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MECHANISMS IN MOLECULAR BIOLOGY

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1. Introduction

While mechanistic explanations are by no means a novelty in biology (see Part I on historical perspectives on mechanisms), their appearance dating back to Harvey’s discovery of the blood’s circulation and Descartes’ mechanistic manifesto touted in The Treatise of Man, it is only in the second half of the twentieth century, with the rise of molecular biology, that mechanistic thinking overtakes the whole of biology, becoming the predominant type of explanation. Explaining biological phenomena as the effects of molecular mechanisms turned out to have a marked influence on philosophy of science on two accounts. First, it motivated a renewed interest in mechanistic explanation, providing philosophers with a wealth of examples that didn’t quite fit the deductive–nomological approach promoted by the logical positivists (Wimsatt 1976). Second, molecular biology motivated a shift in the way we think about mechanisms, fostering a “new” mechanistic philosophy. Unlike the “old” mechanistic philosophy, which was closely linked to the theory of classical mechanics and the clockwork view of the world, the “new” mechanistic philosophy had to come to terms with the notion that most biological mechanisms do not look and behave like eighteenth-century automata, but are much more complex and “noisier” systems composed of hundreds, thousands, and even millions of non-fixed, non-rigid parts whose behavior is nevertheless sufficiently constrained both by the properties of the parts and by the spatio-temporal organizational features of the system as to reliably produce and sustain biological phenomena and, ultimately, life itself.

2. What is molecular biology?

Molecular biology is the field of scientific investigation concerned with the molecular basis of biological activity. Its most significant achievements are the elucidation of the mechanisms of replication, transcription, and translation in the 1950s and 60s, providing an explanation of how cells replicate their genetic material and how genes are expressed as proteins that contribute to the phenotype of the organism. Molecular biologists quickly extended their inquiries to other biological phenomena, most notably gene expression regulation, the cell cycle, and cellular signaling. By the 1970s, molecular biology gained a firm footing in many other fields of biology, with developmental biology, immunology, neurology, and microbiology “going molecular.” In this
respect, molecular biology can be viewed as providing the guidelines of a general explanatory approach which I shall explore in more detail in the subsequent sections of this chapter.

Historically, molecular biology was born from the convergence of work in genetics, biochemistry, and physical chemistry in an attempt to figure out how genes determine phenotypes (Carlson 1967; Darden 1991, 2006a; Fox Keller 2000; Kay 1993; Morange 1998; Schaffner 1993). Such questions fall outside the immediate explanatory scope of classical genetics, which is mainly concerned with the transmission of inherited traits (Morgan 1935; Moss 2003; Waters 1994). They also fall outside the immediate scope of biochemistry, which focuses predominantly on metabolic activities (e.g., the chemical reactions taking place during glycolysis or protein synthesis), as well as that of physical chemistry, which is concerned with the inter- and intramolecular forces shaping the tridimensional structure and the physicochemical properties of macromolecules (Baetu 2012a; Darden 2006b; Morange 2002; Olby 1994).

It is customary to distinguish molecular biology from related fields on the basis of its specific techniques of investigation revolving around the “cloning” of genetic material (creating copies of DNA fragments), along with techniques required to detect (e.g., electrophoresis), sequence (e.g., chain-termination sequencing), amplify (e.g., polymerase chain reaction, or PCR), and manipulate (e.g., site-directed mutagenesis) genetic material, many of which rely on the understanding of the mechanisms of replication, transcription, and translation which are at the core of molecular biology (Astbury 1961; Waters 2008). These techniques involve experimental interventions at the resolution of individual nucleotides—and, via the alteration of codon sequences, of individual amino-acids in a peptide sequence—thus tracking the flow of information within the cell, revealing the functional role of sequence motifs such as promoters, codons, and zinc-fingers relative to the operation of molecular mechanisms, and providing an understanding of how changes in the sequence of various molecular components result in changes in the operation of mechanisms and their ability to produce or sustain biological phenomena.

It should be noted, however, that molecular biology was and continues to be part of a highly integrated cluster of fields. Molecular biologists routinely rely on data, theoretical assumptions, and formal and experimental techniques from genetics, biochemistry, physical chemistry, cell biology, microbiology, statistics, epidemiology, systems biology, systematics, and many others. At the same time, scientists in other fields, from evolutionary biology to psychiatry, rely on explanatory strategies and experimental techniques inspired from molecular biology. As a result, our current understanding of the molecular basis of biological activity integrates findings from a wide variety of fields within and outside biology.

### 3. The nature of molecular mechanisms

In his celebrated essay What is Life?, Erwin Schrödinger tackles the difficult question of the origin of order in biological systems. He argues that biological systems escape entropy because there is information in the system telling it how to assemble itself in an organized fashion. On this account, information is a source of order in what would have otherwise been a thermodynamically disordered system. Genes would be the repositories of information, which is propagated throughout the cell by a series of deterministic mechanisms that preserve order. This view, predating the major discoveries of molecular biology, endures until today, to the point that some philosophers define molecular biology as the study of the mechanisms of information propagation within cells (Darden 2006a, 2006b; Morange 1998).

Schrödinger’s order-generating information was eventually identified with genetic information, while its propagation throughout the cell by means of deterministic mechanisms came to be known as genetic determinism. The best illustration is the “genetic program”
view popularized by François Jacob (1976) and Jacques Monod (1972); for a philosophical discussion, see Baetu (2012b). According to this view, information is unidirectionally propagated via the mechanisms of transcription and translation to peptide sequences, which in turn determine the tridimensional shape of proteins via the folding of $\alpha$-helices, $\beta$-sheets, and other secondary structures, itself determining the specificity of binding to other molecules according to a lock-and-key or induced fit model, thus directing the flow of chemical reactions underpinning metabolic and signaling pathways as well as the self-assembly of the various supramolecular structures that constitute the living cell.

While immensely popular in the 1970s and still echoing today, this view is in fact a special case of a more general concept in molecular biology, namely that of specific binding (Kupiec 2009; Morange 1998). Specificity of binding is assumed to determine not only the preferential pairing of nucleotides in complementary strands of nucleic acids during replication and transcription or between codons and aminoacyl-tRNAs during translation, but also virtually any single activity related to the operation of molecular mechanisms, including enzyme-substrate interactions, the recognition of extracellular ligands by cell-surface receptors, the binding of transcriptional factors to particular DNA sequences, the self-assembly of microtubules and ribosomes, etc. Specificity is determined by chemical affinity, which is typically measured as the average life span of a supramolecular complex in a given chemical environment. When molecules form stable, long-lasting complexes likely to have a marked impact on biological activity, their binding is said to be specific; when the complexes are short-lived, their binding is said to be non-specific. Thus, order-generating information is not restricted to the genome, but is in fact manifest in every single specific molecular interaction taking place in the cell.

Less appreciated by the general public is the fact that binding specificity is an “analog,” or stochastic concept (Rao et al. 2002). Any given molecule always interacts with many other molecules, for some with stronger and for others with weaker affinity, such that specific binding invariably occurs against the “noisy” background of myriad non-specific interactions. Furthermore, it is not uncommon that the same macromolecule can bind with relatively high specificity not only one, but many other molecules (e.g., most transcriptional factors can bind with variable, but relatively high specificity several related DNA sequences). By contrast, genetic determinism assumes an idealized limit case, a “noise-free” or “digital” specificity propagating itself throughout the cell without significant distortion as the inevitable result of the expression of genomic sequences.

“Digital” specificity idealizations are still ubiquitous in the qualitative descriptions of molecular biology. While there are epistemic benefits associated with such idealizations, most notably increased intelligibility, the truth is that, until very recently, molecular biologists had no other choice but to idealize. Traditionally, molecular techniques rely on the amplification of the properties, states, and activities of molecular components up to an unequivocal threshold of detection. This is achieved by studying millions of cells in bulk over (chemically speaking) long periods of time, which means ignoring both time fluctuations, as well as differences from one cell to another. Yet the underlying biochemistry dictates that most molecular activities are chemical reactions controlled by the concentrations, states, and locations of the various molecules involved. If these parameters are not identical in all cells, there will be fluctuations from one cell to another with respect to quantitative and dynamic aspects of the operation and output of mechanisms. Furthermore, chemical reactions are intrinsically stochastic since they rely on random microscopic events that govern how fast reactions occur and in what order. For years, it was assumed that although stochastic fluctuations are bound to occur, they are biologically irrelevant “background noise” cells keep to a minimum. Thus, it was and often still
is customary to assume that what is true of a large population of cells can be safely extrapolated to individual cells within that population. In turn, this justifies the belief that, on average, the same mechanism, following the sequence of chemical events, is synchronously operating in all cells of the same type subjected to the same conditions.

In contrast with this view, recent single-cell experiments revealed that stochastic fluctuations are non-negligible, meaning that cells must rely on noise-suppressing mechanisms, such as negative feedback and DNA “proof-reading” (Elowitz et al. 2002). It also turned out that stochasticity itself can be biologically relevant and is in fact used as a means for generating diversity and histological-level patterns. For example, probabilistic biases in the distribution of adhesion proteins suffice to generate the right amount of twisting in the developing gut, while stochastic gene expression is responsible for generating blue- to ultraviolet-sensitive cells ratios in the Drosophila eye; for discussion, see Baetu (2015b), (Heams 2011), and Merlin (2011). The growing realization that many mechanisms in biology are stochastic motivated a more careful investigation of the extent to which regularity is a distinctive characteristic of mechanisms (Andersen 2012; Darden 2008; DesAutels 2011), with some authors emphasizing the highly irregular (Bogen 2005) and even the singular nature of some mechanisms (Glennan 2010, 2011). The issues of stochasticity, regularity, and singular causation are discussed in more detail in Chapters 10–13. More general implications for theories of causation can be found in Hall (2004) and Psillos (2004).

Specific binding is clearly responsible for generating some supramolecular structures, from the recruitment of polymerase complexes to the self-assembly of proteasomes and microtubules; furthermore, techniques like in vitro translation or PCR would be impossible without specific binding. Nevertheless, specificity is sensitive to the effective concentrations of molecular components, with the “background noise” of non-specific interactions increasing for low copy numbers of molecules. This observation led to a questioning about whether specific binding is the exclusive origin of order in biological systems.

The traditional model, inherited from early twentieth-century biochemistry, is the cell as a “bag of enzymes.” According to this admittedly idealized model, the spatio-temporal organization of molecular mechanisms, from the dynamics of activities to the assembly of supramolecular structures, is driven by specificity of binding in the context of a free diffusion solution chemistry. In short, were it not for differential binding specificities, the molecules inside a cell would display the same amount of order as sugar dissolved in a glass of water. This model turned out to be unsatisfactory. Molecular mechanisms operate within an intracellular environment filled with other molecules. Macromolecular crowding functions as an excluded volume effect, favoring the aggregation of macromolecules while drastically decreasing the rate of any diffusion-dependent molecular activity (Ellis 2001). This strongly suggests that the intracellular environment cannot consist of a disordered collection of molecules, as this would result in the proliferation of noise-generating non-specific interactions at the expense of order-generating specific ones. Instead, it must be structured in such a way as to bring in close proximity proteins and their ligands, thus favoring the specific chemical interactions required for the operation of molecular mechanisms (Hochachka 1999; Mathews 1993). However, if this is the case—and recent evidence supports this conclusion, e.g. the effects of nuclear architecture on transcription (Cremer and Cremer 2001)—then the tridimensional structure of the cell and tissue organization are also a source of order, functioning as a scaffold constraining the behavior of molecular mechanisms by favoring some activities while suppressing others. This “return to holism” in molecular biology did not go unnoticed in philosophy of biology, motivating a renewed attack on genetic determinism on the grounds that gene expression is a stochastic process (Kupiec 2009), that
information is distributed throughout the cell (Jablonka 2001), and that genes alone—or for that matter the properties of individual molecules, such as their binding affinities—cannot fully account for phenotype and development (Dupré 2010; Griffiths and Stotz 2006, 2013; Oyama et al. 2001).

One final twist in the story of the molecular basis of biological activity is the “systemic turn” in biology. Its impact on the way we think about mechanisms is discussed in Chapter 27. The present discussion will focus on one of the many findings that prompted this turn, namely the realization that molecular mechanisms operate in a less modular fashion than initially thought. Molecular biologists often work under the assumption that mechanisms amount to discrete functional modules organized hierarchically, serially or in parallel. While useful as a heuristic of discovery, the modularity assumption came to be questioned by a growing body of evidence revealing that distinct mechanisms responsible for distinct phenomena share mechanistic components. Notoriously, intracellular signaling pathways and gene regulatory mechanisms invariably intersect at some point, forming widespread molecular networks (Davidson and Levine 2005).

It has therefore been proposed that many molecular mechanisms are in fact inextricably interlocked into vast networks of partially overlapping mechanisms, where the sharing of mechanistic components is thought to play a role in the fine-tuning of quantitative-dynamic aspects of the phenomena produced by these mechanisms (Barabási and Oltvai 2004). In some cases, mathematical models were able to account for minute discrepancies between the predicted and observed outcomes by taking into consideration interference from overlapping mechanisms, thus providing some evidence for the biological significance of non-modular modes of organization; for philosophical discussion and references to the original scientific literature, see Baetu (2015b); Bechtel and Abrahamsen (2010, 2011).

In recent philosophical debates, modularity is often understood along the lines of “independent disruptability” stating that the overall effect of a causal system can be decomposed into a set of independent causal contributions attributable to each of the constituents of the system (Steel 2007; Woodward 2002). The systemic turn in biology prompted some authors to reject causal modularity (Bogen 2004; Mitchell 2009), and even interpret it as a vindication of a more holistic approach defended by the old organicist school of thought (Nicholson 2013); for a historical discussion of mechanism vs. organicism, see Chapter 5. It is interesting, however, to note that if molecular mechanisms are constrained by higher-level cellular and histological structures, then significant forms of modularity must prevail in virtue of the physical partitioning of biochemical reactions (Callebaut and Rasskin-Gutman 2005; Hartwell et al. 1999). If so, the relevant issue is not whether cells and organisms are organized in a modular fashion, but the extent to which molecular mechanisms, as described in biology textbooks, amount to functional or causal modules (Baetu on press; Woodward 2010).

4. Mechanistic explanations in molecular biology

One of the explicit aims of molecular biology is to provide a reductive explanation of biological phenomena in terms of molecular mechanisms. It is therefore crucial to investigate more closely the notion of mechanistic explanation: how do mechanisms explain?

According to the ontic view, mechanistic explanations are objective features of the world. To explain a phenomenon is to fit it into the causal structure of the world (Craver 2007). The advantages of this view is that it eliminates the subjective notion of understanding while emphasizing the tight link between explanation and the ability to control effects by intervening on their causes. Notwithstanding, most philosophers prefer an epistemic view, according to which mechanistic explanations are step-by-step descriptions of how mechanisms produce the
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phenomena for which they are responsible, although some authors point out that both ontic and epistemic considerations contribute to a successful mechanistic explanation (Illari 2013). For treatment of ontic vs. epistemic conceptions, see Chapter 16.

In one version of the epistemic view, descriptions of mechanisms, in words or by means of diagrams, convey an intuitive understanding consisting in simulating the working of mechanisms in our imagination (Bechtel and Abrahamsen 2005) or by analogy with more common types of activities (Machamer 2004). While imagination is indispensable for our ability to learn about and understand molecular mechanisms, equating mechanistic explanation with intuitive understanding can be problematic. For one thing, the simulations we perform in our minds are heavily idealized. Detailed quantitative aspects are absent, while known facts are distorted to outline a deterministic sequence of events tracking the fate of single molecules (a more accurate biochemical description would be that of a series of back-and-forth equilibria involving populations of molecules bumping into each other), each assumed to be rigidly structured (ignoring the fact that molecules “breathe,” vibrating and cycling through various configurations), as they modify one another to bring about a change from an initial to a final state of affairs (thus masking an underlying variety of chemical pathways that contribute to the same final state, as well as ignoring alternate pathways where mechanisms fail to contribute to the output).

Such idealizations are due to the fact that intuitive understanding relies on analogies with macroscopic mechanisms more familiar to us. In contrast, examples of mechanistic explanations from the sciences show that the working entities of a mechanism—that is, the parts of the mechanism engaged in the operation of the mechanism (Machamer et al. 2000)—span multiple levels of composition, thus supporting the notion that biological mechanisms combine a wide variety of activities associated with different levels of composition, from push-pull mechanical interactions to chemical reactions and thermodynamic processes (Craver 2007; Craver and Darden 2013; Darden 2006b; also Chapter 14 in the present volume). There is even evidence that some molecular mechanisms harness the quirks of quantum mechanics (Ball 2011); for a philosophical discussion, see Barwich (2015). Arguably, an intuitive understanding of chemical equilibria, thermodynamic processes, and quantum mechanics by means of analogies with macroscopic mechanisms is problematic, as many of these concepts defy our imagination and are best captured by a rather complex mathematical formalism.

This brings us to a third view meant to reflect a relatively recent quantitative turn in molecular biology, namely an understanding mediated by evidence from the testing of mathematical models aimed at demonstrating that mechanisms can in principle produce the phenomena for which they are responsible in close approximation of detailed quantitative measurements (Baetu 2015b; Bechtel 2012; Bechtel and Abrahamsen 2011; Braillard 2010; Brigandt 2013; Gross 2015; also Chapters 20 and 27). This view also qualifies as epistemic, albeit the understanding is more of a theoretical than an intuitive-imaginative nature, as it involves showing how phenomena are consequences of explicit rules and assumptions about the operation of mechanisms. A more comprehensive treatment of representations of mechanisms in general can be found in Chapter 18. Models of mechanisms are discussed in more detail in Chapter 17.

It is interesting to note that mechanistic explanations do not automatically preclude a role for generalizations and regularities in biology. The ability of some mechanisms to regularly produce a phenomenon accounts for some of the generalizations observable in the biological world (Glennan 2002; Illari and Williamson 2012; Machamer et al. 2000). For example, mechanistic constraints can explain why some evolutionary outcomes are more probable than others, and allow for predictions in specific lineages (Baetu 2012c), while the reliance on exemplar organism models supports the notion that general patterns shared by a large number of species exist and play an important role in guiding research (Ankeny 2001; Bolker 1995; Schaffner 2001; Weber 2005).
Conversely, the behavior of mechanistic parts is often characterized by invariant change-relating generalizations (Glennan 1996, 2002; Woodward 2002, 2010). Likewise, mathematical modeling presupposes a set of rules specifying how mechanisms change from one state to another, where some of these rules are laws borrowed from chemistry and physics (Schaffner 1993; Weber 2005). The current tendency to complement experimental research with mathematical modeling is also responsible for reviving the notion that mathematical or, more often, computational derivation contributes to the mechanistic explanation by demonstrating that certain aspects of a phenomenon are the logical consequence of the rules governing the operation of the mechanism. These considerations suggest a rather complicated relationship between mechanisms and regularities in molecular biology, whereby mechanisms both rely on regularities governing the behavior of their components and are themselves responsible for generating novel regularities, typically under the form of recurrent or reproducible phenomena.

Another issue that requires clarification concerns the completeness of mechanistic explanations. This issue is closely linked to the more general problem of how mechanisms are discovered (Chapter 19). In this chapter, I will focus on questions about the levels of composition at which mechanistic explanations bottom-out and top-off—that is, the optimal resolution of detail at which mechanisms should be described and the extent to which mechanisms act as independent modules that can produce (and therefore explain) the phenomena for which they are responsible when separated from the systems in which they are embedded. The decomposition of biological systems reveals a hierarchical organization, with lower-level components organized as mechanisms underlying higher-level components (Bechtel 2006; Bechtel and Richardson 2010; Craver 2007). It might therefore be tempting to conclude that a more complete explanation can be achieved by investigating the components of a mechanism to reveal the finer-grained sub-mechanisms responsible for their properties and activities, as well as understanding how the mechanism fits in the context of progressively more comprehensive systems of mechanisms. Nonetheless, even though such investigations are bound to generate new knowledge—for instance, by explaining why mechanistic components have the properties they have or by providing the structural details necessary to intervene on these components and their properties—they cannot guarantee explanatory completeness. Assuming that the primary objective of a mechanistic explanation is to demonstrate causation—that is, show how an organized system of parts produces a specific phenomenon—then whether a mechanistic explanation is complete is a matter of providing evidence that parts having the properties and organization specified in the explanation can and do produce the phenomenon of interest. This kind of evidence is generated by attempts to build the mechanism in vitro using reconstitution experiments, in vivo using the techniques of genetic engineering and synthetic biology, and in silico by testing mathematical models, as well as more indirectly, by assessing the ability to correctly foresee and correct side-effects of treatments and other technological applications based on mechanistic explanations (Baetu 2015a; Craver and Darden 2013; Morange 2009; Weber 2005).

Another way of looking at the issue of explanatory completeness is from a pragmatic standpoint. There are many ways in which a mechanistic explanation is useful to the scientist, and the purpose will determine when the explanation is deemed to be complete (Craver and Darden 2013). The main advantage of a pragmatic stance is that it can accommodate seemingly conflicting evaluations. For instance, if one seeks to gain control over the phenomenon of interest, then the explanation should focus on the manipulable components of the actual mechanism responsible for the phenomenon, such as gene and protein sequences (Craver 2006; Waters 2007); if prediction is the main goal, then the focus will fall on showing how changes in the components
of a mechanism result in changes in the phenomenon produced by the mechanism (Cartwright 2002; Woodward 2010); if one seeks intelligibility, be it for didactic purposes or to reveal general patterns, then abstracting or even idealizing may be necessary (Levy 2014).

5. Conclusion

Molecular biology was undoubtedly the most influential field of biological research in the second half of the twentieth century, with hardly any branch of biology left untouched by the long-reaching arm of the molecular revolution. At the same time, it is equally important to realize that molecular biology itself changed over time as a result of interactions with other fields, from its origins as interdisciplinary research in genetics, biochemistry, and physical chemistry, to its subsequent integration of ideas from cell and developmental biology, to its current interactions with synthetic, systems biology, and nanoscience. From a philosophical point of view, advances in molecular biology prompted an inquiry about scientific explanation and the nature of biological mechanisms. Under the impetus of the elucidation of the mechanisms of genome replication and expression, molecular mechanisms were initially idealized as thoroughly deterministic devices propagating genetic information. This deterministic conception with a strong reductionistic flavor gave way to a more realistic interpretation endorsed by most molecular biologists today, namely that of molecular mechanisms as deterministic systems with noise, where the spatio-temporal organization of mechanisms is generated not only by specificity of binding (an important part of which is genetic information), but also by cellular and other supramolecular organization constraints.

Notes

1 Among these authors, some take the official date of birth of molecular biology to coincide with the coining of the term by Warren Weaver in 1938 (Kay 1993; Olby 1994), while others postpone it until the elucidation of the structure of DNA in 1953 and the emergence of the modern concept of genetic information (Darden 2006a, 2006b).

2 There are many reasons why molecular interactions are “noisy.” Organic molecules can assume multiple stable configurations, each characterized by its distinct affinities; for instance, spontaneous mutations can occur via the tautomerization of nucleotides. Such variability is expected to be even more pronounced in macromolecules such as proteins, which can fold in a variety of configurations. Binding itself deforms molecules, thus altering their affinities and generating rather hard-to-predict phenomena such as allosterism and cooperative binding. Finally, new discoveries suggest that some proteins are unstructured and assume different folding configurations depending on the partners with which they interact. For references and philosophical discussion, see Kupiec (2009).

3 In many respects, these issues are a continuation of an earlier debate about reductionism in biology. While some philosophers have argued that the best explanations in biology are those bottoming out at a molecular level (Rosenberg 2006; Waters 1994), others replied that descriptions at higher levels of composition are needed to account for organizational features of biological systems (Laubichler and Wagner 2001) or to enhance intelligibility (Kitcher 1984).

4 Some physicists proposed that biological explanations are likely to bottom-out at a molecular level because at this size scale the mechanical, electrostatic, chemical, and thermal energies of objects have similar magnitudes. The convergence of energy values means that mechanical, electrical, and chemical energy can be converted into one another, which can explain some of the most fundamental properties of living things, such as their ability to convert food (chemical energy) into motion (mechanical energy). Furthermore, thermal energy (random molecular collisions) may quite literally “kick start” molecular mechanisms, thus explaining their ability to work autonomously and spontaneously. In contrast, mechanical forces at macroscopic scales or binding forces stabilizing sub-molecular structures such as atoms are largely insensitive to thermal fluctuations at room/body temperature, and therefore phenomena such as spontaneous activation, self-assembly, or change of shape are impossible (Hoffmann 2012; Philips and Quake 2006). This suggests that there is something objectively special about the molecular level in the sense that only molecules, as opposed to atoms or macroscopic objects, have the kind of properties required by mechanistic explanations in biology.
References


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