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Molecular-biological machines: a defense

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Abstract
I offer a defense, albeit a qualified one, of machine analogies in biology, focusing on molecular contexts. The defense is rooted in my prior work (Levy in Philosopher's Imprint 14(6), 2014), which construes the machine machine-likeness of a system as a matter of the extent to which it exhibits an internal division of labor. A concrete aim is to shore up the notion of molecular biological machines, paying special attention to processive molecular motors, such as Kinesin. But I will also try to show how the division of labor account gives us guidance more broadly, both about where and why machine analogies can be expected to prove helpful and about their limitations.

Keywords Molecular machines · Analogies in science · Power-stroke versus Brownian Ratchet

Introduction

Living systems are commonly analogized to machines. This is especially so at the molecular level, where proteins and related macromolecular structures are often likened to motors, rotors, pumps etc. These descriptions seem to be more than mere flourishes or aids to pedagogy. They appear in research articles and review papers and serve to frame results, suggest hypotheses and motivate the use of certain concepts and theoretical tools, primarily from engineering and physics. While common, talk of biological machines often faces criticism as well. Machines are said to be poor guides to living systems, inasmuch as they operate according to different principles. Such critiques allege that viewing biological structures, macromolecules in particular, in terms of machines generates false expectations and misdirects our thinking about how they work.

My goal in this paper is to offer a defense, albeit a qualified one, of machine analogies in biology, focusing on molecular contexts. In so doing, I rely on previous work (Levy 2014) in which I have argued that the machine-likeness of a system is a

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matter of the extent to which it exhibits an internal division of labor. While I will not offer a(nother) detailed description and defense of this account, I will explain its key ideas below.[1] My immediate aim is to shore up the notion of molecular biological machines, paying special attention to molecular motors. I will also try to show how the division of labor account gives us guidance more broadly, both about where and why machine analogies can be expected to prove helpful and about their limitations.

The next section discusses analogies in general, highlighting some points that will prove helpful below. Section 3 discusses the division of labor account and its motivation, relating it to nearby notions, such as mechanism and mechanical device, and to a recent account from Militello and Moreno (2018). Section 4 discusses molecular motors, especially processive motors like Kinesin. This is a context in which machine analogies have been very fruitful, but in which they have also faced criticism; I discuss both issues. The final Sect. (5) looks at three limitations of machine analogies—contexts in which such an analogy, given the present account, is unlikely to prove useful.

A few remarks about analogies

Most writing about analogy in philosophy of science has concerned itself with analogical reasoning and especially with analogical arguments as a form of inductive inference (Hesse 1966; Bartha 2010; Norton 2021, Ch. 4). My focus will be somewhat different, inasmuch as I look at analogies as a means for structuring and organizing inquiry, especially the search for and interpretation of causal-explanatory models. In this section I offer some general remarks on this, setting the stage for the discussion to follow.

When a biological system is likened[2] to a machine this reflects the thought that we can use our familiarity with manmade machines to make intelligible, and to help us investigate, biological systems. In the present context, I will assume that the likeness at issue primarily involves causal structure: to describe a molecule—or, for that matter, any system—as a machine is to say something about how the molecule works by drawing on our knowledge of, and expectations from, machines. To draw an analogy, however, is not just to state that two systems are similar (specifically, causally similar). It is also to suggest that certain conceptual and empirical tools are helpful and that certain expectations are appropriate. Conversely, an analogy can mislead if it generates incorrect expectations or leads us to use ill-suited tools.

Analogies, metaphors and related figurative devices can be understood in terms of framing (Camp 2019, 2020; Levy 2020). A frame is a vehicle of representation and communication which imposes a certain organization on a target subject. A

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[1] Besides 'division of labor', in Levy (2014) I also used the phrase 'causal order'. I've found that this terminology carries unintended connotations, especially in connection with the statistical mechanical concept of order. So I avoid it here.

[2] Some of the cases I discuss in this paper may, strictly speaking, be instances of metaphor or simile, rather than analogy. But I will not worry too much about distinctions within figurative devices.

frame embodies a set of assumptions and expectations about the target. These may be linked to salient forms of explanation and understanding, and, indirectly, to further questions and hence to relevant tools and methods. Frames are often somewhat implicit and inchoate. This is part their (cognitive and communicative) power but may also lead to mistakes, inasmuch as the frame leads one to think of the target in ways that are incorrect but hard to notice and correct for.

At least in science (although perhaps also in general) frames can operate at different levels of organization and detail. At one end, they can play a general, abstract organizing role. At another end, in more concrete terms—they may point us in the direction of particular models, tools and conclusions. Thus, describing something as a machine may be a way of highlighting a generic set of features and of generating a broad set of expectations. To foreshadow the account given in the next section, it would lead one to expect that different parts have distinct roles, to place weight on the relative positions and locations of parts and to expect local interactions among them. Such a view would lead one to search for ways of isolating parts and of examining how there are structured and what the different parts do. One also sometimes sees more concrete, specific uses of machine framing: thinking in terms of specific kinds of machines, such as a motor or even more specifically, a rotary engine. Such a framing creates more concrete expectations—there should be a rotating element and an element that anchors the rotor to some larger structure; there is likely to be a directional source of energy creating the rotation, and a corresponding mechanism for converting the energy of rotation into some further, more useful, form of energy (i.e., do work). Significantly, while an analogy may play a useful and appropriate role as a general organizing schema, it might be less useful (perhaps even positively misleading) when applied in a more specific way. These points will be illustrated by the case of molecular motors, in the "Machine analogies in action: kinesin as a molecular motor" section.

Two additional, interrelated points concern the flexibility and context-sensitivity of analogies. First, they are usually produced with, at least implicitly, a target audience in mind. Someone familiar with fluid dynamics will better understand, and make better use of, a description of an electrical circuit in terms of a system of pipes. This holds for potential pitfalls as well: an audience that is familiar with a certain domain is less likely to misinterpret an analogy pertaining to that domain. This will come up below, as I will argue that some critics of the machine analogy, as applied in the study of molecular motors, do not take sufficient account of its intended audience. They foresee errors stemming from a mishandling of machine analogies that, it seems to me, are unlikely to be made by their intended audience.

Second, the utility and even the content of an analogy may well erode or simply change over time. Often, this is because the concepts on which the analogy draws change. The notion of a machine is certainly one that has undergone historical changes, including in the relatively recent past—machines that compute, for instance, were all but unheard of before the middle of the 20th century. In view of this, my strategy will be to carve out a fairly wide notion, encompassing different sorts of machines, including ones that may not be the first thing to occur to a person upon hearing the term ‘machine’, such as ovens and cars. That said, and as I will explain, I do not think the notion I describe is too wide—it excludes a fairly large and important class of systems, within and outside of biology.

Machine likeness as (localizable) division of labor

The thought that a system is analogous to a machine (*machine-like* is the term I will mostly use) tells us something about how such a system works and hence something about how we can come understand its operation. In previous work I suggested we think in terms of a contrast between machine-like systems and systems that have a more aggregative character. As an illustration of the contrast, we can consider a structural explanation of the workings of the bacterial flagellum, versus a derivation of the second law of diffusion. I will not recapitulate these examples in any detail here. They are meant to illustrate that the first class of systems, but not the second, are appropriate targets for decomposition: the flagellum can be understood by breaking it down into components, characterizing what each component does, and figuring out how the components coalesce into an overall activity or product. Aggregative systems, on the other hand, need to be understood more holistically. They are often modeled via statistical methods, where the contribution of parts is averaged, and there is no defined organizational structure coordinating among the parts.

But what makes for a good target for decompositional analysis and understanding? What types of systems are amenable to this sort of explanation, and thereby fruitfully analogized to machines? Levy (2014) proposed that a machine-like system exhibits two main features, to which I add a third:

> *Different parts play causally distinct roles*. One major aspect of decompositional explanation is the idea of understanding the whole by breaking it down into parts. This will only yield understanding if the parts do indeed play different roles. Here, by ‘parts’ I have in mind spatiotemporally localized causal components – things with a shape, size and location (at any given moment – parts can and often do, of course, move). One way to put this first condition is in terms of difference-making: in a machine, different parts make a distinct difference to the system’s overall effects. Thus, in a homely toaster, the lever makes a different contribution than the coils on the internal walls: the former lowers the bread slices into the toaster whereas the latter heat up and toast the bread.
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> Note that the requirement that parts paly different roles is not identical to a requirement that they have distinct shapes, sizes, masses and related non-relational properties. Two parts with the same size and shape, say, can play distinct roles because they interact with different parts and/or at different times and places within the system. Thus, two cogs with the same size and shape can play different roles in, say, a clock, if they are differently placed. Likewise, the same transcription factor can trigger different protein products if it (they) act(s) at different phases of some cellular process. That said, it is very often

the case that differences in role are at least partly a matter of differences in shape, size, mass, charge and related properties, for they affect a part's causal powers and the interactions it can engage in.

Parts interact locally. For decomposition to work, it is all but necessary that parts come together in a way that confines their interactions to a subset, usually a small subset, of the machine's other parts. If this were not the case, if each part interacted holistically with many (or all) of the machine's other parts, then breaking it down into parts and ascertaining how they interact would not yield much insight. By local interactions I have in mind not just a part's causal neighborhood, so to speak, but also—typically, at least—its spatiotemporal location: parts interact over a specified interval and at a certain place (or places). Like the first condition, this one too can be put in difference-making terms: the difference each part makes depends on interactions with a specific subset of the system's other parts. Typically, it is not the mere fact of local interaction that matters – but the particular nature of it: when the parts interact, in what order etc. As before, manmade machines almost invariably involve local interactions. The toaster's lever interacts with the bread-cage, but not with the heating coils nor with the on/off button.

Relative independence from environment.[3] Most manmade machines are engineered to operate in a way that is relatively insensitive to small differences in external conditions. A toaster will work across a range of room temperatures, moisture levels, lighting conditions and various other situations, so long as it is plugged in. Of course, there are malfunctions, and (more importantly) many conditions the machine is not designed to tolerate (most toasters will not work if drenched in water.) In difference making terms: within the relevant range, changes in the environment do not make a significant difference to the machine's operation. The importance of the independence condition is that, within the relevant range, one need only look *inside* the system to understand its operation. I suggest that this is a significant feature of machines and their explanatory attraction – the limitation to internal factors makes the explanatory task more manageable and the difference-makers more salient.

This analysis is offered as a way of specifying a set of features, or dimensions, that together serve as a guideline for when machine analogies are expected to be useful. Based on this abstract analysis, the next section will discuss machine analogies in action, in the context of molecular motors. But first let me make a few remarks to clarify the analysis.

A (metaphorical) way of summarizing the account is to say that a machine is a system that exhibits *an internal division of labor*, somewhat like organized human endeavors: It has sub-parts that do separate "jobs", and these need to come together in specific ways to form an overall product or effect. To be clear, this division of labor talk must not be taken to imply that the system is in some semi-intentional

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[3] This condition doesn't appear in Levy (2014). It is closely related to Skillings' "isolatability" (2015, 1149–1150).

sense organized *so as* to produce a particular overall effect or product. Labor is divided merely in the sense that the focal overall effect is produced in a manner that allows one to assign roles to parts and local interactions. It is not that some external force, agent or effector has divided labor.

More generally, even though machines of our making are designed artifacts, and despite the fact that machine analogies are primarily drawn in contexts where something like a process of design—either intentional or evolutionary—is thought to have generated the system under study, I think that the role of assumptions about design is pretty far back in the background (Kitcher 1993). That is, I think machine analogies in biology can be discussed largely independently of teleological notions, and from the idea of design. Their cognitive and explanatory utility has to do with features of a system's causal organization, and not directly with the system's origin (Green et al. 2015). To be sure, it does not seem like a coincidence that we find machine-like systems in biology. There may be good reasons why evolution leads to such systems, related to the functional flexibility and evolvability of systems that divide labor. But I suggest that when the machine analogy is employed in biological research, it is geared primarily at understanding its present causal structure, rather than its evolutionary past.[4]

A related point is that machine-likeness is relative to an overall effect or outcome. We will see how this matters for biological machines. But it is true, if often not salient, for manmade machines too: the toaster is a machine for toasting bread, not for generating a gravitational force on the countertop. It does the former, but not the latter, by dividing labor. Indeed, this point is implicit in the claim that the three conditions—distinct parts, local interactions, independence from environment—are difference-making conditions, for whether something makes a difference is always relative to some (potential) change or effect and not others.

Next, note that machine-likeness is a matter of degree. The three features I discussed are, in effect, dimensions which vary in a more or less continuous way, and largely independently of each other. In other words, a system can produce an effect in a more or less machine-like way. This will depend on how distinct its parts are, how local the interactions are and how independent of the surrounds it is. There is no cutoff for being machine-like.

A more subtle point concerns the relation between machines and mechanisms. There is a large body of writing on mechanisms, including several versions of the idea of mechanism per se. I will not enter into an extended discussion of mechanisms. I think it is largely uncontroversial to say that a mechanism is a system of components underlying some overall effect. And while machines are sometimes brought up as examples of mechanisms (a fact that may have led to some confusion

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[4] Daniel Nicholson says that "confronted with a machine, one is justified in inferring the existence of an external creator responsible for producing it in accordance with a preconceived plan or design" (2013, 671). Nicholson's argument rests on a distinction between intrinsic and extrinsic purposiveness, which I do not fully understand. But the key point I would make is that what is relevant to arguments of the sort Nicholson has in mind is not the apparent machine-likeness of the system in question but its *adapted character*—they appear designed in the sense that they are fit for some purpose. Even though humans tend not to, one can design a system in this sense without producing a system that divides labor.

in this area—see Levy 2013) I think that, at present, none of the main advocates of the mechanistic approach view ‘mechanism’ and ‘machine’ as synonyms (Craver and Tabery 2015, § 2). Specifically, a mechanism need not have distinct parts, nor must its components interact locally; and there are many mechanisms that exhibit fairly strong dependence on their environment. Thus, the requirements for being a mechanism are weaker than those for a machine. Put differently, machines are *one kind* of mechanism.

Finally, and by way of segueing into the next part of my discussion, let me compare my view to a recent account from Militello and Moreno (2018). These authors aim to give an account of “the ontology of a machine” (*Ibid*, 4), by which they mean “the structural and physicochemical conditions that allow both macroscopic machines and microscopic devices to work” (*Ibid*, 1). They go on to “define a machine as a meta-stable structure, which can persist in thermodynamic equilibrium, consisting of a number of functional interdependent parts that constrain an energy flow to do work and perform a systemic function.“ (*Ibid*, 7).

There is a partial overlap between this account and mine: Militello and Moreno seem to accept that machine analogies embody something like an internal division of labor. And I have no significant disagreement with the definition they provide. But, as can be seen in the quotations above, they are more concerned with the physical features shared by manmade and biological machines, and so with an attempt to carve out the *literal extension* of the category of machines, showing that it encompasses both artificial and natural cases. For my own part, I think it does not matter a great deal whether the category of machines is ontologically unified in this way. What matters more is whether we can draw on principles and concepts we are familiar with in one case (manmade machines) to understand another (biological systems, whether these count as *bone fide* machines or only as analogs). I think that a definition as broad as Miletello and Moreno’s does not shed much light on this issue, and that is my main reason for seeing their proposal as having a different import. With this in mind, I now move to a more concrete discussion of machine analogies in action.

Machine analogies in action: kinesin as a molecular motor

So far, I’ve outlined a general analysis of what it means for a system to be machine-like. The motivation for this analysis isn’t to allow us to classify biological structures in terms of their machine-likeness. The goal is to say something about when and why drawing machine analogies is helpful, serving as a fruitful guide for investigation. To this end, I will look at molecular motors. While the study of molecular motors—as the reference to motors suggests—is a locus for machine analogies, this has also been a context in which the appeal to machines has been criticized. I will discuss both: on the one hand, I’ll try to show why and how it is useful to view a molecular motor as a machine, with ‘machine’ understood in terms of the analysis given above. On the other hand, I will tackle the critique, attempting to assess the extent to which it poses a problem for machine analogies in this context.

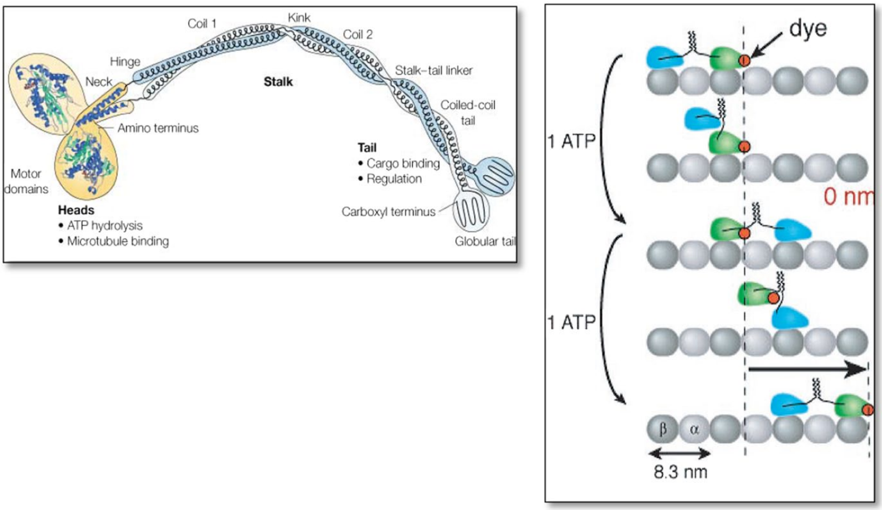

Fig. 1 **a** (Top)—The structure of Kinesin, including two motor, "heads" neck liners and a cargo-associated stalk. **b** (Right)—Kinesin walks in a "hand over hand" manner along the microtubule. Each cycle involves a lagging head detaching from the microtubule and moving forward as it hydrolyzes one molecule of ATP (Drawn from Krukau et al. 2014; Yildiz et al. 2004, respectively)

Molecular motors represent a large class of proteins, performing a range of important roles within cells. The largest sub-class consists of motors that move directionally along the cytoskeleton, typically in a processive manner, i.e. they move many steps in succession without stalling or falling off. These motors consume ATP and convert its energy into a directional force, sufficiently strong that they are able to ferry along with them vesicles, small organelles and other cargo, shuttling them between different regions of the cell. For simplicity I will focus on this class, specifically on the motor protein Kinesin, but the main points apply to most other motor proteins.

Kinesin has a striking structure: it is made of two motor domains, often termed *heads*, which are attached via a connecting structure, typically called the *neck linker* to a long stalk (see Fig. 1b.) Cargo is docked to the stalk, while the protein "walks" heads-down, performing a so-called hand-over-hand[5] movement (Fig. 1b; Yildiz et al. 2004; Howard 2010). Many details of the sequence that constitutes this motion have been revealed in recent years—the location of different elements of the protein at different phases of its walking cycle, the size of steps, the stage at which it hydrolyzes ATP. But some aspects are still under debate (Hancock 2016). One unsettled issue that is of special significance—both in terms of the biophysics of molecular motors and, as I will explain shortly, in terms of the appropriateness of machine analogies—pertains to the manner in which motor proteins are powered.

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[5] A more consistent term would be head-over-head, but I follow standard usage in the field.

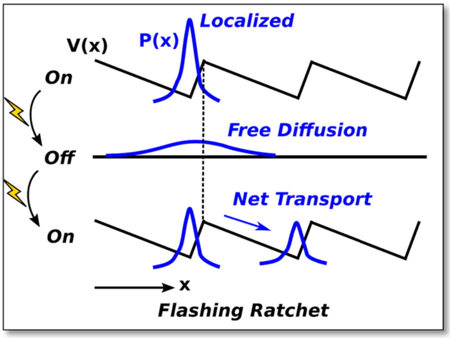

Fig. 2 The energy landscape of Kinesin motion, according to (one version of) the Brownian Ratchet model. What moves the proteins is Brownian forces in its environment. ATP serves to bias diffusion, by making it more likely that the proteins will bind in to sites in the "forward" direction

As noted, all processive molecular consume ATP. But there are two basic models for how ATP consumption is related to motion. They differ in the role they assign to ATP-derived energy relative to thermal energy. The first holds that ATP hydrolysis is converted into a fast directional change in conformation, a so-called *power stroke* (PS), which constitutes a "step" (Howard 2006). To make this more concrete: in a motor like Kinesin, performing a hand-over-hand pattern of motion, the PS model says that each "hand-over" is powered by one ATP molecule (this is also known as 'tight coupling'—because each step is coupled to the energy released by one molecule and vice versa). Specifically, current PS models suggest that the energy from ATP hydrolysis results in a rearrangement of amino acids constituting the neck linker which results in its rotation, relative to the plane of the microtubule. This rotation moves the lagging head forward, where it re-attaches to the microtubule.

An alternative is the so-called *Brownian Ratchet* (BR) model (Reimann 2002; Oster 2002). It depicts motion as powered not directly by ATP but by thermal energy in the motor's surroundings. The role of energy released from ATP hydrolysis is to turn the motor on and off, so to speak. In the 'off' mode, the motor diffuses freely along the cytoskeleton, moved by thermal interactions with its environment, and executing no net motion. However, in the 'on' mode, its motion is biased in the forward direction, because its interaction with the cytoskeletal fiber in the "forward direction" is energetically favored. When in this "on" mode, the forward arm executes a diffusive search for the next available binding site, and eventually docks to the microtubule (Fig. 2.[6]) In the BR picture, Kinesin's motion is only loosely coupled to ATP, and its motion is less directed and more capricious, as it were. It is buffeted about by molecules in its aqueous environment, with ATP-derived energy serving to bias the protein's diffusion in the forward direction.

Some have seen the possibility—indeed, for them, the plausibility—of the BR model as grounds for skepticism about machine analogies in this context. Dick Astumian, a biophysicist who pioneered work on the BR model, suggests that it

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[6] There are different concrete versions of the BR idea. The figure illustrates one version, known as a flashing ratchet model. Note that the figure depicts an energy landscape, not the physical structure of the molecule.

illustrates how "[o]ur physical intuition, formed by everyday observation of large machines, fails when we consider the world of the small." (2001, 57). Likewise, Daniel Nicholson suggests that "[d]ue to their huge disparity in size, mechanical motors and Brownian motors operate according to fundamentally different principles… 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.“ (2020, 57 –58).

Both Astumian and Nicholson portray the difference between the PS and BR models in stark terms; both suggest that the PS model is physically unlikely[7]; and both think that the evidence favors BR models. This is far from the mainstream view. For one thing, there is very strong evidence that ATP hydrolysis results in a rotation of the neck linker (Block 2007), including very recent high-resolution images that practically show this in action (Wolff et al. 2023). Further, many biophysicists hold that Kinesin motion is likely to involve both thermal effects and directed, ATP-induced conformational changes. The thought is that molecular reality is some hybrid of the PS and the BR models (Howard 2010; Hwang and Karplus 2019). That said, I think it is useful to address the applicability of machine analogies to Kinesin under the presumption that PS and BR represent distinct models of its operation, and by taking the latter as empirically plausible. So I will discuss the issue this way.

Recall the account of machine analogies I gave in the previous section: in outline, it says that a machine exhibits internal division of labor, in the sense that it is relatively impervious to environmental influences and that parts interact locally and play distinct roles in bringing about a focal overall effect. It is clear that such a picture has been immensely fruitful in guiding research on Kinesin and similar motors and in framing their overall mode of operation. To be specific—for, recall, division of labor must be relativized to an effect—machine analogies have been very fruitful in guiding work on kinesin's processive motion and its structural basis. This is so whether one accepts the PS or the BR model (or some hybrid).

Early work on Kinesin, during the 1980s, sought to decipher its three-dimensional structure through traditional structural biology methods such as x-ray crystallography. Once the basics of the structure as currently understood were in clear view, in the early 1990s, biophysicists were quick to outline models that linked it to processive motion. Early on, it was suggested that the two-headed structure allowed the protein to move along the microtubule without losing touch with it.[8] This work also involved experimental designs that were directly based on such structural

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[7] Indeed, Nicholson (2019, 117) goes so far as to suggest that advocates of PS models operate under severe misunderstandings of the physics of molecular processes. I think this accusation is an exaggeration, to put it mildly. A range of precise, biophysically sound PS models exist in the literature (Howard 2001).

[8] For more on early work on Kinesin, on how its hand-over-hand motion was characterized and verified, and on the evolution of work in this area see Bechtel and Bollhagen (2021) and Bollhagen (2021).

assumptions, such as the single-molecule motility assay, which fixed the Kinesin and observed the relative motion of the microtubule (Howard et al. 1989). Through such work, it was established that Kinsein motion involves a coordinated movement of both heads.[9]

Through the 1990s models of the exact motion of Kinesin were developed, guided by the details of its structure, rate of motion, approximate step size and other information gleaned from these studies. In the early 2000, a contest between two forms of motion became more clearly defined: a rotational hand-over-hand versus a so-called inchworm motion (in which the leading head is trailed by a lagging head "catching up" with it). The former concept implied that motion generated rotation of the neck and stalk, and it was attempts to detect this feature that clinched the matter (Hua et al. 2002; Yildiz et al. 2004; Bollhagen 2021).

Thus, we can see how thinking of Kinesin as a two-headed motor, and conceiving of the specific role each of its parts, relative to each other and given the precise nature of the interaction between them, was crucial to understanding Kinesin motion. Notice that this work is relevant whether one holds a PS or a BR model. On both, the molecule's basic structure—a homodimer with two motor "heads" connected by neck linkers and a common stalk—is essential to its motion. On both, each element in this structure plays a distinct role: the stalk are associates with the cargo, the heads sequentially attach and detach from the microtubule, and the neck linkers connect the stalk to the heads and rotate in the course of motion. Deciphering the structure, i.e. the relative locations, sizes and conformational details of these parts, has been absolutely indispensable to progress in understanding both the phenomenon of Kinesin motion and to the formulation of various explanatory models (Cochran 2015; Hwang and Karplus 2019).

The importance of linking structure to function, in the manner suggested by the machine analogy, is also evident when we look at current work and, in particular, at some of the questions that remain open with respect to Kinesin's mechanism of motion and which, according to many experts, will play a part in deciding between the PS and BR model (or some combination thereof.) These include, for instance, the precise state at which ATP is hydrolyzed—is it when both heads are bound to the microtubule or when one head is "in the air"? As well the variance among the molecule's steps—are they always of the same size or not?[10] Solving these matters turns precisely on the role of the protein's various parts, their relative positions and the timing of their activities. Indeed, these aspects are at the heart of the considerable progress that has been made on them to date (e.g. Wang et al. 2015). This is what models of kinesin focus on, and this is what techniques for imaging and

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[9] Another motility assay, used primarily in work by Steven Block and associates, involves attaching a glass bead to the Kinesin itself, which can then be captured (with force applied) by optical tweezers. One of the first papers using this method is Block et al. (1990), although it is still being further developed and put to new uses (e.g. Howard and Hancock 2020).

[10] As of the time of writing, and to the best of my knowledge, the clearest evidence on these questions is contained in Wolff et al. (2023). It suggests that ATP is hydrolyzed in the one-head-bound state and that while a full cycle involves the protein moving 16 nanometers, step size varies and can be either 6 nm, 8 or 10 nm.

manipulating Kinesin focus on (e.g., Toprak et al. 2009; Angerani et al. 2021.) In short, work on kinesin processivity is quintessentially decompositional.

In Sect. 2 I said that analogies can be employed at different levels of detail and specificity. In this context, we might ask not only about the general analogy to a machine, but also to *motors*—which I take to be a particular kind of machine. A standard definition of a motor is a machine that converts one or more forms of energy into mechanical energy, typically in order to preform work, i.e. to move something against a force or load. In this sense, all motor proteins are *bone fide* motors. They convert the energy of ATP into motion. The motor domains of Kinesin, in particular, perform work by pulling the protein, and usually some additional cargo, along the microtubule track, as explained before. This level of analogy—it is perhaps more than an analogy—has also proven important to studying motor proteins, including Kinesin. The analogy to motors leads to questions about how various forms of energy—primarily ATP and thermal environmental energy—are converted to work in the form of forward motion. Again, this is so both on the PS and on the BR models: on the former, the primary source of energy is the hydrolysis of ATP, and the energy thereby generated is converted directly into a conformational change that places the leading head further along the track. On the latter, ATP-derived energy generates a confirmational change that facilitates binding to the track in the forward direction, and the energy for motion along the track comes from thermal fluctuations.

Jonathan Howard's 2010 article "Motor Proteins as Nanomachines: The Roles of Thermal Fluctuations in Generating Force and Motion" nicely illustrates this. It considers several aspects of how molecular motors convert free energy into work, suggesting that there is an important role both for ATP and for the thermally-derived diffusion. He does this (as his title suggests) in a framework that highlights the analogy to motors and machines. Indeed, this is what leads him to ask the questions he asks and to suggest answers in terms of findings pertaining to the behavior of the motor's various parts—how they function under load, what happens when concentrations of ATP are modulated, whether and how frequently a motor moves backwards etc.

Howard also stresses, however, that "[m]otor proteins… do what no man-made engines do: they transduce chemical energy directly to mechanical work without using heat or electrical energy as an intermediate." (ibid., 47) This is significant inasmuch as it points to the fact that while Kinesin and similar proteins are helpfully analogized to machines in general, and to motors in particular, it is not the case that motor proteins are similar to any of the variety of (macroscopic) motors that humans have invented and use. It is worth briefly fleshing this out, as this gives further insight into the use and limits of the analogy between proteins and motors. It also serves as a prelude to the discussion of the next section.

When Howard speaks of direct transduction of chemical energy, he has in mind (a disanalogy to) something like a car's internal combustion engine. Such an engine burns a carbon-based fuel like gasoline or natural gas (a chemical reaction) and uses the resultant heat to drive cylinders that—through several mechanical intermediates—drive the car's motion. Direct transduction, which occurs only in molecular motors, means that the motor's motion is a direct product of the reaction that fuels it—ATP hydrolysis is at one and the same time a change to the motor's conformation. (Put differently: the chemical reaction that changes the motor's shape consumes ATP as fuel). One consequence of this is that molecular motors are more efficient than any manmade motor can ever be.[11]

The fact that molecular motors are not fueled by the products of chemical reactions but are themselves molecules that undergo reactions has further important consequences, to do with the role of thermal factors. Manmade motors are designed to work in much the same way over a fairly wide range of temperatures. Molecular motors, like most proteins, are highly sensitive to temperature and other thermal properties. Moreover, molecular motors operate in a much more stochastic way—the exact sequence of steps they undergo varies, they may fall off and recatch to the underlying substrate, move backwards etc. A naïve employment of machine (or motor) analogies might miss or obscure these features but, of course, molecular biologists and biophysicists are not naïve in their use of the analogy. In this respect, I find the statements quoted earlier from Astumian and Nicholson—alleging that machine analogies mislead insofar as they import macroscopic intuitions into studies of the microscopic world—to be unconvincing.

Recall that I said, in the "A few remarks about analogies" section, that in assessing analogies we should keep in mind their intended audiences. Machine analogies, in the context of molecular systems such as motor proteins, are produced and primarily consumed by biophysicists and structural biologists. In view of this, the kinds of misunderstandings Astumian and Nicholson are concerned about seem to me unlikely.[12] Indeed, the idea that biophysicists would import their understanding of macroscopic systems governed primarily by mechanics to this context is belied by central aspects of the work done in the field, which is highly sensitive to the dynamics governing conformational changes, the effects of thermal forces and other factors that are unique to the molecular level. Thus, to use the terminology of the "Machine likeness as (localizable) division of labor" section, biophysicists and molecular biologists are not confusing machines and mechanical devices.

I do think, however, that such criticisms of machine analogies are relevant insofar as they point toward some of the limits of machine analogies. That is the topic of the next, and final, section of the paper.

The limits of machine analogies

My primary aim in this paper has been to provide an account of machine analogies and to illustrate their usefulness. I have focused on molecular motors, where I argued that the machine analogy aids in framing a decompositional-structural

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[11] This is so both on PS and on BR model (Wagoner and Dill 2016) contra Nicholson's suggestion (2020, 58).

[12] It is possible, of course, that some audiences, such as students in relevant areas or the general public, are liable to misunderstanding and errors. But, first, this is not my target in this paper—pedagogy and/or science communication cannot be easily read off from discussions of internal, research-focused questions. And, second, communicating the subtleties of machine analogies to non-specialists, even to lay audiences, is perfectly possible. See, for instance Hoffman (2012).

understanding of their function—in this case, of their motion (and in kinesin, specifically, along microtubules.) There is range of other successful applications of machine thinking in molecular biology. These include other kinds of motors—such as rotational motors (e.g. ATP Synthase, see Boyer 1997) and proteins like helicases and topoisomerases (Dekker and Dekker 2022), which are critical to the maintenance and function of DNA and RNA. The list can be probably be expanded to include the ribosome (Steitz 2008), some catabolic enzymes and various transmembrane proteins such as pumps and other active transporters.

However, I have also made a point of noting differences between molecular machines and manmade ones. In the case of motors, this has to do with the direct conversion of chemical energy to work. More broadly, molecular systems are different from macroscopic ones in important respects. They are subject to thermal and other stochastic influences. This imposes significant limits on machine analogies—they can help us reason through structural features of molecules but we must be more careful when it comes to dynamics, especially if we seek quantitative understanding. Such systems are highly dependent on their environment, especially on features such as temperature and pH, and are thus less machine-like along the third dimension discussed in the “Machine likeness as (localizable) division of labor” section.

Moving to further cases, both at the molecular and at other levels, we can discern explanatory contexts in which the machine analogy is unlikely to be fruitful, and may even be harmful to understanding. In this section I want to look at three classes of such cases. This will be a relatively concise discussion and it is not meant to be exhaustive. The aim is to give the reader an indication of how thinking of in terms of decomposition and internal division of labor affords insight not only into the utility of machine analogies but also into their limitations.

Disordered proteins

The machine analogy, I have argued, is founded on distinguishing systems into their parts, and assigning distinct roles to these parts. In molecular and many other biological contexts, parts play different roles primarily because of their (spatiotemporal) structure. But recently it has been suggested that a fairly large class of proteins lacks a stable, three-dimensional structure. These are so-called *intrinsically disordered proteins (IDPs).* As far as is currently known, they lack a defined conformation. That is, their shape is constantly fluctuating, such that bonds and atom positions are “smeared out” and can be assigned only on average. Mayer et al. (2009) and Nicholson (2019) have appealed to these proteins as part of a critique of machine analogies and I think there is something to this.

Interest in disordered proteins has grown in the 21st century, with improved in vivo detection methods and the discovery of more and more IDPs, and proteins with disordered *regions* (IDRs). Estimates vary as to their abundance (Uversky 2019) but many biologists agree that they are very common, especially among proteins involved in regulation, signaling and control (Dunker and Oldfield 2014). While they have been garnering increased attention, the roles and modes of operation of IDPs and IDRs are still shrouded in substantial mystery. But however research into them turns out, it is likely that these macromolecules represent a break, of sorts at least, with the structure-to-function mapping paradigm that has been central to protein science for decades. On the simplest construal of this paradigm, a protein's amino acid sequence (it's primary structure) determines its three-dimensional (tertiary) structure which determines its functional role(s) in the cell.[13] It is the first "link" in this chain that is disrupted in cases of intrinsic disorder: primary sequence does not determine a unique tertiary structure. If indeed a protein has no stable structure, then this would seem to pose a barrier to machine analogies. For, obviously, if a system has no stable parts, then it cannot be explained by appeal to its parts and the idea of division of labor as I have described it becomes inapplicable. Thus, IDPs and IDRs, if prevalent, may considerably reduce the scope, and potentially the utility, of machine analogies in molecular biology.

It should be noted, however, that it is not currently known how thoroughly divorced structure and function are in IDPs and IDRs. While it is possible that, in some cases, these proteins function in an unstructured way (that is, without a stable structure), many appear to take on a structure either by means of binding to ligands or other molecules (including by clumping together), or in a contextual manner, i.e. depending on the exact conditions in their cellular environment (Uversky 2019; Bondos et al. 2021). When this is the case, we have a situation where the protein can, potentially, be approached with a machine analogy, but the details—how the machine looks and operates—may vary according to context. That would certainly be unusual, relative to ordinary conceptions of machines; our toasters and cars (and their parts) do not change structure and function with context. But until we know more about how and how often such dynamic structural-identity changes occur, it is hard to say how far one can go with the machine analogy in these sorts of cases, or whether it would be stretched beyond breaking point.

Ontogeny and other "comings into being"

Another, more general context in which I think that machine analogies are likely to be less helpful are processes in which a biological structure comes into being—especially from an earlier and relatively homogenous state. These include at least some ontogenetic processes as well as processes in which a cell or a sub-cellular process is generated during the adult form's lifetime. There is, obviously, a wide range of cases that fall into this category, and I cannot hope to provide an extensive discussion of them here. But let me give two examples to illustrate what I have in mind.

A central class of models in developmental biology are reaction-diffusion models. Without delving into technical details, these models depict basic processes in development—from the formation of the back-to-front axis to the generation of

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[13] This is a simplification in several respects, perhaps most importantly because it is well-known that a protein with the same tertiary structure can perform different roles depending on the cellular context, i.e. on cell type, developmental phase, which other cellular constituents are present etc.

patterns in skin and fur coloration—as the result of a dynamic interaction between a small number of diffusing "morphogens" (Kondo and Muira 2010; Lande et al. 2020). The simplest such system, due to Turing (1952) and further analyzed by Gierer and Meinhardt (1972), is a system with two interacting molecules. It can generate diverse patterns and structures, so long as one of them activates itself and is inhibited by the other. Components in such systems usually defy clear assignment of roles to parts—the effect of each component depends on subtle aggregative features having to do with its relative rate of diffusion, relative concentrations and other non-localizable factors. Moreover, the system's structure changes over time, often as a dynamic equilibrium. So decomposition is hard, if not impossible, to perform. Such systems are rather unmachine-like.

Another class of cases in this category involves *self-assembly* processes, which are common at the cellular and molecular level. Nicholson (2019), drawing on Kirchner et al. (2000), described them thus: "Self-assembly involves the physical association of molecules into a static equilibrium structure in the absence of an external energy source. It is driven by local stereospecific interactions between the aggregating 'building blocks', which remain unchanged throughout the process." Since in a self-assembly process parts of a structure come together, without any directed process putting them together, it is difficult to assign each part a role—expect perhaps it's mere being there, ready to take part in the process. Notice, however, this is so *with respect to the assembly process*. A self-assembling system, once in place, may well have distinct roles and stable organization, and thus be amenable to a machine analogy.

In an important sense it is not surprising that these cases defy a decompositional explanation of the sort that underlies machine analogies. Reaction-diffusion systems are designed to explain how an organized system emerges in ontogeny, typically from an undifferentiated (or at least a far less organized) earlier state.[14] Self-assembling systems are not ontogenetic, per se, but involve a similar order-from-homogeneity transition. This kind of process is one in which parts come into being, and roles become defined. So one cannot explain them by appeal to an existing set of roles and local interactions.

Aggregative cell-level processes

A third category of cases in which we see limitations to the machine analogy concerns whole-cell level processes, especially ones of regulation and control. Here I have in mind transcriptional regulation, metabolic control and related processes which affect the overall dynamics of the cell and its central activities. At least insofar as our present-day understanding of cells goes, such processes involve a substantially aggregative aspect. To recall, an aggregative process is one in which the overall effect is a matter of the accumulation of the activities of many elements, with little or no specificity of parts and a relatively minor significance for local

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[14] For this reason they are often described as *self-organizing*. But this term is overused and has multiple, sometimes ill-defined, meanings and so I avoid it.

interactions. Diffusion—which has come up several times in this paper—is a paradigmatic example, and indeed the dynamics of diffusion, whether within the cytosol or across membranes, are central to understanding cell-level activities.

Beyond diffusion per se, the activity of cells is greatly affected by the relative concentration of a host of molecules—from small ions to large proteins—and a key aspect of regulating cellular activities consists in the delicate control exerted over the concentration of various molecular constituents. This is done via controlled trafficking across the cell's membrane, through the modulation of which proteins are synthesized when, and through fine-tuning of the rate at which proteins and other molecules are broken down or evacuated from the cell. Such processes involve a degree of division of labor—decomposing cellular dynamics into distinct players is, often, required for understanding them. But there also an important role for aggregative and holistic relationships. If we are to draw on notions from the human world, then analogues from social and economic processes (market dynamics, cultural evolutionary processes, and the like) may be just as fruitful, if not more, than machines and designed devices.

Summing up, while I have argued that machine analogies have been and continue to be useful in understanding some aspects of molecular processes in biology—primarily dynamic-structural features of single molecules—there are also real limitations to the analogy. An account based on an internal division of labor and its importance for decompositional understanding and explanation can give us a handle both on the machine analogy's power and guidance about where its limits lie.

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