## CHAPTER 8

# The Mystery of an Unexpected Coherence

We heard in Chapter 2 ("The Organism's Story") that living activity has a certain future-oriented (purposive or directive) character that is missed by causal explanations of the usual physical and chemical sort. The end is always more constant than the continually adjusted means. This is true whether we are talking about a dividing cell, the achievement of adult form through development, or the strategy for taking a prey animal for food (or avoiding being taken).

An animal's end-directed activity may, of course, be very far from what we humans know as conscious aiming at a goal. But all such activity, human or animal, displays certain common features distinguishing it from inanimate proceedings: it tends to be *persistent*, so that it is resumed again and again after being blocked; it likewise tends to be *adaptable* — strategies are changed in the face of altered circumstances; and the entire activity *ceases* once the end is achieved.

This flexible directedness — this interwoven play of diverse ends and means within an overall living unity — is what gives the organism's life its peculiar sort of multi-threaded, narrative coherence. Life becomes a story. Events occur, not merely from physical necessity, but because they hold significance for an organism whose life is an unfolding pattern of significances. We are always looking at the *moment-by-moment expression of a present wisdom* — not the automatic playing forward of a pre-existent mechanism.

The idea of a thoughtful wisdom, like the related idea of a governing context (Chapter 6), is a mystery for all attempts at purely physical explanation. This is why even the explicit acknowledgment of an organism's *striving for life* — central as it may be for evolutionary theory — is discouraged whenever biologists are describing organisms themselves. It sounds too much as if one were invoking inner, or soul, qualities rather than material causes — acknowledging a *being* rather than a thing. And it is true that our physical laws as such, however combined, nowhere touch the idea of *striving*.

Biologists much prefer to identify discrete, definitive causes. The cell nucleus with its genome has long been viewed as the seat of such causation. But, as we saw in our discussion of DNA (Chapter 3, "What Brings Our Genome Alive?") and epigenetics (Chapter 7, "Epigenetics: A Brief Introduction"), the single-minded pursuit of genetic causes has forcibly redirected our attention to epigenetics, where we have discovered that genes are circumscribed and given their meaning by the directive life of the entire cell and organism.

In what follows below we will consider this directive coherence in a more detailed way by taking up one of the many activities of the cell that are often considered under the heading of "epigenetics". Then we will look at a startling phenomenon that, already on its face, renders absurd the idea of central genetic control. In both cases we will be focused on molecular-level activity, which is precisely where we have been most strictly taught to expect the absence of any coherence other than that of "blind mechanism".

## *Flexibility and precision in RNA splicing*

The discovery of *RNA splicing* in the late 1970s was one of the transforming moments in the history of molecular biology.[1] To put it in informal terms: the cleanly autocratic mastery of DNA gave way to massive presumption by various scruffy elements of the cellular "rabble". The idea had originally been that a molecule of messenger RNA (mRNA) was produced as a direct image of the "instructions" in a protein-coding gene and was then exported from the cell nucleus to the cytoplasm. There it yielded passively to *translation*, a process whereby a protein was supposedly produced according to the exact specifications of the "genetic code" previously copied from DNA into the mRNA.

Our growing knowledge of RNA splicing has, together with many other developments in molecular biology, exploded just about every aspect of this picture. We now know that, via an elaborately orchestrated improvisational drama, many so-called *epigenetic* elements in the cell (Chapters 7, "Epigenetics: A Brief Introduction", and 14, "How Our Genes Come to Expression") converge to decide what use will be made of any particular gene.

In particular, the cell has innumerable ways to obtain and sculpt its proteins. RNA splicing is just one of these — a massive reconfiguration process whereby a cell decides which portions of an initially produced (*precursor*) RNA to cast aside for other uses, and which ones to "splice" together into a mature mRNA. As we have come to expect by now, these choices are strongly context-dependent, with different protein variants being produced in different kinds of cell or tissue, or under different cellular conditions.

This splicing involves much more than a minor stitch or two. The large human dystrophin gene (whose malfunction is related to some forms of muscular dystrophy) is said to require 16 hours for its transcription from DNA into RNA. Of this time, 15 hours and 54 minutes is required for transcripton of the non-protein-coding RNA sequences that will have to be spliced out of the RNA in order to obtain a mature messenger RNA. That may be a somewhat extreme case, but it remains true that the sequences to be discarded are "commonly orders of magnitude longer" than the remaining portions fit for the synthesis of protein (Papasaikas and Valcárcel 2016).

But perhaps the most dramatic transformation involves the sequence remaining after removal of the non-protein-related ("noncoding") content. The splicing activity can often select from among the parts of this sequence in differing ways, thereby determining which protein-coding portions of the precursor molecule will be included in the mature mRNA. The protein eventually resulting will vary depending on these *alternative splicing* decisions. (The variations of a protein are referred to as *isoforms*.)

The mRNAs generated from over 90 percent of mammalian genes are thought to be alternatively spliced, contributing greatly to physiological complexity (Gehring and Roignant 2021). According to one paper, "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-Fonseca 2012).

Further, “even relatively modest changes in alternative splicing can have dramatic consequences, including altered cellular responses, cell death, and uncontrolled proliferation that can lead to disease” (Luco and Misteli 2011). The title of one technical paper makes the point vividly: “Cell Death or Survival Promoted by Alternative Isoforms of [the protein] ErbB4” (Sundvall et al. 2010).

You have doubtless heard many times how a mutation or engineered alteration of such-and-such a gene “causes” this or that result. How often, by contrast, do you hear that a slight change in the way your cells orchestrate the sculpting of this or that protein can make the difference between life and death?

## The spliceosome

The central player in the sculptural drama of splicing is known as the *spliceosome*, which is not so much a rigidly fixed thing or structure as it is a complex performance. The performers include a few critically important small RNAs and over 150 proteins.[2] Together — although in several, separate, coordinated groups that must continually reconfigure themselves during the process — they excise the protein-unrelated pieces of the RNA and then stitch together a selection of the ones remaining. Misjudging any of the potentially many places to cut the mRNA — shifting the point of severance by a single “letter”, or nucleotide base, out of (in many cases) thousands — could possibly render the resulting mRNA useless for producing protein, if not downright harmful.

We heard a little bit in Chapter 3 (“What Brings Our Genome Alive?”) about the puzzle of topoisomerases. In a way that is difficult to fathom, these molecules make cuts in the DNA double helix in order to release knots and “untangle” the seemingly indecipherable spatial complexity of chromosomes (46 in the human case) that are tightly packed into the cell nucleus. But the challenge for the spliceosome as it does its work seems no less daunting. And the fact that there is indeed coherently describable *work* to do already takes us beyond normal physical explanation to the idea of an unfolding meaning.

The key, chemically active part of the spliceosome complex “is short lived and reconstructed from individual pieces for each splicing event” (Papasaikas and Valcárcel 2016). This is the part that actually cuts and stitches together the RNA once the end-points for the next excision are chosen. Moreover, few of the scores of proteins required for the activity stay together throughout the intricate work on a single RNA. “At all transitions in the splicing process, the spliceosome’s underlying RNA-protein interaction network is compositionally and conformationally remodeled and at each step there is a massive exchange of [spliceosomal] proteins” (Wahl and Lührmann 2015).

But there is more. In multicellular organisms the mRNA being remodeled possesses particular sequences that are supposed to act as signposts for “attracting” the elements of the spliceosome to the correct sites for cutting and stitching. But these signposts are often ambiguous or contradictory, and provide only more or less vague hints.[3] This is despite the extraordinary complexity of the task facing the spliceosome, and the large number of segments that commonly require removal.

“It has been proposed”, write two researchers, “that thousands of different sequences” can function as a certain kind of directive for the spliceosome, but these sequences are highly variable, having only a few loci in common. Further, many sequences that look rather like splice sites are ignored by the spliceosome, while other sequences, despite lying at a distance from the splice sites, nevertheless contextually influence site recognition. So it appears that “hundreds of regulatory motifs may need to be integrated” (and understood) in order for the spliceosome to accomplish its surgery in harmony with current cellular needs (Papasaikas and Valcárcel 2016).

Using the thing-oriented (rather than process-oriented) language available to us, it is difficult not to speak of the spliceosome as a fixed structure, and equally difficult to avoid suggesting that it has a specific and well-defined task. What we see, however, is a remarkable plasticity. This is illustrated, for example, by the fact that “nearly all ‘activators’ of splicing can, in some cases, function as repressors, and nearly all ‘repressors’ have been shown to function as activators … it is clear that context affects function” (Nilsen and Graveley 2010).

This context-sensitivity extends to the very definitions of the various tasks, which can look utterly different, and require wholly different approaches and capabilities on the part of the spliceosome, depending on the situation. Is the task to skip the next protein-coding segment of the RNA? Is it to make sure that a choice is made between two such segments — to retain only one and remove only one? Is it to choose an alternative location for the beginning or end of a particular segment? Is it, in at least some cases, to make the radical choice of preserving a non-protein-coding segment in the final mRNA?

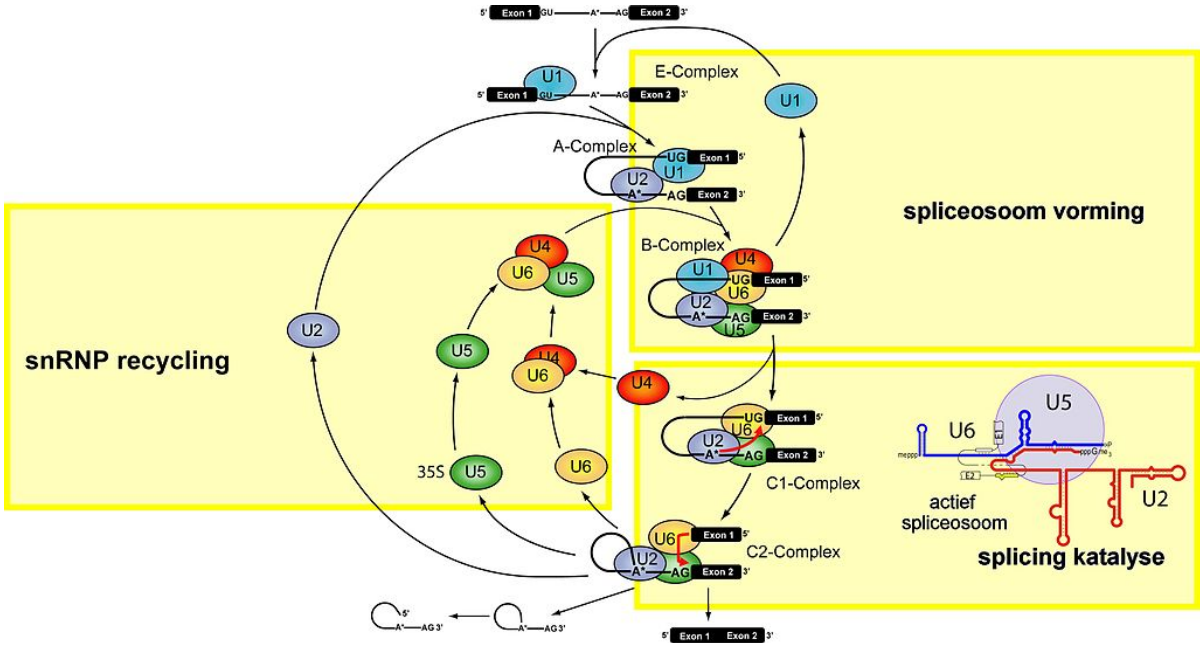


**Figure 8.1**. A Dutch-language figure showing the recycling of some of the molecules involved in RNA splicing. “snRNP” = small nuclear ribonucleoprotein; “spliceosoom vorming” = spliceosome formation; “splicing katalyse” = splicing catalysis. Each snRNP (U1-U6) is an RNA-protein complex. You need only briefly note the complexity of this one (recycling) aspect of the splicing process. Many molecules involved in splicing are not shown here.[4]

Each of these operations demands a different sort of coordination among the many molecules involved, and the ways of approaching the work can vary, one might almost say, "wildly". "Mechanisms of alternative splicing are highly variable, and new examples are constantly being found."[5] So there is not just one "spliceosome machine" (as some would like to call it), and not just one task. The numerous molecules participating (or capable of participating, but "electing" not to) in the various splicing operations face the challenge of working together in an unimaginably sophisticated manner that somehow reflects the wider context and the needs of the cell.

Who will disagree with the researchers who write, in what might even be an understatement: "Working in a highly orchestrated manner, [the many parts of the spliceosome] perform incredible feats of molecular gymnastics with each round of splicing" (Chen and Moore 2014)?

## And further: everything *could* go backward

The entire problem is perhaps most vividly framed when we consider one further fact about RNA splicing. Not only is the spliceosome "a remarkably dynamic and flexible molecular machine; its transitions are so malleable that the whole reaction can eventually be reversed to generate precursor mRNA from spliced products" (Papasaikas and Valcárcel 2016). More particularly:

> Rather than being the one-way pathway typically drawn in textbooks, almost every step in the spliceosome cycle is readily reversible … [For example, regarding the first and second chemical steps in splicing,] not only can the spliceosome catalyze both chemical steps in forward and reverse, it can even convert spliced products … back into unspliced precursor mRNA! (Chen and Moore 2014)

That is, the splicing choreography can take an already spliced RNA along with the sections previously removed from it, and *reinsert* those sections into the RNA.

The reversibility and flexibility underlying the finely gauged, discriminating, and "perceptive"[6] activity of RNA splicing are hard to overestimate. Plasticity is layered upon plasticity, and complexity upon complexity. For example, many of the individual protein "surgical assistants" coming together in continually different ways in the spliceosome are themselves subject to modifications that are often decisive for how they will function within their current context. And these modifications, too, are dynamic and reversible.

They are also mutually entangled, with one kind of modification in one protein likely affecting, or being affected by, diverse modifications in other proteins. The untraceable lines of cause and effect blur into — and become subordinate to — the overall storyline.[7]

## Can DNA coordinate splicing activity?

Despite the fact that a specific splicing process could, with perfect *physical* propriety, go in an infinite number of different directions, it produces, from among all the present possibilities, the particular result that fits the ever-changing cellular context at the present moment. Splicing must, in some extremely significant sense, be guided by this context. If it were somehow being "dictated" to by a specific element or group of elements in the cell, those elements would have to have incorporated within themselves an effective sense for the current state of the entire cell. But then, why not just recognize that a biological whole, in one way or another, informs *all* its parts?

It is worth noticing the great distance between, on one hand, what RNA splicing shows us and, on the other hand, the idea of DNA as a decisive cause of the cell's life (or even merely DNA as a strict determinant of protein synthesis). The notion of a decisive physical cause immediately comes up against questions such as the following:

> Does DNA single-handedly "dictate" that the splicing operation on a particular RNA *this time* should differ in such-and-such a way from how it was done *last time*?
>
> Does DNA (or, for that matter, any other cellular feature) have any possibility of determining the specific and crucial, well-timed chemical modifications or changes in form of just one of the proteins involved in the splicing activity, let alone the mutually interacting modifications that must occur in a great number of them as the splicing "surgery" proceeds?
>
> Does DNA enforce the way these proteins (and other molecules) come together in distinct configurations at one point in the process, or dissociate at other points, or come together in a new configuration at yet another point — all in the temporal order required for the success of the overall procedure?
>
> In sum, are there computer-like lines of communication through which coordinating *instructions* can be conveyed from DNA to the individual protein and RNA molecules?

And what we have said about DNA and splicing can also be said about DNA and just about any of the innumerable other molecular processes of the cell, from metabolism, to energy management, to establishment and management of the diverse structural features of the cell, to gene expression, to cell division and much more. Further, all the complexities of each of these spheres of activity must be harmonized with those of the other spheres so as to yield the overall integral unity of cell, organ, and organism — this in the face of the fact that many molecular players are common to the different processes.

## Shattering the Genome

Our second case is a long way from RNA splicing — and also, it might seem at first, from the human being.

A dose of ionizing radiation equal to 10 grays (a measure of absorbed radiation) is lethal to the human body. Most bacteria cannot survive 200 grays. But then there is the bacterium known as *Deinococcus radiodurans*: it can endure over 17,000 grays and get along just fine. Never mind that its genome is thoroughly shattered by the assault.

Here's what happens. Ionizing radiation can damage DNA in various ways, perhaps worst of all by causing double-strand breaks. These are breaks across both strands of the double helix. The familiar bacterium, *E. coli*, not at all untypically, dies when it suffers about four double-strand breaks per each of its four-to-eight circular DNA molecules. *Deinococcus radiodurans*, by contrast, can survive over a thousand double-strand breaks. This means that it continues life after its genome is broken into many hundreds of small fragments. It does so by proceeding to put its genome back together again when living conditions improve — a daunting task, to say the least.

**Figure 8.2**. A tetrad (group of four) *Deinococcus radiodurans*.[8]

*Deinococcus radiodurans* is one of a small class of single-celled organisms with extreme radiation tolerance. Actually, it tolerates various other extreme conditions as well — some of which, such as dessication, likewise reduce its DNA to genomic shards. It can, for example, survive in a waterless desert for years until moistened again — which could happen, for example, when winds lift it in a cloud of dust from the Sahara, high into the atmosphere (where it is exposed to damaging ultraviolet radiation 100 to 1000 times that on earth's surface), and across the Atlantic ocean to the South American jungles. *D. radiodurans* can be found on Antarctic ice, on dry frozen marble, and in the farthest depths of the sea.

## Who's on first — genes or proteins (or neither)?

Biologists have been intrigued by this peculiar survivor (along with some of its kin) for several decades, and of late they have clarified its story considerably. A central feature of that story is striking, because it points toward a truth about organisms in general, not merely those with extreme survival capabilities. The key finding is this: damage to DNA is not, in the most direct sense, what proves lethal about radiation. The primary issue, instead, is damage to proteins. As long as its proteins remain functional, a cell can reassemble even a badly fractured genome; but with damaged proteins, a cell is done for, with or without an intact genome.

*D. radiodurans* employs a number of strategies for preserving its rather commonplace "proteome", or total inventory of proteins. These strategies include (1) preventing the oxidative damage that results from radiation, a goal it achieves in good part by means of an especially rich supply of antioxidants; (2) eliminating, before they can cause mischief, any proteins that do get damaged, while recycling their constituents; (3) scavenging amino acids and peptides (protein constituents) from the local environment, a capability that, together with the recycling, supports (4) newly synthesizing any proteins that need replenishing.

The proteome thus preserved is then able to go about the task of reconstructing a shattered genome — a task whose complexity at the molecular level is stunning. (Many a bright but befuddled graduate student has twisted his imagination into knots while trying to picture the various textbook processes of DNA damage repair in human cells.) Nevertheless, the task is accomplished in the cells of all organisms. What distinguishes *D. radiodurans* is its ability to carry out this task to an exceptional degree by maintaining its store of proteins intact under extreme duress.

In sum, according to Anita Krisko and Miroslav Radman, researchers at the Mediterranean Institute for Life Sciences who have been studying *D. radiodurans*, "biological responses to genomic insults depend primarily on the integrity of the proteome … This conclusion is the consequence of the fact that dedicated proteins repair DNA, and not vice versa". Moreover, "this paradigm is fundamental in its obviousness (no living cell can function correctly with an oxidized proteome) and, if it is true, must be universal, that is, hold also for human cells".

All this says something powerful about the longstanding genocentric (gene-centered) bias of biologists. Krisko and Radman delicately hint at the issue when they write in their paper:

> The science of molecular biology was dominated by the notion of information, its storage, transmission, and evolution as encrypted in the nucleotide sequence of nucleic acids [that is, DNA and RNA sequences]. But the biological information is relevant to life only to the extent of its translation into useful biological functions performed, directly or indirectly, by proteins (Krisko and Radman 2013).

This truth, as they also point out, applies to our understanding of cancer and its treatment, which have long been focused on DNA abnormalities. But instead, "an effective cancer therapy by tumor cell killing should target the proteome, or both the proteome and genome, rather than the genome alone". Which is almost to say: it should reckon with the coherent living character of the organism as a whole.

## A sense of the whole

It was always a strange thing when biologists, attempting to penetrate the thickly matted tapestry of cellular activity at one or another point and disentangle the threads for analysis, decided that one type of element — the gene or DNA sequence — was the place where all the activity logically begins and from where it is controlled. There is in fact no starting place and no part acting as controller. Any attempt to think in such terms immediately crashes against the facts of cellular behavior. *Deinococcus radiodurans* no more shows proteins to be singularly "controlling" elements than it does DNA.

The work on *D. radiodurans* can remind us that the activity of an organism always reflects something like an immanent "sense of the whole". Surely the protein molecules in this bacterium do not "know" what their "goal" should be in dealing with all those disordered snippets of DNA. But if the overall living context (Chapter 6, "Context: Dare We Call It Holism?") remains sufficiently intact, then the mysterious power of self-realization that we have been gently stalking in these several chapters — the power sustaining the coherent storyline of a life — continues to assert itself. The narrative, whatever its unexpected twists and turns, remains unbroken. If parts can be more fully constituted from their shattered fragments, it is because a functioning whole, with its innate intelligence, was already there.

The information we conceive as *statically* encoded in DNA is a kind of bland abstraction from the living intelligence at work in cellular *processes*. When we occupy ourselves one-sidedly with genocentric information, it is (to employ a rough analogy) as if we elevated a notebook containing selected words, phrases, definitions, and grammatical hints to a pinnacle high above *Moby Dick* or *Faust* or *War and Peace*, worshipping the former as "information" while ignoring the informed and meaningful *activity* through which inert words and phrases are woven into soul-stirring tales.

A phrase-book or dictionary can be an essential resource, but it is the organism (*Deinococcus radiodurans* in the case we have been considering) that uses the dictionary to weave its own story — and even reconstructs the dictionary when the pages fall into a disorganized heap on the floor.

### *Is an unexpected coherence the problem or the solution?*

The problem of what it actually *means* to say, "Molecules accomplish the work of splicing and DNA reconstruction" presents us with one of those vast blanks in scientific understanding that are easily papered over today with informational generalities and convenient pictures of tiny machines busily, and in a "mechanistically" respectable fashion, carrying on the work of a cellular factory.

We already heard about the essential problem from cell biologist Paul Weiss (Chapter 6, "Context: Dare We Call It Holism?"), who spoke about the many degrees of freedom possessed

by the cell's constituents in their watery medium, and about how these degrees of freedom are so remarkably constrained and disciplined toward the expression of biological order at higher levels of observation. The University of Massachusetts geneticist, Job Dekker, was apparently nodding toward the same problem when he asked: "How do cells ensure that genes only respond to the right regulatory elements while ignoring the hundreds of thousands of others?" (Dekker 2013).

It's a good and obvious question. An editor of *Science* amplified it this way: "If you think air traffic controllers have a tough job guiding planes into major airports or across a crowded continental airspace, consider the challenge facing a human cell trying to position its proteins". A given cell, he noted, may make more than 10,000 different proteins under any particular set of conditions, and it typically contains more than a billion individual protein molecules at any one time. "Somehow, a cell must get all its proteins to their correct destinations — and equally important, keep these molecules out of the wrong places" (Travis 2011).

And once more: after a study showed that 70 percent of mRNAs in a cell are specifically localized, Robert Singer of Albert Einstein College of Medicine in New York City called it a "staggeringly large number". He went on: "It's almost as if every mRNA coming out of the nucleus knows where it's going" (quoted in Travis 2011).

Dekker, after posing the problem of a nucleus crowded with diverse regulatory factors bearing on gene expression in different ways, immediately went on to offer what he thought was at least part of the solution to the problem:

> Recent work has revealed a surprisingly simple strategy for matching genes to only some regulatory elements, which involves the spatial organization and folding of chromosomes inside the nucleus.

Certainly this folding, which we encountered in Chapter 3 ("What Brings Our Genome Alive?"), is an important aspect of the cell's performance. But this doesn't resolve, in a mechanistic fashion, the problem Dekker started with. To explain the achievement of crucial regulatory connections in the nucleus by citing chromosomal foldings that bring genetic loci and regulatory molecules together in just the right way is merely to push the problem back one step. We still have to ask the same sort of question with which we began: How are the foldings achieved with such evident wisdom?

It would help if we could get clear about the fact that there are two profound, and profoundly different, descriptive challenges posed by a cell's impressively coherent activities. One has to do with the underlying physical and chemical processes. The other concerns the coordination of those processes as an expression of the organism's needs and interests, intentions and meanings — its entire qualitative way of being. Severe confusions arise when we say that science must concern itself only with the first challenge, while assuming that the second one, if it can even legitimately be referred to, is automatically taken care of by our answer to the first.

Biologists, in their own fashion, do notice the second question. They notice it, as I have repeatedly mentioned, in their putting of questions to themselves ("How does the cell do X?"), where the question generally refers to a meaningful accomplishment. They notice it in their acknowledgment that organisms *behave* and undertake *tasks*, something solar systems and

lake-bottom sediments never do. And they notice it when they grant that every organism acts *as if* it were a purposive being, even if they immediately feel compelled to explain away this purposiveness by appealing to natural selection (Chapters 2, “The Organism’s Story”, and 18, “Teleology and Evolution”). What is not so often noticed is the fact that an organism’s purposive way of being and its pursuit of its own interests require a distinctive manner of understanding that *cannot be assimilated to our understanding of inanimate objects*.

Is the entire matter really so vexing? The mystery of the unexpected coherence that molecular biologists confront, for example, in RNA splicing and DNA damage repair is, from a perfectly reasonable point of view, neither a mystery nor unexpected. The problem arises only at the moment when we refuse to accept life as a foundational fact of the universe and unreasonably demand that an organism’s living performances be explained in an inanimate manner. Then, and only then, do we find it difficult to make sense of things.

But, fortunately, researchers never can wholly resist the urge to make good sense of things. They seek an understanding of whatever issue they are working on by looking for the *coherence* and *meaning* of events. This is necessary in order to provide at least some minimal context for their physical analyses. And it is so natural that it easily occurs without any conscious effort. What then happens, and what so badly distorts the practice of biology, is that this recognized coherence and meaning must be squeezed out of any ultimate explanation, which is allowed to proceed solely in terms of physics and chemistry. The result is rarely pretty.

Listen to how Dekker concludes his reflections about the puzzle of genes and the “hundreds of thousands” of regulatory elements they may or may not interact with: “Future studies will no doubt unveil how [certain chromosome domains] are established and how they insulate genes from the wrong crowd.”

There you see the uncomfortable conflation of two different explanatory challenges: those of physics and chemistry on one hand, and those of living activity on the other. In appealing to future studies, Dekker speaks as though he were unaware of the gap between the idea of physical lawfulness allowed in those studies, on one hand, and that of the “wrongness” of a molecular crowd, on the other. Part of that gap consists of the fact that the lawfulness of events does not explain how those events are meaningfully coordinated, as when genes are insulated from the wrong crowd.

Efforts at reductionism — efforts to reduce biological meaning to the terms of physical lawfulness — never make any progress. Yes, we have dramatically extended our tracing of physical lawfulness in the cell. But, for all the flood of physical data today, the needs, interests, tasks, intentions, and meanings of the organism never become less necessary for structuring our understanding.

What actually tends to happen, however, is not particularly helpful. Once the clarification of physically lawful processes reaches a certain point, the biologist’s deeply ingrained habit of ignoring all questions of meaning leads to the conviction that nothing remains to be understood. And this occurs despite the continuing use, “right under the biologist’s nose”, of a vocabulary of life and meaning well designed to bridge (and conceal) the gap between lawfulness and adequate understanding. (See, for example, the discussion in Chapter 2 of the different vocabularies applied to living and dead dogs.)

Paul Weiss (Chapter 6, “Context: Dare We Call It Holism?”) in addressing the larger

coherence of the “heaving and churning” cell, did not merely stare, transfixed, at the problem of order within “chaos”. He tried to formulate its essence as clearly as possible, often resorting to statements such as this: “The resultant behavior of the population [of cellular constituents] as a whole is infinitely less variant from moment to moment than are the momentary activities of its parts.” And so “the system *as a whole* preserves its character” (Weiss 1962, p. 6). And again: When we examine the form and physiology of an organism, we see how “certain definite rules of order apply to the dynamics of the *whole* system … reflected [for example] in the orderliness of the overall architectural design, which cannot be explained in terms of any underlying orderliness of the constituents” (Weiss 1971, p. 286).

What was the *constraining* power through which all those molecules, possessing all those degrees of freedom at their own level, yielded to a consistent order at a higher level — a *physically* unexpected coherence? This was the question Weiss’ life-long observation of living cells continually brought him up against. But he was too honest to frame an answer in terms of the science of his day. His virtue lay in nevertheless not shrinking from the problem. He spent a long career investigating and describing the physically lawful performances of cells, but he did not pretend that, in doing this, he was *explaining* the order he observed.

I suspect that, with continuing observation and faithful description, the “problem” of order and wisdom (thought-fullness) in cells will more and more fade into nothingness. It is indeed only the effort at reductionism that creates the problem. Cease that effort, and all we have left is the routine scientific task of accurate conceptualization and description. Physicists, after arriving at concepts of law, force, field, and all the rest, do not often complain, “Those are not material things; how can we possibly deal with them?” They simply continue investigating, describing, and thinking until an overall, coherent picture is formed. That is what *making sense* of the world means.

It would be strange if the initially surprising discovery of living and coherent order in the cell persisted as a problem; another name for the discovery of order is, after all, “science”. I suppose that the unexpectedness of at least some forms of order has been part of the scientist’s experience all along. But when we live with it long enough, the unexpected becomes expected. In the end, it simply further strengthens our inalienable sense that we live in a world of coherent meaning.

But this happy ending will not be fully realized in biology until we acknowledge that there are many different ways phenomena can add up to a coherent picture in this cosmos of ours. A sloth is not a lion (Holdrege 2021), ice is not water vapor, and an animal is not a rock. Reductively forcing one sort of coherence into the mold of another by violence is never the answer.

WHERE ARE WE NOW?

### The organism's coherence need not be mysterious

We have arrived at a simple truth: the biologist's sense of threatening mystery (or "mysticism") when confronted with the intentional, purposive, and meaningfully expressive aspects of an organism's life typically arises from the unshakable conviction that there needs to be an essentially inanimate explanation of animate beings. As an *insistence*, this is mere dogma. The requirement of science is that we open-mindedly describe every aspect of every phenomenon in its own terms. It does not require a lot of reflection to see, for example, that organic processes of development and self-realization do not have strictly physical descriptions. Inanimate objects do not persistently and directively engage in efforts to develop and realize themselves.

But this does not mean we are headed toward some kind of mystical conception of the organism. As we will see increasingly in coming chapters, the different aspects of the organism (including the more-than-physical — ideal or archetypal — aspects) require only what all science requires: description in terms that are faithful to the phenomena themselves. To describe the marvelous living coherence of molecular processes in an organism's cells is no more mystical than to describe the very different but just as marvelous coherence of the laws of physics. It merely requires a willingness to embrace what we see, rather than recoil from it.

What I have said in this chapter will raise the question for many readers, "Is merely describing what we see in its own apparent terms an adequate foundation for science?" The question will be appproached in Chapter 11 ("Why We Cannot Explain the Form of Organisms") and addressed more fully in Chapter 12 ("Is a Qualitative Biology Possible?"). An even more fundamental question has to do with the role of thought both in our descriptions of the world and in the world itself. Is the refusal to accept thinking and thought as natural aspects of the world the deepest root of the biologist's unwillingness to take organisms at face value? I will take this up in Chapters 13 ("All Science Must Be Rooted in Experience") and 24 ("Is the Inanimate World an Interior Reality?").

## Notes

1. "RNA splicing was initially discovered in the 1970s, overturning years of thought in the field of gene expression" (Clancy 2008).

2. Estimates of the number of proteins participating in the spliceosome vary widely. Some have said there are more than 300, and others "only" 80 — a good indication of a fluidity of structure that is hard to nail down.

3. The "vagueness" here may be a function of the researcher's habit of looking for a precise

digital code. Yet, without such a code the cell seems to manage the "life or death" business of splicing with great reliability. This is presumably due to the fact that the relevant business of the governing wisdom is the reading of the contextual meaning of the situation, not the mechanical interpretation of an exact digital code. A comparison might be the confirmed party-goer who navigates the exceedingly subtle, complex, and expressive landscape of a cocktail party without giving it a second thought — and without reading off from a "cheat sheet" a set of rigidly encoded, step-by-step instructions ensuring social harmony.

4. Figure 8.1 credit: Jan Medenbach (CC BY-SA 2.0 DE).

5. Wikipedia article, "Alternative Splicing", accessed May 11, 2019.

6. Obviously, I am not referring to our own conscious perceptive capacities. But neither am I referring to something *less* effective in its own way than our power of perception. Whatever brings the biologically coherent and needful results out of the currently inconceivable, creative "chaos" of the cellular plasm is far beyond our efforts to follow, let alone to reproduce. We have to think of a capacity *higher* than anything we consciously possess, even if — as the psychosomatic unity of the organism suggests — our consciousness is somehow contiguous with this higher capacity.

7. There are many other aspects of RNA splicing not considered here — for example, the role played by certain metal ions in the shift between different spliceosomal protein conformations (and therefore between different protein functioning). Such ions are a long way from the macromolecules in which biologists normally invest their sense of cellular information, and yet their well-informed role is crucial to cellular activity.

8. Figure 8.2 credit: BQUB24-Diraheta (CC BY-SA 4.0).

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