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Morphogenetic fields in embryogenesis, regeneration, and cancer: Non-local control of complex patterning

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ABSTRACT

Establishment of shape during embryonic development, and the maintenance of shape against injury or tumorigenesis, requires constant coordination of cell behaviors toward the patterning needs of the host organism. Molecular cell biology and genetics have made great strides in understanding the mechanisms that regulate cell function. However, generalized rational control of shape is still largely beyond our current capabilities. Significant instructive signals function at long range to provide positional information and other cues to regulate organism-wide systems properties like anatomical polarity and size control. Is complex morphogenesis best understood as the emergent property of local cell interactions, or as the outcome of a computational process that is guided by a physically encoded map or template of the final goal state? Here I review recent data and molecular mechanisms relevant to morphogenetic fields: large-scale systems of physical properties that have been proposed to store patterning information during embryogenesis, regenerative repair, and cancer suppression that ultimately controls anatomy. Placing special emphasis on the role of endogenous bioelectric signals as an important component of the morphogenetic field, I speculate on novel approaches for the computational modeling and control of these fields with applications to synthetic biology, regenerative medicine, and evolutionary developmental biology.

1. Introduction and Scope

> "Thus, beyond all questions of quantity there lie questions of pattern, which are essential for the understanding of Nature." – Alfred North Whitehead (1934)

1.1. A Question of Pattern

Embryonic development results when a single cell (the fertilized egg) reliably self-assembles a highly complex pattern appropriate to its species. This process is known as *morphogenesis*—the establishment and creation of 3-dimensional anatomy. During later life, multicellular creatures must maintain their pattern—an active process of *morphostasis* that works to maintain the whole while individual tissues age or are removed by traumatic injury. Some organisms replace large-scale structures during adulthood, illustrating the remarkable plasticity and dynamic control of shape by biological systems. For example, salamanders can regenerate eyes, limbs, lower jaws, hearts, and portions of the brain. The active process of maintaining a complex morphology may likewise be relevant to suppression of cancerous disorganization in favor of cellular activities that are aligned within the morphological needs of the host organism.

A true understanding of the signals underlying this process would enable rational control of growth and form, giving rise to regenerative medicine applications that correct damage done by birth defects, degenerative disease, cancer, traumatic injury, and even aging. Similarly, a mature understanding of the origin and regulation of shape, including its genetic and epigenetic aspects, would deepen our understanding of evolvability (Gilbert et al., 1996; Goodwin, 1994) and have untold benefits for the nascent field of synthetic biology—the bioengineering of functional artificial systems using principles and building blocks abstracted from the biological world (Davies, 2008).

Deciphering and learning to control shape is thus arguably *the* fundamental problem of biology and medicine. Modern molecular cell biology and genetics have made great strides in uncovering the mechanisms guiding cell behavior. However, major questions still remain about the ways in which the activities of individual cells are orchestrated and coordinated to result in large-scale pattern and its regulation (Beloussov, 2010; Gilbert and Sarkar, 2000). This review will discuss classical and recent data bearing on the morphogenetic field as a construct that encapsulates key properties of instructive growth and patterning control. Particular focus is placed on endogenous bioelectrical signals as the physical embodiment of the morphogenetic field.

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1.2. *Defining "Morphogenetic Field"*

The concept of "morphogenetic field" has a number of distinct definitions and a rich history (Beloussov, 2001). For some, it is a descriptive tool not necessarily tied to first principles. For example, D'Arcy Thompson showed a myriad ways in which aspects of living systems often bear striking resemblances to patterns which are obtained as solutions to field equations in physics—potentials of static electricity, magnetism, etc. (Thompson and Whyte, 1942). The discovery of mathematical field-like structures that seem to recapitulate biological patterns (Levin, 1994; Pietak, 2009) does not address directly the question of whether or not those mechanisms are in fact used in biological morphogenesis. In contrast to such "metaphoric" fields, other models explicitly use physical and chemical principles best described by field equations to generate pattern (Brandts, 1993; Brandts and Trainor, 1990a,b; Tevlin and Trainor, 1985), and may describe specific physical or biochemical processes that actually pattern system in question (Briere and Goodwin, 1990; Goodwin, 1985; Goodwin and Pateromichelakis, 1979; Goodwin and Trainor, 1980; Hart et al., 1989).

"Field" denotes both informational and regional relationships (Weiss, 1939). The quintessential property of a field model is non-locality—the idea that the influences coming to bear on any point in the system are not localized to that point and that an understanding of those forces must include information existing at other, distant regions in the system. In a sense, the familiar "morphogen gradient" is already a field model, as it refers to changes of the prevalence of some substance across a spatial domain, as opposed to a single concentration level at some local spot. Cells in vivo are immersed in a number of interpenetrating sets of signals—gradients of chemicals, stresses/strains/pressures, and electric potential (Fig. 1). It remains to be shown in each specific case of pattern formation whether a true field model best explains and facilitates the experimental control of the morphogenetic event in question. In this review, I focus on the spatially distributed nature of instructive patterning signals, discussing the evidence from developmental, regenerative, and cancer biology *for non-local control of pattern formation*. Specifically, these data suggest the hypothesis that many diverse examples of pattern formation are best understood not as cell-level behaviors around any one locale but rather at higher levels of organization.

This way of looking at patterning is far from new. From the perspective of organicism, such fields have been invoked in various guises by Spemann, Weiss, and others (Burr and Northrop, 1935, 1939; Gurwitsch, 1944, 1991; Needham, 1963; Northrop and Burr, 1937; Weiss, 1939). More modern discussions can be found as well, although this is certainly not considered a mainstream subject among the molecular developmental biology community today (Beloussov, 2001; Beloussov et al., 1997; De Robertis et al., 1991; Gilbert et al., 1996; Goodwin, 1982, 1994; Martinez-Frias et al., 1998; Opitz, 1993). While Child was one of the first to propose a physical substratum for these fields—physiological gradients (Child, 1941b), recent data confirm that steady-state bioelectrical properties are likely an important component of this fascinating set of signals (Adams and Levin, 2012b; Levin, 2009, 2012). In addition to these, chemical gradients (De Robertis et al., 1991; Reversade and De Robertis, 2005; Schiffmann, 1991, 1994, 1997, 2008, 2011), shear flows (Boryskina et al., 2011), coherent photon fields (Fels, 2009; Popp, 2009), and gene expression profiles (Chang et al., 2002; Rinn et al., 2006) are additional candidates for mediators of field information during patterning. Nevertheless, formal morphogenetic field models, especially those incorporating specific mechanisms and making testable predictions, are not common. It is hoped that a discussion of modern and oft-forgotten classical data will spur the creation and testing of true field models of pattern formation that will actually be able to predict and explain some of the most remarkable feats of morphogenesis accomplished by biological systems.

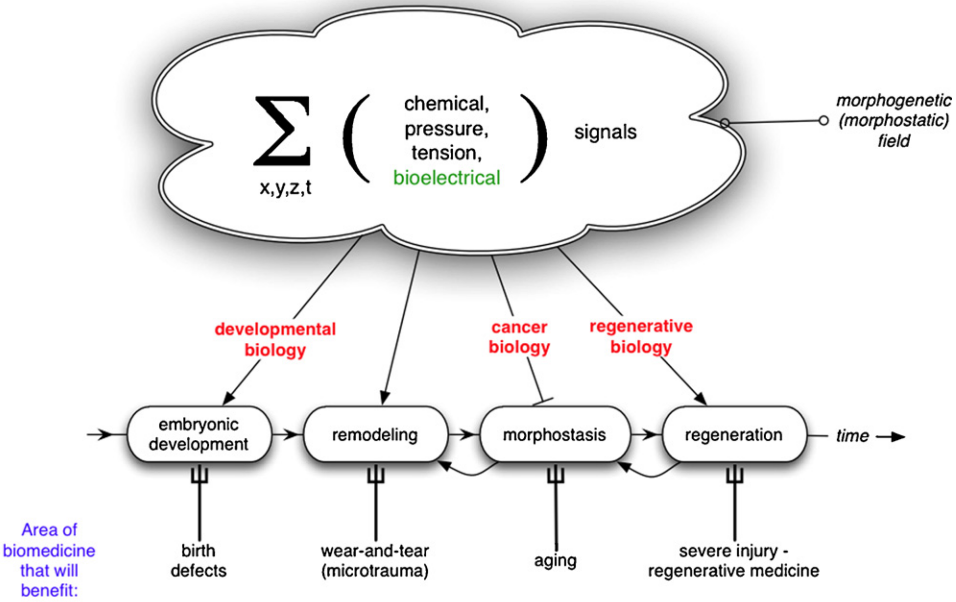

Fig. 1. The morphogenetic field in development, regeneration, and neoplasm and its applications to medicine. The morphogenetic field can be defined as the sum, integrated over 1 temporal and 3 spatial dimensions, of all non-local patterning signals impinging on cells and cell groups in an organism. Functionally, long-range signals (such as planar polarity of proteins on cell surfaces, standing waves of gene expression, voltage potential, and tensile forces, and chemical morphogen gradients) carry information about both the existing and the future pattern of the organism. This allows the initial development of complex form from a single fertilized egg cell, as well as the subsequent maintenance of form in adulthood against trauma and individual cell loss. Errors in various aspects of the establishment and interpretation of these fields result in failures to maintain systems-level properties of anatomical shape, manifesting as birth defects, cancer, aging, and failure to regenerate after injury. Thus, almost every area of biomedicine is impacted by our knowledge of how cells interact with and within this set of complex signals.