DNA and the Whole Organism

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Here are a few excerpts adapted from a very much longer article, "From Genes to Evolution: The Story You Haven't Heard." My intention in that article was to illustrate some of the immediate lessons I've gained from the past several years spent studying gene regulation and related topics, and then to shift attention toward the broader implications. And so I made the most systematic effort I have ever undertaken to picture how DNA and genes actually relate to the rest of the organism, and then I tried to show how this bears on our understanding of organisms and their evolution. If we take the picture seriously, we find ourselves with a biology and an evolutionary theory turned "upside down and inside out." The following excerpts contain nothing about evolution, and not much about DNA; they are mostly drawn from various introductory or summary portions of the article. The full text is available at RediscoveringLife.org/ar/2015/genes_29.htm.

You can hardly turn around today without hearing from this or that biologist or philosopher that we have gone beyond old, narrow conceptions of genes (certain DNA sequences) as the makers of organisms. And ours is indeed a time of great and bracing change—change, even, that portends revolution. Yet genes are still almost universally regarded as the true bearers of destiny within the organism, and "genetic" remains an entrenched synonym for "heritable." In other words, genes retain their status as the one intrinsic factor truly definitive for the life of the organism. Implications of the fact that organisms exist and act as wholes remain taboo.

The taboo is not hard to understand, since we can fully acknowledge an organism's agency only by abandoning the materialism and the machine models that have captivated biologists for so long. This is why we see such widespread efforts today to understand this agency by denying it—that is, by tracing and adding together (in "networks" and "systems") local and momentary causal interactions from which the coordinating agent has been excluded.

Some do acknowledge, it is true, that the "system's" behavior cannot be predicted from its parts—cannot, in fact, be decomposed into stable parts at all. But even they, faced with the question where the actual unity and behavior of the organism reside (Who is doing the behaving?) seem reluctant to acknowledge that the organism's coherence is a coherence of intention, idea, and reason operating at the organic level.

The word "agency" may be infiltrating the vocabulary of some philosophers and biologists, but one guesses that they can mention the necessarily implied *being*, or *agent*, only at peril of their career.

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Genes and Cells: Who's Regulating Whom?

Perhaps you are too cold or too hot, hungry or sated, coming down with a flu or recovering from it, lifting weights or resting, thinking hard or yielding to reverie. Perhaps you have a wound that is healing, or have just now suffered a terrible psychological shock, or are concluding an intense lecture to college students. Or perhaps not much has happened at all, except that the sun has moved from the eastern to the western horizon.

Whatever your changing circumstances, the unseen physiological consequences could hardly be more dramatic. The performances of countless cells in your body are redirected and coordinated as part of a global narrative for which no localized controller exists. This redirection and coordination includes a unique choreography of gene expression in each individual cell. Hundreds or thousands of DNA sequences move (or are moved) within vast numbers of cell nuclei, and are subjected to extraordinarily nuanced, locally modulated chemical activity so as to contribute appropriately to bodily requirements that are nowhere codified—least of all in those DNA sequences.

But let's place before our attention a more concrete picture.

In his little book, *The Directiveness of Organic Activities* (published in 1945), British biologist E. S. Russell describes contemporary work on wound healing in the blood-sucking hemipteran bug, *Rhodnius prolixus*. Beneath the hard, outer cuticle of this insect is a single layer of epidermal cells on top of a basement membrane. If you excise a tiny sliver of these tissues, you set in motion a remarkable series of healing processes.

To begin with, the neighboring epidermal cells become activated and migrate toward the edges of the cut, while red blood cells accumulate in the same area beneath the basement membrane. Having congregated at the site of injury, the epidermal cells then spread into the excised area.

In simple cases, where the wound is small and the basement membrane intact, the wound is quickly covered by a few cells that are spread excessively thinly, with cytoplasmic bridges connecting them. As more cells follow these, they become more and more crowded until the normal density is reached, at which point the spreading ceases. After the migration, cell division continues, but mainly in the now-thinned area from which the migrating cells came. As for the cells that spread over the cut, they initially form a layer several cells thick, but the normal one-layer-thick epidermis is slowly restored through selective degeneration of the unwanted cells in the lower layers. Any overcrowding around the margins of the wound resulting from the migration of cells is similarly relieved by the degeneration of superfluous cells.

Rhodnius prolixus

It's good to imagine this elaborately organized, sequential activity in detail. There can be no doubt that we are seeing a norm—the organism's own unique wholeness and integrity—being reestablished:

> The end-state or terminus towards which the process moves is the restoration of the continuity of the epidermis, the replacement of cuticle and basement membrane, the re-establishment of the normal density of nuclei—a complex result, reached through appropriate activities of cells, which are here the agents concerned. These activities are of several kinds. They are behavioral—as shown in the active migration and spreading of the epidermal cells. They are physiological, as in the secretion of new cuticle. They are "morphoplastic," as in activation and cell division; cells also degenerate where they are superfluous or unwanted.

Most interesting, however, is what happens when conditions are varied, and the same norm is restored, but by a very different route. For example, using heat, it's possible to destroy a group of epidermal cells without injury to the overlying cuticle. In this case there is little migration toward the burn margin from surrounding areas. Rather, the existing cells at the immediate margin begin to fill in over the layer of burned cells—and they do so through multiplication within this zone of spreading rather than through migration from the periphery.

Compare this with the incision, where the injured area was filled to "overcrowding" by migration, with subsequent die-off of excess cells in the injured area. And whereas, with the incision, cell multiplication occurred in the more distant regions from which migration occurred, in the case of the burn, multiplication takes place in the injured area.

It seems that a general truth of healing processes is that they culminate, as far as possible, in the restoration of normal form and functioning. Depending on conditions, there can be a remarkable variation of means toward this end.

The point is not at all that there are no lawfully connected physical processes every step of the way, but only that the immediate causal factors are caught up in a larger pattern that governs them. No study of well-behaved local interactions shows us why those interactions are coordinated in the plastic, goal-directed, context-sensitive manner we observe—a manner that enables them to reach the same end by different pathways, depending on the circumstances encountered.

When we look at pattern in this way rather than adding together separate physical causes, we see a logic of the pattern as such, not a necessity for any particular causal sequence.

It is, of course, a long way from the simplest possible injury of *Rhodnius prolixus* to a complex wound of *Homo sapiens*. Here is a general description of the kind of thing that goes on when you or I suffer the "assaults" of a surgeon—wounds typically of a sort that our species never before encountered during its evolutionary history. It comes from another British biologist, Brian Ford:

> Surgery is war. It is impossible to envisage the sheer complexity of what happens within a surgical wound. It is a microscopical scene of devastation. Muscle cells have been crudely crushed, nerves ripped asunder; the scalpel blade has slashed and separated close communities of tissues, rupturing long-established networks of blood vessels. After the operation, broken and cut tissues are crushed together by the surgeon's crude clamps. There is no circulation of blood or lymph across the suture.
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> Yet within seconds of the assault, the single cells are stirred into action. They use unimaginable senses to detect what has happened and start to respond. Stem cells specialize to become the spiky-looking cells of the stratum spinosum [a layer of the epidermis]; the shattered capillaries are meticulously repaired, new cells form layers of smooth muscle in the blood-vessel walls and neat endothelium; nerve fibers extend towards the site of the suture to restore the tactile senses . . . These

> phenomena require individual cells to work out what they need to do. And the ingenious restoration of the blood-vessel network reveals that there is an over-arching sense of the structure of the whole area in which this remarkable repair takes place. So too does the restoration of the skin. Cells that carry out the repair are subtly coordinated so that the skin surface, the contour of which they cannot surely detect, is restored in a form that is close to perfect. (Ford 2009)

It is well to reflect diligently upon that phrase, "an over-arching sense of the structure of the whole area." It is not a phrase that biologists today know what to do with. Who or what possesses this sense? And if "sense" is the wrong word, what is the right one?

Cells Caught Up in an Intentional Whole

Think concretely about that surgical wound. You're a nearby epidermal cell, and you need to migrate. In which direction? When do you stop? And how do you reorganize all your constituent elements so as to bring yourself into movement—movement away from the place where you've long been settled?

Or you're a nerve cell, and you need to participate in the extension of a nerve fiber. Again, in which direction, and by means of what sort of mobilization of all your internal processes?

Or perhaps you're a stem cell and you need to begin a process of differentiation. But differentiation into what sort of other cell? And how do you go about a radical change in who you are? If change is going on everywhere around you, what gives anything its specific "operational advice"?

Everything needs to be accomplished in the right sequence, and in harmony with everything else going on—all this amid what looks for all the world like a chaotic disaster scene. How are we to imagine the ultimate and nearly incomprehensible *coherence* of the larger picture?

Now, rare is the biologist today who will hear such questions without thinking: "He is trying to suggest that there is no physical explanation adequate to these living processes. So he believes there must be some sort of vital force or miraculous guidance to make things happen."

But this misses the mark entirely. The physical continuity of the entire scenario is unquestioned. Russell, for example, is always looking for immediate physical interactions. In *Rhodnius prolixus*,

> observation shows that the migrating cells are specially attracted towards areas containing dead and damaged cells, and this suggests that the stimulus to activation is provided by chemical substances produced by the injured cells, and that migration towards the wound is a "chemotactic" response to these substances.

Yet Russell does not confuse this physical continuity of local interactions with what he somewhat awkwardly refers to as the "directiveness" of the larger storyline in which these interactions are caught up. It's a confusion that biologists today almost universally consent to.

It's not hard to observe one's own reaction to the statement that migrating cells are activated and directed by a chemical gradient resulting from the death of nearby cells. "Oh, that explains it." But what has happened with this "explanation"? The entire picture of cell migration—a complex mobilization of the cell that biologists have barely begun to understand—has been reduced in thought to an object here and an attractant there. It's an almost mechanical schema—hardly problematic at all! We might as well be thinking of two rigidly interlocking gears, given that we have blocked from our minds the crucial thing: how do all the physical interactions adaptively cohere as part of meaningful, "directive" processes, such as wound healing?

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DNA as Part of a Whole

(This section contains a few summary comments relating to material in the original article.)

A decisive problem for the classical view of DNA is that "as cells differentiate and respond to stimuli in the human body, over one million different proteins are likely to be produced from less than 25,000 genes" (de Almeida and Carmo-Fonseco 2012). Functionally, in other words, you might say that we have over a million genes. But here the word "gene" cannot refer to a defined sequence of genetic "letters." It must refer, in the first instance, to certain characteristic, context-dependent activities of cell and organism—activities in which DNA figures along with innumerable other players.

A useful way to begin thinking about the reality of genes is by overcoming the false picture of DNA as an idealized, geometric configuration. Since Francis Crick and James Watson's elucidation of the structure of DNA in 1953, biologists have been "in denial," according to *Nature* columnist, Philip Ball. "That beautiful double helix, with its genetic information written into the spiral staircase of paired nucleic-acid bases, offers such an elegant picture of the chemical principles of life and inheritance that everyone fell for it."

The Genome in Dynamic Nuclear Space

A few comments from the literature:

- "The dynamic spatial organization of the nucleus both reflects and shapes genome function . . . We now have a picture of a genome that is 'structured,' not in a rigid three-dimensional network, but in a dynamic organization [that] clearly changes during normal development and differentiation" (Fraser and Bickmore 2007).
- Researches have revealed "the astounding degree to which our genome . . . appears to be dynamically utilized for the purposes of gene regulation" (Joanna Wysocka, in Dekker, Wysocka, Mattaj et al. 2013). Of course, the question most immediately implied doesn't get asked: utilized by whom, or by what?
- Although the researchers' first impulse was to find in chromatin modifications (such as histone tail modifications) another "simple code," it eventually became evident, according to geneticist Shelley Berger of Philadelphia's Wistar Institute, that "a more likely model is of a sophisticated, nuanced chromatin 'language' in which different combinations of basic building blocks yield dynamic functional outcomes" (Berger 2007).
- "What was previously known as junk DNA in fact appears a regulatory jungle. In order to understand the laws of the jungle, linear information must now be converted into spatial relationships" (Splinter and de Laat 2011).
- Indeed, the almost exclamatory recognition that "Genomes are incredibly dynamic" (Chalker and Yao 2011) in both space and time has become commonplace today, even if it still seems to surprise many. But the appropriate questions have scarcely been addressed as yet. No one would argue that DNA itself is "incredibly dynamic," for it is just about the most inert substance in the cell, at times approaching an almost crystalline state. It is the cell as a whole that brings our DNA and chromosomes into the movement and directed activity through which they are made to serve the needs of digestion, muscular exertion, sensory perception, and all our other biological functions.
- "The sequence of our genes are [sic] like the keys on the piano; it is the context that makes the music" (Bissell and Hines 2011). Except that the raw sequence does not even contain all the keys; let's say: just the white keys. The flats and sharps, without which the music would lose its savor, are provided by DNA methylation, RNA editing, and more.

The image Ball refers to has become a dominant icon of the modern era, channeling the imagination along the alluring lines of its own geometric perfection. Yet its ubiquity and influence is matched only by its falsehood. For "when we come face to face with DNA in the cell," writes Ball, "it's like meeting a movie star whose airbrushed publicity photos don't look at all like the real thing. You would barely recognise Crick and Watson's perfectly-formed molecule in the tangled, twisted and bent spaghetti that is stuffed inside the nuclei of our cells" (Ball 2008).

In living cells the double helix is "distorted" in every possible way—due, among other things, to the endlessly morphing intricacies of *chromatin,* the massive, ever-changing, protein–RNA complex engaged with DNA in a mutual embrace. We can only assume that this plastic receptivity of the double helix is part of its gift to the life of the organism.

And it is indeed the *life* that we are witnessing at every point and in every detail. The organism manages its DNA with a wisdom, thoroughness, efficiency, and expertise beyond all current possibilities of comprehension. For example, the subtleties of DNA replication rival those of gene transcription [which the main article focuses on] and are, in fact, intimately woven together with processes of gene regulation. But the organism's intentions and activities relative to its DNA are evident on other fronts as well.

There is, for example,

- the play upon chromosomes of mechanical forces from throughout the cell and beyond;
- the infinitely varying electrical forces between DNA and the diverse elements of the dynamically changing chromatin it is bound up with;

- the all-important (if transient) "mooring" contacts between DNA and the more or less stable structures of the nucleus, especially the nuclear envelope;
- the positioning of different parts of the genome in the nucleoplasm relative to significantly gathered concentrations and mixtures of molecules participating in gene expression;
- the looping of chromosomal regions on various scales in order to bring the right "team players" together;
- the formation of all sorts of unusual DNA structures, including three- and four-stranded structures, which play a role in gene regulation—

all this and much else contributes to the cell's management of gene expression, quite apart from the more routinely recognized players: interacting transcription factors, co-activators and co-repressors, promoters and enhancers, splicing factors, and all the rest.

The organism's expertise in managing its DNA cannot be questioned. It is capable of inserting new sequences in DNA, deleting old ones, moving them from here to there, exchanging them between chromosomes, and so on. Even the repair of breaks in DNA is not always merely repair. The cell can make such events the occasion for its own remodeling of the genome. In fact, it is continually *initiating* single- and double-strand breaks, then stitching things back together—a frequent enough requirement, if only to facilitate the organization, disentanglement, and proper physical characteristics of the DNA (such as the degree of double-stranded "twist"). To get a picture of the challenge in simply preventing hopeless entanglement, consider that the amount of DNA in a human cell nucleus is equivalent to twenty-four miles of extremely thin, double-stranded string crammed into a tennis ball.

Sometimes individual genes or sections of a chromosome are duplicated in certain cells. But genome remodeling goes beyond this. Megakaryocytes (cells involved in platelet production in bone marrow) have up to 128 copies of the entire genome; hepatocytes (liver cells constituting some 3/4 of the liver's mass) typically have 4 to 8 copies; trophoblast giant cells in the embryonic outer layer may have up to 1000 copies; and cardiomyocytes (heart muscle cells) usually have 4 copies of the genome. In some cell types such as skeletal muscles, there are many separate nuclei in a single cell, each with its full complement of DNA.

The still-routine statement (I have sometimes acquiesced in it myself) that "all the cells in our body have the same DNA" has been found to fall further and further from the truth. According to a recent report, "perhaps the quantity of nuclear DNA content in human cells is best viewed as a distribution of values" rather than as a single value. New analyses are suggesting that "systematic variation in nuclear DNA content is a more ubiquitous phenomenon in human cells than was previously appreciated" (Gillooly, Hein and Damiani 2015).

Let me then state one lesson clearly: *the organism knows what it is doing* with its DNA, as with all its molecular activities. Yet this living, active, and governing wisdom that we confront face to face in every organism seems to threaten a kind of theoretical paralysis in biologists, who have therefore long since learned to ignore it as they pass by, whistling innocently.

References

Ball, Philip (2008). "Pulling Our Strings," *Chemistry World* (May). Available online: http://www.rsc.org/chemistryworld/Issues/2008/May/PullingOurStrings.asp

Berger, Shelley L. (2007). "The Complex Language of Chromatin Regulation during Transcription," *Nature* vol. 447 (May 24), pp. 407-12. doi:10.1038/nature05915

Bissell, Mina (2011). "Why Don't We Get More Cancer? A Proposed Role of the Microenvironment in Restraining Cancer Progression," *Nature Medicine* vol. 17, no. 3 (March), pp. 320-9. doi:10.1038/nm.2328

Chalker, Douglas L. and Meng-Chao Yao (2011). "DNA Elimination in Ciliates: Transposon Domestication and Genome Surveillance," *Annual Review of Genetics* vol. 45, pp. 227-46. doi:10.1146/annurev-genet-110410-132432

de Almeida, Sergio F. and Maria Carmo-Fonseca (2012a). "Design Principles of Interconnections between Chromatin and Pre-mRNA Splicing," *Trends in Biochemical Sciences* vol. 37, no 6 (June), pp. 248-53. doi:10.1016/j.tibs.2012.02.002

Dekker, Job, Joanna Wysocka, Iain Mattaj et al. (2013). "Nuclear Biology: What's Been Most Surprising?", *Cell* vol. 152 (March 14), pp. 1207-8. doi:10.1016/j.cell.2013.02.041

Ford, Brian J. (2009). "On Intelligence in Cells: The Case for Whole Cell Biology," *Interdisciplinary Science Reviews* vol. 34, no. 4 (Dec.), pp. 350-65. doi:10.1179/030801809X12529269201282

Fraser, Peter and Wendy Bickmore (2007). "Nuclear Organization of the Genome and the Potential for Gene Regulation," *Nature* vol. 447 (May 24), pp. 413-7. doi:10.1038/nature05916

Gillooly, James F., Andrew Hein and Rachel Damiani (2015). "Nuclear DNA Content Varies with Cell Size across Human Cell Types," *Cold Spring Harbor Perspectives in Biology* 2015;7:a019091 (July). doi:10.1101/cshperspect.a019091

Russell, E. S. (1945). *The Directiveness of Organic Activities*. Cambridge UK: Cambridge University Press.

Splinter, Erik and Wouter de Laat (2011). "The Complex Transcription Regulatory Landscape of Our Genome: Control in Three Dimensions," *EMBO Journal* vol. 30, no. 21, pp. 4345-55. doi:10.1038/emboj.2011.344