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Models, theory structure and mechanisms in biochemistry: The case of allosterism☆

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ABSTRACT

From the perspective of the new mechanistic philosophy, it has been argued that explanatory causal mechanisms in some special sciences such as biochemistry and neurobiology cannot be captured by any useful notion of theory, or at least by any standard notion. The goal of this paper is to show that a model-theoretic notion of theory, and in particular the structuralist notion of a theory-net already applied to other unified explanatory theories, adequately suits the MWC allosteric mechanism explanatory set-up. We also argue, *contra* some mechanistic claims questioning the use of laws in biological explanations, that the theory reconstructed in this way essentially contains non-accidental regularities that qualify as laws, and that taking into account these lawful components, it is possible to explicate the unified character of the theory. Finally, we argue that, contrary to what some mechanists also claim, functional explanations that do not fully specify the mechanistic structure are not defective or incomplete in any relevant sense, and that functional components are perfectly explanatory. The conclusion is that, as some authors have emphasized in other fields (Walmsley 2008), particular elements of traditional approaches do not contradict but rather complement the new mechanist philosophy, and taken together they may offer a more complete understanding of special sciences and the variety of explanations they provide.

1. Introduction

Mechanicism is commonly regarded as a version of causalism that is particularly relevant in some special sciences, in particular in molecular biology, biochemistry and neuroscience, in which the notion of explanatory mechanism proves especially useful and is widely used. Although mechanicism is not a homogeneous program, and authors diverge in some relevant respects (cf. e.g., Machamer, Darden & Craver (henceforth, MDC) 2000; Bechtel & Abrahamsen, 2005; and Craver, 2007a for a survey), the main representatives of the new mechanistic philosophy share certain tenets with regard to theorization, explanation and lawfulness. In this paper, we focus on two families of questions. On the one hand, some mechanists claim that in these fields the talk of theories, and laws, is inappropriate, unnatural, or useless (cf. Craver & Darden, 2005; Machamer, Darden, & Craver, 2000), while others defend that one can legitimately talk of theories but that no standard notion of 'theory', either in the Received View or in semantic approaches, is of useful application (Craver, 2001). On the other hand, regarding functions, mechanisms and explanation, some relevant mechanists claim, mainly referring to biochemistry, that mechanistic explanations are fully causal, and that functional explanations that are not fully mechanistically specified are somehow "defective" (provisional, incomplete, elliptical) (Craver, 2006, 2007a,b, 2008; Piccinini & Craver, 2011).

We take as our main case study the Monod-Wyman-Changeux theory of allosterism (MWC), formulated in clearly mechanistic language by the authors themselves, who talk of the "allosteric mechanism" (Monod, Wyman, & Changeux, 1965, p. 103). Although we acknowledge that mechanist philosophers are right in emphasizing that in special sciences most scientists invoke mechanisms

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when they intend to explain a phenomenon (Machamer et al., 2000; Bechtel & Abrahamsen, 2005; Kaplan & Craver, 2011 [1]), we argue, *contra* some of their additional claims mentioned above, in favor of the following four claims. (a) The MWC explanatory set-up can properly be regarded and reconstructed as a theory in a strong sense; more specifically, as a unified net-like theory structurally similar to, yet simpler than, other highly unified explanatory theories such as Classical Mechanics (CM), Phenomenological Thermodynamics or Classical Genetics. (b) The notion of theory applicable here belongs to the semantic or model-theoretic family; more specifically, it is the one explicated by Sneedian structuralism. (c) MWC essentially contains modal, nomological components that can properly be considered law-like in a relevant, though minimal, sense of lawhood. (d) The non-fully mechanistic, functional components are perfectly explanatory, according to a plausible notion of explanation.

In section 2 we introduce the discussion on the use of the notion of theory in molecular biology and biochemistry, and what we take to be the main issues of the debate. In section 3 we introduce the relevant notion of theory at stake; namely, the structuralist notion of *theory-net*. In section 4 we offer a brief historical and conceptual presentation of MWC and informally reconstruct its models and its structure. In section 5, we discuss the relation between theories, laws, mechanisms and functional components in MWC explanations. We conclude by summarizing our main claims and their significance for the debate.

2. Theories and mechanisms

MDC have questioned whether the/any notion of theory is of useful application for many mechanistic explanatory practices, in particular in brain and molecular sciences:

> There are several virtues of the causal-mechanical approach to understanding scientific explanation in molecular biology. For one, it is truest to molecular biologists' own language when engaging in biological explanation. Molecular biologists rarely describe their practice and achievements as the development of new *theories*; rather, they describe their practice and achievements as the elucidation of molecular *mechanisms* (Darden & Tabery 2009, Section 3.2, referring to Machamer et al., 2000; Craver, 2001).

It must be stressed that Craver accepts that a certain broad notion of theory is applicable across all disciplines and that it is useful for understanding scientific practice. However, he doubts that the two dominant accounts of theories, the syntactic or axiomatic and the semantic or model-theoretic accounts, provide any useful notion of theory of general application—and much less so in mechanistic theories (Craver, 2001, p. 55). Here, when Craver refers to "the two dominant philosophical analyses of theories", he is thinking of what he calls the ORV (syntactic) and the MM (semantic) views, and it must be emphasized that, regarding the latter, he only takes into account Suppe's analysis. Craver does not deny that there is a general notion of theory that is applicable, but he confines it to what he calls the *formal aspects/patterns*. Although he does not specify what he understands by 'formal' here, the passage seems to imply that most of the important issues are neglected or excluded.

We think that Craver is right in saying that there are important aspects of theories that cannot be expressed by any (general) notion of theory on the market. For example, the mechanistic (or non-mechanistic) nature of a theory cannot be expressed by any (general) notion of theory; nor can whether a theory is, or is not, causal; or whether it is, or is not, materialist; and so forth. But the problem is not to do with formal *vs* non-formal aspects, but with generality. No *general* notion of theory, already current or forthcoming, can express these facts. If the notion is really general, it should apply to both mechanistic and (if there are any) non-mechanistic theories; to both causal and (if there are any) non-causal theories; to both materialist and (if there are any) non-materialist theories.

We acknowledge that these are very important aspects to be discovered about theories, and thereby agree that there are important features (besides their specific content) that deserve philosophical attention and that have not yet been explicated by a general notion of theory. Such aspects are the subject for other, more restricted notions that apply only to a specific family of theories. For instance, unless one could conceptually exclude the existence of non-mechanistic theories, no *completely general* concept of theory could express the mechanistic aspects. And we know that Craver, and mechanists in general, do not believe that non-mechanistic theories are conceptually impossible (unless we trivialize the notion of mechanism). Nonetheless, we believe that this fact does not imply that a general notion of theory is of little interest in molecular biology, biochemistry and neuroscience—the paradigmatically mechanistic scientific fields. Thus, although it is of great importance to emphasize the relevance of the study of mechanistic aspects in many fields (and mechanist philosophers deserve recognition in this regard), there may be other aspects, even in mechanistic theories, that are more general and of equal or complementary importance. We believe that these other aspects deserve to be analyzed by applying a broader concept of theory.

At this point, especially in these pluralistic times, a mechanist may disagree and claim that there is no general notion of theory that is *both* applicable *and* of interest regarding mechanistic theories. Of course this is true if our interest is confined to the mechanistic aspects of mechanistic theories. But we believe that mechanistic theories involve other non-mechanistic aspects, which are of philosophical interest as well; and that the general Sneedian structuralist concept of *theory-net*, is useful for the analysis of such aspects, or at least of some of them. The following are just three examples of relevant issues concerning which, such a concept has proven fruitful.

- The net-like structure of a theory-net, with its top, essential components and bottom, modifiable ones, is crucial for the understanding of important features related to theory-testing and theory-change emphasized by philosophers and historians of science such as Kuhn and Lakatos, and thus for clarifying whether, or in what sense, theory-nets are falsifiable (Díez, 2007; Kuhn, 1976).
- The distinction between T-theoretical and T-non-theoretical concepts for theory T is essential for responding to some unacceptable versions of theory-ladenness: T-data are T-non-theoretically identified, so they may be theory loaded by another theory, T^*, but never by the same theory, T, in which they behave as the basis for testing (Balzer, Moulines, & Sneed, 1987).
- The hierarchized structure of nomological constraints, introduced in the notion of theory-net, is also useful for clarifying the unified nature of some theories and the related part of the

[1] For example, here the authors claim that Hodgkin and Huxley's (1952) equations do not explain how voltage changes the membrane conductance since the mechanism is not fully specified: "The explanation required the idea of a voltage-sensitive, membrane-spanning channel, which only came dimly into view in the 1970s and 1980s." (Kaplan & Craver, 2011).

debate on the existence of laws in biology (Balzer & Lorenzano, 2000; Díez and Lorenzano 2015).

We thus claim that there already exists a notion of theory that may be found in the current metascientific literature that is both applicable in biology and biochemistry, and that explicates *some* relevant features of MWC that the mechanistic approach (other merits notwithstanding) does not. So now, we first introduce the relevant notion of theory at stake, namely the structuralist notion of *theory*-net, and then we apply it to our mechanistic case study: MWC.

3. Unified theories as theory-nets

The notion of theory we refer to goes back at least to Kuhn and his concept of paradigm (or better: disciplinary matrix). Commenting on his notions of symbolic generalizations (i.e., laws) and exemplars/applications (explananda phenomena), Kuhn introduces a key difference between general or schematic generalizations and specific laws which is essential in unified theories concerning different kinds of phenomena that are all considered explananda of the same theory. Accordingly, in highly unified and developed theories such as CM, there are some generalizations that are not "specific laws", but rather "schemes" that take specific forms for specific problems/applications:

> "generalizations [like $f = ma$ …] are not so much generalizations as generalization-sketches, schematic forms whose detailed symbolic expression varies from one application to the next. For the problem of free fall, $f = ma$ becomes $mg = md^2s/dt^2$. For the simple pendulum, it becomes $mg\ sen\ \alpha = -md^2s/dt^2$. For coupled harmonic oscillators it becomes two equations, the first of which may be written $m_1d^2s_1/dt^2 + k_1s_1 = k_2(d+s_2-s_1)$. More interesting mechanical problems, for example the motion of a gyroscope, would display still greater disparity between $f = ma$ and the actual symbolic generalization to which logic and mathematics are applied." (Kuhn, 1970, p. 465)

This Kuhnian idea has been elaborated in detail by Sneedian structuralism (initiated in Sneed, 1971; canonically presented in Balzer et al., 1987) with the notions of *specialization* and *theory-net*. It has been applied to several sufficiently robust and unified theories in the physical, biological and social sciences, such as CM (Balzer & Moulines, 1981), Phenomenological Thermodynamics (Moulines, 1975) Classical Genetics (Balzer & Lorenzano, 2000), Natural Selection (Ginnobili, 2012; Díez & Lorenzano 2013; 2015) and others (see Balzer et al., 1987 for references to other case studies). For instance, (at a certain historical moment) the CM theory-net appears as follows (only some terminal nodes, and in a simplified version, are shown here, but it suffices for our present exemplification concerns). The theory-net of CM has CMGP, Newton's Second Law, as the top unifying nomic component, and spreads down into different branches for different phenomena/explananda. The branches can be reconstructed in different steps: first, space-dependent forces versus velocity-dependent ones; then the space-dependent branch becomes specialized into direct and indirect space-dependent; the direct space-dependent branch in turn into linear negative space-dependent etc.; the inverse space-dependent branch becomes specialized into square inverse, etc.; finally, at the bottom of every branch we have a totally specific law that is the version of the guiding principle for a specific phenomenon: pendula, gravitation, inclined planes, etc. (Kuhn's "detailed symbolic expressions") (Fig. 1).

Note that the top-to-bottom relation is not one of implication or derivation, but of *specialization* in the structuralist sense (Balzer et al., 1987; ch. IV): lower laws are specific versions of higher ones, i.e., they specify some functional dependences that are left partially open in the laws above them in the branch.

It is worth emphasizing that the difference between top general guiding principles and the other laws has epistemic import. Top general principles cannot be empirically tested "in isolation"; they can be tested, and eventually falsified, only through one of their specific versions for a specific phenomenon. In this sense, guiding principles are "programmatic" or heuristic: they tell us the kind of things we should look for when we want to explain a specific phenomenon, and they provide the unifying nomological factor. But taken in isolation, without their specializations (something that rarely happens in real science), empirically they say very little. When considered alone, they can be regarded as "empirically non-restricted".[2] This peculiar epistemic status of general guiding principles has the consequence that, after a failed prediction, one *may* change the general principle but one can also try to fix the anomaly by modifying only the specific law. A succession of different theory-nets preserving at least the top theory-element constitutes the evolution of a single theory over time (Kuhn's normal science).

When the scientific community changes the top element, we cannot continue speaking of the same theory (Kuhn's revolutions). This picture, elaborated with a high degree of formal precision by the structuralist program, has been acknowledged by Kuhn (1976, 2000) as the best way of putting forward his informal ideas, and by other philosophers (e.g., Cartwright, 2008) as the most fruitful and complete analysis of the structure of scientific theories. We argue that this analysis is also useful to clarify some issues in particular fields such as MWC.

We do not need to enter into all the formal structuralist apparatus in detail here. For our present concerns, the previous and following informal characterizations will suffice. Explananda phenomena are the empirical systems that the theory aims to account for. The identification of explananda does not need or presuppose the theoretical laws or principles introduced by the theory. The relevant structuralist notion here is that of T-theoreticity (related to other more informal, similar notions, e.g., Lewis's (1970) difference between "old" and "new" vocabulary, and Hempel's (1973) division between "characteristic" and "antecedently understood" terms): a T-term (i.e., one used in T-laws) is T-theoretical if every determination of its (qualitative/quantitative) extension presupposes some T-law; a term is T-non-theoretical otherwise, i.e., if it can be determined (at least on some occasions) without presupposing T-laws. Thus, for instance, in CM "mass" and "force" (and other properties defined from them such as "pressure", "momentum", etc.) are CM-theoretical, as their measurement always presupposes some mechanical law or other (e.g., unless we presuppose that the arm-balance satisfies the momentum law, we cannot tell that we are measuring mass), while "space" and "time" are CM-non-theoretical, as, although they are sometimes measured using mechanical laws (e.g., when we calculate space from mass, force and time in a mechanical law), they can be measured independently (e.g., by triangulation).

In order to account for its explananda (e.g., a planetary trajectory in CM), an explanatory theory introduces T-theoretical terms (e.g., mass and force in CM) and postulates non-accidental connections between these theoretical terms and the T-non-theoretical ones mentioned above (e.g., mechanical laws in CM). Structures with the appropriate logical type, which corresponds to T-

[2] This term is Moulines' (1984); Kuhn uses 'quasi analytic' (Kuhn, 1976).

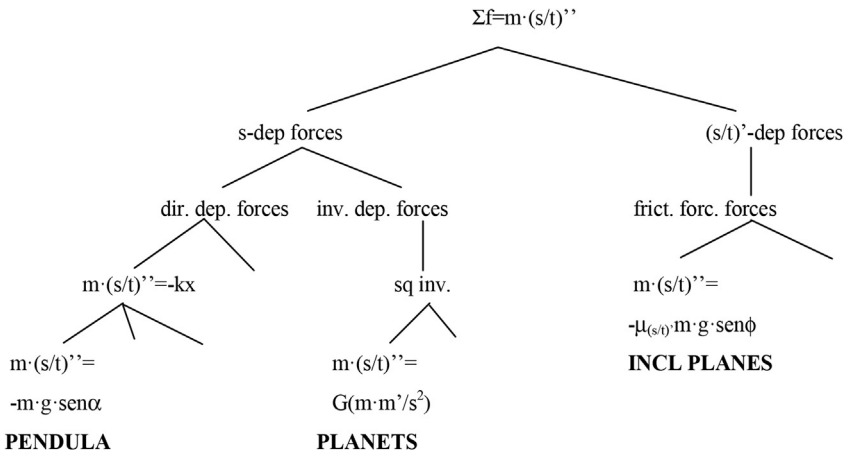

Fig. 1. (Part of) The theory-net of Classical Mechanics.

theoretical plus T-non-theoretical vocabulary, are the *potential models*, i.e., the structures for which to ask whether they satisfy the T-laws makes sense. The potential models that actually satisfy T-laws are the *actual models* of the theory. As noted above, in unified theories, not all nomological generalizations are of the same degree; they are structured in different, hierarchical levels conforming a theory-net with a general, schematic guiding principle at the top. The theory explains a particular phenomenon when the data-model, i.e., the T-non-theoretical description of the phenomenon, is predicted by/embedded in a theoretical structure that is an actual model in a bottom terminal node of the theory-net (e.g., when a CM theory-net has a terminal node with a theoretical actual model whose T-non-theoretical part, i.e., whose empirical prediction, coincides—modulo a certain admissible degree of approximation—with the measured trajectory of the planet).

We can now proceed to show that MWC has the kind of net-like structure that we have seen is characteristic to unified theories.

4. The Monod-Wyman-Changeux theory

4.1. The allosteric mechanism

MWC focuses on a particular regulation of biochemical activity: *allosteric regulation* or, as the authors themselves call it, the "allosteric mechanism" (Monod et al., 1965, p. 103). Jacques Monod came to consider allosteric regulation to be the *second secret of life* on realizing that their innovative hypothesis about protein functioning could explain a complex variety of metabolic pathways, such as hormone action, gene repression and enzyme kinetics, among others. Mechanists have characterized the theory as follows: "The theory of allosteric regulation explains the characteristic pattern of activity (the function) of certain proteins by a specific and reversible sequence of structural change." (Darden & Maull, 1977, p. 59).

Research on protein activity started at the beginning of the 20th century. Many enzyme proteins (the majority of those known up to the 1960s) present a pattern of activity that increases with the amount of substrate up to a certain value, and then remains constant, showing a dose–response curve ('dose' being the amount of substrate, and 'response' the activity measured) with a hyperbolic[3] profile (Fig. 2, grey curve). However, not all proteins present this activity profile; others show sigmoidal dose-response curves (Fig. 2, black curve).

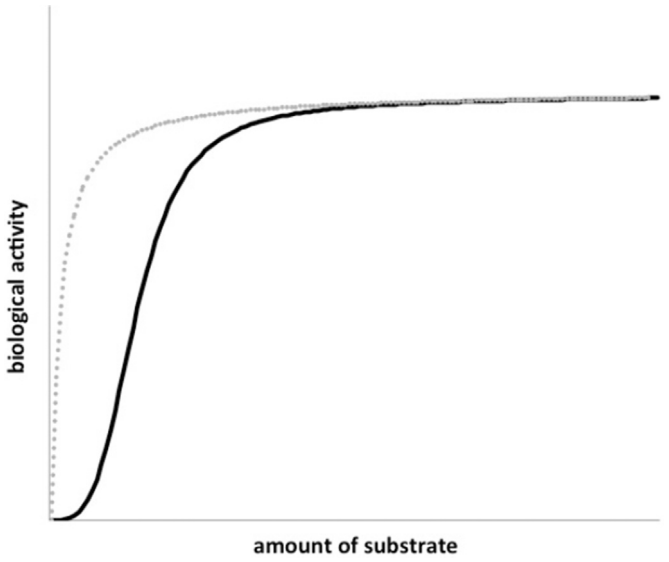

Fig. 2. The figure shows both a hyperbolic profile of biological activity (grey dotted line) and a sigmoidal profile (black continuous line).

As early as 1910, biochemists started proposing different explanations of the sigmoidal behavior (cf. Bindslev, 2008); but it was not until the 1960s that a successful attempt was proposed—MWC theory, which relates the biological response to modifications in the spatial structure, i.e., the conformation, of the protein. The MWC proposal was developed with the aim of explaining how enzyme activity curves with sigmoidal responses might be the consequence of conformational modifications of this kind.

The term 'allosteric'[4] was coined to denote global changes, or allosteric transitions, in protein conformation (Monod & Jacob, 1961; Monod et al., 1965). Interestingly, MWC was initially constructed mainly for enzymes and hemoglobin, but today, other important biological proteins such as transmembrane receptors,

[3] This pattern is known as Michaelis-Menten activity, and the enzymes that behave in this way are called Michaelian enzymes.

[4] The impact of MWC theory was so great that the term 'allosteric' is today polysemic: it is used to denominate different kinds of interaction between a protein with biological activity and its ligands, often named "allosterics" in a loose sense (cf. Bindslev, 2008).

membrane channels and transporters also fall under the scope of MWC. Despite the fact that other theories have been developed to account for some aspects of protein functioning that MWC does not explain, MWC is still a fruitful theoretical proposal that continues to show its resilience in the light of new experimental results (Cui & Karplus, 2008; Viappiani et al., 2014).

As we noted above, the core idea of MWC is that the change in biological activity is due to the changes in the conformation of the protein: proteins have "parts" that may be in different "conformational states" which vary their "affinity" for different substances. These explanatory components obey certain nomological connections that, as a consequence, have the observed patterns of activity. Let us look at this explanatory model in more detail.

MWC introduces the notion of *allostery* to account for the molecular mechanism of changes in biological activity of certain proteins in the presence of different molecules that can be bound by them: *ligands*. The proteins relevant for MWC are *oligomeric* proteins, that is, proteins formed of sub-units. Each sub-unit is named a *protomer*, while the complete protein receives the name of *oligomer*. Each protomer presents "places" or "holes", technically, *sites*, where the ligands can be chemically bound. Ligands can be either substrates of those proteins or modulators (activators or inhibitors) of protein activity; activators increase protein activity, whereas inhibitors decrease protein functionality. MWC aims to account *only* for the variations in activity correlated with the binding of certain substances at protomer binding sites. That is, it does not aim to account for changes in activity due to conditions other than binding, nor for binding with substances that do not affect activity.

MWC postulates the existence of two different conformational states for oligomers with internal symmetry, i.e., there are two possible spatial structures for each oligomeric protein, each one with different biological activity: the tense state (T), with low affinity for substrates and low biological activity, and the relax state (R), with high affinity for substrates and high biological activity (Fig. 3). The symmetry condition implies that all protomers of an oligomer are always in the same conformational state. The theory establishes that an oligomer is in state R or T when all its protomers are in state R or T, respectively. In the absence of a ligand, and only in this case, an oligomer can change its conformational state from R to T, and vice versa; and oligomers in R and T conformational states co-exist in equilibrium when no ligand is present. This equilibrium, called *allosteric transition*, implies that: (i) oligomers are continuously changing from the T state to the R state, and vice versa; but (ii) the ratio between the oligomers in states T and R remains constant. The value of this ratio, a chemical equilibrium constant, receives the name of *allosteric constant* (ι_0) and characterizes each group of oligomers in certain conditions.

The binding of a ligand to the protomers of an oligomer in a certain (R/T) conformational state is the result of a chemical equilibrium, and the constants that correspond to such equilibria are called *microscopic dissociation constants*. Since a ligand molecule binds to a protomer in an oligomer, these microscopic dissociation constants are the parameters that represent the protomer affinity for the ligand in each conformational state. It is important to stress that an oligomer to which a ligand is bound no longer participates in allosteric transition.

The main aspects of MWC are sketched in Fig. 4, in which an allosteric protein is represented with its substrate.

It is important to state that different types of binding situations correspond to different types of activity curves, i.e., to different explananda.[5] The theory then explains these different correlations between changes in ligand binding and changes in activity, roughly by attributing two different "conformational states" to oligomers in which they may have more or less "affinity" for ligands, and postulating some nomological connections between conformational states, affinities, binding states and activity.

Now we can show that the MWC explanatory set-up has the characteristic structure of unified explanatory theories that can be reconstructed as a unified theory-net, with a structure similar to, yet simpler than, other unified theories such as CM, Thermodynamics Classical Genetics and others.

4.2. MWC models and theory-net

In MWC, the T-non-theoretical data models are constituted primarily of "oligomers" (O), each of which is possibly "combined" or bound (β) to one or more "ligands" (substrate, S; activator, A; or inhibitor, I) and shows a certain degree of "activity" (δ) (the kind of activity changes according to the kind of oligomer) which evolves over time (T) as its bonds (σ) with the ligands change. The combining occurs at each of the "binding sites" (ρ) located in the protomer units that constitute the oligomer.

All these MWC-non-theoretical components can be determined independently of the laws of the theory. Of course, this does not mean independently of *any* theory: for example, protomers are identifiable within the theory of the chemical structure of molecules, which involves many highly theoretical principles; but although it is T'-theoretical (for some other theory, T′), the notion of protomer is not MWC-theoretical. This is not a specific, rare case: the same happens in many other fields where a T-non-theoretical term is T'-theoretical relative to another theory T' (for instance, pressure is CM-theoretical but Thermodynamics-non-theoretical). The same happens with other MWC-non-theoretical concepts: clearly with activity δ, but also with bound states, identifiable in structural chemistry, and also activators and inhibitors whose identification as such depends on whether they bind at protomer sites and whether they correlate with increases or decreases in activity. MWC explananda, i.e., MWC-non-theoretical data models whose behavior MWC aims to account for, are then structures of the following type:

$$< O, S, A, I, T, \rho, \beta, \sigma, \delta >$$

These explananda can be graphically summarized in activity curves, with activity on one axis and quantity of substrate on the other (see Fig. 2). These curves may show different type-profiles, which are the explananda that MWC tries to account for. In order to do so, the theory introduces new concepts and some nomological connections, or laws, linking MWC-empirical and MWC-theoretical concepts/entities in different ways. The first MWC-theoretical notion is that of *conformational state*, i.e., the τ (tensed) or r (relaxed) state in which each of the protomers of an oligomer is at a certain moment T, so that a conformational state function (ζ) can be assigned to the oligomer as a unit. Another MWC-theoretical notion is the *dissociation constant* (κ), which represents the affinity of the oligomer for each ligand.

[5] MWC was developed to explain the biological activity of proteins; in fact it does not exactly predict biological activity, but two parameters related to it in some way: the saturation function ($\overline{Y_i}$) and the state function ($\overline{R}$). MWC assumes that biological activity can be qualitatively linked to the saturation function. We (and other authors: cf. Bindslev, 2008) consider that the state function is better suited for representing the biological activity of oligomers (reference suppressed for blind refereeing). It is possible that Monod and coworkers did not consider the state function as preferable in relation to biological activity, since the allosteric systems that they intended to explain at that moment were mainly enzymes and hemoglobin. Today, it has been proved that other oligomeric proteins, such as channels, are also potential applications of MWC, and capturing differences in terms of their biological activity requires use of the state function to represent biological activity.

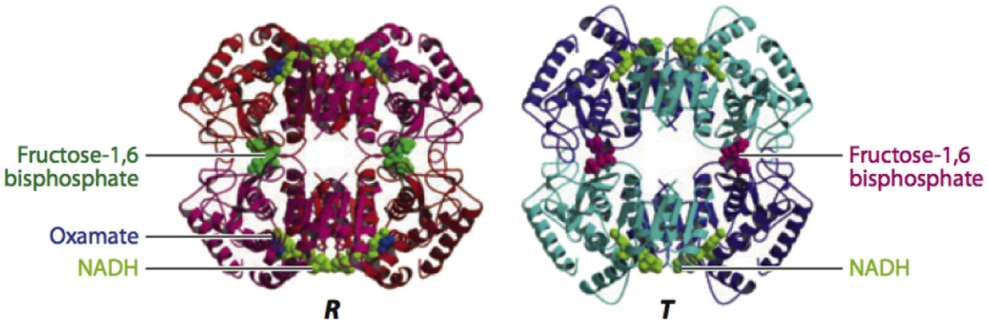

Fig. 3. Example of a specific oligomer in tense/relaxed states. The figure shows the allosteric transition captured by X-ray crystallography of L-lactate dehydrogenase. It must be stressed that at the moment the theory was postulated, these crystallographic data were not available. Adapted from Iwata et al. (1994).

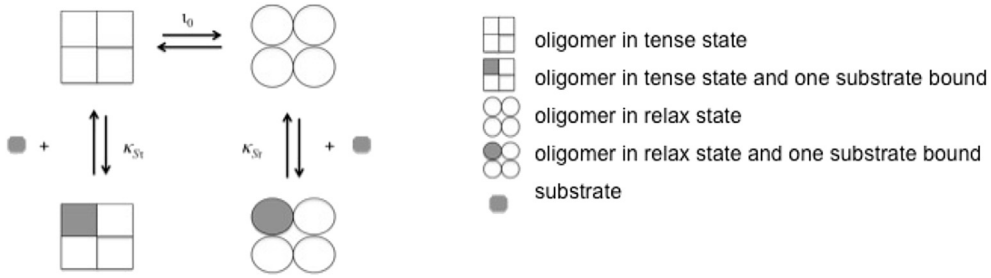

Fig. 4. In this figure, the allosteric transition and ligand binding equilibria are represented for an oligomer with four protomers. The squares denote the protomers in T states, while circles represent protomers in R states. In the upper part, the (ligand-free) oligomer equilibrium between T and R conformations governed by the allosteric constant (ι_0) is shown. The figure also shows the equilibria of oligomers in T and R conformations with substrates; these equilibria are governed by the corresponding constants (κ_{St}, κ_{Sr}). In this case, only one substrate is bound to the oligomer, but of course subsequent equilibria (not shown here) can complete the binding of further substrate molecules to all four protomers.

Thus, MWC theoretical models (including both MWC-theoretical and MWC-non-theoretical constituents) are of the form:

$< O, S, A, I, T, \{\tau, r\}, \rho, \beta, \sigma, \delta, \zeta, \kappa_S, \kappa_A, \kappa_I >$

The theory successfully explains its explananda if, according to the theoretical laws that it postulates, the models that satisfy these laws "coincide" with data, i.e., there are MWC-actual models (i.e., that satisfy MWC-laws) whose MWC-non-theoretical sub-model coincides (modulo admissible approximations) with the data model. This corresponds to the theory succeeding in theoretically explaining the data.

As in many other unified theories, as we saw, not all MWC nomological constraints have the same scope. Some of them are *general* in that they apply to all intended systems/explananda. Some others are *special* in that they apply only to specific systems/explananda.

The first general nomological constraint states that if, at a certain moment, the oligomer is in a certain conformational state and its combinatorial state is "unbound" (i.e., with all its protomers "empty"), then at the next moment it changes its conformational state if and only if it remains unbound; in other words, if at two subsequent moments the oligomer is bound (even if in different ways) then it does not change its conformational state. Thus, binding "fixes" conformational states in the sense that as long as oligomers "remain bound" (to ligands at protomers) they do not change their conformational state. The second general law states that *the proportion* of oligomers in each conformational state is the same at two different moments if and only if all oligomers at these times are unbound/empty (represented by L_0). Finally, the third general law connects chemical activity with conformational and bound states. It states, roughly, that at every moment, the degree of chemical activity "qualitatively" coincides with the proportion of bound oligomers (in either conformational state) over the total population. With these restrictions, the activity is given (where '$\varepsilon\psi_t$' is the normalized concentration of ligand Ψ, i.e., the number of binding sites in the oligomer bound to the ligand in the @ conformation at moment t divided by the dissociation constant κ for that conformation and ligand) by:

$$\delta(t) = \frac{l_0 \frac{(1+\varepsilon_{Itt})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}} \varepsilon_{S\tau t}(1+\varepsilon_{S\tau t})^{\rho_0{}^{-1}} + (\varepsilon_{S\tau t})(1+\varepsilon_{S\tau t})^{\rho_0{}^{-1}}}{l_0 \frac{(1+\varepsilon_{Itt})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}} (1+\varepsilon_{S\tau t})^{\rho_0} + (1+\varepsilon_{S\tau t})^{\rho_0}}$$

These three laws apply to all systems.[6] Yet they alone do not suffice for the explanation; they must be combined with other specific constraints for specific kinds of systems. Which special constraints apply depends on:

(a) The kind of interaction between the protomers of an oligomer, which can be of two different types: (i) non-cooperative (i.e., Michaelis-Menten); or (ii) cooperative (i.e., allosteric).
(b) The kind of ligand that binds to the oligomer: (i) a "homotropic effect", occurs as a result of the binding of similar ligands (substrate); (ii) a "non-cooperative heterotropic effect", results from the interaction (binding) between different ligands, substrate and activator; and (iii) a

[6] Actually, in Monod's theory there is a further condition that applies to all systems: that there is non-zero activity only in the presence of a substrate. Yet, since later on systems were discovered that exhibit spontaneous activity at initial stages, in the absence of a substrate (e.g. channels), we do not include it as a general law; it is a theorem of every specialization in which whenever activity is non-null, a substrate is present.

"cooperative heterotropic effect", which is a result of the interaction (binding) of different ligands, substrate and inhibitor.

Let us see the specializations they give rise to in turn.

(ai) Michaelis-Menten systems (MMs), Special Law 1

The constraint here specifies that the affinities for ligands are the same in both conformational states, and there are far fewer unbound oligomers in state τ than in state *r* before the addition of substrate. With these additional constraints, it follows that the biological activity δ has the form of the General Law 1 in (Monod et al., 1965, p. 92) for MMs,

$$\delta(t) = \frac{\varepsilon_{Srt}}{1+\varepsilon_{Srt}}$$

and the biological activity profile is that previously shown in Fig. 2 (grey dotted line).

(aii) Allosteric systems (ALs), Special Law 2

In this case, there are more unbound oligomers in state τ than in state *r* before the addition of substrate, and the affinity for the substrate is much higher in *r* than in τ.

With these restrictions, the activity is given by:

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1+\varepsilon_{S\tau t})^{\rho_0{}^{-1}}}{l_0\frac{(1+\varepsilon_{Irt})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}}(1+\varepsilon_{S\tau t})^{\rho_0}+(1+\varepsilon_{S\tau t})^{\rho_0}}$$

which corresponds to sigmoidal curves in Monod et al., 1965, p. 93 (Fig. 2, black continuous line), where the greater the difference in affinities, the more sigmoidal the curve.

ALs may satisfy additional constraints, depending on whether the substrate is the only ligand or is bound together with activators or inhibitors. We then have the following three allosteric subsystems.

(bi) Homotropic systems (HOs), Special Law 3

These systems satisfy Special Law 2 and other constraints which state that no oligomer is bound to activators or inhibitors at any protomer. The activity is given by:

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1+\varepsilon_{Srt})^{\rho_0{}^{-1}}}{l_0+(1+\varepsilon_{Srt})^{\rho_0}}$$

(bii) Non-cooperative heterotropic systems (NCHEs), Special Law 4

These systems also satisfy Special Law 2, but instead of Special Law 3, they satisfy a different constraint: oligomers are bound to activators in addition to the substrate, the affinity for the activator is much higher in *r* than in τ. In these cases, the implied activity is:

(biii) Cooperative heterotropic systems (CHE), Special Law 5

In these systems the oligomer is bound to inhibitors, in addition to the substrate, and the affinity for inhibitors is much lower in *r* than in τ. In these systems the activity is:

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1+\varepsilon_{Srt})^{\rho_0{}^{-1}}}{l_0\frac{1}{(1+\varepsilon_{Art})^{\rho_0}}+(1+\varepsilon_{Srt})^{\rho_0}}$$

The different possible profiles of biological activity that emerge for each situation are shown in Fig. 5:

We can summarize the explanatory structure of MWC with Fig. 6, which has the typical tree-like theory-net structure of unified explanatory theories, showing general explanatory principles applicable to all systems and special explanatory constraints applicable to specific cases.

5. Discussion

The first issue we need to address is whether the mechanists are right when they claim that the old approach in the philosophy of science, in terms of laws and formal theoretical structures, should be replaced by an account that emphasizes "the material structures that scientists endeavor to describe" (Craver & Kaiser, 2013, p. 143). Our answer, in a nutshell, is: *yes* and *no*. *Yes*, since the mechanistic account highlights specific features that are essential for a proper understanding of the many biological and biochemical theories. *No*,

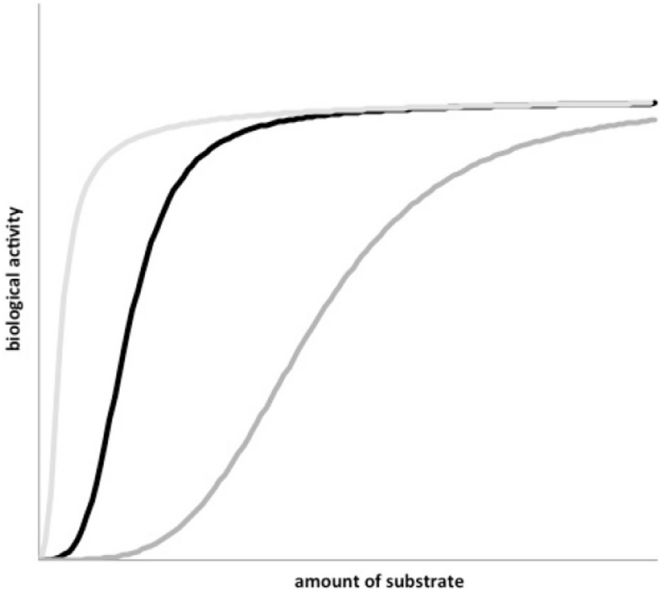

Fig. 5. The figure schematically shows three possible biological activity profiles: in light grey, the non-cooperative heterotropic (NCHE) effect; in black, the homotropic effect (HO); and in dark grey, the cooperative heterotropic (CHE) effect.

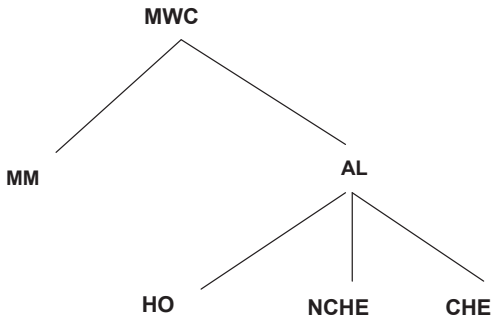

Fig. 6. MWC theory-net tree. MM: Michaelis-Menten systems, AL: allosteric systems, HO: homotropic systems, NCHE: non-cooperative heterotropic systems, CHE: cooperative heterotropic systems.

if what they claim is that more traditional, formal notions of theoretical structures have nothing important to contribute to our best understanding of theoretical endeavors in such fields. Our claim is that the two approaches are complementary, and that there is at least one formal notion of theory on the market that sheds light on some important features of theories such as MWC.

We think that the informal reconstruction we have presented suffices to show that the notion of theory-net, broadly applicable across different fields to highly unified explanatory set-ups, also applies in biological sciences—not only in "macro-biology" (e.g., Natural Selection, Mendelian Genetics, etc.) but also in biochemistry and molecular biology, as the MWC case demonstrates. MWC possesses the main traits that highly unified theories such as CM, Thermodynamics, or Natural Selection have: a hierarchized structure with a general guiding principle at the top that becomes specialized as we move downwards in different branches, ending in bottom elements that explain different, yet similar, phenomena.

Thus, if within the semantic family one includes, as one should, Sneedian structuralism, Craver's quoted above, claiming that no semantic notion of theory is both applicable and useful, is at least highly controversial, as the foregoing reconstruction shows. At this point, one might complain that we are simply artificially applying the extremely flexible notion of theory-net to MWC, a notion that may be accommodated to any theoretical constructs and thus lacks any real explicatory power.[7] A complete defense of the non-triviality of the notion of theory-net is beyond the limits of this paper (see Balzer et al., 1987 for a detailed exposition and defense), but the following clarification may help for our present concerns. On the one hand, it is true that the notion is flexible enough to apply to any *unified* theory, in the above Kuhnian sense. It is a *general* notion that explicates key features of unified theories, thus as flexible as needed. What else can a general notion be? If this were a defect of general notions, there could not be non-defective general notions in meta-theoretical analysis. On the other hand, however, it does trivially apply to any theoretical construct or web of beliefs. It applies to *unified* constructs: theoretical systems such as CM, Thermodynamics, Classical Genetics, Natural Selection Adaptationism and MWC (see Balzer et al., 1987; for some examples). It does not apply to "disconnected" explanatory webs in a field. Certainly, when a theoretical discipline reaches a sufficient degree of complexity and fruitfulness, it is highly unlikely to remain disconnected and sooner or later will unify explanatory principles that were previously isolated. But the non-unified period may last for quite some time. For instance, thermodynamics was a set of relatively independent theoretical practices until Gibbs' work allowed for the unification of some of the preexistent principles, laws and generalizations (Moulines, 2013. Of course, unification is a matter of degree, and the resulting theory-nets may then be more or less complex. Moreover, since it is a matter of degree, there may be ways of trivializing it and applying it to degenerate cases, such as Galilean kinematics, where it does not seem possible to find any interesting net-like structure. But a trivial application of a notion is not a problem for the notion, but for that application. Our claim is that this notion can be interestingly applied to MWC, as we think the informal reconstruction of the MWC net above demonstrates. It is not as complex a net as that of CM, but still non-trivial, and we believe it is useful to shed light on the relations between different MWC theoretical principles/laws/regularities and different MWC explanatory models.

Starting with lawhoodness, there is an important debate as to whether the notion of law can be usefully applied in biochemistry, molecular biology, neuroscience and other mechanistic disciplines. In their influential work, MDC question the utility of the notion of law in these fields:

> The traditional notion of a universal law of nature has few, if any, applications in neurobiology or molecular biology. Sometimes the regularities of activities can be described by laws. Sometimes they cannot. For example, Ohm's law is used to describe aspects of the activities in the mechanisms of neurotransmission. There is no law that describes the regularities of protein binding to regions of DNA. (Machamer et al., 2000, p. 7).

Similar claims have been made by other mechanist philosophers (cf. Glennan, 1996, 2002, 2005; Bechtel & Abrahamsen, 2005; Craver 2007a,b.; also cf. Leuridan, 2010; Craver & Kaiser, 2013 for more recent debate). Note that MDC start the passage quoted above by talking of the notion of *universal* law. There is a strong tradition against the existence of laws in biology (cf. e.g., Beatty, 1995; Rosenberg, 2001; Smart, 1963), and following this line, mechanisms furnish additional examples. Yet, the main arguments are based on the failure of this universality, and also of exceptionlessness; for in biology, regularities are not universal and exceptionless, but domain-restricted and have exceptions. Yet even in physics it is hardly the case that laws are always universal and exceptionless (Dorato, 2005). In the philosophy of biology, but also in philosophy of physics, many philosophers have proposed a weaker, and more realistic notion that does not require regularities to be universal and exceptionless in order to qualify as laws (e.g., Carrier, 1995; Mitchell, 1997, p. 200; Lange, 1999; Dorato, 2005, 2012; Craver & Kaiser, 2013).

With regard to mechanists, even if in general they question the notion of law *as traditionally conceived*, many accept that mechanisms essentially involve *non-accidental generalizations* (no matter how domain-restricted) (e.g. Bechtel, 2011; Craver & Kaiser, 2013; Glennan, 1996; Machamer et al., 2000). Thus, terminological issues aside, it is uncontroversial that mechanistic explanations make essential reference to non-accidental regularities. To us, this is the essential feature of lawhoodness, but we do not want to argue this here. It suffices that mechanists themselves seem to agree that generality (even if domain-restricted and with exceptions) and non-accidentality are also central in mechanistic explanations. And these traits are also present in our reconstruction of MWC. The authors of MWC themselves eventually use the word 'law' to refer to some components of the specializations explained above, for instance: "most real systems will exhibit appreciable deviations from the theoretical function, as indeed is very often the case for the much simpler Michaelis-Henri saturation *law*" (Monod et al., 1965, p. 24, our emphasis). But we do not think we need to rely on such terminological practices (that we acknowledge as infrequent in the MWC literature) to defend the idea that there is a minimal, but relevant, notion of law as non-accidental, counterfactual-supporting regularity applicable in biology in general, and in MWC in particular; and that our reconstruction identifies the presence of them and their relations in the MWC theory-net.

Of course, the non-accidental, modal nature of the regularities that define MWC theoretical models at various levels of the theory-net is not *formulated* in the net. But theory-nets, *all of them*, must be understood as imposing series of hierarchized *modal, non-accidental* constraints on the *potential models* in order to become *actual models* (the whole difference between potential models and actual models is the difference between conceptual and nomological modalities). Given our terminological preferences, we referred above to these constraints as *laws*, but we could have talked simply of a net of non-accidental general constraints instead; nothing essential hinges on this. And the reconstruction also shows that, in

[7] We thank an anonymous reviewer for raising this criticism.

sufficiently interesting theories, these non-accidental constraints are structured in a hierarchy. Not all constraints have the same force: some are designed to apply to any intended application of the theory; others are designed to apply only to specific subtypes. We do not claim that in all mechanistic explanatory set-ups one can find this unified, hierarchized structure of non-accidental regularities, but our example shows at least that relevant mechanistic explanatory set-ups may have this nomologically hierarchical structure (characteristic of highly unified theories). We grant that there are less systematic mechanistic explanations to which this net-like structure does not apply, but the same happens in non-mechanistic cases. Thus, contrary to MDC and other mechanist philosophers, we think there is a pretty clear and useful notion of law present in biochemistry, as our reconstruction of MWC shows.[8]

This last point is important, as it shows a sense in which the reference to laws in MWC (and other unified theories in special sciences) is essential in order to account for the unified nature of the theory, i.e., to explicate what different explanatory models have in common. In our reconstruction, this is explicated by the specialized hierarchy of laws (if you prefer, of non-accidental constraints): some apply to all models, some are specific of certian models. We think that the reference to mechanistic aspects, important as it is for explicating other features, is of little use here: if we specify the mechanisms in all allosteric systems sufficiently, we find different mechanisms for the same MWC model (e.g., the heterotropic branch above); but if we do not specify all the way down and stop at an abstract mechanistic description, then the same abstract mechanistic description applies to different MWC explanatory models that differ in the modal regularity that specializes the general top common laws. The *lac operon* mechanism proposed by Monod and Jacob (the aforementioned regularities of protein binding to regions of DNA) is a case in point, described by the MWC explanatory model: when allolactose is present (the inhibitor), it binds to the lac repressor (a tetramer), causing an allosteric change in its shape; in its changed state, the lac repressor is unable to bind tightly to its cognate operator.

We thus believe that such analysis of the outcomes of scientific research in terms of the Kuhnian-structuralist notion of theory-net, serves to explicate some relevant features that cannot be accounted for in terms of mechanisms. That is, in order to capture the similarities and differences between different MWC models presented in the literature as different δ values, we need to refer to the hierarchy of nomological constraints that makes the nomological dimension of the allosteric explanation explicit.[9] We think that this hierarchical analysis of the nomological structure of unified theories contributes to a better understanding of their explanatory role, and that it is different from, and complementary to, the aspects highlighted by mechanistic analysis.

At this point some might argue that certain mechanists also acknowledge and emphasize a similar hierarchical structure at the level of mechanisms. Craver, for instance, clearly refer to "levels of mechanisms" in contemporary cognitive neuroscience:

> The top level is a mechanism as a whole engaged in a spatial memory task, such as learning to run efficiently through a maze. One component in that mechanism, and so one level down in this description, is the hippocampus, a region of the brain thought to form a "map" of locations and orientations within the maze. The capacity of the hippocampus to acquire such an internal map of local spaces is thought to be explained, in part, by changes in synapses between pyramidal cells, specifically by a process known as Long-Term Potentiation (LTP). And it is now known that n-methyl D-aspartate (NMDA) receptors (n-methyl D-aspartate is a pharmacological agonist that binds these receptors preferentially), contribute to LTP. This story could continue downward, looking into aspects of protein chemistry and the structural changes thought to underlie channel functioning. (Craver, 2015, p. 17).

Important as these levels of mechanisms might be for a mechanistic analysis, it is worth emphasizing that such a hierarchy of mechanisms, when it exists, is totally different from and independent of the hierarchy of nomological constraints represented by our theory-net. As this quote shows, "levels of mechanisms" refer to the levels of organization of matter (atoms, molecules, organelles, cells, tissues, organs, etc.) at which mechanisms operate. In contrast, the nomological levels in a theory-net such as that we present here for MWC, refer to levels of generality among the set of nomological constraints that apply to theoretical models: more general at the top, more specific at bottom. These two hierarchies and levels of organization are of a completely different natures. The different levels in a theory-net structure are not such that posterior levels refer to entities that are made of entities referred to by the corresponding previous level. That is, specification of mechanistic levels is "materially compositional" in the sense of indicating how certain entities in a mechanism are "materially made of" some other, more basic entities. Meanwhile, specification of nomological levels has conceptually nothing to do with material composition. In order to demonstrate the conceptual difference, it suffices to show that the different nomological constraints that apply at different levels in a theory-net apply, as in MWC, to the same kind of materially organized entities. This is clearly so since different laws at different levels of a theory-net can apply to the same set of models/structures that represent the material organization in reality.[10] Thus, the nomological hierarchy in a theory-net is radically different from, and not reducible to, an alleged compositional hierarchy of mechanistic organization.

With regard to the importance of laws themselves in mechanisms, however, we think that the difference, at least with respect to some mechanists, may ultimately be a matter of emphasis and not of principle. Responding to Leuridan (2010), who argues that models of mechanisms must incorporate regularities and that, actually, mechanists mention regularities either explicitly or implicitly, Craver & Kaiser reply, appealing to a defense of their program as a "gestalt-shift":

> Against this backdrop, mechanists should be read as suggesting something of a gestalt-shift in which mechanisms are moved into the foreground. Such a shift leads attention away from the formal structure of scientific theories (and questions about the logical structure of law statements and models) and toward the

[8] Of course, our notion is as clear as the notion of "non-accidental, counterfactual-supporting (domain-restricted, non-exceptionless) regularity" is. All these concepts are philosophically intriguing and need further explication, but what we have said suffices for our present concerns (an exhaustive explication is beyond the limits of this paper; but see Mitchell's (1997, 2000) pragmatic approach for an account of lawhoodness that we are sympathetic to).

[9] This sense of unification is inter-modelic: it explicates what different models have in common. It is thus different from that analyzed in Fagan (2012), whose jointness/unificationist proposal is intra-modelic: it analyses the sense in which different parts of a mechanism work together.

[10] This is *compatible* with the possible existence of unified theories with some specialization in the theory-net introducing a specification of the organizational structure of some constituent of the potential models; but we do not know of any such case and, more importantly, this would not undermine the conceptual difference mentioned here at all.

> material structures that scientists endeavor to describe. Attention to such material structures provides resources for thinking about how generalizations and mechanisms are discovered, evaluated, and extrapolated and into how such concepts are deployed in explanation, prediction, and control. The perceived need to defend laws, no matter how much they have been weakened and stripped of their once robust metaphysical content, reflects a conservative refusal to acknowledge that perhaps the philosophy of science might benefit from coming at its subject matter from a fresh perspective. Mechanists decenter laws in their thinking about science because the old paradigm, centering laws, has become mired in debates that are inconsequential and, as a result, have stopped generating new questions and producing new results (Craver & Kaiser, 2013, p. 143).

We agree that this mechanistic gestalt has been extremely beneficial to our better understanding of most scientific practice in biology and neuroscience. But this does not imply that at least some notions of the pre-mechanistic era are of no interest at all. Different explicanda deserve different analytical tools; so we maintain that there should not be conflict here, but a division of labor. Conservatism should not be a problem *per se*, at least not in epistemology; and conservative or not, we think that our reconstruction shows that the net-like notion of a theory, and the broad notion of law associated with it as non-accidental generalizations, and structured in unified theories in a hierarchized theory-net, explicate *some* important features of scientific explanatory practice, including in biological sciences. To repeat: not all the important features are explicated in this way; there are many others (of equal, or if you like more, importance) with regard to which our analysis remains silent. To understand those other aspects, the mechanistic analysis is, needless to say, of great importance. This ecumenical attitude is not a tactical move, we certainly believe that different explicanda deserve different conceptual tools and that a division of labor in epistemology, as in the rest of philosophy as well as in the sciences, is the correct methodology.

The net-like structure brings us to our final point, namely, whether mechanisms, as described in mechanistic explanations, are "fully mechanistic" or may rather include components that are functional and play an essential role in the explanation without specifying their particular mechanistic realizers. We believe that the latter is the case, and that our allosteric mechanistic explanations are a case in point. The allosteric mechanism has several components that are mechanistically specified, such as the "holes" in protomers that may or may not be bound to certain substances (ligands). Some mechanistic elements are often not completely mechanistically specified, and are thus described partially functionally and are multiply realizable[11] (for instance, the same allosteric models, e.g., the "heterotropic allosteric" branch above applies to a materially/causally very varied kind of systems: enzymes, hemoglobin, membrane channels and receptors). Nevertheless, their mechanistic character is, despite their level of abstraction, unquestioned. Yet, they may also involve other elements that are essential for the explanatory power, whose mechanistic nature is not clear at all and which are better described in purely functional terms. The affinity of protomers for ligands in MWC explanatory models is a case in point. We believe that such functional components are widespread in biological explanations, including mechanistic ones. And we note that in cases such as the one we mention, *affinity* is not simply a functional/abstract characterization of a mechanistic element that could eventually be made mechanistically more concrete. *Affinities* are purely dispositional/functional; and despite this, they do not seem to make allosteric models non-explanatory.

Craver considers that functional explanations are sketches of mechanistic explanations, and in so being they are defective, incomplete or elliptical explanations (Piccinini & Craver, 2011, p. 284, p. 298). It then seems that according to these mechanists, functional models are somehow explanatorily defective, or at least "in need" of mechanistic specification.[12] For the above-mentioned reasons, we disagree. Both functional components, those derived from the abstract level of description (e.g. holes in oligomers bound to ligands) and those that are essentially functional (e.g. affinities), are perfectly fine as they are. It is true that we might know something more with regard to the former, for instance when we know that the same "heterotropic allosteric" model is multiply realized by enzymes, hemoglobin, membrane channels or receptors (Fig. 7); but this does not make the explanatory import of the abstract/functional level defective. Quite the contrary, in MWC the explanatory import is due to what all these different realizers have in common: what the heterotropic allosteric model specifies. And if we focus in the differences between the realizers, we lose the MWC explanatory power.

Granting that in some cases abstract description may be provisional and call for mechanistically better specified models, we claim this is not *always* the case: abstraction, functionality and multiple realizability may be explanatory essential, even in mechanistic explanations in biological sciences. Aizawa (2007) has emphasized the importance of the multiple realizability of mechanisms, even at the molecular level. According to him, the biochemistry of memory consolidation provides empirical evidence regarding the non-unique physicochemical realizations of cognitive processes such as memory consolidation. And it is well known in biochemistry that proteins constituting one biochemical pathway or one biological mechanism consist of distinct sequences of amino acids in each species, or even in different organs in the same organism. In our case, it is worth noting that sodium channels differ in terms of their amino acid composition, and their allosteric characteristic can be conserved in the mechanisms in which they are involved.

In scientifically interesting cases such as MWC, mechanisms that are multiply realizable are the norm rather than the exception.

We believe that the moral is that mechanisms are specified mechanistically *and* functionally, i.e., they are functionally described, in terms of their nomological behavior, as in MWC. So the functional description of the mechanism, like that of the channel mentioned above, is the norm, not the exception. We further claim that *contra* what Craver seems to suggest, functionality is not in tension with mechanicism, but usually the opposite: it is the way in which sufficiently interesting mechanisms are described. Mechanistic descriptions that are not multiply realizable have a very narrow scope and are very rare, even in microbiology; it is more usual to find mechanistic theories with a trade-off between specificity and generality: two explanatory virtues that a good mechanistic explanation must balance (cf. Barberis, 2013 for a discussion of these two virtues in neuroscience).

[11] Kaplan and Craver (2011) acknowledge multiple realizability in mechanistic models, though they add that, from a realist perspective, it is descriptions of mechanisms (that may be more or less abstract) which are multiply realizable, not mechanisms "themselves" in the world, which are not. We do not emphasize this distinction here as we think nothing that is essential to our point hinges on it (our discussion aims to be orthogonal to the realist debate).

[12] Craver also claims that mechanistic models "allow for idealization and abstraction" (Kaplan & Craver, 2011). If abstraction amounts to functionality, then functional parts in mechanistic descriptions would be (genuinely?) allowed; the question then being in what sense are they sketchy, incomplete or elliptical?.

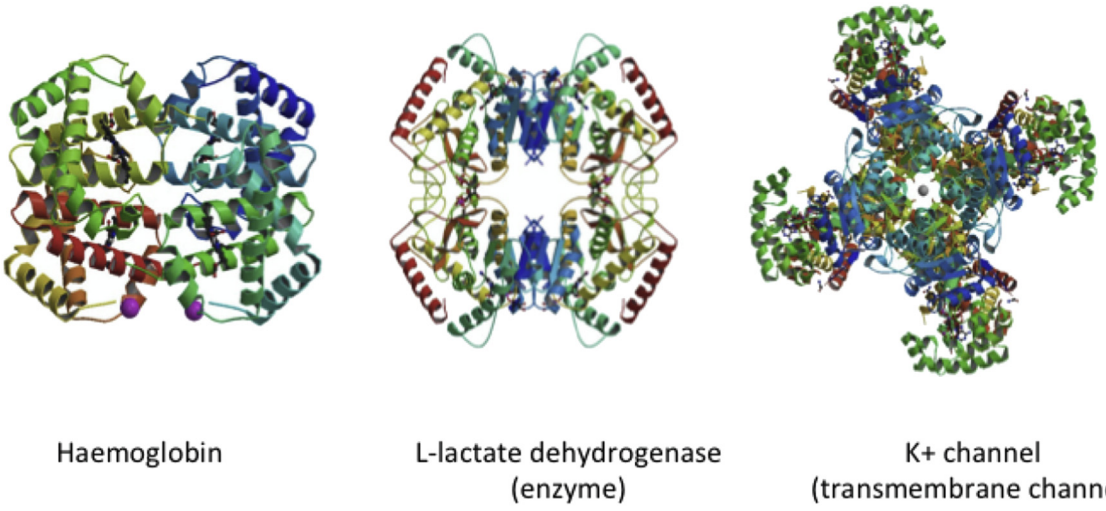

Fig. 7. MWC bottom specializations (HO, NCHE, CHE) apply to materially/causally very different kinds of systems, such as hemoglobin, enzymes, and membrane channels. The structures shown correspond to 2HHB (hemoglobin), 1LTH (L-lactate dehydrogenase) and 2A79 (K^+ channel) from the Protein Data Bank.

Moreover, it could happen that even within special sciences *some* explanations are merely functional, not mechanistic. No matter how important mechanistic explanations are in fields like biochemistry and neuroscience, we do not think that in those fields non-mechanistic explanations are conceptually impossible or should be conceptually excluded. In discussing dynamical and mathematical models in neuroscience, Kaplan and Craver (2011) claim that since they do not want to be imperialistic, they allow for non-mechanistic explanations in other fields, but neuroscience "is a domain in which the demands of mechanistic explanation ought to be met" (612), thus making non-mechanistic explanations in neuroscience conceptually redundant. We do not see why. In fact, there seem actually to be some cases of such a non-mechanistic kind in physiology and neuroscience: Harman's free radicals theory of ageing (Harman, 1956), Anderson's ACT-R theory of declarative memory (Anderson, 1983), or (more controversially) the Hodgkin-Huxley model of neuron action potential, accepted as explanatory by Weber (2008), refuted by Craver (2006, 2007a,b, 2008; Kaplan & Craver, 2011).

It is worth emphasizing that we do not refer to merely descriptive models: those that simply provide a general description of a phenomenon. We agree with Kaplan and Craver (2011) that mere descriptive models/regularities, no matter how general and systematic, do not explain. In discussing the explanatory import of dynamical and mathematical models[13] (a kind of functional models) in neuroscience, they claim that phenomenal models "describe the phenomenon [, t]hey do not explain" (616); and in virtue of this they qualify as non-explanatory the Haken-Keslo-Bunz model of bimanual coordination, the difference-of-Gaussians visual spatial receptive-field organization model, and the Hodking-Huxley model of the action potential mentioned above. As we have just said, we agree that merely descriptive models are not explanatory, and we also agree with the diagnosis with respect to the first two models Kaplan and Craver mention. But we think that the Hodking-Huxley case is more controversial, for it is arguable that it does not merely describe the change in action potential across membranes, but also introduces membrane conductance as functionally responsible for action potential changes. Whether the model is explanatory depends on what the explanandum is taken to be. If the explanandum is how membranes change their conductance, the model is uncontroversially non-explanatory, for it says nothing about that (in fact, Hodking and Huxley actually posited "activation particles"; but Kaplan and Craver, p. 609, are right in considering this just a "filler term" with no explanatory import). But if the explanandum is why potential changes, we believe that the model provides "some" explanation, namely, that conductances change in such a way and they are related to potentials in a specific manner.

The difference between merely descriptive and explanatory models is not specific of neuroscience, or other special sciences: it is widespread in all disciplines. In physics, for instance, Galilean kinematics and Keplerian astronomy are merely descriptive; while Newton, or Einstein, mechanics are explanatory (with respect to the same phenomena, e.g. free fall or Uranus' orbit). Kaplan and Craver draw the divide between merely descriptive and explanatory models in the causal component of the latter, implemented in neuroscience (and presumably in other special sciences) in a mechanistic manner. Since they are not imperialistic, they allow for non-mechanistic explanatory models in other domains. This restricted scope makes their claims more moderate, but it also leaves some questions unanswered. They claim that the "signature of a phenomenal model is that it describes the behavior of the target system without describing how the mechanism underlying that behavior works" (p. 608). As a general claim this cannot be true, for Newton is explanatory and there is no underlying mechanism, for instance, in his theory of gravitation (on pain of trivializing the notion of mechanism). It probably needs to be read as referring only to neuroscience; but then we remain ignorant about these differences in other domains such as physics. Kaplan and Craver also claim that there is an essential connection between explanation and control: "this connection between explanation and control might help to explain why scientific explanation remains prized as a distinct scientific virtue" (p. 613). Yet control can hardly be the mark for explanatoriness with respect to mere description; for even in descriptive models, we can control variables (for

[13] For a different approach to dynamical and computational models by another prominent mechanist, which we think suits better with our conciliatory position, see Bechtel, 2011 (e.g., "the basic mechanistic account must be extended in the direction of dynamic mechanistic explanation in which computational modeling and dynamic systems analysis is invoked to understand the dynamic behavior of biological mechanisms", p. 554). His differences with Craver in this regard are orthogonal to their widely discussed differences with respect to the ontic and epistemic accounts of mechanisms (for a recent survey of this debate and a conciliatory proposal, see Illari, 2013).

instance, we can modify distance in free fall and we obtain different a time; likewise with Kepler's descriptive laws). As mechanists who allow for non-mechanistic explanations in some other fields, they probably think that causation is the mark of explanatory models vis-à-vis mere descriptive ones. But there are many examples of explanatory models whose causal nature is doubtful, General Relativity to start with (see e.g. Hoefer, 2009; for other cases of non-causal explanatory models see e.g. Ruben, 1990; Thalos, 2002).

To conclude: it is true that descriptive models are not explanatory; it is also true that mechanistic models are explanatory.[14] But we do not agree that the difference lies in the mechanistic components of the explanans, nor even in the broader causal component. Causal models, and mechanistic models in particular, are explanatory, but not all explanatory models are causal, much less (fully) mechanistic. Providing mechanistic details is one adequate way of giving satisfactory explanations, maybe it is even the most frequent way in biochemistry and neurosciences. But it is not the only satisfactory way; there are models that are not merely descriptive, that are explanatory, but that are not mechanistic, at least not fully, including essentially nomological functional, not mechanistically specified, components.[15] Where does the explanatory power lie in these cases?

Referring to dynamical/mathematical models in general, Kaplan and Craver claim that "there is no currently available and philosophically tenable sense of 'explanation' according to which such models explain even when they fail to reveal the causal structures that produce, underlie, or maintain the explanandum phenomenon." (2011, p. 602). We think that the answer to their challenge must be: "it depends". Functional models may be merely descriptive or not. If they are merely descriptive, Kaplan and Craver are right, no acceptable notion of explanation applies to them. But there are functional models that are not merely descriptive, and they can be explanatory, even if they do not "reveal the causal structure that produces the explanandum phenomenon". And there is a notion of explanation that accounts for this. It is a notion of explanation that sits well with the structuralist net-like analysis presented above, and sketched in the last paragraph of section 3 (implicit in Balzer et al., 1987; developed in some respects in Bartelborth, 2002; and fully elaborated in Díez, 2014). Briefly: to explain a phenomenon is to embed it in a theoretical model defined making essential use of (i: ampliation) new conceptual/ontological machinery not present in the description of the phenomenon/explanandum and (ii: specialization) non-accidental, nomological generalizations—including non-universal and non-exceptionless ones—that modally connect the new machinery in the explanans and the content of the explanandum in a *specific*, non-ad hoc manner (see references for details). In planetary motion, for instance, the kinematic trajectory is explained by embedding it in a mechanical model defined by laws of motion and gravitation that essentially involve the new machinery of masses and forces. In MWC, variation in biological activity is explained by embedding it in an allosteric model defined (in every specialization) by the laws mentioned above that essentially involve the new machinery of conformational states, affinities, etc.

This account of explanation draws the line between descriptive and explanatory models in conditions (i) and (ii) above, and we think it accounts for the differences in the examples we have mentioned. The theories of Galileo and Kepler are merely descriptive with respect to kinematic phenomena as their kinematic laws use only kinematic concepts: they just systematize kinematic phenomena. Those of Newton and Einstein, in contrast, are explanatory with respect to kinematic phenomena for they introduce new non-kinematic machinery (masses and forces) connected with the kinematic content through special laws. We think that it also explicates why the Keslo-Bunz and the difference-of-Gaussians models mentioned above are not explanatory: they do not introduce new theoretical machinery with respect the phenomenon they model. And why the Hodking-Huxley model is taken as explanatory or not, depending on whether the explanandum is the variation of the potential or it also includes the conductance of the membranes.

Although this account makes essential use of laws (including non-universal and non-exceptionless ones), and is a form of expectability account (yet permitting low expectability in some probabilistic cases), it is not simple Hempelianism. It is not merely a covering-law model, as it introduces the two essential new conditions (i) and (ii) that block traditional counterexamples to mere nomological expectability (see Díez, 2014 for details). Finally, it is compatible with causal explanations, and with mechanistic explanations in particular, but does not make mechanisms conceptually necessary for explanation, neither in general nor in neuroscience or biochemistry in particular (even if we can acknowledge that in these fields most explanations—or even all, if this were the case, which we doubt—were actually mechanistic). Neither does it make causation conceptually necessary. Maybe most explanations are causal, even non-mechanistic ones such as Newton's gravitation; but there is room for alleged non-causal explanations, such as General Relativity. The key is conceptual/ontological ampliation with nomological specialization, which may come via causation or mechanisms, but does not to. This is the way in which we answer the part of Kaplan and Craver's challenge that is answerable!

6. Conclusion

We have argued, *contra* some representatives of the new mechanicism, that: (a) The MWC explanatory set-up can properly be regarded as a theory in a strong sense—more specifically, as a unified net-like theory structurally similar to, yet simpler than, other highly unified explanatory theories such as CM, Phenomenological Thermodynamics or Classical Genetics; (b) the notion of theory applicable here is one that belongs to the semantic or model-theoretic family, specifically the one explicated by Sneedian structuralism; (c) the MWC theory-net essentially contains non-accidental, nomological regularities that can properly be considered as laws in a relevant, though minimal, sense of lawhood; (d) the mechanistic nature of the explanation is not only compatible, but necessarily accompanied by a functional characterization; and (e) the functional-mechanistic explanation involved here consists of making the explanandum that can be expected by introducing to the explanans T-theoretical concepts/entities connected with the explanandum via special laws (or in the alternative terminology, special non-accidental regularities). The reconstruction of MWC presented here supports these tenets, and it also shows that the reference to non-accidental, modal regularities (or laws, in accordance with our terminological preference) is also essential for explicating the unified nature of the theory, and thus accounting for what is common and what changes in different explanatory MWC models.

The conclusion, though, is not that our account is better than the mechanistic one, nor vice versa. We do not believe that the mechanistic and our model-theoretic accounts are in opposition;

[14] Depending on the explanans, they are causally explanatory if the explanandum is—as we believe is the more natural option—the phenomenon produced by the mechanisms, or constitutively explanatory if the explanandum is—as Fagan, 2012 defends—the functioning of the mechanism.

[15] These nomological functional explanations need not always be presented in the inferential manner they usually appear in physics, see e.g., Jones and Wolkenhauer (2012) for the role of diagrams in nomological and functional explanations in biology.

quite the contrary. We advocate a plural, syncretic perspective in which every relevant aspect is explicated according to its specific nature. Biological, neurophysiological and cognitive theories are too complex to reduce to either mechanisms or hierarchical models, and a complete understanding of such theories may call for complementary analyses. We are not alone in this ecumenical methodological pluralism. For instance, Green, Fagan and Jaeger (2015) advocate, from a different perspective, a complementary account in evolutionary biology that integrates mechanistic and dynamical nomological explanations; and Walmsley (2008) defends the complementarity of covering-law explanations in dynamical cognitive science. Our goal here is to contribute to this complementary methodology, calling attention to some model-theoretic net-like features that our reconstruction highlights and that, we believe, contribute to understanding some important aspects of a biochemical theory that mechanistic analysis, important as it is in shedding light on other features, cannot capture. We also believe that our case study is paradigmatic in biochemistry and that it is worth exploring whether this complementarity applies to other theories in these is fields.

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