2 On being the right size, revisited

The problem with engineering metaphors in molecular biology

Daniel J. Nicholson

In 1926, Haldane published an essay titled *On Being the Right Size* in which he argued that the structure, function, and behavior of an organism are strongly conditioned by the physical forces that exert the greatest impact at the scale at which it exists. This chapter puts Haldane's insight to work in the context of contemporary cell and molecular biology. Owing to their minuscule size, cells and molecules are subject to very different forces than macroscopic organisms. In a sense, macroscopic and microscopic entities inhabit different "worlds": the former is ruled by gravity and inertia, whereas the latter is governed by Brownian motion. One implication is that we should be extremely skeptical of models and analogies that seek to explain properties of microscopic entities by appealing to properties of macroscopic ones. Unfortunately, this is precisely what the appeal to engineering metaphors in molecular biology attempts to do. Molecular biologists routinely resort to such metaphors because they are familiar and intuitively intelligible. But if our machines were the size of molecules it would be impossible for them to function the way they do. It follows that we should avoid distorting biological reality by construing it in engineering terms. In this chapter I examine four key metaphors in molecular biology – "genetic program," "cellular circuitry," "molecular machine," and "molecular motor" – and I argue that their deficiencies derive from their neglect of scale. I also try to explain why many biologists today appear to have forgotten the importance of scale that Haldane drew attention to in his essay. I suggest that the reason has to do with the influence of Schrödinger's argument in *What is Life?* regarding the stability of the gene.

Introduction

Machines have been used as sources of metaphorical and analogical explanations for as long as organisms have been the subject of empirical investigation. Aristotle compared the bones and tendons of the forearm to the arms of a catapult drawn back by tightening ropes. Descartes was so impressed by the life-like movements of hydraulic automata that he concluded that the movements of the body were machine-like. And Liebig's view of digestion as combustion relied on his understanding of the body as a heat engine and of food as fuel. In more recent times, the advent of cybernetics, electronic engineering, and computer science has furnished

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biologists with an even richer array of technological devices to employ as models in their explanations of the phenomena they investigate (cf. Grmek 1972; Vartanian 1973; Keller 1995; Canguilhem 2008; Reynolds 2018).

However, despite their undeniable heuristic value in certain experimental contexts, machine metaphors can be seriously misleading when they are used to ground the conceptualization of biological phenomena. The reason is that, some superficial similarities notwithstanding, living systems are fundamentally different from machines. Ontologically speaking, the *machine conception of the organism*, as I have referred to it in the past, is fraught with problems. In previous work (Nicholson 2013, 2014, 2018), I have advanced two major arguments against the theoretical understanding of organisms as machines, which still pervades many areas of contemporary biology. The first, which can be referred to as the Argument from Teleology, states that organisms are intrinsically purposive (in the sense that their activities and internal operations are directed toward the maintenance of their own organization), whereas machines are extrinsically purposive (given that their workings are geared toward fulfilling the functional ends of external agents). The second, which can be referred to as the Argument from Thermodynamics, states that organisms exhibit dynamic stability (due to their need to constantly exchange energy and matter with their surroundings to keep themselves in a negentropic steady state far from equilibrium), whereas machines exhibit static stability (given that they do not require to constantly expend free energy to ensure their continued preservation as they slide back and forth from equilibrium to near-equilibrium conditions). I have shown that the former argument has especially salient consequences for development and evolution (see Nicholson 2014), whereas the latter argument has particularly important implications for morphology, physiology, and bioenergetics (see Nicholson 2018).

In this chapter, I draw inspiration from a classic essay by Haldane titled *On Being the Right Size*, first published in 1926, to propose a third argument against the ontological identification of organisms as machines that is especially relevant for current research in cell and molecular biology. I shall refer to it as the Argument from Scale. Roughly, this states that, owing to their minuscule size, cells (and their macromolecular components even more so) are subject to very different physical conditions compared with much larger objects like machines. Machine metaphors and analogies draw on our intuitive familiarity with the macroscopic world of our everyday experience, but such intuitions fail us when we attempt to grasp the structure, function, and behavior of microscopic entities, as these exist in drastically different environments from our own (and our machines).

In the ensuing sections I will illustrate this argument by critically examining four core conceptual models of molecular biology that were originally imported from electronic and mechanical engineering (namely, "genetic program," "cellular circuitry," "molecular machine," and "molecular motor") and by showing that their explanatory deficiencies ultimately derive from their neglect of the impact of scale.[1] But first, it shall be useful to remind ourselves of the claims that Haldane put forward in his essay to better understand how they can be fruitfully redeployed in a contemporary context. At the end of the chapter, I will try to explain why so many

molecular biologists today appear to have forgotten the importance of scale that Haldane famously drew attention to in his essay.

Redeploying the argument of Haldane's *On Being the Right Size*

Although Haldane is primarily remembered for his foundational contributions to theoretical population genetics, he was also a prolific essayist and an avid popular science writer who wrote numerous articles on a variety of topics for a lay audience. *On Being the Right Size* is one of them. Its message is simple, but it has profound consequences. "For every type of animal," Haldane writes (1928, 20), "there is a most convenient size, and a large change in size inevitably carries with it a change of form." Size directly constrains the shape and structure that an animal can assume, as well as its behavior. An animal's way of life is conditioned by the physical forces that exert the greatest effect at the scale at which it exists.

For example, gravity poses no danger to a small animal, but it is a very serious threat to a large one.[2] As Haldane memorably puts it, "[y]ou can drop a mouse down a thousand-yard mine shaft; and, on arriving at the bottom, it gets a slight shock and walks away, provided that the ground is fairly soft. A rat is killed, a man is broken, a horse splashes" (ibid., 21). An insect is not afraid of gravity, as it has a negligible effect on its way of life; it can fall without danger and crawl up a wall or cling to a ceiling with remarkably little trouble. Conversely, surface tension is of little significance to a large animal but is of critical importance to a small one. A man coming out of a bath, Haldane observes, carries with him a film of water that is about half a millimeter thick and weighs about half a kilogram. A wet mouse, however, has to carry its own weight in water. And a wet fly has to lift many times its own weight. In fact, once a fly gets wet and falls in the grip of the surface tension of water, it is likely to remain there until it drowns. "An insect going for a drink is in as great danger as a man leaning out over a precipice in search of food" (ibid., 22), which is the reason why most insects keep well away from their drink by means of a long proboscis.

Many of Haldane's examples are based on the square-cube law, which states that the volume of a shape increases much faster than its surface area. Specifically, volume increases as the cube of length, while surface increases only as the square. A large organism has a far lower surface-to-volume ratio than a smaller organism of comparable shape. This explains why large animals have less trouble keeping warm than smaller animals, which cannot help dissipating more heat because of their higher surface-to-volume ratio. A mouse must eat about a quarter of its own weight in food every day just to keep warm. And although five thousand mice weigh as much as a man, their combined energetic consumption (through food and oxygen) is about seventeen times a man's. But small animals exploit their high surface-to-volume ratio in other ways. Insects have no need for complex circulatory systems; the oxygen their cells require can be directly absorbed by diffusion of air through invaginations in their external surface. In order to become larger, animals have had to evolve oxygen-carrying

bloodstreams as well as pulmonary alveoli (to increase the surface area available for the exchange of gases) and a gastrointestinal tract (to increase the surface area available for the absorption of food). Haldane realized that "[t]he higher animals are not larger than the lower because they are more complicated. They are more complicated because they are larger" (ibid., 23). And the same can be said for plants. In general, "[c]omparative anatomy is largely the story of the struggle to increase surface in proportion to volume" (ibid.).

Such geometric relations determine the morphology and physiology of organisms and impose unbreachable limits on their possible dimensions. Given their existing morphology and physiology, it is simply not possible for insects to grow to be much larger than they already are. For the same reason, the giant creatures found in fantastical stories – from *Gulliver's Travels* to *Godzilla* – are impossible. Haldane calculated that a giant ten times as high as man, and also ten times as wide and ten times as thick, would weigh a thousand times more than man. But because the cross-sections of its bones would be only a hundred times those of man, every square centimeter of giant bone would need to support ten times the weight supported by every square centimeter of human bone. The consequence of this is that the giant would break its thighs every time it tried to take a step.

Of course, Haldane was not the first to reflect on the impact of size in biology.[3] Three centuries earlier, Galileo had made strikingly similar observations in his *Dialogues Concerning Two New Sciences*. Galileo already understood that size imposes fundamental constraints on the possible proportions of an organism, as well as of its parts. In his own words,

> An oak two hundred cubits high would not be able to sustain its own branches if they were distributed as in a tree of ordinary size; [similarly,] nature cannot produce a horse as large as twenty ordinary horses or a giant ten times taller than an ordinary man unless by miracle or by greatly altering the proportions of his limbs and especially of his bones, which would have to be considerably enlarged over the ordinary.
>
> (Galileo 1914 [1638], 4)

Galileo illustrated this by graphically depicting how the bone of a large animal must thicken *disproportionally* to provide the same relative strength as the corresponding bone of a small animal, as shown in Figure 2.1. As size increases, skeletal structure needs to become much stronger and more robust. This and many of Haldane's examples I have discussed above demonstrate the inevitability of allometric scaling. Animals are not isometric. Large animals do not look like small organisms scaled up in size, and vice versa. No one would mistake an elephant for a mouse, or a fly for an albatross, even if they are portrayed as being the same size. Quantitative changes in size necessarily entail qualitative changes in form and function. And this is as true for organisms as it is for other kinds of physical objects, such as ships, buildings, and *machines*.

Let us now see how these old insights can be put to work in the context of current cell and molecular biology. The most obvious feature of cells and molecules,

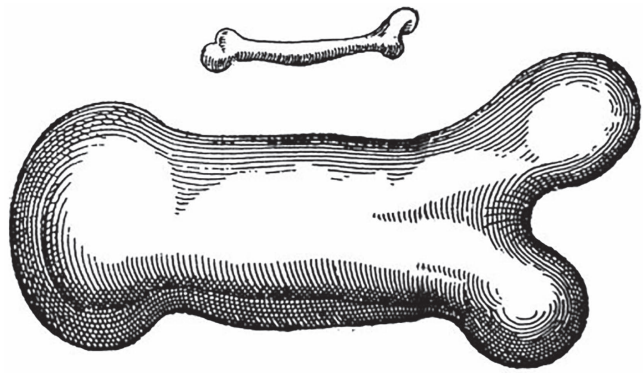

Figure 2.1 Galileo's drawings showing the extent to which the shape and proportions of a bone would need to be modified for it to perform its function if its length was increased by a factor of three.

Source: Figure adapted from Galileo 1914 [1638]. Reproduced with permission.

especially when we compare ourselves to them, is that they are extraordinarily small. The difference in size between a man and a paramecium is several orders of magnitude greater than the one between a man and a giant, or between a mouse and an elephant. As a result, the morphological and physiological differences between them are also far more dramatic. I have already indicated that the structure, function, and behavior of every organism are adjusted to the scale at which it lives. This scale defines the physical environment in which each organism finds itself and determines the forces that have the greatest impact on its way of life. Cells and molecules are so miniscule that they exist in an environment that is *completely different* to our own. It is not an exaggeration to say that macroscopic and microscopic entities inhabit different "worlds." Whereas the macroscopic world is ruled by gravity and inertia, the microscopic world is governed by Brownian motion, which results from the thermal agitation of molecules above absolute zero. This has serious implications for the explanations we formulate of cellular and molecular phenomena. Most importantly, our imagination and intuition, based as they are on our experience of the macroscopic world, fail us when estimating the adaptive problems that cells and molecules have to overcome, as they inhabit a world that is utterly alien to us.

The main lesson that I wish to draw from this is that we should be extremely skeptical of analogies that seek to explain properties of microscopic entities by appealing to properties of macroscopic ones. Unfortunately, this is *precisely* what metaphorical appeals to machines in the modelling and explanation of molecular and cellular phenomena attempt to do. We routinely resort to machines to shed light on microscopic structures and processes because machines are familiar and

intuitively intelligible macroscopic objects of our everyday experience. To conceptualize something as a machine is already to assume that we have a basic epistemic handle on how it works. The problem is that if our machines *were* the size of molecules they would not be able to function the way they do, as their physical environment would make it impossible for them to do so. It follows, therefore, that we should try to avoid distorting the reality of cells and molecules by construing it using concepts and models borrowed from the domains of electronic and mechanical engineering. Indeed, the reason why engineering metaphors in molecular biology mislead more than they illuminate, as the following four case studies will illustrate, is that they are not appropriately calibrated to the scale of the target domain they are called upon to explicate.

Metaphor #1: "genetic program"

The first engineering metaphor I shall discuss is the perennially popular notion that every cell contains a *genetic program* that directs and controls its functions by executing a predetermined set of operations according to instructions encoded in its genes. This idea was proposed, seemingly independently, by Jacob and Monod (1961) and by Mayr (1961), and it quickly garnered widespread acceptance among molecular biologists.[4] Jacob (1973, 9) admitted that the genetic program "is a model borrowed from electronic computers. It equates the genetic material of the egg with the magnetic tape of a computer," adding that "everything urges one to compare the logic of heredity to that of a computer. Rarely has a model [. . .] proved to be more faithful" (ibid., 265). Mayr (1982, 106), for his part, remarked that "all manifestations of development and life are controlled by genetic programs," noting that "[n]othing comparable to it exists in the inanimate world, except for manmade computers" (ibid., 55). More than half a century after it was first proposed, the metaphor continues to pervade the specialist as well as the popular scientific literature (e.g., Danchin 2009; Bray 2009).

Despite its enduring popularity, the problems with the genetic program have long been pointed out by biologists and philosophers (e.g., Webster and Goodwin 1982; Atlan and Koppel 1990; Nijhout 1990; Moss 1992; Keller 2000; Oyama 2000; Longo and Tendero 2007; Nicholson 2014). It has been repeatedly argued, for example, that the metaphor is conceptually incoherent, as the genetic program requires its own output to be executed: the protein "hardware" that runs the genetic "software" is not independent of it but is itself produced by that very software. What has received far less attention, however, is the fact that the difficulties involved in theoretically transferring the idea of a program governing the operation of a computer to the way genes are involved in specifying the cellular phenotype have a great deal to do with the physical scale at which the latter process takes place. It is because of this, for instance, that the deterministic assumptions of the genetic program model of development are completely unrealistic. It is just not possible, physically speaking, to "compute the embryo" from a complete description of a fertilized cell's DNA sequence and the location of all its proteins (cf. Wolpert 1994; Rosenberg 1997). One reason for this is very simple.

Gene expression is first and foremost a *molecular* process, and like all molecular processes it is subject to the dampening stochastic effects of Brownian motion. Let me elaborate this point a little.

Gene expression is an extremely intricate process. Consider how it gets started: an inducer, which can be an intracellular or extracellular signal, triggers a chain of biochemical reactions that causes proteins called activators to bind to specific sites in the DNA known as enhancers. Upon binding, the activators interact with other proteins that recruit RNA polymerase and its associated transcription factors to the promoter region of the target gene, where it begins the process of transcription. Numerous additional steps need to be strictly followed after transcription, including RNA processing and export, translation, and protein folding and sorting (Alberts et al. 2008). The point is that for even a single protein to be successfully expressed in the cell, a huge number of molecules need to interact with one another in exactly the right way, at exactly the right time, and in exactly the right order. And it should not be surprising that the likelihood that all of this happens in a perfectly efficient and precisely timed fashion (as one would expect of the programmatic execution of an algorithmic sequence of coded instructions) is virtually zero once we take into account the random and ferocious buffeting that all molecules are subject to inside the cell by virtue of their size.

The impact of stochasticity on gene expression is exacerbated even further by the fact that a cell, unlike a test tube, contains very low copy numbers of the relevant molecules. There are only one or two copies of any given gene in a cell, just a few copies of each mRNA molecule, and a few dozen copies of the required polymerases and transcription factors (Xie et al. 2008). Consequently, it is not possible to appeal to the law of large numbers to make accurate predictions about the process. Of course, it is still possible to make predictions when gene expression is measured across a *population* of cells, as the individual differences between cells are averaged out, but this becomes impossible when measuring the expression of a gene in a single cell. The recent introduction of methods capable of tracking individual molecular reactions on a cell-by-cell basis has confirmed that even genetically identical cells subject to the same external conditions exhibit substantial variability in their gene expression profiles due to the inherent stochasticity of the process (Altschuler and Wu 2010). This finding makes perfect sense given the scale at which gene expression occurs, but it is difficult to reconcile with the genetic program model, as two identical computers running the same software program are expected to execute it in exactly the same way.

Frustratingly, instead of questioning the theoretical adequacy of the genetic program (or the assumptions that underlie it), molecular biologists initially reacted to the discovery of the stochastic character of gene expression by borrowing an additional idea from the realm of engineering to make sense of it; namely, the concept of *noise* (e.g., Elowitz et al. 2002; Rao et al. 2002; Raser and O'Shea 2005). In engineering, noise refers to an undesirable random disturbance that garbles the transmission of a message. Noise is therefore a nuisance that engineers strive to overcome by designing machines that filter out its detrimental effects. The rationale for appropriating this term seems to have been that stochasticity thwarts the capacity of molecular biologists to perfectly predict cellular

behavior in the same way that noise thwarts the capacity of engineers to design and manufacture totally predictable machines. In any event, the analogy does not hold because cells, unlike machines, actually benefit from the "noisiness" of gene expression. Far from being disruptive or detrimental, recent research has shown that gene expression noise plays many critical biological functions. In microbial cells it is a key generator of phenotypic diversity within populations and therefore serves to increase their adaptability to new environmental conditions. And in eukaryotic cells, among other things, it helps to determine cell fate decisions, thereby shaping the way in which cells differentiate during development (Eldar and Elowitz 2010; Balázsi et al. 2011).

Overall, the genetic program can only be understood as a rather crude approximation of what happens during gene expression. Although the metaphor does compellingly capture the order, reliability, and robustness of this process, it does so at the expense of abstracting away the messy molecular details that enable it to take place. Upon close inspection, the analogy with how a computer executes a program breaks down. Lewontin (2000, 17), as ever, puts it best when he declares that "[a]ny computer that did as poor a job of computation as an organism does from its genetic 'program' would be immediately thrown into the trash and its manufacturer would be sued by the purchaser." It is worth pointing out as well that the genetic program metaphor misrepresents not just the phenomenon it seeks to explain but also the way in which scientists investigate it: molecular biologists are simply not in the business of deducing computable functions, either mathematical or algorithmic, from their empirical studies.[5]

Metaphor #2: "cellular circuitry"

Another engineering metaphor commonly used by molecular biologists, and which is to some extent implied by the genetic program, is the notion of *cellular circuitry*. This is the idea that the programmatic instructions encoded in the genes are carried out in a logical fashion by fixed, solid-state circuits inside the cell that mimic the circuit boards of electronic engineering. The metaphor of cellular circuitry goes beyond that of the genetic program because it argues that computers are not merely functionally analogous to cells and other biological systems but also *structurally* analogous. In other words, not only does a cell behave in a programmed way, but its internal architecture also displays the modular organization that is typical of the hardware of an electronic computer.

There are two main areas of current research in which the cellular circuitry metaphor is regularly employed. The first is in relation to gene regulation, particularly as it pertains to embryonic development. Here the metaphor provides the conceptual foundation for the understanding of gene regulatory networks (GRNs). GRNs are comprised of cis-regulatory elements (i.e., the regions in the vicinity of each gene that contain the specific sequence motifs at which the regulatory proteins that affect its expression bind) plus the set of genes that encode these specific regulatory proteins. Conceptualized through the lens of electronic engineering, GRNs are characterized as hierarchical assemblies of "modular

subcircuits and their interconnections" (Davidson 2009, 535), where each subcircuit is an "information processing unit" (Davidson 2001, 7) that produces a discrete developmental output, which is defined in terms of the effect it has on the spatial or temporal expression pattern of a particular gene. Importantly, these outputs can be mathematically represented as combinations of Boolean operators (e.g., AND, OR, NOT), so that the entire GRN can be viewed as "a logic processing system" made up of distinct "computational devices, the functions of which are conditional on their inputs" (Davidson and Levine 2005, 4935). The GRN for the early development of the sea urchin embryo is shown in Figure 2.2, which illustrates just how complex and detailed these models have become, and also just how uncanny, and intentional, their resemblance is to the wiring diagrams of electronic engineering.

The first thing to bear in mind when evaluating GRN circuits is that they include only a fraction of the genes, cis-regulatory elements, and proteins involved in the developmental process. Moreover, despite their seemingly robust design, the depicted circuits have rather restricted predictive capabilities, as their computing power is dependent on the presence of very specific environmental conditions. As GRN researchers readily admit, "[w]e do not know how they [i.e., GRNs] would

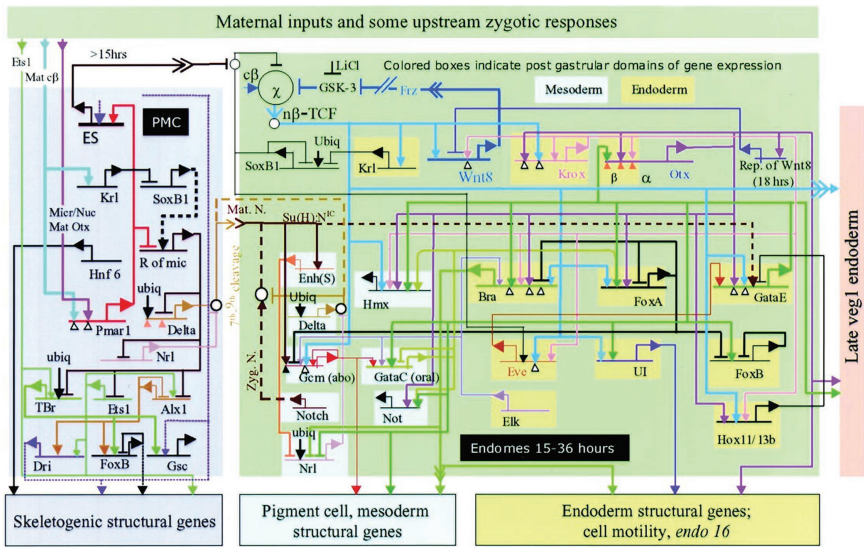

Figure 2.2 Gene regulatory network for the early development of the sea urchin embryo. The circuit is divided according to the embryonic region in which each gene is expressed. The lines with bent arrows represent the transcription pattern of the genes named beneath them, as inferred from experimental studies.

Source: Figure adapted from Davidson et al. 2003. Reproduced with permission.

Note: This figure can be accessed in color via the eBook version of the book and eResources at www.routledge.com/9780815380788.

behave even in a slightly different context (both abiotic and biotic)" (Wang and Buck 2012, 382). Still, the most serious problem with GRN models is that they misinterpret our ability to describe certain patterns of transcriptional activity in terms of Boolean operators as empirical proof that cis-regulatory elements in the genome and their associated regulatory proteins causally interact in a perfectly reproducible, deterministic manner. It is a blatant – even if often convenient – idealization to characterize molecular processes such as transcription and differentiation in terms of computable logic functions, and the reason, as I have already discussed, has to do with the scale at which they take place. Every single step in these processes (as with every biochemical reaction in the cell) relies upon probabilistic collision events between small numbers of randomly moving molecules, and these stochastic effects are amplified in regulatory cascades. This imposes absolute limits on the predictive capabilities of these models, and it is also why the analogy with electronic circuit boards is inappropriate and frequently misleading.

The second context in which the cellular circuitry metaphor is widely used is in the study of protein-protein interactions, particularly signal transduction pathways, which enable cells to make decisions, such as whether to grow, differentiate, move, or die. "The analogy between cell signaling and man-made machines," Mayer et al. (2009, 81.1) observe, "is all-pervasive, frequently adopting the imagery of [. . .] electronic circuit boards." The reason, according to Dueber et al. (2004, 690), is that signal transduction pathways "have information-processing capabilities that rival computers: they can perform complex signal integration [and] switch states in a manner that retains memory or generate complex temporal behaviors, such as oscillations." They are also presumed to be analogous in their organization: "[j]ust as electronic circuits are built of simpler components cellular signalling circuits are composed from a modular toolkit of components" (ibid.). Specifically, "transistors are replaced by proteins (e.g., kinases and phosphatases) and the electrons by phosphates and lipids" (Hanahan and Weinberg 2000, 59). Figure 2.3 shows a typical example of how these pathways are represented in the literature.

It is hard to resist the appeal of diagrams of this kind. Besides economically summarizing a wealth of information about how particular proteins interact, by deliberately imitating the design charts of electronic circuits, with their neat modular structure and their reassuring arrows, these attractive representations convey the comforting impression of understanding and control. However, in order for them to be as explanatorily useful as the diagrams of engineering, they must assume a very high degree of specificity in the molecular interactions that are depicted as arrows. The trouble is that this assumption is not well supported empirically. A growing body of experimental evidence suggests that exquisite specificity in protein function is the exception rather than the rule (Nobeli et al. 2009; Kupiec 2010).[6] What a protein does in the cell is determined as much by the milieu it finds itself in as by its amino acid sequence. The same polypeptide chain can partake in a wide variety of cellular functions depending on where and when it is expressed; a rather unexpected phenomenon that has been dubbed "moonlighting" (Jeffery 2003; Copley 2003). Moonlighting occurs because proteins *in*

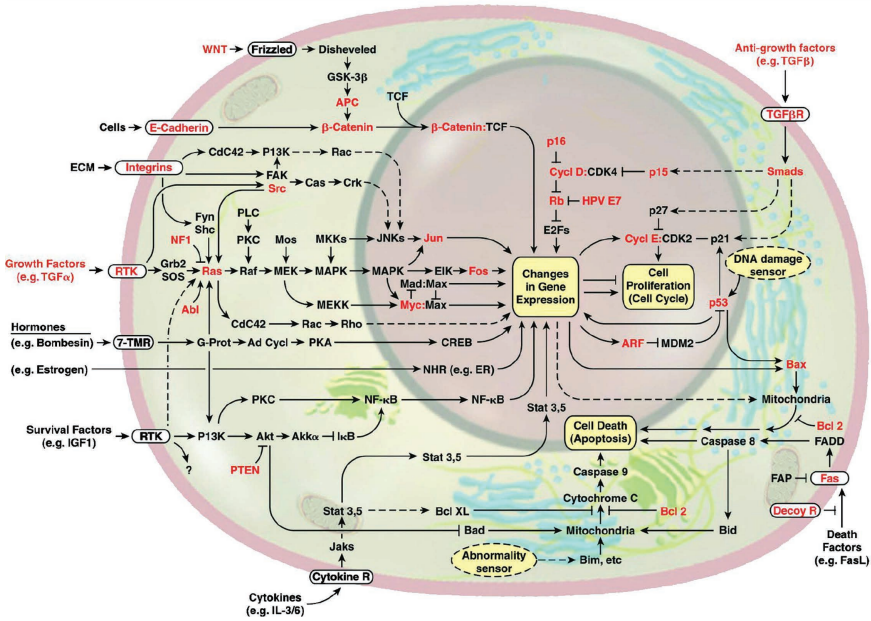

Figure 2.3 Signal transduction pathways represented as wiring diagrams to reflect what Hanahan and Weinberg (2000: 59) call the "integrated circuit of the cell."

Source: Figure adapted from Hanahan and Weinberg 2000. Reproduced with permission.

Note: This figure can be accessed in color via the eBook version of the book and eResources at www.routledge.com/9780815380788.

vivo actually interact with many more binding partners than was previously supposed (Gierasch and Gershenson 2009). Nevertheless, reports of moonlighting become far less surprising when we bear in mind that most proteins are constantly colliding with one another as a result of being violently knocked about by Brownian forces. This is all a consequence of the strange, stochastic world that proteins inhabit by virtue of being so small.

The fact that every protein in the cell can potentially associate with a large number of other proteins leads to a dazzling explosion of combinatorial possibilities that is exceedingly difficult to faithfully represent in diagrammatic form. The problem with circuit-like characterizations and representations is that signal transduction pathways do not exist as discrete, mutually exclusive subcellular compartments, given that the proteins that constitute them participate in many other pathways, as well as in other, altogether different cellular processes. Signaling cascades in the cell are deeply interconnected; they interact, or "cross-talk," with one another in numerous ways (Knight and Knight 2001). Even the most straightforward textbook representations of linear sequences of protein-protein interactions tend to mislead, as "the simple causal links that are being depicted hide

an underlying complexity that is often essential to explain real world functionality: so much is swept under the rug" (Blinov and Moraru 2012, 3). A dramatic illustration of this was provided by Dumont and colleagues, who, in an attempt to diagrammatically represent experimentally verified cross-signalings between four distinct cascades (as reported in the literature during the previous two years), produced a remarkable, yet utterly unreadable, "horror graph," shown in Figure 2.4, in which, according to the authors, "everything does everything to everything" (Dumont et al. 2001, 457).

When visualizing cellular circuit diagrams, it is important to understand that they represent only one of the many potential ways in which a given set of proteins can interact with one another. Tweak the intracellular or extracellular context ever so slightly and the wiring between the proteins will change. And, of course, we should not forget that there is no actual wiring physically connecting proteins as there is in a real electronic circuit. Instead – and this is, again, a consequence of their size – proteins exist in a fluid and dynamic environment in which they rely on probabilistic collision events with appropriate partners to reliably perform particular cellular functions at particular times. Diagrams such as Figure 2.3 wrongly imply that the proteins featured in them always form the same exact networks of interactions, which are envisaged as

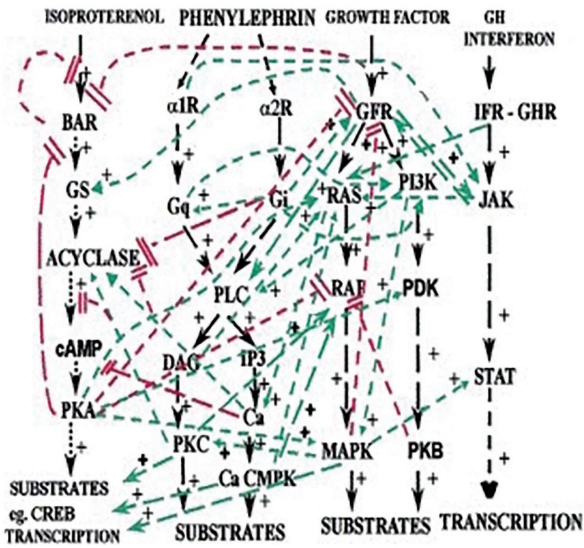

Figure 2.4 "Horror graph" indicating cross-signalings between four signal transduction cascades. The black arrows show the "textbook" representation of the cascades. The remaining arrows denote all the experimentally verified cross-signalings reported in the literature in the space of only two years. Despite featuring only four cascades with four to six steps each, the total number of possible interaction combinations is 760!

Source: Figure adapted from Dumont et al. 2001. Reproduced with permission.

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fixed, solid-state circuit boards. In doing so, these diagrams prevent us from appreciating the vast spectrum of alternative interaction networks that the same set of proteins can and do form in different cells, and even in the same cell at different times. The majority of protein-protein interactions are contingent and opportunistic (Misteli 2001; Kurakin 2009). There is no predetermined "design" that specifies the way in which the proteins in a cell interact any more than there is a program of genetic instructions that is deterministically computed by the cell (or the embryo). Conceptualizing protein-protein interactions as circuits may seem like a harmless heuristic simplification, but it can mislead us into thinking that we understand more than we actually do. Worse still, it can inadvertently direct our attention away from the factors and causal relations that may turn out to be most relevant for explaining the phenomena we are interested in.

Metaphor #3: "molecular machine"

A further engineering metaphor that has completely permeated the molecular biology discourse is the concept of *molecular machine*. This notion, which borrows more from mechanical than from electronic engineering, has become central to the way protein complexes and many other subcellular assemblies are conceptualized (Block 1997; Piccolino 2000). The success of this metaphor lies in its versatility. As Table 2.1 illustrates, an extremely wide range of machines can be summoned on its behalf to give substance to descriptions of the structure and function of macromolecular assemblies, thereby rendering them more tractable and familiar.

But what exactly is the rationale for using the term "machine" to designate macromolecular assemblies? According to Nogales and Grigorieff (2001, F1), "this designation captures many of the aspects characterizing these biological complexes: modularity, complexity, cyclic function, and, in most cases, the

Table 2.1 Examples of the different kinds of machines that molecular biologists draw upon as conceptual resources to ground their characterizations of macromolecular assemblies in the cell.

Macromolecular assembly	*Machine*
Cilium, flagellum	Propeller
ATP synthase	Generator
Ribosome	Factory assembly line
Ion channel, nuclear pore	Gate, key, pass
Polymerase	Copy machine
Ligase	Chain coupler
Spliceosome	Film editing machine
Protein targeting mechanism	Mail sorting machine
Proteasome, apoptosome	Bulldozer, destroyer
Magnetosome	Compass

consumption of energy." Frank (2011, 1), for his part, argues that " '[m]achine' is useful as a concept because the molecular assemblies [. . .] share important properties with their macroscopic counterparts, such as processivity, localized interactions, and the fact that they perform work toward making a defined product." And Browne and Feringa (2006, 26), when asking "What makes a molecule a machine?", answer that in "a molecular machine we are able to switch between two [or more] molecular states (shapes) in a controlled manner as part of a repetitious mechanical cycle." Finally, Alberts, who has been one of the most influential advocates of the molecular machine metaphor in molecular biology during the last two decades, gives the following explanation:

> Why do we call the large protein assemblies that underlie cell function protein *machines*? Precisely because, like the machines invented by humans to deal efficiently with the macroscopic world, these protein assemblies contain highly coordinated moving parts. Within each protein assembly, intermolecular collisions are not only restricted to a small set of possibilities, but reaction C depends on reaction B, which in turn depends on reaction A – just as it would in a machine of our common experience.
>
> (Alberts 1998, 291)

The idea, then, is that macromolecular assemblies in the cell can be legitimately thought of as machines because they effectively capture in their operation the high degree of coordination and precision that is typical of mechanical devices. However, the scale at which these macromolecular assemblies operate makes this comparison hard to uphold from a physical point of view. Perfectly orchestrated mechanical movements are simply not possible in a world that is governed by Brownian motion. Even the structure of a macromolecule cannot be compared to that of a machine. Machines tend to rely on a hard and rigid constitution for their operation. Proteins, on the other hand, exhibit very high degrees of structural flexibility. In fact, it is becoming apparent that, in their native environments, proteins behave more like liquids than solids; they can be characterized as "dense liquids" or "melted solids," consisting of a "near-solid interior" and a "full-liquid exterior" (Rueda et al. 2007, 798; see also Zhou et al. 1999). What is more, it is now widely acknowledged that most proteins do not have a single ordered conformation. What we refer to as *the* conformation of a protein actually comprises an entire spectrum of well-defined configurations separated by low-energy barriers that the protein continuously samples by means of stochastic fluctuations (Yang et al. 2003). Even more counterintuitive is the discovery that many proteins do not have an ordered conformation *at all*. These have come to be known as "intrinsically disordered proteins" (Uversky 2013; Wright and Dyson 2015) and they empirically refute the longstanding mechanical assumption that a protein needs to have a clearly defined three-dimensional structure for it to perform its function; a requirement that is, of course, crucial for the operation of a mechanical device. Macromolecular assemblies, which are primarily composed of protein subunits, therefore lack most of the structural characteristics that we associate

with machines, often exhibiting instead fluid, ever-flickering, "fuzzy" structures (Fuxreiter and Tompa 2012).[7]

The fundamental shortcomings of the molecular machine metaphor have far-reaching consequences for how macromolecular assemblies in the cell are studied and represented. For example, they call into question the adequacy and usefulness of virtual movies that purport to faithfully depict how these assemblies modify their structure as a result of their operation. Such movies are made by using cryo-electron microscopy to visualize a frozen population of isogenic macromolecules in a near-native state, categorizing each macromolecule in the snapshot according to its reconstructed three-dimensional structure, and ordering these static reconstructions so as to create the impression of motion. "Morphing" computer software is then used to interpolate additional hypothetical frames to smoothen the transition between reconstructions and prevent the resulting movements from appearing excessively jerky (Moore 2012; Nogales 2016). Thus, unlike conventional live imaging microscopy techniques in which what one sees more or less reflects what is really happening, in molecular movies the temporal dimension is introduced *virtually* by linking unrelated reconstructions of different macromolecules to plausibly infer a coherent "time line" of a single macromolecule.

An important limitation of these movies is that it is not possible to conclusively determine whether the conformational trajectories devised by morphing programs are accurate, let alone that such trajectories are always followed by every macromolecule of the type depicted in the movies. The problem is that, because macromolecules are so often thought of as molecular machines, molecular biologists tend to assume, incorrectly, that they move in a mechanical fashion. This has been forcefully pointed out by Moore (2012) with regard to movies of the ribosome – that most paradigmatic of molecular machines (Garrett 1999; Frank 2000). Moore argues that a virtual movie makes the ribosome appear to be something it is not:

> Like the structures on which it is based, the movie will actively invite viewers to think that the ribosome works the same way as a clock, or a machine for making candy bars. *It is no help that macromolecules* [. . .] *are commonly called molecular machines*. The use of the word 'machine' in this context is pernicious because of its implication that the functional properties of macromolecules can be explained mechanically, *which is simply not true*.
>
> (Moore 2012, 7–8; emphasis added)

Due to their minuscule size, ribosomes (and smaller macromolecules even more so) cannot possibly operate in the orderly and reproducible manner that is characteristic of machines. In a machine, as we noted earlier, the motions of the various parts are perfectly coordinated. For example, when a gear rotates, the shaft to which it is connected rotates in synchrony, a spring is compressed, a latch is released, etc. All of these movements are purposeful and predictable and are always precisely executed in exactly the same temporal sequence. Macromolecular assemblies, by contrast, are subject to continuous Brownian motion, which means that the vast majority of conformational changes they undergo are the result of "random walks"

that have nothing to do with their function.[8] This is very significant because if the usefulness of a virtual movie is predicated on its ability to explain the function of a macromolecule on the basis of its conformational changes, then it follows that a *perfectly accurate* movie (i.e., one that realistically depicted all of the macromolecule's random motions) would be of no explanatory value whatsoever. Virtual movies of mechanically moving macromolecules are undoubtedly fun to watch, but they are also misleading – especially when shown to impressionable students or to the unsuspecting general public. As Moore (2012, 15) himself concludes, "[s]tructure-based movies of ribosome function should have a surgeon-general's warning attached to them because they are more likely to deceive the unwary than enlighten them."

Metaphor #4: "molecular motor"

The final engineering metaphor I shall examine is the concept of *molecular motor*, which is used to characterize proteins responsible for transporting cargo to specific destinations inside the cell. Although it is generally regarded as a subclass of the more general notion of molecular machine, its usage poses its own set of distinct challenges that merit separate attention. For a start, it could be argued that the concept of motor does not necessarily imply the concept of machine. If we understood a motor simply as an entity that imparts motion – which is actually the first definition of "motor" listed in the *Oxford English Dictionary* – then there would be nothing metaphorical about referring to kinesin, dynein, and myosin as motors. In practice, however, the designation "molecular motor" in molecular biology tends to carry clear connotations of machines and of mechanical engineering. When proteins capable of directional movement are described as molecular motors in the literature, what is typically implied is that that they resemble macroscopic mechanical motors with regard to their structure and to their operation. In fact, it is not unusual for them to be compared to automobiles. Both, it is argued, consume fuel to power their motion. Moreover, Vale and Milligan remark that:

> Just as in an automobile, the site that processes the chemical fuel [in a molecular motor] must be linked through intermediate components to the site that ultimately generates the motion. In the automobile, the breakdown of the chemical fuel is coupled to the stroking of a piston, which in turn is linked through the crankshaft and transmission to the turning of the wheels. A somewhat analogous situation for translating chemical changes into mechanical motions exists in molecular motors.
>
> (Vale and Milligan 2000, 90)

Specifically, the claim is that the energy released from the chemical fuel is used to induce a large-amplitude conformational change in the motor protein, which generates a mechanical force – a "power-stroke" – that drives the molecule forward relative to a polymeric track (Howard 2001; Tyska and Warshaw 2002). Sometimes, this power-stroke is compared to the mechanical release of a viscoelastic

spring (e.g., Howard 2006). In the case of kinesin, which has dimeric "legs" that alternatively attach to tubulin, the repetitive power-strokes result in directed movement that makes the protein appear like a tiny robot walking along the microtubule, and this is indeed the way in which its motion is usually represented in diagrams and animations (e.g., Asbury 2005).

Once again, the problem with these familiar mechanical models inspired by our everyday experience of the macroscopic world is that they fail to recognize the drastically different physical conditions that characterize the microscopic world. When we are walking, the two major physical forces at play are gravity and inertia. Most of the motive power is expended by repeated cycles of acceleration, as the foot that was in touch with the ground is brought forward to a position in front of the torso. Friction plays only a minor role as far as the energetics are concerned. In the microscopic world, however, the impact of inertia (which is proportional to volume and mass) is completely dwarfed by the impact of friction (which is proportional to surface area). The high viscous friction (or drag) of water at the molecular scale means that, for a bacterium, swimming in water feels like what swimming in molasses would feel to us (Bier 2003; Astumian 2007). Moreover, although we might (just about) be able to imagine what it would feel like to be immersed in molasses, it is much harder to imagine another feature of aqueous solutions that cells and their macromolecular components experience by virtue of being so small: the molasses that surrounds them is furiously moving about as a result of the thermal agitation of the water molecules. We have to remember that a motor protein does not experience water as a fluid continuum in the way that we do, but as an extremely dense array of rapidly moving particles that are constantly striking it from all sides. "Even a freak hailstorm," Astumian (2001, 58) writes, "does not come close to the tempestuous bombardment that is routine in the molecular world, but the effects can be analogous."

From a physical perspective it is difficult to understand how a motor protein could possibly walk in a directed manner by means of mechanical cycles of precisely coordinated power-strokes once we realize that "[f]or molecules, moving deterministically is like trying to walk in a hurricane: the forces propelling a particle along the desired path are puny in comparison to the random forces exerted by the environment" (ibid., 57). Recently, a growing number of researchers have come to appreciate that if we are to understand the way in which motor proteins move, we need to "[i]magine living in a world where a Richter 9 earthquake raged continuously" (Oster and Wang 2003, 207). So how exactly do motor proteins manage to move directionally in such a turbulent and chaotic environment? There are two alternatives: motor proteins must either work with the raging Brownian storm that engulfs them or fight against it, and in light of the above considerations, the former appears to be the preferable option. This has led to the hypothesis that motor proteins are not mechanical motors but *Brownian motors*. Instead of moving directionally by generating a large mechanical force that overpowers the stochastic effects of Brownian motion, motor proteins are thought to move by biasing the existing Brownian motion in a particular direction.

Figure 2.5 illustrates how Brownian motors harness stochasticity to move directionally. According to this model, motor proteins use the energy released from the chemical fuel they consume to switch between two alternative conformational states – "on" and "off" – with different energy profiles. When the motor proteins are on, their energy landscape has a jagged, sawtooth shape, and consequently random collisions jostle them overwhelmingly to the right, where they get trapped in the nearest energy minima. When the motor proteins are off, their energy landscape has a flat shape, and consequently random collisions cause them to perform random walks, with equal probabilities of moving to the left or to the right of their initial position. Thus, by periodically switching between on and off states through the repeated consumption of chemical energy, and by taking advantage of the incessant Brownian motion that characterizes their environment, motor proteins are able to move directionally in the absence of mechanical forces (Ait-Haddou and Herzog 2003).

When trying to comprehend how a motor protein moves along a cytoskeletal track, the assumption has long been that at least some of the mechanical principles "that have been derived by the engineers who analyse the machines of our common experience are likely to be relevant" (Alberts 1998, 291). But if the Brownian motor model of intracellular transport is even partially correct, then this attitude is bound to lead researchers astray. Due to their huge disparity in size, mechanical motors and Brownian motors operate according to fundamentally different principles. The former use energy to drive motion, whereas the latter use energy to restrain it. The former move despite stochastic fluctuations; the latter move because of them. The structure of the former must be hard and rigid, while that of the latter can be soft and plastic. In addition, Brownian motors are far more efficient than mechanical motors because they convert chemical energy directly into work without using heat or electrical energy as intermediates. An important upshot of

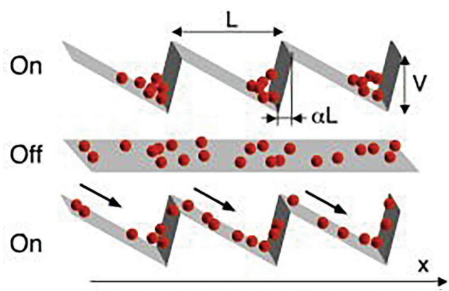

Figure 2.5 Directed movement by Brownian motors. During the on phase, Brownian motors (shown as particles) move toward the closest energy trough. During the off phase, they undergo one-dimensional isotropic diffusion. Stochastically alternating between the two states results in net movement along the x axis.

Source: Figure adapted from Linke et al. 2005. Reproduced with permission.

Note: This figure can be accessed in color via the eBook version of the book and eResources at www.routledge.com/9780815380788.

relying on stochasticity for their operation is that the directional movements of Brownian motors are purely *statistical* occurrences. The timing of their individual journeys, as well as their precise trajectories, is non-deterministic and therefore impossible to predict. Every Brownian motor performs a unique "dance" despite moving in the same general direction. Overall, it is clear that attempts to draw on the properties of macroscopic motors to shed light on the properties of microscopic ones (such as the motor proteins inside the cell) are more likely to cloud and obfuscate than they are to clarify and illuminate.

How did molecular biology come to neglect the impact of scale?

Before bringing this chapter to a close, it is worth pausing for a moment to consider the intriguing historical puzzle that the examination I have provided suggests. A growing number of molecular biologists are beginning to question the value of using metaphors and models imported from electronic and mechanical engineering, and this undoubtedly reflects an increasing awareness of the importance of adjusting explanations of molecular and cellular phenomena to the scale in which they take place. The odd thing about this is that it has taken molecular biologists so long to start taking the importance of scale seriously. Haldane was not a lone voice when he drew attention to the importance of size in his essay of 1926. The impact of scale was widely recognized at the time, remaining an important consideration in biological discussions during the first half of the 20th century. Take, for example, the second chapter of the revised edition of Thompson's celebrated magnum opus, *On Growth and Form*. It is titled "On Magnitude" and it presents a wonderfully detailed analysis of the numerous ways in which physical forces at various scales affect the lives of organisms of different sizes. In fact, its final paragraph eloquently articulates the basic thesis I have sought to defend in this chapter:

> [The world of] Man is ruled by gravitation. [. . .] [But in the] world where the bacillus lives, gravitation is forgotten, and the viscosity of the liquid, the resistance defined by Stokes's law, the molecular shocks of the Brownian movement, doubtless also the electric charges of the ionized medium, make up the physical environment and have their potent and immediate influence on the organism. *The predominant factors are no longer those of our scale; we have come to the edge of a world of which we have no experience, and where all our preconceptions must be recast*.
>
> (Thompson 1942, 77; emphasis added)

These remarks were written over three quarters of a century ago, so why do they now seem more relevant than ever? Or, to put it slightly differently, how did we come to forget what we used to know? It is obviously not possible to do justice to such a complex question here. In what follows I only wish to propose and briefly discuss a factor that might have contributed to molecular biology's neglect of scale

during the second half of the 20th century; namely, the influence of Schrödinger's argument regarding the stability of the gene laid out in his famous little book *What is Life?* published in 1944.

Like all science classics, *What is Life?* is far more often cited than read. But if one bothers to go back and actually read how Schrödinger arrives at his well-known characterization of genes as "aperiodic crystals," the striking thing about his argument is that it is based primarily on considerations of size and scale! Schrödinger begins his book by noting that atoms, as a consequence of being so small, are incapable of exhibiting orderly behavior on their own because they are continuously subject to the stochastic effects of thermal agitation at any temperature above absolute zero. This is why physical laws are statistical in nature. Order and regularity can only emerge upon consideration of enormous numbers of atoms (or molecules), which collectively display macroscopic patterns of order. Schrödinger calls this the "order-from-disorder" principle, and he discusses several physical examples to illustrate it.

One of them, shown in Figure 2.6, concerns what happens when you fill a glass vessel with fog consisting of minute droplets. Over time, the fog gradually

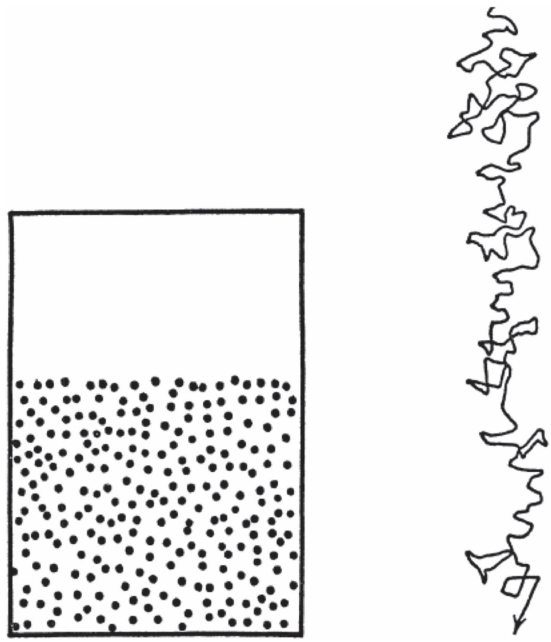

Figure 2.6 One of Schrödinger's own illustrations of the "order-from-disorder" principle. The vessel on the left shows the regular, orderly sinking of fog over time. The arrow on the right delineates the irregular and disorderly trajectory of an individual droplet. The law-like behavior of the fog reflects a statistical average of the collective behavior of all the droplets of which it is composed.

Source: Figure adapted from Schrödinger 1944. Reproduced with permission.

sinks to the bottom with a well-defined velocity, determined by the viscosity of the air and the size and specific gravity of the droplets. Still, if you observe one of the droplets under the microscope you find that it does not permanently sink with constant velocity, but instead performs highly irregular movements – Brownian motion – as a consequence of thermal agitation. So, although the behavior of any given droplet is stochastic and disorderly as it sinks, the behavior of the fog *as a whole* is regular and orderly. In general, the larger the number of participating particles in a physical process, the more accurate the lawful prediction of its behavior. This is what mathematicians refer to as the law of large numbers.

Now, a "naïve physicist," Schrödinger writes, might be forgiven for thinking it self-evident that the astounding regularity and orderliness displayed by an organism must also be based on the macroscopic law-like patterns of behavior exhibited by large ensembles of interacting molecules. However, Schrödinger continues, "this expectation, far from being trivial, is wrong" (Schrödinger 1944, 20). His reasoning is as follows. The order of an organism is essentially determined by its genes, and we know from experimental studies that a gene molecule is not much larger than a few thousand atoms. This number, Schrödinger observes, "is much too small (from the [law of large numbers] point of view) to entail an orderly and lawful behavior according to statistical physics" (ibid., 21). Because genes are so tiny, they should not be able to reliably code for heritable traits, given that they are firmly in the grip of thermal agitation. And yet we know for a fact that genes *are* remarkably stable, "with a durability or permanence that borders upon the miraculous" (ibid., 49).[9] So how do we reconcile the small size of genes with their extraordinary stability in the face of constant stochastic perturbations?

Schrödinger's answer is that the genetic material must have the rigid, solid-state structure of a crystal, as only then would it be able to effectively withstand the relentless disruptive effects of Brownian motion. But unlike normal crystals, which display regular and periodic configurations, the structure of the genetic material must be "aperiodic" so that it can contain within it the "code-script" that specifies the organization of the organism. Schrödinger refers to the kind of order displayed by organisms as a manifestation of an "order-from-order" principle, which he explicitly contrasts to the aforementioned order-from-disorder principle described by statistical mechanics. Interestingly, he argues that in this crucial respect organisms are analogous to machines, as the latter likewise exhibit rigid, solid-state structures capable of resisting random fluctuations, enabling them to operate in an orderly way. Indeed, Schrödinger ends *What is Life?* by declaring that "the clue to the understanding of life is that it is based on a pure mechanism, a 'clock-work' [. . .] [that] also hinges upon a solid – the aperiodic crystal forming the hereditary substance, *largely withdrawn from the disorder of heat motion*" (ibid., 82, 85; emphasis added).

Schrödinger's deliberations led him to conclude that the solid-state, crystal structure of the genetic material renders it impervious to the physical forces that exert the greatest effect at the microscopic scale. Genes behave as if they were at absolute zero, as they do not appear to be affected by thermal agitation. And

although he does not go into detail, his argument implies that the order encoded in the aperiodic crystal must somehow be reliably transmitted to the rest of the cell's components, especially to the proteins, so that these can individually express it through their functions in a way that similarly eludes or overcomes the raging Brownian storm of the molecular realm.

What I want to suggest here is that the influence of this idea – which is central to Schrödinger's argument in *What is Life?* – is responsible, at least in part, for molecular biology's subsequent neglect of the importance of scale. Just as Schrödinger had done with genes, molecular biologists went on to focus on the structure of proteins and other macromolecular assemblies (using methods such as X-ray crystallography), drawing attention to their crystal-like stability and rigidity, emphasizing their functional specificity, and ignoring the chaotic, destabilizing influences of their surroundings. One can easily see how this attitude might have encouraged the appeal to conceptual models borrowed from the macroscopic domain, such as the four engineering metaphors I have considered in this chapter. Indeed, Schrödinger himself, as I have just discussed, acknowledged the deep resemblance between organisms and machines with respect to the kind of order they exhibit, as well as to the negligible impact of the physical environment on their operation.

Some fairly compelling evidence for this hypothesis can be found by considering the case of Monod, one of the main intellectual architects of the molecular biology revolution. The reason is that Monod appears to have changed his mind about the nature of biological order partially as a consequence of reading *What is Life?* which he regarded as a work of genius (see Loison 2015). Though initially committed earlier in his career to a statistical and non-deterministic understanding of biological regularities (consistent with the aforementioned order-from-disorder principle), Monod later came to regard the order of the cell as a product of the static, clockwork-like precision of its macromolecular components. "The whole trend of modern molecular biology," Monod declared in a 1958 lecture, "makes it every day clearer that structural stability and rigidity rather than dynamicity are the most essential and characteristic properties of the typical cellular macromolecules" (Monod, quoted in Loison 2015, 395). Monod also commented in his notes for that same lecture, where he explicitly mentioned Schrödinger in a parenthetical remark, that even when examining large macromolecules (e.g., ribosomes) and complex subcellular processes (e.g., protein synthesis), one can confidently disregard the disruptive effects of stochasticity due to the imposing stability and rigidity of the participating molecules:

> The protein-synthesizing process appears to work with very high precision, and the concept of molecular micro-heterogeneity due to errors or fluctuations in this process appears unwarranted. Putting it otherwise: even in the formation of such a very large and complex molecule [i.e., a protein], the synthesizing system [i.e., the ribosome] appears to work mechanically, like a clock or a precision machine tool, rather than statistically (Schrödinger).
>
> (Monod, quoted in Loison 2015, 396)[10]

By the time he wrote his renowned treatise on molecular biology, *Chance and Necessity*, Monod had become even more forceful in his dismissal of stochastic environmental effects, noting that "a living being's structure [. . .] owes almost nothing to the action of outside forces, but everything, from its overall shape down to its tiniest detail, to [. . .] interactions within the object itself" (Monod 1972, 10). Note that this is precisely the view that I have repeatedly challenged over the course of this chapter.

In any case, more historical research is needed to corroborate this interpretation. Still, I cannot resist making the provocative observation that if the proposed hypothesis is correct, we shall be forced to draw the utterly paradoxical conclusion that one of the greatest physicists of the 20th century was responsible for making several generations of molecular biologists forget about the importance of *physical forces* on the phenomena they study.

Conclusions

Despite its importance in the historical development of biological thought, the machine conception of the organism is deeply problematic from an ontological point of view. In this chapter I have drawn on the insights that Haldane offered in a classic essay from the 1920s to propose a new philosophical argument against this conception that is particularly relevant for current work in cell and molecular biology, and which I have called the Argument from Scale. This states that, owing to their minuscule size, cells and their macromolecular components are subject to drastically different physical conditions compared with macroscopic objects like machines, and that using machine metaphors to explain microscopic phenomena is consequently more likely to obscure and deceive than it is to elucidate and enlighten. I have illustrated this argument by analyzing four central conceptual models in molecular biology that were originally imported from electronic and mechanical engineering – genetic program, cellular circuitry, molecular machine, and molecular motor – and by showing that their explanatory deficiencies ultimately derive from their neglect of the impact of scale. Once scale is seriously taken into account, it becomes hard to defend the theoretical adequacy of these models (which, of course, is not to say that they cannot sometimes serve useful heuristic purposes as convenient, experimentally tractable idealizations).

Although there will be many that will continue to believe that "[t]he engineering sciences, particularly electronic and control engineering, are likely to have an ever increasing and pervasive impact on molecular biology" (Sauro and Kholodenko 2004, 37), the fact is that the physical dimensions of the cell and the milieu it finds itself in impose fundamental constraints on what is possible and what is not, both structurally and functionally. The rigidity, stability, and deterministic precision that we typically associate with the machines of our macroscopic world simply cannot exist in the messy, turbulent, and chaotic world that cells and molecules inhabit. "The clockwork mechanism of the cell," if that is what we insist on calling it, is "built not of precisely engineered solid cogs, but of vague and uncertain particles whose generation, diffusion, and reaction can not provide any precision"

(Hallett 1997, 105). Perhaps the most serious obstacle in coming to terms with molecular and cellular phenomena is the lack of a good analogy from our daily experience. It is for this reason that we should learn to trust what physics tells us about the molecular realm, despite being strange and counterintuitive, over the more familiar and comforting picture that traditional appeals to engineering have tended to suggest.

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Notes

1 For a more technical and detailed examination of the numerous theoretical problems with the machine conception of the cell that complements and extends the analysis I provide in this chapter, see Nicholson 2019.
2 To a terrestrial one, at any rate. The threat that gravity poses to a large aquatic animal (such as a whale) is greatly reduced, as it can use its buoyancy to counteract gravitational effects.
3 Nor was he the last. A highly accessible contemporary account of the impact of size in biology can be found in Bonner 2006.
4 In a fascinating historical examination of the genesis of the genetic program metaphor, Peluffo (2015) explores the potential intellectual connections between Jacob and Monod on the one hand and Mayr on the other prior to their respective 1961 publications.
5 The genetic program is not, of course, the only metaphor biologists have used to characterize gene expression or embryonic development. For a discussion of alternative, non-machine-based conceptualizations of these processes, see Nicholson 2014.
6 Even enzymes, which have traditionally been regarded as extremely specific catalysts, exhibit varying degrees of catalytic promiscuity, as well as the ability to perform a wide range of non-catalytic functions, including cell motility, membrane trafficking, chaperoning, activation and inhibition of metabolic pathways, and chromatin organization (Babtie et al. 2010; Khersonsky and Tawfik 2010).
7 In a recent paper, Militello and Moreno (2018) have defended the legitimacy of the term "molecular machine" in the characterization of macromolecular assemblies – even after recognizing their patently nonmechanical features – by proposing to define a machine as "a meta-stable structure consisting of interdependent parts which constrain a flow of energy and matter in order to do work and perform a systemic function" (ibid.: 35) and showing that this definition can accommodate what we know

about these subcellular entities. While I agree that such a broad definition is capacious enough to encompass many (though perhaps not all) macromolecular assemblies in the cell, my own preference, following Mayer et al. (2009) and others, is to embrace an alternative, explicitly nonmechanical conceptualization of them as *pleomorphic ensembles* (for details, see Nicholson 2019).

8 Indeed, it is highly unlikely that a given ribosome ever repeats its exact same movements as it elongates a polypeptide.

9 Schrödinger illustrates this with the example of the "Habsburg lip," a genetic trait afflicting the Habsburg dynasty that persisted for hundreds of years despite having a molecular basis and consequently being permanently subject to the turbulence of thermal agitation.

10 Compare Monod's characterization of the operation of the ribosome with the radically opposing one offered half a century later by Moore (2012), which I quoted earlier in this chapter. The contrast between the two is extraordinary.

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