CHAPTER 4

The Sensitive, Dynamic Cell

Throughout a good part of the twentieth century, cell biologists battled over the question, “Which exerts greater control over the life of the cell — the cell nucleus or the cytoplasm?” (Sapp 1987). From mid-century onward, however, the badge of imperial authority was, by enthusiastic consensus, awarded to the nucleus, and especially to the genes and DNA within it. “Genes make proteins, and proteins make us” — this has been the governing motto, despite both halves of the statement being false (which will become ever clearer as we proceed).

The question for our own day is, “Why would anyone think that any part of a cell must possess executive *control* over all the other parts?” We have already caught our first glimpse of the performances in the nucleus (see Chapter 3, “What Brings Our Genome Alive?”) and these hardly testify to domination by a single, controlling agent. Now we will broaden our outlook by making a first approach to the rest of the cell — the cytoplasm, along with its organelles and enclosing membrane.

It would be well to remind ourselves before we proceed, however, that, whatever else it may be, an organism is a physical being. Its doings are always in one way or another *physical* doings. This may seem a strange point to need emphasizing at a time when science is wedded to materialism. And yet, for the better part of the past century problems relating to the material coordination of biological activity were largely ignored while biologists stared, transfixed, into the cell nucleus. If they concentrated hard enough, they could begin to hear the siren call of a de-materialized, one-dimensional, informational view of life. life.[1]

The idea of a genetic *code* and *program* proved compelling, even though the program was never found, and even though the supposedly fixed code became many different codes and these were continually modified by the cell in every phase of its activity. So long as one lay under the spell woven by notions of causally effective information, logic, and code, the complex, causal realities of the material organism tended to disappear from view, or seemed unimportant. An overall, never clearly observed logic was assumed to *govern* all the messy particulars, which did not need to be studied too closely.

Unfortunately for conventional thought, the particulars *did* come into view, however slowly, and however much they were at first ignored. Eventually and inevitably they undermined the much too neat story of a clean, all-determining, informational logic.

Surely, even if genes are not the decisive logical and informational causes usually imagined, they must connect in *some* manner with the features they were thought one-sidedly to explain. But this just as surely means they must connect physically, via movements and transformations of substance testifying to the deeply meaningful, underlying narrative we actually observe in every organism (Chapter 2, “The Organism’s Story”). And the picture we were exposed to earlier (in Chapter 3, “What Brings Our Genome Alive?”), detailing some of the significant movements and gesturings of chromosomes, is only the beginning of the story.

Does the cell possess its own "senses" and "limbs"?

Let's continue by taking note of the cytoskeleton (Figure 4.1), which plays a key role in the cell's physical movement. It consists of many exceedingly thin molecular filaments and tubules, visible only under powerful microscopes. Many of these are growing at one end and perhaps shrinking at the other end, or else disassembling altogether even as new filaments are establishing themselves. Through this dynamic activity — this constant growth and dissolution of minuscule fibers — the cell gains its more or less stable shape and organization.

Cellular organelles, to which the cytoskeleton attaches, are positioned and re-positioned as the cytoskeleton somehow "senses" internal needs, while also responding to external stresses such as stretching or compression. Beyond that, the filaments and tubules, by dynamically managing the distribution of forces within the cell as a whole, help to enable and guide its movements so that it can find its proper place among the millions of cells in its nearby environment.

And the cells of our bodies do move. Literal rivers of cells shape the young embryo. So, too, migrating cells in and around a wound cooperate in restoring the damaged architecture. In every tiniest hair follicle niche, as well as throughout our tissues generally, cells move, replace dying neighbors, and reorganize themselves. And even while remaining in one place, cells must continually adapt their form to their immediate environment — certainly a major task in the rapidly growing embryo and fetus. But the stresses and tensions of that environment are in turn the partial result of interconnected cytoskeletal activities in all the cells of the local tissue.

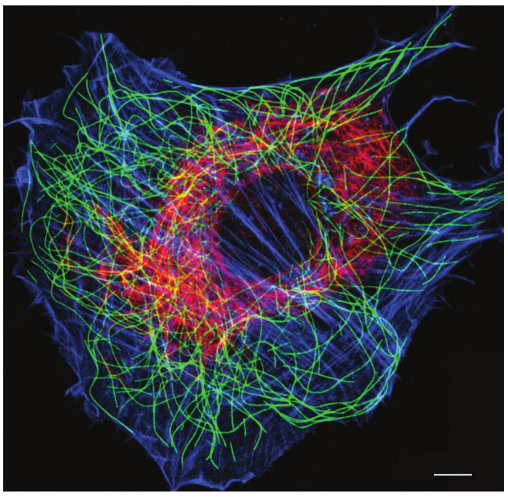

Figure 4.1. A cultured fibroblast cell, specially prepared so as to show features of the cytoskeleton in artificial color: narrow actin filaments (blue); wider microtubules (green); and intermediate filaments (red). The dark and roughly circular (spherical) region near the center is the cell nucleus.[2]

The cytoskeleton not only supports cell migration, but also provides pathways for the orchestrated movement of substances within the cell. A protein molecule is not of much use if it cannot find its way to where it is required. Individual molecules and protein complexes are shifted about along these cytoskeletal pathways, as are the relatively voluminous contents of membrane-enclosed transport structures ("vesicles"). These latter can "bud off" various internal membranes of the cell and then move, along with their cytoplasmic contents, to a particular destination where, having released their contents, they are degraded and recycled.

Such directed movements are essential to the life of the cell. Where an enzyme or signaling molecule goes in a cell is decisive for its function. Some molecules, for example, are outward-bound to, and through, the cell surface on signaling missions to distant reaches of the body. Meanwhile, others are inward-bound on different signaling missions. (Hormones, secreted by cells of a gland at the start of their journey, and then received by cells in various other parts of the body, illustrate both sorts of movement.) Some molecules produced in a cell are destined for a particular locus on the highly differentiated cell membrane, while others are targeted to any of a virtually infinite number of possible stopping places somewhere in the cell's "intricate landscape of tubes, sacs, clumps, strands and capsules that may be involved in everything from intercellular communication to metabolic efficiency."[3]

But the cytoskeleton is not just a cytoskeleton. The filaments and tubules themselves are teeming with associated regulatory molecules. As of a decade ago more than 150 proteins capable of binding to just one type of filament — actin — had already been identified. As one researcher has put it: "Despite the connotations of the word 'skeleton', 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" (Fletcher 2010).

There is scarcely any aspect of cellular functioning in which the cytoskeleton fails to play a role. On the exterior side, it connects with the cell's outer ("plasma") membrane, where it helps to import substances from the environment while also facilitating the adhesion of extracellular molecules and other cells. Through its interaction with the extracellular matrix, it contributes to the mechanical stiffness and coherence of entire tissues. On the interior side, it engages with the nuclear membrane and the specialized filaments underlying that membrane. These filaments are vital regulators of gene expression. In this way the cytoskeleton links various sorts of extracellular signals, both mechanical and biochemical, to the nucleus and its chromosomes, providing a foundation for holistic behavior involving much more than the individual cell.

There are many ways to affect gene expression, and they do not all occur in the cell nucleus. For example, a key part of this expression is the translation of RNA molecules into proteins, which occurs in the cytoplasm. Evidence suggests that "the physical link between cytoskeletal and translational components helps dictate both global and local protein synthesis". But it's not just that the cytoskeleton affects translation. As is all too typical, the causal effects work both ways: "specific translation factors are able to affect the organization of cytoskeletal fibres".[4]

The cytoskeleton plays many other roles, not least by ensuring the proper separation of mitotic chromosomes, the division of a cell into two daughter cells, and the correct allocation of chromosomes to those daughter cells. (See Figure 3.3, where the mitotic spindle, shown in green, consists of cytoskeletal fibers.) It is perhaps unsurprising, then, that some have seen the cytoskeleton, with its nuanced organizational "skills", as the seat of cellular intelligence or the "brain" of the cell. However, we need not invite a misleading anthropomorphism in order to acknowledge the subtle and nuanced organizational activity — the *narratively intelligible* activity (Chapter 2, "The Organism's Story") — realized through the dynamics of cytoskeletal movement.

One thing is certain: neither the cytoskeleton's moment-by-moment dynamics nor the coherent and intelligible aspect of its activity can be ascribed to "instructions" from genes — or even to the physical laws bearing on cytoskeletal proteins. As the matter was summarized by Franklin Harold, an emeritus professor of biochemistry and molecular biology at Colorado State University, "One cannot predict the form or function of these complex [cytoskeletal] ensembles from the characteristics of their component proteins". And yet, Harold went on, "When seen in the context of the parent cell the arrangement of the molecules becomes quite comprehensible". He then raised the obvious question: "How is the cytoskeleton itself so fashioned that its operations accord with the cell's overall 'plan' and generate its particular morphology time after time?"[5]

Harold answered the question merely by expressing confidence that understanding will eventually come. And surely it will. But we can be equally sure that it will not come before we have penetrated more deeply this problem: How does a living context, or whole — in this case, the cell with its "overall plan" — manage to express itself through all its parts?

In an integral, organic whole, we can assume the "viewpoint" of many parts in such a way as to make each one *momentarily* seem to be the coordinating "master" element. This is why the cytoskeleton, just as much as our genes, might appear to explain everything that goes on. With wonderful sensitivity it "feels out" the surfaces of the cell and all its organelles. The balance of forces maintained by the fibers shapes the cell, dynamically positions the organelles, and both guides and helps to power the critical movement of the cell within its environment. As we have seen, the cytoskeleton likewise plays a key role in moving substances to their functional locations within the cell. And it is a decisively important regulator of gene activity.

And yet, this does not make the cytoskeleton a *master* regulator. The truth is simply that, to one degree or another, each part of an organic whole bears that whole within itself — is informed by, and expresses, the whole. The idea of a master regulator arises only when we insist on viewing a specific part in isolation from the whole so as to identify single, local, and unambiguous causal interactions. We then say that this part *makes* certain things happen. The fact that the part is itself made to happen by the very things it supposedly accounts for then tends to be ignored. We lose sight of the fluidity and physical indeterminism of the living context — an indeterminism whose meaning and coherence become visible only when we allow particular physical causes to "disappear" into the unifying *narratives*, or stories, of the organism's life (Chapter 2, "The Organism's Story"). In much the same way, we experience physical sounds and gestures disappearing into the *meaning* of the speech we hear.

The sensitive "skin" and organelles of the cell

Interestingly, the cell membrane ("plasma membrane") is likewise a highly dynamic feature that has been seen as a decisive coordinator of cellular activity, and even as a seat of cellular intelligence. It is here that we see "decisions" continually being made about which substances and signals — from among the endlessly streaming crowds passing through the neighborhood — are to be admitted into the cell and which ones are "foreign", or else unnecessary at the moment. Here, perhaps more than anywhere else, is where cellular identity is established and "self" is distinguished from "other". This happens partly by means of protein receptors ("sensors") embedded in, or attached to, the lipid matrix of the membrane.

Here, too, everything flows (which is one reason why any image like the two below is a kind of frozen lie, despite being useful when approached with the right awareness). Molecules continually associate with, and dissociate from, the membrane, even as they undergo various modifications that redirect their functioning. They also migrate within the membrane, forming specialized communities that are in no two locales exactly the same. All the while portions of the membrane, along with cytoplasmic contents, are "pinched off" as more or less spherical vesicles that, once they are fully detached, move elsewhere, either externally to the cell or internally. At the same time, selected vesicles from external sources fuse with the membrane and release their contents into the cell's interior.

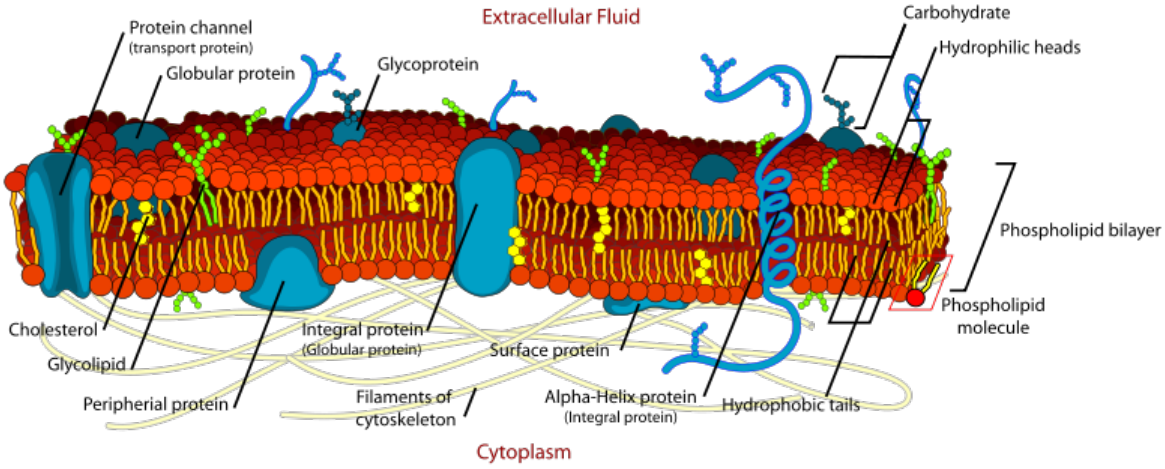

Figure 4.2. Schematic repesentation of a portion of a lipid bilayer and its associated molecules, endless variations of which constitute the cell membrane. See main text.[6]

Much the same is true of all the interior membranes delimiting the various organelles of the cell (Figure 4.3). These, too, "harbor sensitive surveillance systems to establish, sense, and maintain characteristic physicochemical properties that ultimately define organelle identity. They

… play active roles in cellular signaling, protein sorting, and the formation of vesicular carriers" (Radanović et al. 2018).

Membranes, then, not only structure the cell into distinctive compartments and organelles, but they also "oversee" the characteristic and essential contents of those compartments and play decisive roles in managing the ceaseless and massive intercommunication among them.

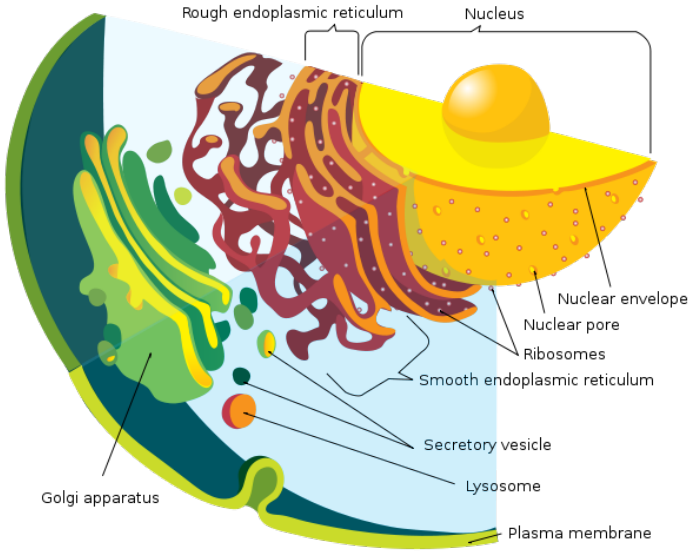

Figure 4.3. Schematic representation of the internal membrane systems of a nucleated cell.[7]

All this finely discriminating activity is going on, as the eminent cell biologist, Paul Weiss, wrote in 1973, while "the cell interior is heaving and churning all the time" (Weiss 1973, p. 40). Everything is watery movement of substances and transformation of organizational structure, and yet the cell's identity and unified character are maintained. The movement expresses the character and constitutes the life of the cell. The intricately choreographed flows and chemical transactions in plasm and membrane are responsive to the ever-unpredictable conditions of the moment, and are the means by which the cell not only stays true to itself, but also remains in harmony with its larger environment.

The dynamics of this material accomplishment are a long way from the clean, informational logic commonly associated with genes. Lenny Moss, a molecular biologist who transformed himself into one of our most insightful philosophers of biology, had this to say about the relation between cellular membranes and genes:

> The membranous system of the cell, the backbone of cellular compartmentalization, is the necessary presupposition of its own renewal and replication. Cellular organization in general and membrane-mediated compartmentalization in particular are constitutive of the biological "meaning" of any newly synthesized protein (and thus gene), which is either properly targeted within the context of cellular compartmentalization or quickly condemned to rapid destruction (or cellular "mischief"). At the level of the empirical materiality of real cells, genes "show up" as indeterminate resources ... If cellular organization is ever lost, neither "all the king's horses and all the king's men" *nor* any amount of DNA could put it back together again.[8]

From information to life

Returning for a moment to our introductory question about the control of the cell by its genes: perhaps we have by now gained a feeling for how the cell and organism as a whole can flexibly and contextually express itself through any one of its parts, including its DNA and chromosomes — a fact we will get much more specific about in Chapter 7 ("Epigenetics: A Brief Introduction") and Chapter 14 ("How Our Genes Come to Expression"). If we think of the genome as an almost infinitely complex informational structure, there is no reason not to think, for example, of the cytoskeleton and membranes of a cell as at least equal bearers of vital information. However, it is also important to recognize the illegitimate aspects of this comparison.

In particular, the concept of information as normally applied to DNA is a quantitative one. It depends on the existence of discrete, iterated elements ("letters" of the "code"), any one of which can take on certain precise values. But everything we know about the "heaving and churning" interior of the cell — including even the coiling and looping of chromosomes we saw in Chapter 3 ("What Brings Our Genome Alive?") — tells us that we are looking at boundless and continuous variations of form and gesture whose depth of meaning is both non-quantifiable and more profoundly expressive than any quantifiable features we can abstract from it.

To ask about the amount of information in various aspects of the cellular performance (including the performance of chromosomes) is rather like asking about the amount of information in Stravinsky's ballet, "The Rite of Spring". It would be one thing to define informational quantities in terms of some more or less arbitrary method of choreographic notation ("code"), and quite another to consider the expressive content of the ballet itself.

So, too, our means for quantifying the informational content of a genomic sequence bears little relation to the material gestures expressing the cell's life. The truth here will become even more vivid when we look (in Chapter 6, "Context: Dare We Call It Holism?") at the context-dependence that biologists freely acknowledge at every turn.

WHERE ARE WE NOW?

The cell is reflected in its parts

In this chapter (as will happen throughout much of the book) we have had thrown at us the question of the relation between part and whole. Both the cytoskeleton and the collection of cell membranes participate in and seem to represent the whole cell to such a degree that some biologists are inclined to see one or the other — and not the genetic material — as the "controlling" element of the cell. But neither point of view is satisfactory. We are continually forced back to nothing less than the whole itself, not as a mechanistically controlling entity, but rather as the narrator of the ongoing drama that is the organism's life.

We will hear more about the cytoskeleton and membranes in Chapter 5 ("Our Bodies Are Formed Streams"). The main lesson for the moment is that the cell is a material whole in its own right. In a multicellular organism it is, of course, a *relative* whole. But the fact is — as we will take specific note of in Chapter 6 ("Context: Dare We Call It Holism?") — even every *organism* is a relative whole: it is not only reflected in its parts, but it is itself caught up in, and is a reflection of, its encompassing community and environment.

By noting the complementary manner in which the cytoskeleton and membranes work together to express a cell's living character, we can get a feeling for the integral unity of a biological whole. Perhaps (although I do not discuss this here) the linear, ray-like character of the cytoskeletal filaments and the more globular, enclosing character of the membranes tell us something about the fundamental polarity out of which the living unity of the cell arises.[9]

Notes

1. "In 1989, the gene was in the process of being disembodied, increasingly informaticized and formalized; it was very much swimming upstream to suggest that genes had physical embodiment and dynamic behaviours. (Landecker 2015).

2. Figure 4.1 credit: courtesy of Harald Herrmann, University of Heidelberg, Germany.

3. Kwok 2011. Here is a further description (from Plankar et al. 2012) of the various roles of the cytoskeleton:

> The cytoskeleton, in addition to its classical structural-mechanical role, integrates many signalling pathways, influences the gene expression, coordinates membrane receptors and ionic flows, and localizes many cytosolic enzymes and signalling molecules, while at the same time it represents an immense, electrically active catalytic surface for metabolic interactions. Together with cell adhesion molecules and the extracellular matrix, it forms a tensionally integrated system throughout the tissues and organs, which is able to coordinate

> gene expression via mechano-transduction. Given the strong relationship between mechanical and electromagnetic excitations in the microtubules (piezoelectricity) and their well-established organising potential, a weakened EM field may thus influence both cell and tissue aspects of carcinogenesis.

4. Kim and Coulombe 2010. The use of words such as "dictate" to suggest unambiguous, one-directional causation is extremely common in all the literature of molecular biology. And almost as common is the immediate contradiction of this language, as we see here. For more on this, see Chapter 9 ("A Mess of Causes"). There is also this from two biologists in McGill University's Department of Physiology, pointing to the two-way interaction between the cytoskeleton and the ubiquitous signaling activity through which the cell's diverse activities take place:

> Filamentous actin, microtubules, and intermediate filaments regulate cell shape, motility, transport, and interactions with the environment. These activities rely on signaling events that control cytoskeleton properties. Recent studies uncovered mechanisms that go far beyond this one-directional flow of information. Thus, the three branches of the cytoskeleton impinge on signaling pathways to determine their activities (Moujaber and Stochaj 2019).

5. Harold 2001, p. 125. Harold makes his question more emphatic with a little elaboration:

> How, for instance, do [the cell's] famously fluid membranes hold their shape? How does the endomembrane system as a whole acquire its spatial orientation and location, while the cell of which it is a part grows, divides and moves around? ... In a nutshell, the cytoskeleton is responsible for the mechanical intergration of cellular space; unpacked, this phrase covers a host of actions and interactions, mediated by a large and growing ensemble of proteins. ... [Moreover, the cytoskeleton itself] is subject to frequent remodelling. Mitosis, for instance, entails the dissolution of much of the cytoskeleton; its components are redeployed in the service of cell division, and subsequently reconstituted in their former order. Everything is in flux, but in a regulated purposeful manner (pp. 123-24).

6. Figure 4.2 credit: LadyofHats Mariana Ruiz (Public Domain via Wikimedia Commons).

7. Figure 4.3 credit: LadyofHats Mariana Ruiz (Public Domain via Wikimedia Commons).

8. Moss 2003, p. 95. Pages 76-98 in Moss' book provide an excellent overview of the dynamics associated with cellular membranes. There is also this from Harayama and Riezman 2018: "We are beginning to understand why even small changes in lipid structures and in composition can have profound effects on crucial biological functions":

> Although our knowledge of lipid metabolism and function has improved, we have so far revealed only the tip of the iceberg. We have only a limited understanding of the biological consequences of slight structural differences in lipids, but the known cases suggest that small structural changes will be very important. Many of these cases were unpredictable when the research started, suggesting that exciting new findings lie ahead.

9. One thing these opposing qualitative characters remind me of is a rather bold saying by Samuel Taylor Coleridge at the beginning of the famous Chapter XIII of *Biographia Literaria*:

> Grant me a nature having two contrary forces, the one of which tends to expand infinitely, while the other strives to apprehend or *find* itself in this infinity, and I will cause the world of intelligences with the whole system of their representations to rise up before you (Coleridge 1906).

And this in turn might remind us of a remark by Jakob Boehme (whose work was important to Coleridge):

> Nothing without contrariety can become manifest to itself; for it has nothing to resist it, it goes continually of itself outwards, and returns not again into itself (quoted in McFarland 1981, pp. 323-24).

And again from Boehme: if a thing has only one will and "finds not a contrary will, which gives occasion to its exercising motion, it stands still" (*ibid*.). We need only think of the importance of gravity and the resulting friction of our feet upon the ground, to realize that we walk and move forward by "pushing off" against the force of gravity. We could ourselves accomplish no movement forward if we were floating in space with nothing to resist us.

This lack of contrariety sounds rather like a fanciful picture of a cell with growing and unrestrained cytoskeletal fibers, but no enclosing membrane, or like the inertness of a cell with enclosing membrane but no dynamic cytoskeleton.

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