Penultimate draft. Accepted for publication in *The British Journal for the Philosophy of Science*

'MODELS OF' AND 'MODELS FOR': ON THE RELATION BETWEEN MECHANISTIC MODELS AND EXPERIMENTAL STRATEGIES IN MOLECULAR BIOLOGY

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Abstract

Molecular biologists exploit information conveyed by mechanistic models for experimental purposes. In this contribution, I make sense of this aspect of biological practice by developing Keller's idea of the distinction between 'models of' and 'models for'. 'Models of (phenomena)' should be understood as models representing phenomena and they are valuable if they explain phenomena. 'Models for (manipulating phenomena)' suggest new types of material manipulations and they are important not because of their explanatory force, but because of the interventionist strategies they afford. This is a distinction between aspects of the same model; in molecular biology, models may be treated either as 'models of' or as 'models for'. By analyzing the discovery and characterization of restriction-modification systems and their exploitation for DNA cloning and mapping, I identify the differences between treating a model as a 'model of' or as a 'model for'. These lie in a *cognitive disposition* of the modeler towards the model. A modeler will look at a model as a 'model of' if he/she is interested in its explanatory force, or as a 'model for' if the interest is in the material manipulations it can possibly afford.

1. INTRODUCTION

Models can be used in many ways to achieve a number of different purposes (Morrison and Morgan 1999). For instance, models are used to draw inferences about a target system, as measuring instruments, as experimental systems (1999, p 20-21), to explain, or to construct other models. In molecular biology, models are used not only as tools to shed

light on phenomena or theories, but also to design new experimental strategies (Morange 1998). In Rheinberger's own words, "molecular biology (…) is governed by methods rooted in the molecular tools that operate in the living cell itself" (2007, p 220). Here Rheinberger is implicitly saying that *knowledge* of tools operating in the living cell can provide solid grounds for biological experimental methods. Since knowledge in molecular biology is expressed mainly in the form of *mechanistic models* (Craver and Darden 2013), Rheinberger's claim can be interpreted as saying that molecular biologists take advantage of (or take inspiration from) mechanistic models to develop new experimental strategies. This aspect of mechanistic models has not been properly appreciated in philosophical studies of biology. Philosophy of biology has mainly focused on explanatory aspects of mechanistic models. To fill the gap in the literature, here I aim to understand the role that mechanistic models have in the development of experimental strategies. In particular, the question I am interested in is: *What is the relation between mechanistic models and experimental strategies in molecular biology?*

I will answer this question by borrowing and developing a distinction made by Evelyn Fox Keller. In (2000), Keller discusses the relation between theory and practice in biology and she mentions a distinction between 'models of' and 'models for'. 'Models of' (phenomena) should be understood as models representing phenomena, while 'models for' (manipulating phenomena) are models that suggest new types of material manipulations, i.e. tools for material change. In Keller's terms, 'models of' are *theoretical* in the sense that they are aimed at explaining accurately specific aspects of biological phenomena, while 'models for' are valuable not because they represent accurately or explain phenomena (though they might), but because they suggest strategies for manipulating phenomena. In my understanding, this distinction is not between two types of models; rather it is between different *aspects of models*, especially in molecular biology, where mechanistic models might explain but they might also suggest new interventionist strategies. However, only a few mechanistic models in molecular biology have been directly involved in the development of experimental strategies. Therefore, certain mechanistic models must possess virtues that make them better 'models for' rather than simply 'models of'. In this article I want to understand *in virtue of what* models may be a good 'models for'.

The structure of this article is as follows. In Section 2, I will introduce the received view on 'models of' in molecular biology (2.1) and some preliminary considerations on why we should distinguish them from 'models for' (2.2, 2.3, 2.4). In Section 3, I will discuss more in detail 'models for' by reconstructing the history of the development of the model of the restriction-modification systems which embeds important aspects of 'models for'. The main thesis is that whether a 'model' counts as a 'model of' or a 'model for' depends on a *cognitive disposition* of the modeler towards the model. A modeler will look at a model as a 'model of' if he/she is interested in its explanatory force, or as a 'model for' if the interest lies in the material manipulations it affords. In section 4, I will distinguish two cognitive dispositions behind 'models of' and 'models for', namely an *epistemic disposition* and a *disposition towards affordances*. Such dispositions 'prescribe' the way the model will be treated, developed, and evaluated. In other words, these cognitive dispositions 'prescribe' the virtues that modelers usually look for in a model. In section 5, I will identify 'portability' as a complex and fundamental virtue of 'models for'.

2 'MODELS OF' AND 'MODELS FOR' IN MOLECULAR BIOLOGY

Although the distinction between 'models of' and 'models for' captures important aspects of models in molecular biology, philosophy of biology has mainly focused on models considered under the (epistemic) aspects of 'models of'.

One may object that in philosophy of biology the relation between mechanistic models and interventionist/manipulative strategies has been extensively analyzed. However, in these cases philosophers have focused on material manipulations with explanatory or realist issues in mind, rather than being concerned about what models in molecular biology allow us to do independently of these epistemic issues. Let me introduce more precisely the distinction.

2.1 'Models of' in molecular biology

The aim of molecular biology is to explain biological phenomena (e.g. protein synthesis, cell cycle) in light of macromolecules (e.g. nucleotides, amino acids, etc) that compose it.

In philosophy of biology, the received view (Tabery, Piotrowska and Darden 2015) assumes that the unit of explanation of molecular biology is the mechanistic model (Bechtel and Abrahamasen 2005), namely a description *of* how biological components are organized in order to produce a specific biological phenomenon (Machamer et al 2000). The more a mechanistic model (or a description) can depict precisely the way macromolecules are organized to fully account for the phenomenon, the more the biological phenomenon is explained. This view is also endorsed by prominent molecular biologists (Weinberg 1985; Alberts 2012). Therefore, *models of* phenomena - in the sense of accurate representations of phenomena – play a crucial explanatory role in molecular biology. Consider for instance the model of CRISPR-Cas system (Figure 1).

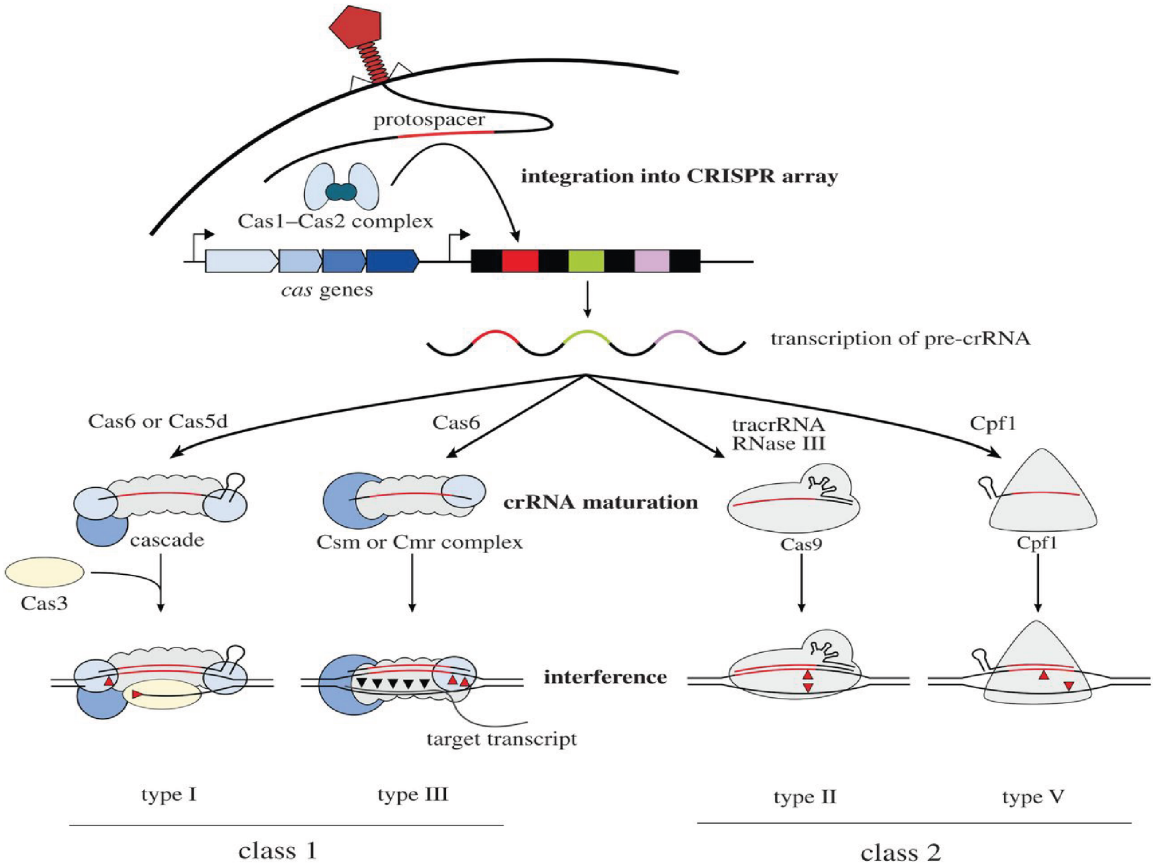

Figure 1. Mechanistic model of CRISPR-Cas system (Picture taken from Hille & Charpentier 2016)

The CRISPR-Cas system is the immune system of specific bacteria and archea (Hille and Charpentier 2016). The CRISPR-Cas9 model was originally conceived as a 'model of'; the target system (CRISPR-Cas9 system) of the model was studied by microbiologists in order to explain the functioning of such a system (Zhang 2015, p 409).

This immune system works as follows (I draw extensively from Makarova et al (2015)). A CRISPR locus consists of a CRISPR array ('Clustered Regularly Interspaced Short Palindromic Repeats') – namely a series of nucleotide repeats - separated by short variable DNA sequences called 'spacers'. Such spacers are composed by integrated foreign DNA sequences. The CRISPR array is flanked by several *cas* genes (Cas stands for 'CRISPR-associated'). The mechanism of CRISPR-Cas is composed of three main stages. The first stage has been called *adaptation*, when fragments of foreign DNA from invading viruses are incorporated into the CRISPR array as new 'spacers'. These provide the sequence memory for a targeted defense against subsequent invasions by the corresponding virus. The second stage is *expression*, namely when the CRISPR array is transcribed and matured to produce CRISPR RNAs (crRNAs). Finally, there is the *interference*. This is when crRNAs, aided by Cas proteins, function as guides to specifically target and cleave the nucleic acids of specific foreign viruses. Figure 1 provides the typical diagram used to represent such a mechanism. If mechanistic models explain, then the model of Figure 1 is seen as explanatory of how the immune system of certain bacteria and archea works. This model describes how certain entities (DNA molecules, proteins, etc) work together to produce a specific phenomenon. Describing and representing *accurately* the causal structure of a phenomenon is here explanatory of the phenomenon itself.

How should 'accurate' be understood? Why is CRISPR-Cas9 model a good model? Such questions have fuelled a vivid debate, in particular around Craver's work (Bechtel and Abrahamasen 2005; Craver 2006; 2007; Kaplan and Craver 2011; Levy and Bechtel 2013; Levy 2014).

First, successful mechanistic explanations describe *the causal structure of the world*, i.e. how a phenomenon is *constitutively* produced and/or maintained by *causally relevant* components. In Craver's work (but in Bechtel and Richardson 2010 as well), causal relevance and explanation are intimately connected, and the idea of 'control' plays a pivotal role. Craver draws extensively from Woodward's account of causation (2003), in the sense that causal relationships can be identified by the fact that they are "potentially exploitable for the purpose of manipulation and control" (Craver 2007, p 94). For this reason, the account is related to the idea of 'intervention', i.e. a manipulation that

changes the value of a variable[1]. To simplify, X is causally relevant to Y if we can manipulate Y in conditions W by manipulating X[2]. Entities described in the CRISPR-Cas9 model are causally relevant to bacterial immunity in this sense.

Next, according to Craver (2006; 2007), a mechanistic model is accurate (i.e. it explains) when the description of the causal structure of a phenomenon is not just a mere conjecture of how that phenomenon could be produced. It must involve a description of a causal structure involving real components and real activities. When I say 'real' I mean that they have to correspond to entities *in the world* causally relevant to the phenomenon (Kaplan and Craver 2011). The gold standard for a mechanistic explanation is that it should include *all the relevant features* of the mechanism we investigate. This is what distinguishes a 'complete' and adequate mechanistic explanation from a mere *how-possibly* model or a mechanistic sketch. However, including all relevant features is not an easy concept to spell out. Craver (2006; 2007; Kaplan and Craver 2011) provides detailed discussions of this issue, and even though he is focused in neuroscience, his accounts works for disciplines such as cell biology or molecular genetics as well (see Craver and Darden 2013). The model should account for the *explanandum* by describing its causal structure in terms of components (both entities and activities) that should be clearly identified. In (2007, chapter 4) he enriches this picture by adding that an adequate explanation needs to spell out precisely the nature of constitutive explanatory relevance of components. In (Kaplan and Craver 2011) he further reinforces such norms by clarifying that – at least in neuroscience – there is a 'model-to-mechanism-mapping' requirement (i.e. *3M constraint*) that rules out inadequate explanations; variables in the models should correspond to real entities and activities that are deemed relevant to the phenomenon, and dependencies among components should capture relations among real components.

Craver's claims of 'completeness' of explanations have attracted criticisms (Levy and Bechtel 2013; Levy 2014). First, a 'complete' description is impossible. As Levy and Bechtel (2013) point out, "[m]any, perhaps all, descriptions are abstract in some respects and degrees" (p 242). Moreover, Levy (2014) emphasizes the distinction between

[1] The idea of 'intervention' and 'manipulation' should not be conflated with 'human agency'
[2] *Importantly*, one does not need to be able actually manipulate X, i.e. the intervention can be simply 'ideal' and a variable may not be accessible directly for several reasons

sketches (i.e. models lacking *relevant* details) and *abstractions* (i.e. models leaving out *irrelevant* details) by emphasizing that in neuroscience some models may be explanatory when they leave out (irrelevant) details.

In my opinion, there are *two debates* here that should not be conflated. First, there is a debate internal to the philosophy of neuroscience. Levy criticizes Craver for his interpretation of Hodgkin-Huxley model and of modeling strategies in neuroscience, in particular when it comes to Craver's emphasis on molecular details. Next, there is the debate about abstraction and mechanistic explanation *in general* and this looks less controversial than the former. This is because even Craver stresses that claims on 'how-actually' models and 'completeness' have to be understood with two important limitations. First, they are always *relative* to a certain context. Second, 'how-actually' and completeness are regulative ideals which cannot be achieved and that "[b]etween sketches and complete descriptions lies a continuum of *mechanism schemata*" (2006, p 360). Furthermore, too many details can make difficult the task of clearly depicting the organization. Even if we have the ideal of completeness in mind, "practices of abstraction and idealization sit comfortably with the realist objectives of a mechanistic science" (Kaplan and Craver 2011, p 610).

In molecular biology (and specifically cell biology or molecular genetics), the issue of completeness and abstraction is not as problematic. Typical molecular biologists (such as cell biologists, etc) focus on the components and activities that make a difference or that they are causally relevant in a specific context (Love and Nathan 2015). This can be done by emphasizing the aspects relating the notions of 'intervention' and causal relevance as stressed by Craver (2007) or analogously by other authors (e.g. Strevens 2008). But unlike Levy's remarks about neuroscience, in the case of disciplines as cell biology or molecular genetics depicting precisely the properties of (causally relevant) components is *often* very important. Abstracting from irrelevant details and having in mind Craver's discussions of what counts as a good 'model of' should not be understood as in tension, because such features would apply only to the causally relevant components.

2.2 'Models for': The case of CRISPR-Cas9

Let us consider again the model of the CRISPR-Cas system (Figure 1), though from another perspective.

The model of CRISPR-Cas meets the criteria that a model must possess to be explanatory, but its importance hardly lies in its explanatory force. It is worth knowing more about bacteria and archea, but the attentions received by this model have nothing to do with bacteria and archea *per se*. As Zhang says, "[i]n the past 5 years (…) attention shifted to developing CRISPR/Cas9 as a powerful tool for biological research (…) for genome editing and manipulation" (2015, p 409). Apart from its explanatory purposes, this model is a 'model for' when we focus on how it suggests new potential ways of doing genome editing. To use Jiang and Doudna's own words, this bacterial defense mechanism has been, "*repurposed* as a powerful RNA-guided DNA targeting platform for genome editing, transcriptional perturbation, epigenetic modulation, and genome imaging" (p 507, emphasis added). This means that components of the model of CRISPR-Cas9 have been 'resituated' in a different context. By *context* here I mean the *biological context* for which a model is deemed to be relevant. In the case of 'models of', the biological context is defined by the phenomenon to explain[3]. For instance, the material modifications exercised on the 'real' components are evaluated and interpreted in light of the whole response of the *explanandum*, i.e. how modified components modify the *explanandum*. When I say that the context of 'models for' is different, I mean that we do not evaluate the model – as a 'model for' – in light of the phenomenon that the model – as a 'model of' – is purported to explain. Instead, the context of 'models for' is any biological context where the interventionist strategies they suggest can be useful.

When I say that components of CRISPR-Cas9 model have been resituated in another context, I mean that a single RNA-guided Cas9 that can cleave specific targeted DNA sequence has been 'redirected' for programmed DNA cleavage (Jinek et al 2012). Such a single RNA-guided Cas9 does in other contexts the same thing that it does in the context of bacterial immunity, but it does this *with different purposes* (i.e. it does not contribute to bacterial immunity), where 'purposes' are specified by *those who exploit its*

[3] This aspect is emphasized in several works about mechanistic explanation (see in particular Craver 2007; Craver and Darden 2013; Darden 2006).

capacities. Unlike in mechanistic 'models of', interventionist strategies *must* be actual and they are *strictly related to human agency*.

The same model can be used both to represent/explain and as a guide to manipulate experimental systems in multiple contexts; it is the same model but looked in light of different desiderata and aims. In other words, instead of looking at models to establish if they explain, we look at models to find something that can be 'repurposed' elsewhere. The components of the model are used with different purposes in mind; when models are considered 'models of', components are considered as parts of an explanation, unlike in models as 'models for' where components are seen as potentially triggering specific effects in other contexts.

2.3 Importance of 'models for'

Models like CRISPR-Cas9 - as 'models for' - play a prominent role in molecular biology. Biologists, by reasoning on them, develop new ways of manipulating biological entities, which are then used to investigate phenomena that were at first inaccessible. The history of molecular biology is replete with such examples. For instance, the model of reverse transcriptase in 1970 (Temin and Mizutani 1970) has been used to develop tools for gene cloning. As Morange puts it, "its discovery (…) in fact provided one of the most important tools of genetic engineering" (1998, p 172). Another important example is DNA polymerase which was characterized by Arthur Kornberg in 1955, and then it has been 'repurposed' in many ways, which will be exposed in detail below.

These examples are related to the importance of experiments in molecular biology. In several cases, strategies of discovery in science have been characterized by philosophers of science as (cognitive) strategies for discovering mechanisms (Bechtel and Richardson 2010). When it comes to molecular biology, these strategies are instantiated mostly in terms of experiments. For instance, to localize causally relevant biological entities in a phenomenon, we need to *materially* stimulate or inhibit the phenomenon itself (Bechtel and Richardson 2010; see also interlevel experiments in Craver 2007). This is related to the observations that Craver does about the idea of intervention and causal relevance as developed by Woodward (2003). However, in molecular biology what count are only *actual* manipulations and interventions, and not also 'ideal'

interventions. The importance of experiments is that they *actually* (and not possibly) provide a *material access* into biological systems; only by interpreting the responses of such systems, do we elaborate a mechanistic description of how the system works. As just mentioned, in the history of molecular biology (Rheinberger 2007; Morange 1998), models have been exploited to elaborate more precise and effective ways of materially manipulating biological phenomena[4]. These in turn could lead *in principle* to the elaboration of more precise mechanistic models. 'Models for' are the engine of progress in molecular biology, because they facilitate the possibility of more precise experimental manipulations, which are a prominent means for elaborating explanations.

2.4 'Models for' and philosophy of experimentation in biology

Before turning to a more detailed analysis of the characteristics of 'models for', let me now distinguish my interest in this aspect of models from seemingly similar analyses.

Consider for instance the notion of 'build-it test' developed by Craver and Darden. In (2013), they interpret the ability to modify biological phenomena on the basis of their mechanistic models (after all, mechanistic descriptions look like 'recipes' for constructing phenomena) as a sign of the explanatory force of models. By hypothesizing what would happen if entities of a mechanistic description were overexpressed or inhibited, and then by materially intervening on the target system accordingly, we would have indications about the quality of the mechanistic model. By 'constructing' the phenomenon, we understand if the model is explanatory. In the case of CRISPR-Cas9 model, this test would reconstruct the immune system of bacteria in the same context where it usually happened (i.e. in prokaryotes). However, my focus is on how mechanistic models can be used to elaborate manipulative/interventionist strategies that are applied to contexts (in the sense meant above) that are different from the specific context for which the model – as a 'model of' - is considered relevant. The important aspect of the CRISPR-Cas model is that we do not use its specific 'DNA-cutting' workflow (in the sense of 'procedure') to reproduce a phenomenon in order to understand

[4] Please note that models, 'as models for', are not the experimental strategy itself. Rather, they are a source used to develop the strategy/experimental protocol

if we have a good explanation of it (i.e. the 'build.it' test), but rather we want to use the workflow to manipulate other phenomena.

The same could be said also for scholarships focused on the experimental nature of molecular biology. For instance, Weber's *Philosophy of Experimental Biology* (2005) is centered on issues that "concern the ways in which scientific knowledge is structured, how it explains natural phenomena, how it is generated and evaluated, and how it connects to the world" (p 5). As in the 'build-it' test, the interest is directly in epistemic issues. Surely, 'models for' are important tools to devise experimental strategies which in turn will be used to explain other phenomena. But models as 'models for' are not interesting because they answer directly to epistemic problems. Rather, they inspire interventionist strategies that, *per se*, are not intended to show the causal relevance of the components of the model involved. While for some scholars successful and robust experimental use of entities (Hacking 1983) are intended to show that certain entities exist[5] and/or they are causally relevant, seeing models as 'models for' *assumes* that the components of the model are real.

Moreover, one may connect the idea of 'models for' to the rich discussion made by Rheinberger about experimental systems (understood as the phenomenon to explain and the material tools to constrain it) and practices of molecular biology (1997a; 1997b). Biologists reduce the epistemic complexity of biological phenomena (i.e. the fact that they have limited access to the phenomenon itself) by constraining and manipulating systems (both conceptually and materially) in various ways. For this reason, Rheinberger focuses his research on the details of epistemic and experimental practices. He also emphasizes different ways in which experimental systems *may be combined*. This sounds similar to the idea of 'models for', in the sense that we combine pieces of different models (or experimental systems, even though they are not exactly the same thing) in order to do something different from the aims of the contexts where the pieces have been extracted. However, in my understanding Rheinberger's descriptions of such combinations (i.e. *conjunctures*, *linkages* or *hybridizations*) focus especially on how the combination of techniques or concepts from different disciplines/communities leads to

[5] For the philosophy of biology, see in particular the project *From Biological Practice to Scientific Metaphysics* at http://biological-practice-to-metaphysics.org/

new concepts or new representations of a phenomenon. When 'models for' are concerned, my focus is directly related to what these models allow us *to do*, and only indirectly related to the epistemic consequences.

3 'MODELS FOR' AND THE DISCOVERY OF RESTRICTION-MODIFICATION SYSTEMS

The characteristics of good 'models for' will be further investigated by reconstructing an important episode of the history of biology. This is the characterization of restriction-modification systems of bacteria and their exploitation for developing various techniques widely used in molecular biology, (e.g. DNA cloning and mapping). This particular episode shows very well how the scientists' interest can shift to different aspects ('model of' and 'model for') of the same model.

3.1 Material access through restriction enzymes: a tale of three Noble Laureates

The *restriction-modification system* (RM-system) is a mechanism of defense of bacteria used against bacteriophages (i.e. a virus infecting and replicating in bacteria). Such a mechanism of defense works as follows (see Figure 2). First, a bacteriophage invades a bacterium (from now on, the host cell). Once this happens, the host cell stimulates the production of two types of enzymes. The first is called *restriction enzyme*. A restriction enzyme (type II[6]) cleaves DNA at specific sites. This means that it cuts only specific short sequences of DNA. Therefore, restriction enzymes 'recognize' DNA sequences of the invading entities, and by cleaving they block the invasion. However, a restriction enzyme does not distinguish between the DNA of the bacteriophage and the DNA of the host cell. Hence, restriction enzymes may also cleave the DNA of the host cell. For this reason, the host cell stimulates the production of another enzyme, called *modification enzyme*. This enzyme methylates the DNA of the host cell where the restriction enzyme would cleave. By doing that, the specific DNA locus of the host cell is not recognized by the restriction enzyme. Werner Arber, Hamilton Smith and Daniel Nathans were awarded

[6] There are at least five types of restriction enzymes. The most relevant here are Type II because they are the most commonly exploited

the Nobel Prize in 1978 for the characterization of this phenomenon and its exploitation. Yet, Arber and Smith on the one hand, and Nathans on the other were awarded the prize for different reasons, which in part reflect the distinction between 'models of' and 'models for'.

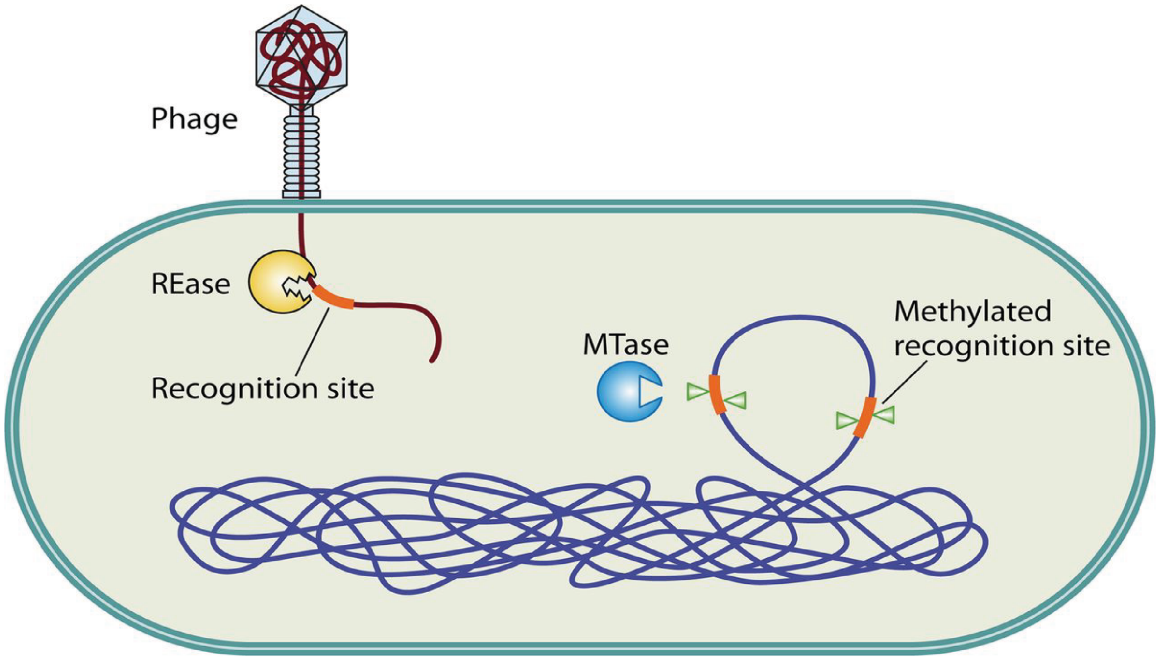

Figure 2. Mechanistic model of RM-system. Bacteriophage enters a bacterium cell. Specific sequences of its DNA are cleaved by restriction endonuclease/enzyme (REase). Simultaneously the modification endonuclease/enzyme (MTase) methylates a specific sequence in the DNA of host so that REase does not cleave the genome of the host too. Picture taken from Vasu and Nagaraja 2013.

The origin of the discovery of RM-systems lies in some studies in the 1950s showing that bacteriophages grown on one strain of bacteria could not grow similarly in others (Roberts 2005, p 5905). At first, this seemed to suggest that "the efficiency with which phage infected new bacterial hosts depended on the host on which they previously grew" (Loenen et al 2014, p 4). Therefore, the hypothesis was that certain abilities of bacteriophages – acquired by means of an unknown mechanism - created this difference.

Later, Arber accumulated enough evidence to support the idea that *host cells* were responsible for the curious phenomenon. Arber's lab proposed a new model to fully account for the mysterious phenomenon. He hypothesized that bacteria cells *must* contain two specific types of enzymes. The first (later identified as an endonuclease) has the function of cleaving specific sequences of DNA. The second (later identified as a methyltransferase) recognizes and modifies the same *specific* sequence on the host DNA

preventing its destruction by the restriction enzyme (Arber 1965)[7]. Arber proposed this mechanism as a sketch rather than a *schema* or as a *how-plausibly/actually* model because the two enzymes were only later isolated. Therefore, Arber's model is not a case of *abstraction*, because he failed to identify relevant components. If Arber had just elaborated a sketch, it is not clear why he was awarded the prize in the first place. The Nobel Academy said it was both for the discovery of restriction enzymes and because he "postulated that these enzymes bind to DNA at specific sites containing recurring structural elements made up of specific base-pair sequences (…) He proposed that DNA molecules contain specific sites with the capacity to bind both types of enzymes"[8]. However, this is imprecise. While he postulated the existence of restriction enzymes, he discovered in 1968 a specific restriction enzyme (i.e. *Eco*BI) that is not sequence-specific. This was in a sense a self-defeating discovery, because at first he postulated the existence of a specific type of entity with specific features, but later that entity turned out to have different properties. Therefore, the main reason why Arber was awarded was because he "had provided the theoretical framework that described the biology of restriction and modification" (Roberts 2005, p 5907). Since in 1978 The Nobel Academy decided to award the prize "for discoveries with far reaching consequences for genetics"[9], despite the 'black boxes' in Arber's model the importance of this work was apparent.

Hamilton Smith won the prize as well. Smith (Smith and Wilcox 1970) characterized and isolated the first sequence-specific restriction enzyme (a Type II restriction enzyme called *R endonuclease*) in the immune system of *Haemophilus Influenziae*, thereby filling a black box in Arber's model[10], and then *he moved to other research interests*. The Academy motivated the award by saying that Smith "verified Arber's hypothesis with a purified bacterial restriction enzyme and showed that this

[7] In (Arber 1965) methylation is proposed as "a likely basis for modification" (Gitschier 2014, p 4). In other articles before that, Arber hypothesized several other mechanisms for the modification part of RM-systems

[8] https://www.nobelprize.org/nobel_prizes/medicine/laureates/1978/press.html

[9] https://www.nobelprize.org/nobel_prizes/medicine/laureates/1978/press.html

[10] Another important black box was filled in 1972 by Kuhnlein and Arber himself when they isolated the first modification enzyme

enzyme cuts DNA in the middle of a specific symmetrical sequence"[11]. To use the mechanistic jargon, Smith improved Arber's sketch towards a how-actually model.

Nathans was awarded the prize for a work on RM-systems too, but not because he further improved the model by identifying other entities. Strictly speaking, Nathans did not discover anything. Rather, he used the model as inspiration to elaborate a technique to obtain the first 'physical' map of the DNA of a virus (Nathans and Danna 1971). The Academy drew a contrast between Arber and Smith on the one hand, and Nathans on the other. Nathans was not awarded for a discovery, but because he "pioneered the application of restriction enzymes to genetics (…) and developed and applied new methodology involving restriction enzymes to solve various problems in genetics"[12]. By Nathans's account, Arber's model suggested new interventionist strategies:

"From the incisive work of Arber and his colleagues (…) and the biochemical characterization of purified restriction enzymes by (…) Smith & Wilcox, it seemed likely (as first suggested by Arber) that restriction enzymes could be used to digest DNA molecules into specific fragments" (1978, 2)

Therefore, Arber's model has been used to develop new techniques to facilitate the manipulation of biological systems which are different from bacteriophages. Since restriction enzymes cut and paste at specific recognition sites, Nathans exploited this workflow "to cleave DNA from the SV40 virus into fragments, and thus make what would be later called 'a physical map' of the viral genome," (Morange 1998, p 187). Note that Nathans 'moved' restriction enzymes from the context of bacteria to the context of tumor viruses (i.e. SV40). If in the 'model of' the biological context is the bacteriophage's RM-system (i.e. the *explanandum*), in 'model for' the context is any system where the restriction enzyme could be used (in this case, tumor viruses). But 'repurposing' restriction enzymes in this way goes beyond tumor viruses. Weinberg (1985) stresses the usefulness of restriction enzymes in other contexts; they "establish convenient, fixed, landmarks along the otherwise featureless terrain of DNA molecules" (p 51). Restriction enzymes are used to cut *any* long DNA molecule into discrete

[11] https://www.nobelprize.org/nobel_prizes/medicine/laureates/1978/press.html
[12] https://www.nobelprize.org/nobel_prizes/medicine/laureates/1978/press.html

fragments, which are smaller and more amenable to be analyzed, and they have been used also to develop early sequencing technologies and techniques of gene cloning (Weinberg 1985).

3.2 RM-system model as a 'model for' and a 'model of'

Arber's model, understood as a 'model for', has been *repurposed* in a different biological context in order to manipulate other biological entities. Which are the features of RM-system model that made it a successful 'model for'?

The model of RM-systems was conceived and treated as a 'model of' both by Arber and Smith. Starting from Arber's sketch, biologists tried progressively to complete it in a way that could make sense of the phenomenon observed. As I have already noticed, the philosophical literature has a list of criteria that mechanistic models – conceived as 'models of' - should met to be good models. Let us see whether some of these virtues were embedded by Arber's model and whether they can explain why this model was successful as a 'model for'.

It seems to me that Arber's model originally was a paradigmatic case of an incomplete how-possibly model because the two most important entities (the restriction enzyme and the modification enzyme) were merely hypothesized. This is *not* abstraction, since the enzymes were causally relevant in Arber's interpretation of the phenomenon. Moreover, Arber speculated that restriction and modification enzymes had to be sequence-specific but the first restriction enzyme he isolated was not sequence-specific. Even when Smith isolated the sequence-specific endonuclease R, Arber's model remained largely incomplete, since evidence of the first 'modification' enzyme was reported only in 1972. To use mechanistic jargon, in 1971 – when Nathans exploited RM-system model – the RM-system model was just a *mechanism sketch*; it could not fully account for the phenomenon and most of its entities and activities were merely hypothesized. The idea, for instance, of the *3M constraint* and in general the fact that entities and activities must be real is not met. Hypothesized components are understood as being causally relevant, but establishing causal relevance requires that such components should be more than fictional. The only aspect that Arber (and Smith as well) correctly spelled out was the organization (i.e. the causal connectivity) between the

hypothesized key entities. However, understanding correctly the organization is not enough for a mechanistic model to be adequate and hence good 'models of' and 'models for' do not share necessarily the same features.

4. EPISTEMIC DISPOSITION AND DISPOSITION TOWARDS AFFORDANCES

Let me now turn again to the fact that the model is treated both as a 'model of' and 'a model for' by scientists (Evelyn Fox Keller in 2000 suggests a similar idea); it seems that *scientists themselves decide whether a model should count as a 'model of' or a 'model for'*. This can be explained by appealing to a sort of *cognitive disposition* of the scientist towards the use of the model. The disposition establishes whether we should focus on the explanatory force of the model or if components of the model should be 'repurposed' elsewhere. By 'cognitive disposition' I mean a tendency to look at and reason over things through a particular lens or from a specific angle. By 'reasoning over' I mean that these dispositions somehow *prescribe* the criteria employed to analyze and appraise the specific *analysandum* under scrutiny.

4.1 Two cognitive dispositions towards models

Smith treated Arber's model as a 'model of', and in that respect he aimed to complete the model by identifying specific enzymes postulated in the model. If we treat the model as a model *of a biological phenomenon*, then we look for specific features of the model and not others. I call the cognitive disposition of looking at models as 'models of phenomena' *epistemic disposition* because it focuses scientists' attention to matters of explanatory force or representational adequacy of a model with respect to the target system. Because of this disposition, the biologist will only ask specific questions such as "Does this model fully account for the phenomenon under scrutiny? Is this model explanatory?". Therefore, Smith looked at RM-system model as something lacking some important components that needed to be identified. In other words, he looked at Arber's model as something to be *improved* in its explanatory force. If we have to work on Arber's model from the standpoint of the epistemic disposition, we will ask fir whether that model meets Craver's criteria adequately.

By contrast, Nathans looked at Arber's model (improved by Smith) as a 'model for', trying to 'resituate' (Morgan 2014) some components into a different biological context to design a new experimental technique. Nathans treated this model and the kind of information embedded in it as a vehicle for potential material manipulations in other contexts.

Smith and Nathans had different interests. This is clear both from Nathans' Nobel Prize Lecture and other sources[13]. As a matter of fact, Nathans was not interested in bacteriophages *per se*, but rather he was interested in tumor viruses. In particular, while he was trying to understand "how to approach the genetics of SV40 in a sort of combined genetic and chemical way" (Schlesinger 1979), he received a letter from Smith about the restriction endonuclease in *Haemophilus Influenzae*. While Smith abandoned the topic of restriction enzymes, Nathans continued the research with a different spin, and he focused on how Arber's model and Smith's work could be used to study the DNA of SV40 (Brownlee 2005). This is looking at Arber's model as something to be 'repurposed' in another context. In particular, Nathans and one of his students assayed "the activity on SV40 DNA of various restriction enzymes" (Schlesinger 1979). Therefore, the appeal to 'cognitive dispositions' is supported by Nathans' account of the episode since it is Nathans' aims and intentions that had him to treat the model as a 'model for' and not necessarily some features of the model itself.

To qualify this further, Nathans looked at Arber's model from the standpoint of what I call *a disposition towards affordances*[14]. The idea of 'affordance' comes from psychology. It has been introduced by James Gibson and later popularized in the context of Human-Machine Interaction by Norman (1999). Though there is an evolution of the concept, here I will use just the basic meaning of the concept of 'affordance'. An affordance is a property of an object that suggests how to interact with or use that object. While for Gibson 'affordances' exist independently of the observer, the fact that they can be 'exploited' depends on the actor interacting with the environment. Models, when

[13] See in particular Schlesinger's interview to Nathans in 1979 at http://beckerexhibits.wustl.edu/oral/transcripts/nathans.html

[14] By drawing a distinction between the two different cognitive dispositions, I do not mean to say a biologist in his/her life cultivates either the one or the other. Actually, molecular biology curricula emphasize both aspects

considered as 'models for', may *afford* experimental strategies, but the fact that one can see them depends on whether she has the right disposition towards the model. In molecular biology, it is common to look for affordances in mechanistic models to solve experimental problems in a different context. Therefore, Nathans 'imagined' a component of Arber's model in a different biological context serving a different purpose than in the original context, i.e. to solve the problem of how to reduce the length of DNA strands in a controlled way. Through this disposition towards affordances, a scientist is not interested in whether a model accurately explains a phenomenon. Rather, this disposition sets scientists' focus on how we can use a part of a model to solve a problem raised in another context. It is important to stress this idea once more; it is up to human agency whether to treat a model as a 'model for' because nothing in the model *per se* discriminates between 'model of' and 'model for' (even though there are models that are better 'equipped' to be 'models for' or 'models of'). As I said, 'models of' and 'models for' are not two types of models, but rather *aspects* of the same model. It is in light of scientists' aims and interests that a model is treated in a way or another and the scientist can go back and forth depending on her interests and intentions. Moreover, we need the appeal to cognitive dispositions and intentions in order to make sense of the fact that resituating a model in a specific context rather than another is a function, again, of scientists' interests and intentions.

4.2 Intentions in philosophy of science and studies of scientific cognition

The appeal to (cognitive) dispositions or intentions and the inclusion of the agent in the equation of modelling are hardly new things (Giere 2004; Van Fraassen 2008). However, my impression is that some philosophers of science have for the most part only invoked – rather than analyzed in detail – the role of agents and intentions.

For instance, Giere (2004; 2010) focuses on the *activity* of representing. He says that the mere focus on the representation and the target system is not enough, because the activity is done by agents; "[s]ince scientists are *intentional* agents with goals and purposes, I propose explicitly to provide a space for purposes in my understanding of representational practices in science" (Giere 2004, p 743). His attention is on the purpose of learning something from models, and how models represent reality. My analysis

differs from Giere's in *at least* two respects. First, I provide a 'taxonomy' (though preliminary) of different types of 'intentions' within a specific scientific field. I show precisely how specific intentions/dispositions can make sense of different practices within the same discipline. Moreover, unlike in Giere's account, here I am not interested in explaining how models represent and how similarity should be understood, but rather in why and how mechanistic models are used in different ways.

Intentions and purposes make one important appearance in Weisberg's discussion of *similarity* (2013) as well. When one has to establish which features should be considered to measure similarity between a model and the target system, Weisberg says that we should make explicit modeler's *intended scope*. This is a mixture of intentions, purposes (e.g. research goals) and background theory. Weisberg's discussion of purposes is rich, and it is spelled out in terms of *representational ideals*, namely those goals governing modeling. However, intentions play only an indirect role, and in my understanding they are invoked to make sense of the claim that scientists choose among ideals. Here I am more explicit about the specific contribution of dispositions and intentions. Moreover, the intended scope and fidelity criteria Weisberg considers in modeling are related to what I call the *epistemic disposition*. This is clear from the components of representational ideals, namely inclusion rules and fidelity rules. These specify properties of the target system to include in the model, and the degrees of precision and accuracy used to judge the model, but only under similarity concerns which, in a sense, are typically concerns of the epistemic disposition. Weisberg's representational ideals are all related either to similarity or to explanatory purposes, while my interest, as I have emphasized, is not entirely in such goals.

Knuuttilla's works on models (2005; 2011) is relevant here. I am sympathetic with her emphasis on the multitude of activities on models *beyond* representation and the relation of 'model/target system'. However, we have different goals. Knuuttilla is interested in understanding the complex relation between intentionality and materiality in the diverse uses of models beyond the mere representational activities. While here I want to show how specific types of cognitive dispositions can make sense of the practices of a specific discipline, Knuuttilla is more focused – as far as I understand - in uncovering the

multiple relations between the medium of models and their intended uses and how one informs the other and *viceversa*.

I should also emphasize that studies of scientific cognitions can in principle shed light on some of the cognitive dynamics of 'models of' and 'models for' (Nersessian 2002). First, studies on scientific cognition are grounded in a problem-solving framework. Philosophical studies in molecular biology (Bechtel and Richardson 2010) assume that problem-solving is a fundamental way biologists reason. Next, I have interpreted Nathans' narrative of his work (but Kary Mullis' account of PCR might be interpreted similarly) as embedded in the 'mental modelling' framework (Nersessian 2002). Mental modelling based on the idea that "in many instances people reason by carrying out thought experiments on internal models" (p 139), and this is especially true for reasoning about causality in physical systems. It seems that when biologists treat models as 'models for' and they abstract components of a model and imagine them in another context, they exhibit several types of mental modelling types listed in cognitive science literature, such as analogical, visual and simulative modelling. Finally, studies of scientific cognition in biomedical engineering in particular (see for instance MacLeod and Nersessian 2013) have shown how scientists abstract and combine pieces of models to create new epistemic or material tools.

5. VIRTUES OF 'MODELS FOR'

Being a good 'model for' does not necessarily require Craver's epistemic virtues. However, this is just a negative characterization. Which are exactly the virtues of good 'models for'? Here I sketch a preliminary taxonomy of such virtues. Since I have emphasized that the unit of analysis is not only the model and the target system, but that also the 'modeler' plays a role, I first establish that there are two categories of virtues for 'models for'. First, there are virtues of models connecting the model to its target system, and next there are virtues connecting the model to the modeler.

5.1 'Models for', target systems and portability

In the case of 'models of', the target system is the phenomenon we want to explain. In the case of 'models for', the target system is the set of experimental systems where the dynamics described by the model can be successfully implemented.

When 'models for' and their target systems are concerned, an important virtue is what Floridi calls *portability* (2011; but see also Leonelli 2015). In a different context, Floridi defines *portability* "as to the ease with which a piece of software or a file format can be 'ported', i.e. made to run on a new platform and/or to compile with a new compiler" (2011, p 357)[15]. *Portability* here is the ease with which pieces of mechanistic models could be used and combined to solve problems in a different biological context. When one looks at Arber's model from the standpoint of the disposition towards affordances, one does not consider whether Arber's model scores high in Craver's virtues, but rather if some of its components could plausibly have interesting functions in other contexts or can be *implemented successfully* in a different context in order to supply a stimulus to the new target of study[16].

In order for a model to be portable, there are a few requirements that should be met. *First*, not the entire model must be portable. In fact, only a few components will do, but it is the entire model that is a model 'for' because the biologists think about resituating components by reasoning on the model *as a whole*, and by abstracting something *from it*. *A consequence* of this is that the components that we want to 'resituate' must be *real*. The whole model does not need to be 'complete' or 'how-actually', but specific components should be clearly identified. As I mentioned above, entity realism (in the sense of components of the model corresponding to real entities in the world) in 'models for' is not the aim, but it is an assumption. We do not manipulate entities for the purpose of showing that they are real, but we use such entities in another context *under the assumption* that they are real. Nathans was not in the position to treat

[15] Floridi's context is the evaluation of ontologies. A portable ontology is one that could be made 'run' in many possible worlds.

[16] Something akin to 'portability' may work also for 'model of', though it has a different function, and it has a different name. A 'models of' is highly portable if it can capture the dynamics of several target systems. This has been called *schema*, and portability in such a context has been also named *generality*, namely "the number of (…) target a particular model applies to" (Weisberg 2013, p 109)

Arber's model as a 'model for' until Smith filled a black-box in Arber's model with the identification of the restriction enzyme. In CRISPR-Cas9 model there is 'something' that cleaves DNA and it is guided in an effective way, but unless we identify this 'something' as a RNA guided by a specific protein, we would not be able to use it in another biological context because we would not know what to use. *Moreover*, while not all the components must be real, still the organization of the model must be correctly spelled out. This is because knowing the type of causal relevance that a component has for a phenomenon can give us an idea of whether such role can be fulfilled in another context. In the case of restriction enzymes and crRNAs, their function is to cut DNA and it seems that they do selectively not necessarily because of the specific organization of the mechanism embedded in the *explanandum*; this suggests that they can be easily resituate elsewhere to do the same thing (even though for a different purpose). *Relatedly*, the components of the original target system that correspond to the components in the model have to fulfill the intended activities in the new context. For instance, imagine that the single RNA-guided Cas9 could work *only* in the context of bacteria and archaea. Even though the model of CRISPR-Cas9 suggests new strategies of genome editing, the fact that such components do not do the same thing in other contexts (notably eukaryotes) would make the model way less portable. Therefore, the real components and activities that we select should be able to fulfill the same (or a similar) function in many other contexts[17]. *Finally*, the components of the model we want to resituate must be *accessible*. This is because the interventions we are interested in must be *actual*. If a component is not accessible, it cannot be resituate elsewhere. The more a model is portable in the way I described, the more the model is a better 'model for'.

An example of high degree of portability is the class of models of DNA replication and synthesis. A component of such class of models that has a history of successes in being 'repurposed' is DNA polymerase. This enzyme is essential for DNA replication because it can synthetize molecules of DNA from deoxyribonucleotides. DNA polymerase performs its function across many contexts, and this is why its properties may be exploited virtually anywhere. The component 'DNA polymerase' is *highly portable* because the enzyme has been 'identified' (i.e. it is real), it is required anytime there is cell

[17] Being a portable model is not a yes-or-no quality; being portable is a matter of degree

division (i.e. it is compatible with almost every experimental system biologists use) and it is accessible. Arthur Kornberg identified the enzyme in the 1950s. Among the other applications, DNA polymerase has been 'repurposed' by Kary Mullis to develop the so-called polymerase chain reaction (PCR) (Rabinow 1996). Mullis in the 1980s was working for Cetus Corporation to develop an efficient technique to isolate and identify a specific sequence of DNA. PCR can amplify a targeted DNA molecule over several orders of magnitude, and this can aid the analysis of a targeted molecule. What has been 'ported' of the model of DNA polymerase is its capacity to synthesize DNA molecules; in Mullis' own words "I did not see why one could not use the enzyme DNA polymerase" (1990, p 57). Interestingly, Mullis presented the protocol to Lederberg in 1984, and Lederberg admitted that Kornberg and he "had considered the notion that the enzyme could somehow be harnessed to make large quantities of DNA. They had not figured out exactly how to do it, however" (Mullis 1990, p 65). In other words, the issue is how to control certain components and their function in another context, and this was most of Mullis' work. To generalize this point, the important thing about 'resituating' is to be able to control the activity of a component in a novel context.

5.2 How-possibly models and schemas

Affordances suggested by models may be difficult to see. However, sometimes models have some characteristics that facilitate the detection of affordances. These characteristics, though not necessary for good 'models for', are *helpful to modelers*.

One of these is being a *'how-possibly' model*, strange as this may sound since the received view is that being 'how-possibly' is actually a deficiency of models[18] (Craver and Darden 2013). However, a 'how-actually' model is so replete with details that is very difficult for the biologist to mentally abstract some of its parts and to resituate them in other contexts. Therefore, a 'how-possibly' model affords better (if, of course, it is

[18] Again, the way I understand here how-possibly models is not related to abstraction (Levy and Bechtel 2013; Levy 2014). For instance, Arber - to use Craver's jargon -, had no idea if the "conjectured' parts" (2006, p 6) like the enzymes exist. A how-possibly model is a model that depict the organizational structure of a phenomenon, but it fails to identify some relevant components. This is not the same as in abstraction, where relevant features are identified

portable[19]) than a 'how-actually' model because it easier to decontextualize. *This is true under the condition emphasized above that even if the model is 'how-possibly' still the component to resituate must be real*. Also, this does *not* mean that good 'models for' are necessarily 'how-possibly' model. Being 'how-possibly' is simply a characteristic of the model that help the modeler to see the affordances, *if there are* affordances. However, whether the model is a good 'model for' *will depend on portability*, and whether a model is portable will depend on the nature of the components of the model.

Something similar may be said about *schemas* (i.e. *abstract descriptions* of mechanisms that can apply across several contexts). The case of schemas make even more sense if we look at the literature on how scientific knowledge is transferred from one context to another. For instance, Morgan (2014) describes several ways of 'resituating knowledge' to different contexts. In particular, when resituating is from local-to-many, modelers have first to desituate "local findings into a somewhat broader level (above local but less than general), which can then be available for resituation in another local level" (p 1014). To see whether something can work in a different context, we have to abstract or decontextualize it from its local context; at a more general level 'pieces' of mechanistic models are less constrained by the locality of the models themselves.

CONCLUSION

Sometimes molecular biologists exploit knowledge of phenomena for experimental purposes. In this contribution, I tried to make sense of this by developing Keller's distinction between 'models of' and 'models for'. 'Models of (phenomena)' should be understood as models representing phenomena, while 'models for (manipulating phenomena)' are models that suggest new types of material manipulations and experimental strategies. The aim of the article was to identify the differences between 'model of' and 'model for' and in particular to provide a preliminary characterization of the characteristics that make a model a good 'model for'. However, a study combining

[19] This means that how-possibly models are *not* necessarily more portable. Facilitating affordances and portability are *not* connected

the perspectives of philosophy of science in practice, studies of scientific cognition and history of molecular biology will be fundamental to enrich the picture I proposed.

By analyzing the history of the characterization of restriction-modification systems, I claimed that whether a model is treated as a 'model of' or a 'model for' will depend on a scientist's *cognitive dispositions* towards the model. A modeler will look at a model in the sense of a 'model of' if he/she is interested in the explanatory force of the model (i.e. epistemic disposition), or as a 'model for' if the interest lies on model's affordances for manipulative strategies (i.e. disposition towards affordances). Such dispositions 'prescribe' the way the model would be treated and evaluated.

Virtues of models as 'models of' in molecular biology have been extensively characterized. On the contrary, the characterization of models from the standpoint of the *disposition towards affordances* has been elusive. For this reason, in the last section I have identified an important virtue of 'models for'. This is called *portability*, namely the ease with which components of mechanistic models could be used and combined to solve problems in a different experimental system. Finally, I have also noticed that if a model is a 'how-possibly' model or a schema, then it is easier to resituate elsewhere, though under the assumption that it is portable.

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