Promising Themes in Molecular Biology

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Step back and survey the philosophical commitments evident in the major biological journals, the massive biological research community, and the huge public and private funding organizations, and you may be forgiven for feeling a certain discouragement. It sometimes seems as though the entire world of institutional biology speaks with a unified voice — a voice testifying to the apparently unstoppable inertia of an oppressive and misconceived materialism, and an obsession with explanatory *mechanisms*. And this orthodoxy has managed to erect seemingly impregnable barriers to protect itself against fundamental change.

I will not quarrel with this picture. But pay closer attention and you will hear some unexpected notes sounding a hopeful counterpoint to the monotonous drumbeat of orthodoxy. I would like to highlight, ever so briefly, a few signs of potential health and transformation, particularly in the literature of molecular biology.

Putting Molecules in Context

In one way or another nearly the entire body of current biological research at the molecular level has come down to a reckoning with problems of context. And there seems to be a growing consciousness of this fact, even if its radical implications have not yet dawned on many. For example, the editors of *Nature Reviews Genetics* recently asked, "How much complexity is being concealed by doing research on gene regulation and function in a limited range of biological contexts? ... biology is rarely simple, and studies in multiple contexts often reveal a fuller picture."[1]

Similarly, bioinformatics researcher Alberto de la Fuente, discussing the ever more vexed topic of the relation between genes and disease, reminds us that "To understand the roles of genes in complex human diseases, genes need to be studied in the context of the regulatory systems they are involved in." Further: "Gene networks are context specific: the regulatory structure among genes depends on the developmental stage, cell type, environment, genotype and disease state."[2]

And again, Neil Greenspan, an immunologist and clinical pathologist at Case Western Reserve University, wrote that "A crucial aspect of molecular function, whether with respect to proteins, nucleic acids, other macromolecules or even small molecules, is that function, as normally understood, is generally not a completely intrinsic attribute of a molecule. Most function arises out of the interactions between molecules or between forms of energy and molecules."[3]

The point may seem painfully obvious to many readers of *In Context*, yet it is laden with revelation in a world where the expression, "DNA *makes* RNA and RNA *makes* protein" has become a truism — as if a given molecule could carry the decisive responsibility for *making* anything! And so, as the reality of context and interaction — the reality that life is characterized most essentially by complex *processes*, not *things*, and that the organism as a whole is the organizer of these processes — begins to sink in, we hear countless "wake up calls" of the following sort (to take a few isolated examples):

- "The array of axonal glycoproteins acting as receptors for growth signals may be far more complex than we thought."
- "Induction of cellular immunity seems to be even more complex than we thought 15 years ago."
- "The numerous recent reports of stem cell plasticity suggest that human stem cells will be even more complex than we thought a year or two ago."
- "Obesity and hypertension–the issue is more complex than we thought."
- "Transcriptional networks for lignin biosynthesis: more complex than we thought?"
- "To explain the differences with previous renal studies on this topic, one has to point to several important differences with respect to species, type of stem cells, time course of renal injury, etc .... matters are much more complex than we thought only a few years ago ... Currently, to quote G.B. Shaw, "We have the privilege to be confused on a much higher level."

Of course, taken by themselves, such isolated remarks, extracted from a search engine, don't mean much of anything. But what strikes anyone looking at the current literature is the dramatic way virtually every topic — *every* type of molecular interaction — is being "opened up" to a wider world of exchange in previously unanticipated ways. Connections are being forged in all directions, so that the *crosstalk* between different processes has become an incessant theme, and everywhere one finds the acknowledgment that *context matters*.

The problem in conveying what is going on today is that the only way to do so is to describe the kind of contextual complexity these biologists are talking about — and this would quite naturally require extraordinarily complex descriptions! The cellular interactions are so remarkable, so extensive, so stunning in the coordinated and meaningful play of interweaving factors, that it would take a huge article to do any sort of justice to the reality of even "one" process, and that article would be stuffed with unfamiliar technical terms. I am, therefore, reduced to the unfortunate position of offering a few relatively bland generalities.

One increasingly common theme is that a given factor known for playing some particular role in a cellular process will eventually be found also to play a more or less opposite role in some circumstances. For example, there has been a great deal of excitement in recent years about "epigenetics" — and, specifically, the way various molecular groups (or "marks") attached to the protein structure of chromosomes can affect whether or how a nearby gene is expressed. It turns out, however, that not only do different marks have entirely different associations with gene expression, but the *same* mark can have quite opposite associations, depending on the context. In fact, the innumerable possible combinations of these marks are now presenting biologists with an expressive potential that begins to rival that of the genome itself. The closer we look at chromosomes, one group of researchers wrote, "the more these canonical associations between a given mark and gene expression become nuanced and idiosyncratic."[4]

But it's not just a matter of divergent pictures regarding one particular function. A striking theme in the literature has to do with the fact that almost any given element of the cell is caught up in many different functions, reflecting at its own level the overall contextual unity of the cell. For example, the FOXL2 transcription factor (transcription factors are proteins that bind directly to DNA to help regulate gene transcription) plays a major role in sex determination and female fertility; in its absence the ovaries develop characteristics of testes. But FOXL2 is also involved in the oxidative stress response, the maintenance of cholesterol balance (homeostasis), and steroid hormone production.

Likewise, the p53 protein has received huge attention as a transcription factor with a major role in suppressing tumors. Cancers often involve defects in this protein. But "emerging studies have shown that, in addition to its ability to function as one of the most important tumor suppressors, p53 also controls many other biological functions, including implantation [of the embryo in the uterus], cell-fate decisions, metabolism, and aging."[5]

Again, histones are proteins that form a crucial part of the DNA/RNA/protein complex comprising the structure of chromosomes. Many of the chemical groups ("marks") mentioned above as modifying chromosomes, attach to these histones, with dramatic effects on chromosome structure and gene expression. However, the "so-called histone-modifying enzymes have other roles in the cell beyond histone modifications."[6] So it's not just that differently contextualized marks exert different influences; it's also the case that the enzymes supplying these marks do many other things in the cell. And those enzymes in turn are powerfully affected in their function by yet other molecules that modify *them* ... and such lines of influence, when followed up, eventually merge untraceably into the sum total of the life of the organism. It's a story being told over and over in every field of molecular biology.

And as for genes themselves, they can hardly be thought of as discrete, neatly causal entities. "Diverse genetic loci are organized hierarchically into interconnected genome-wide networks which function dynamically. Not confined to a single pathway, many genetic loci are active at different times, participating in the expression of more than one phenotypic [observable] trait."[7]

In sum, the intense focus of a great mass of today's research has to do with networks, interactivity, dynamism, plasticity, and context. Nothing has just one meaning, and nothing means anything all by itself. One hears "systems biology" being invoked on every hand.

Unfortunately, in common usage "systems biology" today means little more than "we should use computers to try to track the myriad interactions bearing on any given process" — which is fine as far as it goes. But it does not go nearly far enough. Researchers typically pursue interactions in the cell and organism only to the degree they are forced to, and they consider the job done when they think they have "nailed down" local causal factors. The old governing conviction remains strong: we understand the organism by adding isolated cause to isolated cause.

But that's not how the organism works. Every organism is telling a story, not merely being "pushed around" by physical causes. This is why the biologist has to reckon with *contexts*. A collection of parts, or even of words, as in a

dictionary, is not a context in any relevant sense. It becomes a context by being woven into a coherent, meaningful narrative. And our understanding of this narrative arises, not only by considering the causal impact of part upon part or word upon word, but also by entering into the meaning of the whole as it works its way down into, and gives specific content to, all the individual words.

If biologically significant causation flows from the whole to the part, then we must learn, not merely to isolate all the words of the context, but to *think the context as such*, which is also to think the organism as such. This requires us to think qualitatively, a challenge that has as yet scarcely even been formulated as a possible goal within biology.

The Fluent Organism

The old logic — DNA makes RNA and RNA makes protein (and protein makes the organism), all operating in obedience to a kind of mechanistic encoding that originates with DNA and rules the whole organism from the bottom up — while still clearly shaping the mindset of many biologists, is now falling apart. Or, rather, it is being caught up in *fluid* movement. You can glimpse this clearly enough by reading through a single article in *Nature* that briefly traced some of the relevant history. Written in 2003, it talked about the then-dawning awareness of dynamism in the cell nucleus: DNA can "gyrate like a demonic dancer"; the nucleus presents us with "endless acrobatics" and a "subcellular waltz"; whereas the nucleus "was once thought to be fairly static ... now we know it to be a very lively place"; the knowledge of dynamism among DNA-associated proteins "changed the way we thought about the nucleus. The word 'static' is disappearing from our vocabulary."[8]

The organism is above all an organism of movement, or flow. Studies of protein movement have "revealed much more rapid and/or more extensive dynamics than would have been anticipated from either earlier in vitro ["test tube"] work, or from the apparent stasis of certain nuclear bodies, constituting a true paradigm shift in the nucleus field ... Even the nuclear lamina, which had long been viewed as one of the most stable structures in the nucleus, was found to undergo dynamic exchange of subunits ... it was amusing to recall the incredulity expressed by some that interphase chromosomes [chromosomes during the main period between cell divisions], relatively giant structures, are moving, and with no dependence on metabolic energy."[9]

This kind of dynamism is being documented in one domain after another. For example, signaling complexes "typically have half-lives on the order of seconds or less," and the all-important secondary modifications of the molecules in those complexes through the attachment of various chemical groups are "similarly dynamic."[10] The crucial transcription factors — proteins that bind to DNA in order to facilitate or repress gene expression — engage in "highly dynamic interactions ... with their binding sites on the timescale of seconds."[11] Even the structures that give cells their strength and load-bearing ability, such as the plasma membrane and the filamentous cytoskeleton, are caught up in flows. Regarding the cytoskeleton: "Recent work has demonstrated that these structures are dynamic, undergoing assembly, disassembly and movement, even when ostensibly stable."[12] And, again: "The cytoskeleton is not a fixed structure whose function can be understood in isolation. Rather, it is a dynamic and adaptive structure whose component polymers and regulatory proteins are in constant flux."[13]

But it's not just a matter of movement. The rhythm and timing of the movement are coming in for analysis, and are proving to be critically important. The transcription of many genes "has been described to occur in short, discontinuous episodes, called 'bursts'," separated by periods of quiescent resistance to transcription.[14] Perhaps more dramatically, rapid imaging of fertilization in the mouse egg has revealed that "fertilization induces rhythmical cytoplasmic movements that coincide with pulsations of the protrusion forming above the sperm head." Crucially, the character of these movements was found to predict the viability of the eggs.[15]

Oscillations have likewise been noted in key signaling pathways, and "there is growing evidence for the importance of an oscillator's frequency in controlling downstream biological events."[16] And again, "dynamic interactions between oscillators with different frequencies may be a key component of signaling cross-talk in cells. Thus, like cogs in a watch, these networks may interconnect in order to robustly regulate cell fate."[17]

This last remark illustrates the strange mix you often get when new understandings are imported into old mindsets — in this case, when the idea of living flow comes into contact with mechanistic habits of thought. The one thing we do not in fact find in the organism is anything faintly answering to the image of mechanical cogs. The rhythms of the cell are living rhythms, continually modulated by everything going on in the larger surroundings.

There is no place better than the nucleus to show how far from being a mechanism the cell is. The nucleus is populated by numerous organelle-like "bodies" — Cajal bodies, nucleoli, nuclear speckles, paraspeckles, Polycomb bodies, and so on — none of which is in fact an organelle. They all lack a surrounding membrane. But despite this fact, they retain their distinct identities. Moreover, they keep these

identities in the presence of a remarkable in-and-out flow of constituent elements. As one example: nuclear speckles play a role in the storage, assembly, and modification of splicing factors — molecules and molecular complexes that cut apart and stitch together (often in varying patterns) the premature RNA molecules that will eventually participate in the production of proteins. When the turnover rate of a particular splicing factor in speckles was measured, it proved to be on the order of 3 – 5 seconds for replacement of one half of the molecules.

Such rapidity of movement is more the rule than the exception within all the nuclear bodies. "It is a remarkable feature of nuclear organization," write two researchers, that "the overall structure of speckles, as well as other nuclear domains, persists despite the large flux of their components."[18] These bodies seem more like standing waves than mechanical structures.

Fluidity and *plasticity* coming to expression under the influence of a governing *context* — these constitute one pole of the creative tension between plasticity and limitation within which every organism finds its way through the world.[19] The pole of limitation, all too commonly thought of in terms of fixed material structure, rigid causation, and mechanistic determinism, has, of course, long held central place in the biologist's understanding. But the whole idea of a true polarity is that the opposite poles weave through each other and qualify each other. They are held in a tensive unity. Today we can hope that the foundation is being laid for a restoration of balance whereby the organism is perceived as a creature in its own right, bringing its unique character to dynamic expression within the "permissively restrictive" or "restrictively permissive" terms of its physical existence.

On context, meaning, and the organism, see my two articles, "The Unbearable Wholeness of Beings" and "What Do Organisms Mean?" available at http://natureinstitute.org/txt/st/mqual.

On the "fluency" of the organism, especially with reference to genetics and epigenetics, see "Getting Over the Code Delusion" at the same website. All three articles have also been published in The New Atlantis *and are available at http://thenewatlantis.com.*

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