Chapter 6
Explaining in Contemporary Molecular Biology: Beyond Mechanisms

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Abstract Over the past decade, the concept of mechanism has drawn considerable attention in the philosophy of biology. This interest stemmed from the recognition that mechanistic explanations are central to the practice of biologists. So far, most discussions have aimed at defining the mechanism and characterizing mechanistic explanations, rather than assessing the genuine significance of these explanations in the overall explanatory activity of biologists. This reinforced the view that in functional biology, and in particular in molecular biology, explaining a phenomenon mostly consists in showing how this phenomenon is produced by its causes, by describing the mechanisms that maintain and underlie it. From this perspective, mechanistic explanations appear to be the most relevant causal explanatory scheme in functional biology. However, in this chapter, I argue that causal explanations have been mistakenly reduced to mechanistic explanations. I focus on current research on the regulation of genetic expression by microRNAs to suggest that in contemporary molecular biology, explanations increasingly describe some features of causal processes that mechanistic explanations are not meant to grasp. Given this, I characterize two types of explanations – namely, quantitative explanations and systemic explanations – that do not rely on the concept of mechanism. Altogether, these considerations prompt the reconsideration of the status of the concept of mechanism in biological practice, as well as the development of a pluralistic approach of explanations in molecular biology.

Keywords Mechanism • Mechanistic explanation • Quantitative explanation • Systemic explanation • Pluralism • Network • MicroRNAs • Genetic regulation

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1 Introduction

Since the twentieth century, the mechanistic perspective has been used successfully to explain how a wide range of biological phenomena is causally brought about. This perspective has distinctly dominated research in the field of molecular biology, following its rise in the 1950s. Recently, the realization by philosophers of science that the concept of mechanism plays a crucial role in biological practice has motivated discussions about the characteristics and the explanatory value of mechanistic explanations. These discussions hold the concept of mechanism as central to explanations in neuroscience, molecular biology, cell biology, and genetics. Remarkably, the debate intersects with major philosophical issues, including causation, reduction, and function, bringing interesting new perspectives to these issues.[1]

Here, I wish to examine how the mechanistic perspective fits into the explanatory activity in contemporary molecular biology,[2] following the recent development of postgenomic biology and of systems biology. To address this issue, I focus on recent work on microRNAs, a class of small non-coding RNAs that appear to be key players in the regulation of gene expression. Over the past decade, research on microRNAs has spawned an abundant literature that overlaps with many biological issues. This research has already been proven to be an excellent case study to show the need for exploratory experimentation in post-genomic molecular biology (Burian 2007), and to develop a pluralistic model of scientific inquiry (O'Malley et al. 2010). I shall argue that microRNA research also provides solid ground for defending a pluralistic account of explanations in contemporary molecular biology.[3] Indeed, central explanations of the regulatory role of microRNAs do not rely on the concept of mechanism. They have their own explanatory specificities, which lead me to define what I call quantitative explanations and systemic explanations. These types of explanations are becoming increasingly important in molecular biology, because they compensate for some limits of the concept of mechanism to grasp particular features of molecular processes.[4] In the end, my analysis leads to a reconsideration of the status that has so far been ascribed to the concept of mechanism by philosophers, as well as to the development of a pluralistic account of explanations that more accurately fits biological practice.

[1] See for example: Machamer et al. (2000), Machamer (2004), Craver (2001), and Craver (2005).

[2] I define molecular biology broadly as the study of biological processes at the molecular level.

[3] The issue of explanatory pluralism in contemporary biology is also discussed in this volume: Mekios (2015), Morange (2015), Brigandt (2015).

[4] For related discussions of possible limitations of mechanistic models in systems biology, see in this volume: Baetu (2015), Breidenmoser and Wolkenhauer (2015), Issad and Malaterre (2015).

2 Explaining with Mechanisms in Contemporary Molecular Biology

2.1 The Concept of Mechanism in the New Mechanistic Philosophy

In the philosophy of science, issues about the nature of scientific explanation have long been dominated by the deductive-nomological model, according to which explanation takes the form of a deductive argument with at least one natural law among its premises. The debate took a decisive turn when Machamer et al. (2000) claimed that much of the explanatory activity in the biological sciences implies the discovery and the description of mechanisms, which they defined as "entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (p. 3). Their analysis triggered important discussions about the characteristics of mechanisms and mechanistic explanations. More specifically, philosophers have debated the possibility of providing a unified characterization of the concept of mechanism across biology, and several accounts of this concept have been proposed (Bechtel and Abrahamsen 2005; Glennan 2002; Torres 2009). Despite their differences, these accounts all share the following core elements (reviewed in Craver and Bechtel 2006):

(i) A mechanism explains how a *phenomenon* is produced, how some *task* is carried out, or how some *function* is performed.
(ii) A mechanism is composed of *parts*, *entities*, or *component parts*, with their properties.
(iii) In virtue of their properties, the parts of the mechanism *interact*, engage in *activities*, or perform *component operations*. Activities or operations are the causal components of mechanisms.
(iv) The parts of the mechanism and their causal relations are spatially and temporally organized, so that they produce the phenomenon.

This new mechanistic philosophy arose from the realization by philosophers of science that the concept of mechanism plays a central role in biological practice. Therefore, the development of the mechanistic framework is meant to grasp scientific practice more adequately, especially in the fields of neuroscience, genetics, and molecular and cell biology, where mechanism-talk is pervasive. However, this recent interest in the concept of mechanism does not stem from new developments within biological sciences, since the mechanistic perspective has been used to explain biological phenomena throughout the twentieth century. Rather, the introduction of the concept of mechanism in philosophical debates was prompted by the need to offer an alternative to the traditional law-based approaches of scientific explanation that fail to account for most of biological practice (Bechtel and Abrahamsen 2005).

A widely shared assumption within the new mechanistic philosophy is that describing mechanisms is the bulk of explanatory activities in biology. Although the possibility that researchers may draw on other types of explanations is not denied,

it seems to be taken for granted that, at least in functional biology, explaining a phenomenon usually requires the identification of the mechanism responsible for this phenomenon. For instance, Bechtel (2006) asserts that in many domains, "the aim of inquiry leads to meticulous accounts of complex mechanisms. This is particularly true in the functional domains of biology" (p. 2). Craver, who is interested in explanations in neuroscience, makes a similar claim: "in the final analysis, even if it is false to state that all explanations must describe mechanisms, many of them do" (2007, p. xi). In what follows, I offer a critical examination of this widely shared, mechanism-centered account of biological explanations by examining current research on the regulation of gene expression by microRNAs. As I shall argue, this case study provides an illuminating insight into explanatory activities in contemporary molecular biology.

2.2 Explaining miRNA Regulation with Mechanisms

MicroRNAs (miRNAs) are a class of small non-coding RNAs, approximately 21–23 nucleotides long, found both in plants and animals. They have emerged over the last decade as key regulators of gene expression that act post-transcriptionally to inhibit gene expression. The total number of human miRNAs is estimated to be close to 800 (Bentwich et al. 2005), and about one third of all genes are predicted to be under miRNA regulation (Lewis et al. 2005). MiRNAs are involved in the regulation of virtually all biological processes, including development, cell proliferation, immune responses, and metabolism, to give but a few examples.[5]

After miRNAs were reported to represent a wide class of small non-coding RNAs in animals (Lau et al. 2001; Lee and Ambros 2001; Lagos-Quintana et al. 2001), research efforts mainly concentrated on the mechanisms responsible for their biogenesis and their regulatory role.[6] It appears that in animals, miRNA genes are transcribed into primary miRNA transcripts that undergo processing in the nucleus by the Microprocessor complex to generate precursor miRNAs. Precursor miRNAs are then exported into the cytoplasm, where they are further processed by the Dicer enzyme to form mature miRNAs. MiRNAs associate with the RISC complex (RNA-Induced Silencing Complex) and bind to mRNA targets in a sequence-specific manner, thereby guiding the RISC to these mRNAs. This results in either translational repression or mRNA degradation by the Argonaute protein of the RISC complex.

This description is a simplistic outline that does not reflect the complex accounts of miRNA biogenesis and regulatory action found in scientific literature. However, it provides sufficient grounds to claim that at least part of the research on miRNAs fits

[5] See for example: Stefani and Slack (2008), Lodish et al. (2008), Rottiers and Näär (2012).

[6] For a review on miRNA biogenesis and function, see: Ghildiyal and Zamore (2009), Pasquinelli (2012).

the mechanistic framework. Indeed, the explanation above involves parts, such as miRNAs, Dicer, Argonaute, that engage in activities, such as binding or processing. These parts and activities are organized so that their productive order is responsible for miRNA biogenesis or miRNA regulation. However, although the mechanistic perspective is undoubtedly successful in explaining miRNA-mediated regulation, I shall later demonstrate that explanations in the field of miRNA research encompass far more than describing mechanisms. Before doing so, I shall briefly review how philosophers conceptualize the diversity of explanatory schemes in biological sciences.

2.3 Mechanisms, Nothing But Mechanisms?

The new mechanistic philosophy has undeniably improved our understanding of scientific inquiry and explanatory practice in the biological sciences. Nevertheless, the claim that explaining biological phenomena consists in identifying and describing mechanisms seems to rule out, or at least downplay, the extent to which biologists draw on a variety of types of explanations. This perspective seems to be at odds with the one advocated by Morange (2005), who distinguishes between three explanatory schemes in biology: the mechanistic scheme, the Darwinian scheme and the physical non-causal scheme. Morange argues that these different types of explanations should be articulated in order to provide complete explanations of biological phenomena.

More recently, Braillard (2010) pointed out that part of the explanatory practice in systems biology cannot be accounted for by the mechanistic framework. He characterizes a non-causal type of explanation that consists in showing how a system's function determines its structure. Braillard's work highlights how the development of systems biology has influenced and transformed the explanatory activity of biologists. Following this analysis, it seems legitimate to wonder how the transition from classical molecular biology to postgenomic biology has impacted the way biologists explain phenomena at the molecular level. This issue is particularly relevant to our concern, since miRNA research has greatly benefited from genomic and transcriptomic analyses. Indeed, these analyses allow researchers to systematically identify all miRNAs and their targets in organisms, as well as study the impact of miRNA-mediated regulation on gene expression at a large scale, in different cell types and under various conditions. However, the consequences of the transition to post-genomic biology regarding the explanatory practice in molecular biology have been poorly investigated. More precisely, philosophers have insufficiently explored the possibility that the status of the concept of mechanism in scientific investigation may have significantly evolved during the last decade.[7] In this regard, the strong emphasis placed on mechanistic explanations by the new mechanistic philosophy

[7] However, see: Moss (2012).

seems problematic. The concept of mechanism has undoubtedly been at the core of research in classical molecular biology; however, the centrality of this concept in contemporary molecular biology has still to be assessed. I shall indeed suggest that the current role played by the concept of mechanism in biological practice has been overrated, and therefore, that the explanatory weight of this concept has been wrongly assessed, at least in molecular biology.

One reason for this failure, I contend, results from the misleading view that at the molecular level, causal explanations boil down to mechanistic explanations. This view is most salient in Craver's work. Following Salmon (1984), Craver defends a causal-mechanical account of explanation in neuroscience, according to which good explanations in neuroscience show how phenomena are situated within the causal structure of the world, by describing mechanisms. In line with this perspective, Craver alludes to causes and mechanisms in an interchangeable way: "Mechanistic models describe the relevant causes and mechanisms in the system under study" (Kaplan and Craver 2011, p. 608). Similarly, when mentioning the "virtue of the causal or mechanistic view of explanation" (Kaplan and Craver 2011, p. 606), he seems to conflate causal and mechanistic explanations. This opinion is not peculiar to Craver. Nicholson (2012) recently noticed that "it is increasingly the case that philosophers employ the term 'mechanistic' simply as a synonym for 'causal' when characterizing scientific explanations" (p. 154). Even Morange, who is most concerned with the diversity of explanatory schemes in biological sciences, seems to take for granted that causal explanations accounting for biological functions at the molecular level are basically mechanistic explanations. However, in what follows, I show that explanations of the regulatory roles of miRNAs do not solely consist in describing mechanisms. I sketch out a richer account of explanations in the field of miRNA research, by characterizing two explanatory contexts in which biologists avoid using the concept of mechanism. This leads me to define two kinds of non-mechanistic explanations, namely, quantitative and systemic explanations, which overcome some limits encountered by the concept of mechanism when describing causal processes at the molecular level.

3 Explaining miRNA Regulation with Quantitative Explanations

3.1 Beyond Mechanisms: Molecular Populations and Their Quantitative Properties

In molecular biology, the basic idea underlying the use of the concept of mechanism is that of a description of the causal patterns that bring about the phenomenon of interest. In that respect, the process of discovering a molecular mechanism always requires identifying the parts involved in the production of the phenomenon. To put it differently, it always involves a qualitative description of causal patterns.

Only some mechanistic explanations also describe quantitative features of molecular systems. By quantitative, I mean here exclusively either the number of copies or the concentration of a molecule or molecular complex.[8] My point is that in contemporary molecular biology, the concept of mechanism is basically used to place emphasis on the qualitative component of the causal structure of molecular systems, rather than on its quantitative component.[9] For instance, mechanistic explanations of miRNA biogenesis or miRNA regulatory action describe the molecular components responsible for these phenomena, but they do not specify the concentrations of these parts, such as miRNA or mRNA concentrations. Thus, in order to provide an account of the concept of mechanism that properly grasps contemporary biological practice, one should stress the qualitative component of causal relations, rather than their quantitative component.

Yet, at the molecular level, quantitative properties of living systems are of crucial importance, since most molecules inside cells are present in multiple copies. Therefore, it is appropriate to talk about 'populations' or 'pools' of molecules. For instance, many miRNAs are present at levels more than 1,000 molecules per cell, some of them exceeding 50,000 molecules per cell. As I shall now argue, quantitative features of miRNA regulation have become a major focus of attention in miRNA research. I will suggest that there has been a concomitant shift in the explanatory discourse toward explanations that depart from the mechanistic framework.

3.2 Quantitative Explanations of miRNA Regulation

Research on miRNAs encompasses far more than a mere qualitative description of the causal processes in which these RNAs are embedded. Many quantitative studies based on accurate assessments of miRNAs and mRNAs concentrations are currently performed. This interest in the quantitative features of miRNA-mediated regulation straightforwardly stems from the phenomenon to be explained, namely the regulation of gene expression. Indeed, explaining gene regulation can be addressed from two complementary perspectives: a qualitative one, which consists in describing how particular molecular components are responsible for the activation or inhibition of gene expression; and a quantitative one, which consists in explaining how a gene product is expressed at a given level. This quantitative aspect should not be deemed less important than its qualitative counterpart. Indeed, alterations in the precise level of most proteins can impair cell functions and cause diseases, such

[8]However, it is clear that many other features of molecular systems can be quantitatively characterized.

[9]This does not mean that mechanistic explanations never assume some quantitative characterizations of the activities, but rather that the qualitative description of causal patterns is the common core of all mechanistic explanations in molecular biology.

as cancers. Up to now, aberrant miRNA expression has been reported in various diseases, ranging from cancers to metabolic disorders (Lujambio and Lowe 2012; Rottiers and Näär 2012), and therapeutic strategies that aim at restoring normal miRNA levels are currently developed (Esteller 2011). Thus, quantitative analyses of miRNA-mediated regulation are fully relevant in order to gain insight into the regulatory roles of miRNAs, and to account for their involvement in diseases. These analyses have become easier to perform in the post-genomic era, due to the development and improvement of techniques allowing precise measurements of the expression levels of individual miRNAs and of their mRNA targets. Besides, the advent and refinement of microarray and sequencing technologies have made it possible to carry out high-throughput transcriptome analyses that provide an overview of miRNA expression on a large scale and under various conditions.

Quantitative studies have brought very interesting results regarding the quantitative features of miRNA regulation. First, the effect of miRNAs on the expression of their targets is usually modest, with most targets being down-regulated by less than a half (Baek et al. 2008; Selbach et al. 2008). This result is consistent with a role of miRNAs as fine-tuners of gene expression. Nevertheless, the effects of miRNAs on their targets expression actually exhibit some kind of diversity, and, based on these effects, miRNA-mRNA interactions can basically be categorized into three classes (Bartel 2009; Wu et al. 2009; Ebert and Sharp 2012). First, a miRNA can repress its target expression to inconsequential levels, thereby acting as a 'switch'. Switch interactions have been shown especially to help sharpen developmental transitions and maintain cell fates. Second, a miRNA can adjust the mean expression level of its target to a lower level, thereby acting as a 'fine-tuner' of gene expression. Third, a miRNA can reduce the variance of its target expression, thus contributing to buffer stochastic fluctuations in gene expression. A recent study has further clarified how miRNAs can act either as switches or as fine-tuners of gene expression, by demonstrating that miRNA regulation establishes a threshold level of target mRNA (Mukherji et al. 2011). Below this threshold, translational repression is high, and the miRNA acts as a switch; near the threshold, the protein output responds sensitively to target mRNA transcription, and the miRNA acts as a fine-tuner; above the threshold, translational repression is weak. Therefore, given a miRNA-mRNA interaction, the miRNA can either act as a switch or as a fine-tuner, depending on the mRNA concentration. This can be accounted for by titration effects: as target abundance increases, target mRNAs interact with available miRNAs and titrate them away, so that fewer free miRNAs are able to repress additional targets. This titration effect highlights that the relative concentrations of a miRNA and of all its targets are important to explain miRNA regulation. Indeed, since miRNAs partition among all their target mRNAs, miRNAs that have a higher number of available targets in a cell will repress each individual target to a lesser extent: this effect is known as the dilution effect (Arvey et al. 2010).

Recently, the discovery of competitive endogenous RNAs (ceRNAs) has further complicated the overall picture of the quantitative characteristics of miRNA regulation (Salmena et al. 2011). ceRNAs are targets of common miRNAs, and they can therefore compete with each other for the same pool of miRNAs, which results in

a reduction of the inhibitory action of these miRNAs on other targets. Competition between different targets for binding to the same miRNA may widely influence the regulation efficiency for each individual target.

Altogether, these data show that a qualitative description of the interactions between miRNAs and their targets is not sufficient to provide a complete explanation of miRNA regulation. Indeed, the regulatory function of miRNAs crucially depends on the relative cellular concentrations of these small RNAs and of their targets. The basic reason underlying this property is that molecular components are present in cells as populations. However, the concept of mechanism is not primarily meant to grasp this property. In line with this interpretation, biologists tend to avoid using the concept of mechanism in this research context. They have to think of miRNAs and of their targets as populations of molecules, and this conceptual shift is mirrored in the literature by the idea that these molecules form 'pools' inside cells. I refer to the resulting explanations as quantitative explanations. Such explanations describe the relations between quantitative properties of populations of molecules that are causally related: changes in miRNA concentrations cause changes in the expression level of their targets.

Quantitative explanations have their own explanatory specificities. Whereas mechanistic explanations focus on the qualitative interactions between miRNAs and mRNAs, as well as the properties in virtue of which these interactions occur, quantitative explanations focus on the quantitative features of these interactions. To put it differently, mechanistic and quantitative explanations study biological phenomena from two different perspectives: the former are mostly interested in the qualitative relations between molecules, whereas the latter deal with the quantitative relations between populations of molecules. I contend that when the phenomenon to be explained includes a quantitative component, as it is the case for the regulation of gene expression, an adequate explanation of this phenomenon will require both a mechanistic explanation and a quantitative explanation.

3.3 Mechanistic Explanations and Quantitative Explanations

Quantitative explanations highlight features of miRNA-mediated regulation that are not accounted for by the descriptions of parts and activities that lie at the core of mechanistic explanations. As such, they bear genuine explanatory relevance, and they successfully overcome a major limit of the mechanistic framework. Since mechanistic and quantitative explanations provide insights into different aspects of biological phenomena at the molecular level, they complement each other, and are to be articulated. Thus, quantitative explanations should not be considered as an alternative to mechanistic explanations. They are interested in properties of molecular systems that are not the primary focus of mechanistic explanations. However, one could argue that instead of distinguishing between two different types of explanations, the mechanistic framework could be extended so as to include quantitative explanations. To support this view, it could be stressed that

quantitative explanations describe relations between populations of molecules that are related in a mechanism. For instance, mRNA concentrations depend on miRNA concentrations because there is a mechanism of post-transcriptional gene silencing in which miRNAs causally interact with mRNAs to inhibit translation.

This solution has recently been advocated by both Craver and Bechtel (Kaplan and Craver 2011; Bechtel and Abrahamsen 2010; Kaplan and Bechtel 2011), who consider mathematical descriptions of dynamical systems as part of mechanistic explanations in cognitive neuroscience. Craver elaborates a model-to-mechanism-mapping constraint, according to which a dynamical or mathematical model explains a phenomenon if elements in the model plausibly map onto elements in the mechanism. In so doing, he states that "mechanisms are frequently described using equations that represent how the values of component variables change with one another" (Kaplan and Craver 2011, p. 606). He later supports the view that, in successful mechanistic explanations, "the (perhaps mathematical) dependencies posited among these variables in the model correspond to the (perhaps quantifiable) causal relations among the components of the target mechanism" (Kaplan and Craver 2011, p. 611). Bechtel and Abrahamsen have developed a similar perspective. The growing use of the tools of quantitative computational modeling to investigate the dynamic behavior of mechanisms led them to extend the mechanistic framework to accounts of dynamics. Dynamic mechanistic explanations, as they refer to them, do not merely describe the parts, operations, and organization of the mechanisms responsible for biological phenomena; they also explain how the parts and operations of complex mechanisms are orchestrated in real time to produce dynamic phenomena. Bechtel clearly endorses the view that dynamic descriptions should be embedded in mechanistic explanations: "the mechanistic perspective on dynamical models is uniform and remarkably clear: dynamical explanations do not provide a separate kind of explanation; when they explain phenomena, it is because they describe the dynamic behavior of mechanisms" (Kaplan and Bechtel 2011, p. 440). The mechanistic account defended by Craver and Bechtel conflicts with my claim that quantitative explanations should be articulated rather than conflated with mechanistic explanations. I shall provide grounds for holding mechanistic and quantitative explanations distinct in molecular biology. Before doing that, though, it is worth pointing out that Craver and Bechtel have developed their 'quantitative mechanistic' framework in response to claims that dynamical models explain phenomena independently of the mechanisms underlying these phenomena, and consequently that dynamical models are an alternative to mechanistic explanations. There is no such need to defend the explanatory relevance of the mechanistic framework in molecular biology, where the concept of mechanism remains strongly entrenched in the explanatory practice. Instead, my analysis stems from a careful examination of the specific research contexts where biologists favor or avoid the use of the concept of mechanism. This examination is, I believe, necessary in order to develop a mechanistic perspective that is consistent with biological practice. However, the fact that biologists distinguish between mechanistic and quantitative descriptions in their explanatory discourse does not legitimate my claim that

these descriptions should be held distinct in a philosophical account of biological explanations. Thus, I now provide some grounds for this claim.[10]

First, from a pragmatic standpoint, mechanistic and quantitative analyses are often carried out separately. Indeed, because they investigate different aspects of the same phenomena, they usually rely on different sets of techniques. Quantitative analyses of miRNA regulation involve techniques that allow accurate measurements of concentrations or copy numbers of miRNAs and mRNAs. They are not designed to investigate the precise mechanisms responsible for the regulatory role of miRNAs. Rather, they complement mechanistic studies by providing quantitative features associated with these mechanisms. Besides, quantitative studies have therapeutic implications on their own, since they lead to develop treatments that could restore adequate levels of miRNAs. The basic principle underlying such treatments is not to change the processes occurring in cells qualitatively, but rather to change their quantitative features.

Second, a hallmark of miRNA regulation lies in the diversity it exhibits in different cell types, at different developmental stages, and in various physiological and pathological conditions. This diversity is both qualitative, since different miRNAs may be expressed in different environmental conditions, and quantitative, since the same miRNA may be expressed at different levels in different conditions. In this latter case, the same qualitative pattern of entailment operates, but with various quantitative characteristics. However, if one chooses to extend the mechanistic framework so as to include quantitative relations between parts of mechanisms, then it is legitimate to wonder whether quantitatively different occurrences of the same interaction between parts should be treated as different mechanisms. Unfortunately, this issue has not been addressed by the new mechanistic philosophy. Nevertheless, it should be kept in mind that in molecular biology, the concept of mechanism is used to emphasize some kind of regularity in the occurrence of a causal sequence of events. This regularity requirement is central to the role played by mechanisms in biological explanations, since it provides the basis for generalizations from one instance to another (Andersen 2011). Because of the quantitative variability exhibited by biological processes, conflating mechanistic and quantitative explanations might weaken the ability of the concept of mechanism to stress such regularity, which in turn might lead to give up on a major epistemic interest of this concept.

Third, according to my analysis, mechanistic explanations at the molecular level can be regarded as idealized representations of causal processes, in which the idea of 'pools' of molecules is generally irrelevant. They describe how molecular components engage in activities, with little regard for the populations of molecules in which these components are embedded. It follows that mechanistic explanations are mostly interested in properties of molecules, whereas quantitative explanations

[10]In this volume, Baetu (2015) discusses how mathematical modeling relates to mechanistic explanations. Issad and Malaterre (2015) also offer an interesting critical examination of the concept of dynamic mechanistic explanation.

are interested in properties of populations of molecules. Philosophical accounts of the concept of mechanism rightly insist on the properties in virtue of which parts engage in activities. However, it is important to distinguish between properties of parts and properties of populations of parts: the quantity or concentration of a molecular component is a property of the population of this component, not of the component itself. As such, quantitative properties of molecular systems do not fall straightforwardly within the scope of the mechanistic framework. In the recent refinement of their account of mechanistic models, Bechtel and Craver inadvertently conflate these two kinds of properties. This is most apparent in Bechtel and Abrahamsen's revised definition of the mechanism, according to which "the orchestrated functioning of the mechanism, manifested in patterns of change over time in properties of its parts and operations, is responsible for one or more phenomena" (p. 323). In this definition, the properties of the parts actually refer to the properties of the populations of parts. This is probably why Bechtel fails to identify the different contributions of mechanistic and quantitative explanations to the explanatory practice of biologists.

Finally, the parts and operations involved in quantitative explanations may not be confined within the boundaries of a particular mechanism. For instance, explanations involving dilution effects, which rely on the relative concentrations of miRNAs and of all their targets, span multiple mechanisms, and could be seen as relating to the system level. In this regard, a major limit of the concept of dynamic mechanistic explanation developed by Bechtel is that it only fits cases where dynamical models are used to understand the behavior of a particular mechanism. Yet, if one takes into account the diversity of quantitative explanations, it becomes clear that it is not relevant to merge the quantitative and the mechanistic perspectives. When quantitative explanations relate to the system level, it could, however, still be argued that the mechanistic perspective adequately accounts for explanations at this level. I now discuss whether explanations at the system level should be considered mechanistic explanations.

4 Explaining miRNA Regulation with Systemic Explanations

4.1 Explaining miRNA Regulation at the System Level

After the discovery of miRNAs and of their regulatory action, specifying how cellular functions are regulated by miRNAs has become a pressing issue. As the connections between particular miRNAs and these functions have been uncovered, a new terminology has emerged to account for the roles of miRNAs. Explanatory texts describe how miRNAs "orchestrate" cellular functions, how they are "integrated" in cellular "networks" or "circuitry", how they "mediate" biological phenomena, how the miRNA pathway "crosstalks" and is "coordinated" with other cellular pathways. Concomitantly, the concept of mechanism tends to be less frequently used. This terminological shift has already been noticed by Moss (2012), who rightly relates

it to a scientific interest in interrelatedness of function: "the hallmark of leading edge research in biomedical sciences has become that of seeking to understand how the very many low-level basic pieces of chemistry are responsively, flexibly, and contingently weaved together (*orchestrated*, *mediated*, *regulated*, etc.) into coherently global responses to developmental and environmental cues, internal and external perturbations." (p. 168). In miRNA research, the current interest in the interplay between miRNA-mediated regulation and cellular processes results in a shift from mechanistic explanations to a type of explanation that emphasizes how causal processes interact with one another. I shall outline the main features of this explanatory scheme, and highlight its importance with regard to miRNA biology.

Current research on miRNAs investigates how previously characterized mechanisms, those responsible for miRNA regulatory action and those involved in various cellular functions, are interconnected. Interactions between miRNA-mediated gene silencing mechanisms and other cellular mechanisms directly follow from the regulatory function of miRNAs. Indeed, miRNAs have an impact on the cellular functions in which their target genes are involved. Far from being incidental, this impact is widespread, due to the high number of genes that are targeted by miRNAs. Descriptions of the interactions between miRNAs and cellular functions are not detailed mechanistic descriptions. Rather, they span multiple mechanisms, and they characterize causal relations in cells at the systemic level. That is why I refer to them as systemic explanations. Surprisingly, Moss did not insist on the importance of a systemic thinking in this explanatory framework.

It has been suggested, quite provocatively, that the impact of miRNAs is always at the system level (Jost et al. 2011). The reason underlying this claim is that most miRNAs target multiple genes, which results in the coupling between the expression of genes involved in the same cellular function, or in a crosstalk between seemingly unrelated biological processes. Moreover, since many protein-coding genes are predicted to be targets of multiple miRNAs, distinct miRNAs can act cooperatively to regulate gene expression. This systemic perspective of miRNA regulation has implications for the explanatory discourse. Braillard (2010) has stated that both mechanistic and systemic approaches aim at explaining biological phenomena "by studying the molecular components, their properties and their interactions", and that "systems biology is clearly concerned with large and complex mechanisms, but they are still mechanisms" (p. 45). I wish to point out some limits of this assertion, by stressing important differences between mechanistic and systemic explanations in the context of miRNA research. Consider the following explanation of the role of miRNAs in the resolution of inflammation:

> Later, the induction of miR-146a[11] and miR-9 resolves the pro-inflammatory response by targeting TNFR-associated factor 6 (TRAF6) and IL-1R-associated kinase 1 (IRAK1), which are key components of TLR signaling pathways, and the nuclear factor-κB (NF-κB) subunit p50, respectively. miR-132 expression has also been shown to be increased by TLR signaling and would limit the antiviral response by targeting p300. (O'Neill et al. 2011, p. 172)

[11] Under the standard nomenclature system, the prefix «miR» refers to mature miRNAs.

This explanation differs from detailed mechanistic explanations in several important respects. First, it only reports two kinds of molecular components, miRNAs and their targets, without much interest in their binding, or in the properties by virtue of which this binding occurs. Moreover, most of the causal chain responsible for the inhibition of gene expression, such as the sorting of miRNAs into the RISC complex or the interaction between the RISC and mRNA targets, is not described. Rather, this explanation shows how previously characterized mechanisms (the mechanisms responsible for the expression of specific miRNAs and those involved in immune responses) interact with one another to resolve inflammation. In this respect, there is no need to describe the complete causal processes, since mechanistic descriptions already did so. Instead, in systemic explanations, biologists only focus on portions of the causal processes they deem relevant to explain how these processes interact to fulfill the biological function of interest. Here, in order to explain how cellular functions are regulated by miRNAs, it is only relevant to describe the set of miRNAs that regulate the expression of the genes involved in these functions. The resulting explanation is not at a higher hierarchical level than mechanistic explanations, but at a systemic level. More importantly, this explanation possesses its own explanatory specificities, especially regarding the features of the patterns of entailment that are picked out as relevant.

The concept of network is particularly well equipped to describe the interactions between mechanisms that lie at the core of systemic explanations. Accordingly, this concept has become ubiquitous in miRNA research. Sometimes, it is used in a loose way to convey the idea that biological processes are interconnected in an intricate way:

> Clearly, miRNAs cannot independently perform a single task in cells. Instead, miRNAs regulate cellular networks as network components in many cellular functions. (Li et al. 2011, p. 1)

More frequently, the concept of network is used to describe specific gene regulatory networks involving miRNAs. These networks usually depict the interactions either between miRNA regulation and cellular functions, or between the regulation by miRNAs and by transcription factors. They consist of nodes that can be genes, proteins, mRNAs, or miRNAs, and of links connecting the nodes that indicate the regulatory relations (activation or inhibition) between nodes. These networks do not exhaustively describe the causal processes of interest, but they show how several causal processes interact with one another.

4.2 Mechanistic Explanations and Systemic Explanations

In molecular biology, mechanistic explanations are used to describe continuous causal chains that produce or maintain the phenomenon to be explained. Consequently, they satisfy two requirements. First, the description of the component parts, their relevant properties, and the activities they engage in must be exhaustive.

Second, mechanistic explanations only describe the relevant causal relations that are responsible for the production of the phenomenon under investigation. Craver has formulated these requirements: "Complete explanatory texts are complete because they represent all and only the relevant portions of the causal structure of the world" (Craver 2007, p. 27). Systemic explanations describe how previously characterized processes that together perform a function interact with one another. In miRNA research, they tackle the issue of the biological functions of miRNAs from a different perspective than mechanistic explanations do, and accordingly, they often draw on a different set of investigative tools. As such, they fruitfully complement the mechanistic approach, but they should not be conflated with it.

In contemporary molecular biology, the concept of mechanism is primarily used to individualize some portions of the causal structure of the cell. This fragmentation of living systems into autonomous mechanisms has a heuristic interest that has already been put forward by Nicholson (2012): "The idea of autonomous causal mechanisms operating within the organism is, I suggest, nothing more than a pragmatic idealization that biologists appeal to in order to narrow their focus on the particular parts of the organism they happen to be investigating" (p. 159). However, in the case of miRNA-mediated regulation, the description of a regulatory mechanism does not provide, on its own, a complete explanation of how a cellular function is regulated by miRNAs at the molecular level. This is why researchers are currently increasingly interested in the interrelatedness of causal processes, which is better investigated and described with the concept of network than with the mechanistic framework.[12]

So far, I have characterized two explanatory schemes that do not rely on the concept of mechanism. This analysis has important implications regarding the status of the concept of mechanism in contemporary molecular biology.

5 Reassessing the Status of the Concept of Mechanism in Contemporary Molecular Biology

My account of the explanatory practice in miRNA research ensues from a careful examination of explanatory texts and diagrams found in scientific literature. This perspective has been motivated by the assumption that in order to provide a characterization of the mechanistic framework that is grounded in biological practice, one has to bear heavily on these texts and diagrams. This focus on explanatory texts, rather than on the causal structure of the world, departs from the perspective adopted by Craver. Indeed, Craver places much more emphasis on objective explanations, which are the mechanisms in the world, than on explanatory texts, which describe these mechanisms:

[12]For a different perspective regarding networks and the mechanistic framework, see Bechtel (2015) in this volume.

> There are perhaps many interesting things to be said about explanatory texts, but one crucial aspect of their adequacy has to do with whether explanatory texts accurately characterize the causal structure of the world. (Craver 2007, p. 27)

Giving more prominence to explanatory texts results in a mechanistic framework that differs from the one offered by the new mechanistic philosophy in two important respects. First, it shows that in biological practice, causal explanations do not boil down to mechanistic explanations. Second, it highlights the epistemic component of the concept of mechanism. In what follows, I provide more details about these claims.

5.1 Causal Explanations in Contemporary Molecular Biology

I previously argued that in the context of miRNA research, biologists tend to not use the concept of mechanism when quantitative or systemic properties of molecular systems are being investigated. Accordingly, I distinguished between three explanatory schemes in contemporary molecular biology: mechanistic, quantitative, and systemic explanations. New mechanistic philosophers have failed to notice the explanatory shift that resulted in this diversity of causal explanations in postgenomic biology. This may be because they embrace a causal-mechanical view of scientific explanation, according to which the causal structure of the world is characterized through the concept of mechanism. Besides, little attention has been paid to the specific research contexts in which researchers actually use the concept of mechanism and those in which they prefer employing other concepts. This could result in accounts of scientific explanation that somehow move away from actual explanatory practice.

I do not claim that explaining a phenomenon does not require showing how it is produced by its causes, although it should be kept in mind that not all biological explanations are causal (Morange 2005; Braillard 2010). Rather, my critical examination of some claims made by new mechanistic philosophers aims at developing an account of explanations that more adequately characterizes explanatory practice in contemporary molecular biology. Indeed, in this field, the concept of mechanism is less prevalent than it used to be in classical molecular biology. This is because biologists increasingly study molecular causal processes from different perspectives, each focusing on a specific feature of these processes: their qualitative component, their quantitative component, or their interrelatedness. Therefore, I advocate a pluralistic approach of biological explanations that accurately fits explanatory practice in contemporary molecular biology in two important respects. First, it emphasizes the fact that mechanistic, quantitative and systemic studies of molecular systems are often performed separately, and rely on different methodological and conceptual backgrounds. Second, it is consistent with explanatory texts, in which biologists prefer articulating the results coming from these studies, rather than merging them into a unique complete explanation.

The categorization of explanatory schemes I sketch out offers a basis for developing a richer and finer conceptual framework of explanations in molecular biology. However, it should be stressed that it is also simplistic, insofar as the different types of explanations overlap to some extent. Indeed, some explanations belong to more than one of these types. For instance, explanations involving the dilution effect can be regarded either as quantitative explanations or as systemic explanations. Indeed, they focus on the relative concentrations of miRNAs and of all their targets, and as such, they deal with the systemic level. This overlap suggests that the different types of explanations should not be conceived of as mutually exclusive, but rather as a continuum of explanatory practices.

5.2 The Epistemic Component of the Concept of Mechanism

I related the use of the concept of mechanism to specific research contexts where qualitative aspects of causal patterns are the primary (but not necessarily the sole) focus of attention. If this analysis is correct, it implies that the concept of mechanism is used to make salient some properties of the living system under investigation, and consequently that this concept has an epistemic component that should not be ignored. When molecular biologists study causal processes, they often decompose their properties into several categories for heuristic purposes. In this respect, the concept of mechanism makes it possible to put some properties of biological processes in the foreground, while other properties are overlooked. Concomitantly, it helps mobilize methodological and conceptual tools that are well equipped to study these properties; it also provides a conceptual background to analyze experiences and to draw up explanations. Therefore, the wrong appreciation of the status of mechanistic explanations by the new mechanistic philosophy may be related to its defense of an ontic view of the concept of mechanism. Craver and Bechtel, who consider mechanisms as real things in the world, explicitly advocate this view. This may be why they fail to realize that the concept of mechanism is mostly used to place emphasis on specific features of the patterns of entailment occurring inside cells. This may also account for their choice to include quantitative explanations into the mechanistic framework. As a matter of fact, their conceptualization of mechanisms includes the three features of causal patterns I distinguished. The problem is that in so doing, their definition of the mechanism does not grasp what most biologists mean when they use this concept.

Other philosophers have already stressed the epistemic component of the concept of mechanism. According to Nicholson, mechanisms are epistemic models used to explain how biological phenomena are produced. In this view, mechanisms are idealized representations of causal processes, which capture some features of living systems at the expense of others. More precisely, mechanisms are individuated both temporally and spatially in the specific context of the explanation, and consequently, mechanistic explanations abstract away the complexity of the organismic context. Powell (2012) also rejects an ontic conception of mechanisms. Instead, he develops

a characterization of mechanisms that heavily relies on cognitive and psychological dispositions. Nicholson and Powell's views both have attractive features. Yet, the characterization of mechanisms I am most sympathetic to is the one embraced by Moss (2012). According to Moss, mechanism-talk in biology draws metaphorically on the knowledge of the workings of macroscopic machines. This helps biologists to grasp and make intelligible phenomena occurring in the microscopic world. Moss' assumption is supported by the fact that biologists never define (nor try to define) the concept of mechanism. Rather, this concept seems to be used quite intuitively, more as an explanatory metaphor than as a scientific concept. Accordingly, Moss denies the possibility (as well the philosophical interest) of offering a normative account of mechanistic explanations that would specify standards to evaluate explanations. Moss' thesis is helpful to make sense of the idea that mechanistic explanations are primarily used to foreground the qualitative component of causal patterns, rather than the quantitative features and interrelatedness. Indeed, if he is right, then the concept of mechanism cannot be satisfactorily accounted for without reference to the workings of machines. This view strongly contrasts with the new mechanistic discourse, which insists on differences between mechanisms and machines (Craver 2007; Craver and Darden 2005). Keeping in mind that biologists do not provide any definition of the concept of mechanism, it follows that the way biologists conceptualize mechanisms must be at least partly influenced by their individual experience of machines, and most certainly by their knowledge of emblematic machines such as the clock. In this respect, it is noteworthy that describing the working of a clock consists in a qualitative description of how its component parts interact to perform a task. A quantitative characterization would not be relevant, because these parts are not present as 'populations'. Besides, one can straightforwardly describe all the parts and operations of the mechanism of the clock, with no need to examine how different mechanisms are interconnected in an intricate way. Therefore, it is tempting to come to the conclusion that the working of emblematic mechanical devices has been heuristically transposed onto the descriptions of molecular mechanisms. In this respect, the current conceptual shift towards explanations that depart from the mechanistic discourse highlights some limits faced by the metaphor of the machine to accurately describe causal patterns occurring in cells.

6 Conclusion

Throughout the twentieth century, the mechanistic framework has been very successful in providing explanations of a wide range of biological functions. The new mechanistic philosophy has rightly shed light on this success. However, recent developments in molecular biology reveal that biologists are, with increasing frequency, investigating properties of living systems that the concept of mechanism captures only poorly, and that provide different insights into biological phenomena. This gives rise to explanatory schemes that stress the quantitative and systemic

properties of molecular systems and that have their own explanatory specificities. Rather than considering these schemes as part of the mechanistic framework, a more fruitful standpoint consists in developing a pluralistic approach of explanations that better fits biological practice. Such a pluralistic approach requires us to give more emphasis to the epistemic properties of the concept of mechanism.

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