Form and the Electrified Organism

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We trust our readers understand that our reporting on current research—even when we find profound significance in it—does not always imply happiness about all the various aspects of the work. We are, in fact, currently looking at some of the issues raised by the kind of experimentation now being conducted on "model organisms," and also at the issues involved in reporting on these experiments. On a separate matter: from a phenomenological perspective, terms such as "molecule," "ion," and "electric field" raise interesting questions concerning what sort of reality one is actually talking about, and how it might best be described. These are matters requiring an ongoing and critical self-awareness as we go about our work.

Since the earliest days of biological science the question, "How does the organism develop and maintain its form, or morphology?" has vexed human inquirers. Today we understand that a zygote (fertilized egg) possesses the ability to become a full-grown organism. But how does this more or less spherical and undifferentiated zygote, with all its contents, "know" to shape itself into a trout or red oak or grey wolf? How do all the dividing cells "know" where and when in the developing mass of the embryo to change into the appropriate cell types and form the appropriate organs?

It's a mystery that has intrigued and puzzled the greatest minds in biology. In the nineteenth century, that fierce defender of Darwin's theory, Thomas Huxley, described his loving observation of the development of one particular organism:

> Examine the recently laid egg of some common animal, such as a salamander or a newt. It is a minute spheroid in which the best microscope will reveal nothing but a structureless sac, enclosing a glairy fluid, holding granules in suspension. But strange possibilities lie dormant in that semi-fluid globule. Let a moderate supply of warmth reach its watery cradle, and the plastic matter undergoes changes so rapid and yet so steady and purposelike in their succession, that one can only compare them to those operated by a skilled modeller upon a formless lump of clay. As with an invisible trowel, the mass is divided and subdivided into smaller and smaller portions, until it is reduced to an aggregation of granules not too large to build withal the finest fabrics of the nascent organism. And, then, it is as if a delicate finger traced out the line to be occupied by the spinal column, and moulded the contour of the body; pinching up the head at one end, the tail at the other, and fashioning flank and limb into due salamandrine proportions, in so artistic a way, that, after watching the process hour by hour, one is almost involuntarily possessed by the notion, that some more subtle aid to vision than an achromatic, would show the hidden artist, with his plan before him, striving with skilful manipulation to perfect his work. (Quoted in Barfield 1963, pp. 144-5)

Today, in this age of molecular biology and invisible "building blocks," you can hear very different descriptions of embryonic development. A great deal is said, for example, about gene networks and cascades of gene expression producing proteins, which then diffuse throughout cells and tissues, creating various chemical gradients. Then, depending on the nature of the interacting gradients at particular locations, the proteins at those locations stimulate the expression of further genes, and so it goes on.

But there is no more *explanation* of form in this kind of description than there was in Huxley's rather more poetic one. It's just that patterns of gene expression and chemical gradients are substituted for the patterns produced by finger tracings and the invisible trowel. Certainly it is right to dismiss the fanciful finger and trowel, but they were merely a way of drawing attention to significant form. And far from being *explained* by genes and chemical gradients, this form is now simply being *described* at another level of observation. For, after all, the complex patterns of gene expression and chemical flows are no less manifestations of form than the precisely corresponding form they are meant to explain. (How could it be otherwise?) And this process of explanation seems to go on forever, since those gene expression patterns and elaborately structured chemical gradients need their own explanations, and on the trail of such explanations we find ourselves pursuing pathways that lead us further and further throughout the entire organism and invoking ever new manifestations of form (Talbott 2007).

The organism can at times seem to be almost nothing but interweaving fields of form. There are the forms of individual chromosomes, elaborately structured by the seemingly endless modifications that now are being related to gene expression as "controlling" factors. There is the way chromosomes position themselves in the nucleus, writhing and interacting with each other and with other nuclear "bodies" under all the influences working into the nucleus from the cell as a whole. There is the finely detailed transport and localization of RNAs and proteins to the "correct" places in the cell; the continual shaping and re-shaping of the cell's outer and internal membranes, each with its own significant and ever-changing mosaic of embedded proteins and other molecules; the spatial and temporal rhythms of various signaling processes; and so on without end.

And now, after several decades of low-key investigation—long kept in the background due to the prevailing fixation upon genetics and related molecular studies—another kind of form is suddenly and dramatically breaking in upon the awareness of biologists. Dynamically changing electric fields, it is now becoming evident, can play a crucial role in structuring the developing organism.

The Shaping Power of Bioelectric Fields

Last July a team of researchers at Tufts University near Boston produced a startling, time-lapse video in association with a paper they published in *Developmental Dynamics* (Vandenberg et al. 2011). It showed a developing tadpole embryo, and due to the use of special dyes that reported the electric potential across cell membranes, areas of the image successively lit up brightly and then went dark. The researchers' focus was on the development of craniofacial features, and what was striking was the way something like an image of the face lit up prior to the actual development of the corresponding features. Regional changes in electric potential, these scientists concluded, "regulate expression of genes involved in craniofacial development."

The electric fields at issue here need to be distinguished from those routinely studied in nerve and muscle cells. Whereas nerve impulses act on a scale of milliseconds, the fields now getting attention can be maintained from minutes to days. They result from, among other things, the flow of ions across cell membranes, and because of the communication channels between cells, entire groups of cells can develop roughly the same membrane potential at any particular time.

According to Michael Levin (2012), director of the Center for Regenerative and Developmental Biology at Tufts, where the tadpole research was performed, "Ion flows and the resulting V_{mem} [membrane voltage] changes are components of long-range conversations that orchestrate cellular activities during embryonic development, regeneration, and ... tumor suppresion." He adds that "bioelectric cues are increasingly being found to be an important regulator of cell behavior," controlling the proliferation and death of cells, their migration and orientation, and their differentiation into different cell types. "We are," he writes, "just beginning to scratch the surface of the bioelectric code—the mapping between voltage properties and patterning outcomes, akin to the genetic, epigenetic, and perhaps other codes remaining to be discovered."

Bioelectric fields are the result of physiological processes at a considerable remove from gene expression. While genes are certainly required, for example, in the production of the ion-transporting proteins that help produce electric fields, bioelectric signaling of the sort involved in craniofacial patterning of the tadpole is, Levin emphasizes, not in the first instance a genetic event, but "a *physiological* event ... causally responsible for a given patterning outcome." Bioelectric states, in other words, "are an important source of *non*-genetic heterogeneity." Cells in which genes have produced the same set of ion-transport proteins can generate completely different membrane potentials, while cells differing in their gene-expressed proteins can generate the same membrane potential. And, in either case, the potentials—so Levin and the tadpole researchers are arguing—can stimulate cascades of gene expression leading to the formation of entire organs.

But the most dramatic development is still more recent. A second group of researchers in Levin's laboratory (Pai et al. 2012) has now manipulated the membrane potentials of tadpole cells destined to become eyes, with the result that the eyes became deformed. The extent of deformation (all the way to complete loss of the eyes in some cases) was correlated with the extent of deviation from the normal, eye-associated electric field.

Moreover, the researchers did the reverse: on the back and tail of a frog embryo they altered the membrane voltage to be that of normal eye regions, and by this means they succeeded in producing more or less eye-like formations in these decidedly unexpected places. It is indeed a startling and surprising discovery, which is the way the researchers themselves seem to have experienced it. Surely the experiments pose many puzzles and will require a lot of reckoning from the community of biologists in the coming months and years.

Looking for Explanations

Electrical phenomena in organisms have been recognized for a very long while. It's not only the dominance of genetics during the era of molecular biology that has moved this field of inquiry to the background, but also the appeal electrical effects have had for the ignorant and deceptive.

As University of Aberdeen biologist Colin McCaig and colleagues (2009) write, "In the past, bogus electrical therapies to 'cure' ailments ranging from impotence to baldness were common. 'Electric air baths', for example were a popular Victorian spa treatment and, when Mary Shelley was writing *Frankenstein*, public demonstrations using electrical shocks to raise corpses were popular for their theatrical impact. Much of the bad reputation associated with bioelectricity is rooted in this quackery."

The more recent work will surely change this. McCaig et al. note many of the now well-established findings in the field of bioelectricity (some of which were first recognized many decades ago):

> Bioelectricity influences cellular processes as fundamental as control of the cell cycle, cell proliferation, cancer-cell migration, electrical signalling in the adult brain, embryonic neuronal cell migration, axon outgrowth, spinal-cord repair, epithelial wound repair, tissue regeneration and establishment of left-right body asymmetry. In addition to direct effects on cells, electrical gradients interact with coexisting extracellular chemical gradients. Indeed, cells can integrate and respond to electrical and chemical cues in combination. (McCaig 2009).

One thing I'm confident of is that the range of interactions and contextual dependencies will continually expand as the research continues. Nevertheless, old habits die hard, so that one reads in the literature, for example, how "transmembrane voltage gradients *determine* anatomical polarity and function as *master regulators* during appendage regeneration and embryonic left-right patterning." Similarly, electric fields are said to *control* this or that, and biologists are urged to *crack the bioelectric code*. It recalls the way particular genes have been designated master regulators, only to be caught up in sprawling networks of interacting, fluid, bi-directional causes as the whole field of gene regulation research has explosively expanded to encompass just about anything and everything going on in the organism.

The habit of mechanistic thinking received a huge impetus during the era of molecular biology, and will not disappear quickly. Every new discovery is supposed to cause, control, or determine something. Its action is supposed to be definitive, corresponding to a one-dimensional code. Yet what we always find is meaningful context, significant form, a weaving together of causes that are never precisely repeated in the same pattern and therefore are never precisely the same causes. Causes of the moment are forever being transformed and adapted to the particular character and strivings of the organism (Talbott 2010; 2011).

The fact is that we understand the organism through the elucidation of its many dimensions of form. We do not so much explain form, as explain by means of form. Even the physicist, in applying mathematically formulated laws, is invoking a kind of abstract form. The problem the biologist (curiously, much more than the physicist) has with this is that dynamic form is not a physically graspable thing, and therefore is not accepted as a principle of explanation, but rather is thought to need explanation. But the organism is what it is, and therefore biologists will continue along the path they have really, in their best work, been traveling from the very beginning: recognizing the character and functioning of organisms by exploring at every level and in every dimension the expressing, gesturing, forming, and transforming "speech" by which each organism declares its own distinctive way of being.

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