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CONCEPTUAL RECONSTRUCTION AND EPISTEMIC IMPORT: ALLOSTERIC MECHANISTIC EXPLANATIONS AS A UNIFIED THEORY-NET

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SUMMARY: The goal of this article is to show that formal analysis and reconstructions may be useful to discuss and shed light on substantive meta-theoretical issues. We proceed here by exemplification, analysing and reconstructing as a case study a paradigmatic biochemical theory, the Monod-Wyman-Changeux (MWC) theory of allosterism, and applying the reconstruction to the discussion of some issues raised by prominent representatives of the new mechanist philosophy. We conclude that our study shows that at least in this case mechanicism and (some version of) more traditional accounts are not rivals but complementary approaches.

KEY WORDS: allosterism, Monod, mechanisms, theory-nets, structuralism, explanation

RESUMEN: El objetivo de este artículo es mostrar que los análisis y reconstrucciones formales pueden ser de utilidad para discutir e iluminar cuestiones metateóricas sustantivas. Precedemos aquí por ejemplificación, analizando y reconstruyendo una teoría bioquímica paradigmática como caso de estudio, la teoría del alosterismo de Monod-Wyman-Changeux, y aplicando la reconstrucción a la discusión de algunas cuestiones planteadas por prominentes representantes de la nueva filosofía mecanicista. Concluimos que nuestro estudio muestra que al menos en este caso la aproximación mecanicista y (alguna versión de) otras aproximaciones más tradicionales no son rivales, son complementarias.

PALABRAS CLAVE: alosterismo, Monod, mecanismos, redes teóricas, estructuralismo, explicación

This paper aims to show, through a detailed case study, that formal analysis and reconstructions may be useful to discuss and shed light on substantive meta-theoretical issues with regard to explanation, mechanisms, lawfulness and theoryhood. We proceed by exemplifi-

cation, analysing and reconstructing as a case study a paradigmatic biochemical theory, the Monod-Wyman-Changeux (MWC) theory of allosterism, and applying the reconstruction to the discussion of some issues raised by prominent representatives of the new mechanist philosophy. In section 1 we summarize the main elements of MWC so as to provide sufficient background for the non-specialized reader. In section 2 we present the meta-theoretical tools that we use in our reconstruction, mainly the structuralist notion of theory-net. In section 3 we start the analysis with the definition of MWC potential and partial models, and their components. In section 4 we conclude the reconstruction with the definition of MWC actual models and the network of nomological constraints and the associated hierarchical theory-net. In section 5 we apply the reconstruction to the discussion of the usefulness, questioned by some mechanists, of the notions of *theory* and *law* for a proper understanding of the explanatory practice in biochemistry and related fields where the use of mechanisms is widespread. We defend (a) that the unified aspects of allosteric explanations, which are essential for a correct understanding of such practice, cannot be accounted for merely in mechanistic terms and are well explicated by the notion of *theory-net*; and (b) that the notion of law, in the weak sense of non-accidental —and possibly domain-specific— generalization, as they appear in the allosteric theory-net, is essential for allosteric explanations. We conclude that our case study shows that at least in this case mechanicism and (some version of) more traditional accounts are not rivals but complementary approaches; we also claim that this result plausibly generalizes in other cases in molecular biology, biochemistry and neuroscience —although this hypothesis should be tested by future work.

1. *The Monod-Wyman-Changeux Theory*

The Monod, Wyman and Changeux theory (MWC) focuses on a particular regulation of biochemical activity, *allosteric regulation* or, as they themselves call it, the "allosteric mechanism" (Monod, Wyman and Changeux 1965, p. 103). The theory was first published more than fifty years ago, but remains "the basis for nearly all attempts to analyze the mechanistic basis of regulation not only for enzymes such as aspartate transcarbamoylase, but also for similar but different systems, such as ion channels" (Cornish-Bowden 2014). Indeed, allostery has remained as a key theory in biology and biochemistry since the quantitative explanation this theory allows regarding the biological activity of oligomeric proteins is fundamental for understanding a

variety of cellular processes such as hormone action, gene repression and enzyme kinetics, among others. For this reason, allostery has been referred to by Jacques Monod as the "second secret of life" (Ullman 2004, p. 201). Although to the best of our knowledge we offer the first detailed meta-theoretical analysis and reconstruction, the theory has already been a subject of interest to meta-theorists, some of whom are mechanists (Darden and Maull 1977).

Jacques Monod and François Jacob coined the term "allosteric" in a summary article for the Cold Spring Harbor Symposium on Cellular Regulatory Mechanisms (Monod and Jacob 1961). They first used the term "allosteric" for naming the inhibitory mechanism triggered by the binding of a ligand to a site in an enzyme distinct from the binding site for the substrates; however, the concept of allosterism was substantially modified in a later paper (Monod, Wyman and Changeux 1965); the application of the new version of allosterism presented in 1965 has grown continuously and today applies to a whole variety of protein behaviors not involving enzymes, such as trans-membrane receptors, membrane channels and transporters. The theory is still considered a fruitful proposal and continues to show its resilience in the light of new experimental results (Cui and Karplus 2008; Viappiani *et al.* 2014).

The core general idea of MWC is to explain a particular pattern of biological activity showed by certain enzymes. Most enzymes show a biological activity with a hyperbolic dose-response profile ("dose" being the amount of substrate, and "response" the activity measured): the activity increases with the amount of substrate up to a certain value, and then remains constant (grey curve in Fig. 1). However, not all enzymes present this activity profile; others show sigmoidal behavior (black curve in Fig. 1). The variety of sigmoidal behaviors is what MWC aims to explain, introducing two main ideas: the occurrence of a relevant *oligomeric* structure for signal-transducing proteins, and a pre-existing equilibrium between two *different conformations* of oligomers depending on different *affinities* for different *ligands* (Changeux 2012). Roughly: the theory postulates that proteins have "parts" that may be in different "conformational states" which modify their "affinity" for different substances, obeying certain nomological connections that imply the observed patterns of activity.

The theory applies to proteins, named *oligomers*, having several sub-units, named *protomers*. Protomers have *sites* for the binding of *ligands*, which can be either substrates or modulators (i.e., activators

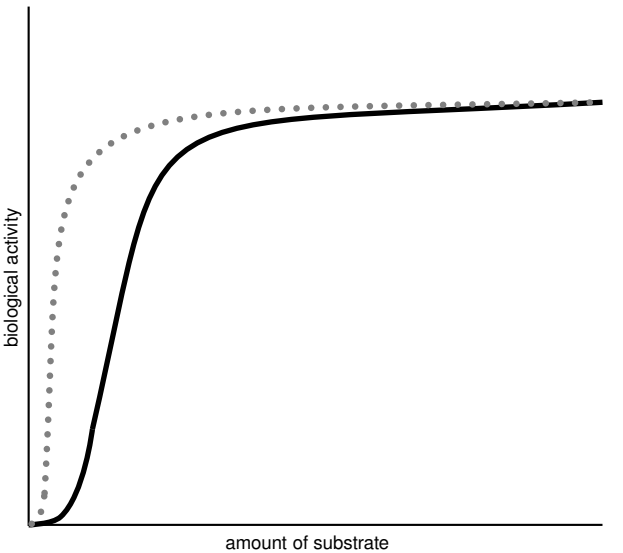

FIGURE 1. The figure shows a representation of both the hyperbolic profile of the biological activity (grey dotted line) and a sigmoidal profile (black continuous line).

that increase protein activity or inhibitors that decrease it). According to MWC, there are two possible spatial structures or *conformational states* for each oligomeric protein, each one with a different biological activity: a tense state (τ), with low affinity for substrate and low biological activity, and a relaxed state (r), with high affinity for substrate and high biological activity.

A symmetry condition is central to the theory and implies that all protomers of an oligomer are always in the same conformational state. The theory also claims that a change in conformational states is possible only in the absence of ligands (thus an oligomer that has bound a ligand no longer participates in allosteric transition), and that oligomers in r and τ conformational states co-exist in equilibrium when no ligand is present. This equilibrium, called *allosteric transition*, implies that: (i) oligomers are continuously changing from τ to r state and vice versa, but (ii) the ratio between oligomers in τ state and oligomers in r state is 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. Oligomers may behave differently with different ligands,

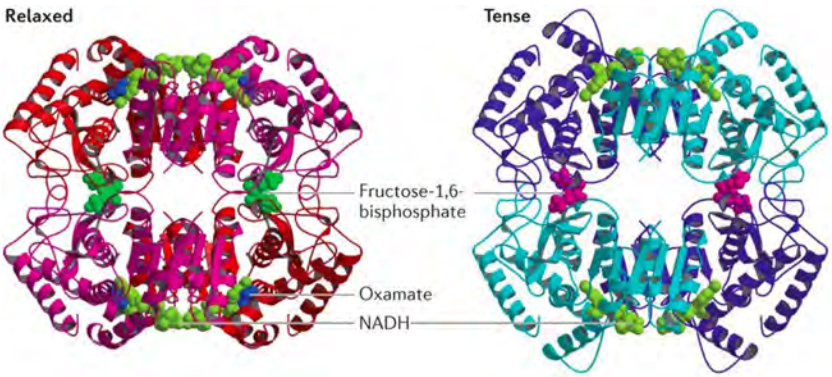

FIGURE 2. Example of a specific oligomer in tense/relaxed states. The figure shows the allosteric transition captured by X-ray crystallography of L-lactate dehydrogenase (Iwata 1994). It must be stressed that at the moment of the postulation of the theory these crystallographic data were not available. (Adapted by permission from Macmillan Publishers Ltd: *Nature Rev Mol Cell Biol*, Changuex 2013.)

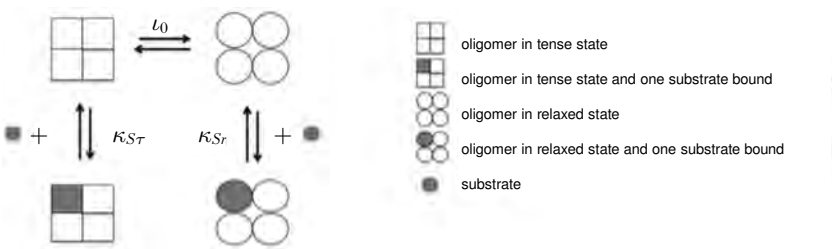

FIGURE 3. The allosteric transition and ligand binding equilibrium are represented for an oligomer with four protomers in the figure. The squares denote the protomers in τ states, while circles represent protomers in r states. In the upper part the empty oligomer equilibrium between τ and r conformations governed by the allosteric constant (ι_0) is shown. The figure also shows the equilibria of oligomers in τ and r conformations with substrates; those equilibria are governed by the corresponding constants ($\kappa_{S\tau}, \kappa_{Sr}$). In this case, only one substrate is bound, but of course subsequent equilibria (not shown here) can complete the binding of the four protomers.

reaching different equilibria, which are conceptualized as the specific "affinities" that the oligomer has for the specific ligands, and are formally represented by *microscopic dissociation constants*.

This is the general theoretical framework of the theory that allows it to explain different types of activity curves by different types of binding situations. The theory then explains different correlations between changes in ligand binding and changes in activity by, roughly, attributing to oligomers two different "conformational states" in which they may have more or less "affinity" with respect to ligands, and postulating some nomological connections between conformational states, affinities, binding states and activity.

It must be stressed that, initially, when MWC theory explained the biological activity of certain proteins it did so by referring to two parameters, the saturation function (the proportion of bound sites for all conformational states) and the *r* state function (the proportion of proteins in the relaxed state *r*, see below), linked to protein biological activity. The MWC model assumes that the biological activity can qualitatively be analogous to the saturation function. According to our point of view, shared by other authors (e.g., Bindslev 2008), in order to represent the biological activity of the oligomers the *r* state function is more appropriate, since it expresses the fraction of relaxed states that are responsible for the activity in the oligomer. On the other hand, the *r* state function is able to capture the spontaneous biological activity that some oligomers, such as channel proteins, might have. This function, however, was not considered by the authors of the model to account for the biological activity of the systems. We believe that this could be due to the fact that the allosteric systems to which the model was intended to be applied when the theory was created, comprised only enzymes and hemoglobin, proteins that do not have any spontaneous activity. The use of the saturation function for representing biological activity has been the object of controversy (Bindslev 2008). This controversy notwithstanding, in the original presentation of the theory, the authors themselves accept that using the saturation function depends on "assumptions about the mechanism of the reaction itself" and that "the saturation function cannot be determined directly but inferred form kinetics results" (Bindsley 2008, p. 94) —for enzymes. In this regard, our reconstruction helps to clarify that the corresponding concept here is biological activity.

This brief summary suffices for showing that the MWC explanatory set-up has the characteristic structure of other unified explanatory theories and can then be reconstructed as a unified theory-net

in the precise sense announced above and that we are now going to specify.

2. *Theory-Nets*

The structuralist notion of theory-net originates in the Kuhnian concept of paradigm/disciplinary matrix. When Kuhn introduces the two first components of disciplinary matrices, namely symbolic generalizations (i.e., laws) and exemplars/applications (explananda phenomena), he makes a crucial distinction between general or schematic generalizations and specific laws, which is essential in unified theories that account for different kinds of phenomena all considered explananda of the theory. In such unified theories, like Classical Mechanics, there are some generalizations that are not "specific laws" but, rather, "schemes" that take detailed form for specific applications:

> generalizations [like $f = ma \ldots$] 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 $mg \sin \alpha = -md^2s/dt^2$. For coupled harmonic oscillators it becomes two equations, the first of which may be written $m_1 d^2 s_1/dt^2 + k_1 s_1 = k_2(d + s_2 - s_1)$. 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)

Sneedian structuralism (Sneed 1971, Balzer *et al.* 1987) elaborates this Kuhnian idea with the notions of *guiding-principle*, *specialization* and *theory-net*, which have been applied to several theories in a variety of fields.[1] In Classical Mechanics (CM), for instance, at a certain historical moment the CM theory-net appears as shown in Figure 4 (for current exemplification goals this simplified version suffices).

This theory-net has Newton's Second Law as the top unifying nomic component, and opens down different branches for different

[1] For instance, Classical Mechanics (Balzer and Moulines 1981), Phenomenological Thermodynamics (Moulines 1975) Classical Genetics (Balzer and Lorenzano 2000), Natural Selection (Ginnobili 2012, Díez and Lorenzano 2013), and others (see Balzer, Moulines and Sneed 1987 for references to other case studies).

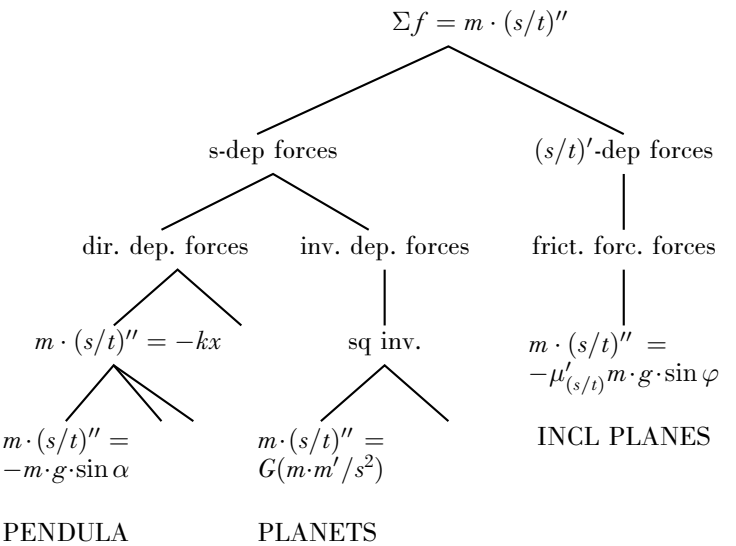

FIGURE 4. (Part of) The theory-net of Classical Mechanics.

phenomena/explananda. These branches introduce different hierarchized nomological constraints in different steps: first, space-dependent forces versus velocity-dependent ones; then the space-dependent branch specializes into direct and indirect space-dependent; the direct space-dependent branch specializes in turn into linear negative space-dependent, etc.; the inverse space-dependent branch specializes into square inverse, etc.; 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": see the above quote).

Note that top-bottom relations are not of implication or derivation, but of *specialization* in the structuralist sense (Balzer *et al.* 1987, ch. IV): bottom laws are specific versions of top ones, i.e., they specify some functional dependences that are left partially open in the laws above in the branch. It is also worth emphasizing that the difference between top general guiding principles typically present in highly unified theories —such as CM and its Newton's Second Law— 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 "pro-

grammatic" 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-restrict".[2] This peculiar epistemic status of general guiding principles has the consequence that, after a failed prediction, one *may* change the general principle but 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); and when the scientific community changes the top element, we cannot continue speaking of the same theory (Kuhn's revolutions).

An additional component of this picture, not present in Kuhn and essential for explicating theoretical explanatoriness, is the structuralist notion of T-theoreticity (related to other more informal, similar ones, e.g., Lewis's 1970 between "old" and "new" vocabulary, and Hempel's 1973 between "characteristic" and "antecedently understood" terms): A T-term (i.e., a term used in T-laws) is T-theoretical if every determination of its (qualitative/quantitative) extension presupposes some T-law; otherwise, a term is T-non-theoretical, i.e., if it can be determined (at least on some occasions) without presupposing T-laws.[3] The structures with the appropriate logical type, i.e., with elements that correspond to (primitive) T-terms, both T-theoretical and T-non-theoretical, are the *potential models*, i.e., the structures for which to ask whether they satisfy the T-laws makes sense. The substructures of potential models made just of T-non-theoretical com-

[2] This term is Moulines' (1984); Kuhn uses "quasi analytic" (Kuhn 1976) and, later, "relativized synthetic apriori" (Kuhn 1993); with regard to this notion, see also Friedman (2000, 2001, echoing Reichenbach 1920), and in the structuralist framework, Díez (2002), Lorenzano (2006, 2008) and Falguera (2012). Although the structuralist literature distinguishes between guiding principles and general or fundamental laws, the former being a special kind of the latter, we shall not take this distinction into consideration here since nothing in what follows hinges on it.

[3] For instance, in CM "mass" and "force" (and other terms defined out of them such as "pressure", "momentum", and others) are CM-theoretical, for 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 CM-mass), while "space" and "time" are CM-non theoretical, for, although they are sometimes measured using mechanical laws (e.g., when we calculate a distance from mass, force and time in a mechanical law), they can be measured independently (e.g., by triangulation).

ponents are the *partial (potential) models*. And the potential models that actually satisfy the T-laws are the *actual models* of the theory (T-laws that, as noted above, in tree-like unified theories come in different, hierarchical levels conforming a theory-net having a general, schematic guiding principle at the top).

The difference between T-theoretical and T-non-theoretical components is essential for explanatoriness. Explananda phenomena are the empirical systems that the theory aims to account for; for instance, in CM, kinematic trajectories such as planetary movement or free fall. Crucially, explananda are describable/identifiable/measurable with just T-non-theoretical machinery; that is, we identify T-explananda without assuming the correctness of T-laws. In the above jargon, explananda are (some, intentionally specified) partial models. 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.[4]

We are now in a position to apply this meta-theoretical picture to our case study showing that MWC has the unified structure just drawn.[5]

3. *MWC Potential and Partial Models*

In MWC, the T-non-theoretical data models are constituted by oligomers, each of which is possibly "combined" or bound to one or more "ligands" (substrate, activators, inhibitors), shows a certain degree of "activity" (the kind of activity changes according to the kind of oligomer) and evolves over time as its bounds with the ligands change. The union takes place in each of the "binding sites" located in the protomer units that the oligomer possesses. The formal description of these data models involves, then, the following components:

1. O is a (non-empty) set, a population of oligomers
2. S,A, $I(S \neq \varnothing; A \neq \varnothing; I \neq \varnothing; S \cap I = \cap A = A \cap I = \varnothing)$ are (non-empty, and disjunct) sets of kinds of ligands. S is the set of substrate ligands —the ligands which, when bound to oligomers,

[4] Cf. Díez 2014 for details.

[5] This picture, elaborated with high 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.

allow them to have biological activity. A is the set of activator ligands —molecules that increase oligomer activity. I is the set of inhibitor ligands —molecules that decrease oligomer activity when bound to them.

3. T is a discrete time sequence (i.e., isomorphic with a subset of $\mathbb{N}$).

4. ρ represents the number of protomers or binding sites that oligomers have. It is thus formally represented by a function ρ: $O \to \mathbb{N}$. It is essential to this theory that in each system all the oligomers in the population have the same number of protomers or binding sites, so ρ is a constant function: $\forall\, o,\ o' \in O\ \rho(o) = \rho(o')$. Since ρ assigns the same number to all oligomers of the population, we can define "the number of protomers that the oligomers of the population have", $\rho(O)$, as follows:

$$DfAux1: \quad \rho(O) = n \text{ syss}_{\text{df}} \exists\, o \in O\ \rho(o) = n.$$

5. β represents all *possible* combinations of bound states of the oligomers of the population. Every oligomer o has $\rho(O)$ protomers or binding sites, and in each binding site different ligands may be bound, with the following restriction: there can never be activators and inhibitors together without a substrate. That is, in every protomer there may be either all three; substrate, activator and inhibitor; substrate and activator; or substrate and inhibitor; or just substratum; or nothing. Thus:

$\beta = \{\langle o, \langle s, a, i\rangle_1, \ldots, \langle s, a, i\rangle_{\rho(O)} / \forall\, o \in O$ and such that $\forall\, j : \langle s, a, i\rangle_j \in (S \times A \times I) \cup (S \times A \times \{\varnothing\}) \cup (S \times \{\varnothing\} \times I) \cup (S \times \{\varnothing\} \times \{\varnothing\}) \cup (\{\varnothing\} \times \{\varnothing\} \times \{\varnothing\}, [1 \leq j \leq \rho(O)]\}$

6. At every moment each oligomer is in one of the bound states. We represent by $\sigma(o,t)$ the bound state of the oligomer o at moment t; that is, $\sigma : O \times T \to \beta$. Thus $\sigma(o,t) = \langle o, \langle s, a, i\rangle_1, \ldots, \langle s, a, i\rangle_{\rho(O)}$ this means that oligomer o, at moment t, is bound in binding site 1 to ligands..., in binding site 2 to..., and in binding site $\rho(O)$ to ligands... For future reference, it will be useful to have a notation for "the j-th ligands bound to o at t", i.e., the ligands bind to o at t in the j-th binding site:

$$DfAux\ 2: \quad \sigma(o,t)_j =_{df} \text{ the j-th indexed component of } \sigma(o,t)[1 \leq j \leq \rho(O)]$$

7. The last component of empirical or data models is *biological activity*. It is a positive real value assigned to the whole population of proteins, representing the "intensity" of certain biological activity at a time. As explained above, different types of oligomers show different biological activities: for example, the biological activity of enzymes is to catalyze a chemical reaction, the activity of an ionic channel is the transportation of ions, and so on. We can then represent this value by a positive real function δ. Since this value varies with the change in bound states of the population over time, δ is a function of time. Note that δ is a value for the "global" activity of a specific population O , a fact that is formally expressed by specifying a particular δ in the model that has the specific population O as its domain. Thus, it suffices to characterize δ thus: $\delta : \sigma \rightarrow \Re^{+}$.

All these MWC-non-theoretical components can be determined independently of the laws of the theory. This of course does not mean independently of *any* theory: for example, protomers are identifiable within the theory of 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. As we noted above, 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 Classical Mechanics-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,[6] and activators and inhibitors whose identification as activators / inhibitors depends on whether they are bound in protomer sites and whether they correlate with increases/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 are graphically summarized in activity curves with activity on one axis and quantity of substrate on the other (see

[6] Although the analysis of general intertheoretical relations between MWC and other theories is an interesting issue per se, and crucial for other metatheoretical goals, it is not essential for the goal of this paper and we thus will not focus on it here. The same applies to other important structuralist tools, inter-modelic constraints, which are not essential for current dialectics and are left aside for simplicity's sake.

Figure 1). If successive values of the substrate axes are values at successive moments of time, then the values of the activity axes are time-successive degrees of activity. Yet, there is no need for the values to be interpreted as "time ordered": the graph shows a correlation between quantity of substrate and activity regardless of whether prior/posterior values in the axes are also prior/posterior temporally considered. These curves may show different type-profiles, which are the explananda that MWC tries to account for.

In order to account for these data, the theory introduces new concepts and some nomological connections, or laws, linking MWC-empirical and MWC-theoretical concepts/entities in different ways. The new MWC-theoretical notions are the following ones:

8. The first MWC-theoretical notion is that of *conformational states*, i.e., the τ (tensed) or r (relaxed) state in which all protomers of an oligomer are at a certain moment (recall that in this theory, all the protomers have the same conformational state —this is the "symmetry" condition). We'll use $\{\tau, r\}$ to refer to the set of these two conformational states.

9. We can then associate a conformational state function, ζ, directly to the oligomer as a unit. Every oligomer in a certain bound state at a given time is in one of the two conformational states (and the same oligomer in the same bound state can be in different conformational states at different times). That is:

$$\zeta : \beta \times T \rightarrow \{\tau, r\}$$

10. The third MWC-theoretical notion is the *dissociation constant*. There is one such "constant" κ for each ligand representing the affinity of the oligomer for the ligand in question, i.e., the tendency or disposition to bind this ligand at its binding sites. This tendency is postulated to be: (i) the same for all binding sites, so that it can be assigned to the oligomer as a unit: (ii) dependent only on the conformational state, that is, all oligomers in the population in the same conformational state have the same affinity for the same ligand. We can then characterize the three dissociation "constants" in each model as three different real functions on $\{\tau, r\}$:

$$\kappa_S : \{\tau, r\} \rightarrow \Re^+$$
$$\kappa_A : \{\tau, r\} \rightarrow \Re^+$$
$$\kappa_I : \{\tau, r\} \rightarrow \Re^+$$

Since $\{\tau, r\}$ is the range of ζ, we have that e.g., $\kappa_A(\zeta(\langle o, \langle s, a, i\rangle_1, \ldots, \langle s, a, i\rangle_{\rho(O)}, t\rangle))$ reads "the affinity of oligomer o (in a certain bound state) for the ligand A at the moment t in which it is in the conformational state $\zeta(\langle o, \langle s, a, i\rangle_1, \ldots, \langle s, a, i\rangle_{\rho(O)}, t)$. Note that all oligomers in the population of the system have the same S/A/I-affinities when they are in the same conformational state, but the reverse (i.e., oligomers in different conformational states have different S/A/I-affinities) may or may not be true, depending on specific systems (cf. the Michaelis-Menten specialization below). We abbreviate the affinity of the oligomers of the system for ligand ψ when they are in stat r, respectively τ, by "$\kappa_{\Psi r}$", and "$\kappa_{\Psi\tau}$":

$$DfAux\ 3: \quad \kappa_{\Psi r} =_{\text{def}} \kappa_{\Psi}(r)$$
$$\kappa_{\Psi\tau} = \kappa_{\Psi}(\tau)$$

This completes the presentation of the components (domains, relationships and functions), both MWC-non-theoretical and MWC-theoretical, of our theory. Thus, MWC potential models, which extend the MWC partial models (which had only MWC-non-theoretical elements) with these "new" MWC-theoretical components, are of the following form:

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

These potential models are the kind of entities that *may* satisfy MWC nomological constraints. The subset of MWC potential models that *actually* satisfy MWC laws will constitute MWC *actual models*. The theory then successfully explains its explananda if, according to the theoretical laws that it postulates, the models that satisfy these laws "coincide" with data: that is, if there are MWC-actual models whose MWC-non-theoretical sub-model coincides (modulo admissible approximation) with the data model, i.e., the phenomenon summarized by a specific activity curve. Let us now reconstruct the net of MWC-laws that define the different sets of actual models that account for different MWC-explananda.

4. *MWC Laws, Actual Models and MWC Theory-Net*[7]

As we have advanced, not all MWC nomological constraints have the same scope. Some of them are *general* in that they apply to all

[7] This section partially follows Alleva, Díez and Federico 2012.

intended systems/explananda. Some others are *special* in that they apply only to specific systems/explananda. Let us see them in turn:

General Laws

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; binding "fixes" conformational states in the sense that as long as oligomers "remain bound" (to ligands in protomers) they do not change their conformational state. Formally:

$$GL1 \quad \forall t \in T \, \forall o \in O : \\ \zeta(\sigma(o,t),t) \neq \zeta(\sigma(o,t_{+1}),t_{+1}) \text{ iff } \forall j \sigma(o,t)_j = \langle \phi, \phi, \phi \rangle = \sigma(o,t_{+1})_j [1 \leq j \leq \rho(O)]$$

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. To simplify notation, let's abbreviate "the number of oligomers in conformational state @ at moment t" by "$\eta(o, @, t)$" (now we use "@" as a variable for conformational states):

$$DfAux4: \quad \eta(o, @, t) =_{def} | \{o / \zeta(\langle \sigma(o,t), t \rangle) = @\} |$$

Then the second general law reads as follows:

$$GL2 \quad \forall t, t' \in T \, \forall o \in O : \\ \eta(o, \tau, t) \div \eta(o, r, t) = \eta(o, \tau, t') \div \eta(o, r, t') \text{ iff } \forall j \sigma(o,t)_j = \langle \phi, \phi, \phi \rangle = \sigma(o,t')_j [1 \leq j \leq \rho(O)]$$

The third and last general law connects chemical activity with conformational and bound states. It claims, 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. For the sake of exposition, let's introduce the following abbreviations: "ι_{0t}", naming the ratio at t between unbound oligomers in the two different conformational states; "$|\Psi_t|$",

naming the number of binding sites of oligomers in the population actually bound to ligands of type Ψ at time t; and "$\varepsilon_{\Psi@t}$" naming the normalized concentration of ligand Ψ, which corresponds to the numbers 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.

$DfAux5:$ $\iota_{0t} =_{def} \eta(o,\tau,t) \div \eta(o,r,t)$ for oligomers $\forall\, j\sigma(o,t)_j = \langle\phi,\phi,\phi\rangle$

$DfAux6:$ $|\Psi_t| =_{def} |\{x \in \Psi x$ is bound in t to a protomer in n oligomer o in $O\}|$

$DfAux7:$ $\varepsilon_{\Psi@t} =_{def} |\Psi_t|/\kappa_{\Psi@}$

With these abbreviations, the third law takes the typical form that we find in articles and textbooks:

$GL3 \quad \forall\, t \in T:$

$$\delta(t) = \frac{\iota_0 \frac{(1+\varepsilon_{I\tau t})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}} \varepsilon_{S\tau t}(1+\varepsilon_{S\tau t})^{\rho_0 - 1} + (\varepsilon_{S\tau t})(1+\varepsilon_{Srt})^{\rho_0 - 1}}{\iota_0 \frac{(1+\varepsilon_{I\tau t})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}} (1+\varepsilon_{S\tau t})^{\rho_0} + (1+\varepsilon_{Srt})^{\rho_0}}$$

These three laws apply to all systems.[8] Yet, they alone do not suffice for the explanation; they must be combined with other specific constraints for specific kinds of systems.

Special Laws

Special constraints apply depending on:

The kind of interaction between protomers of one oligomer, which can be of two different types: (i) non-cooperative (i.e., Michaelis-Menten); (ii) cooperative (i.e., allosteric).

(a) The kind of ligand that binds to the oligomer: (i) "homotropic effect", as a result of binding of similar ligands (substrate); (ii) "non-cooperative heterotropic effect", as a result of the interaction (binding) between different ligands, substrate and activator; and (iii) "cooperative heterotropic effect", as the result

[8] Actually, in Monod's theory there is a further condition that applies to all systems, namely that there is non-zero activity only in presence of a substrate. Yet, since later on there were systems with spontaneous activity at an initial stage in the absence of a substrate (e.g., channels), we don't include it as a general law; it is a theorem of every specialization in which, when activity is non-null, a substrate is present.

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 (MM)

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:

$$SL1 \quad \kappa_{S\tau} = \kappa_{Sr} \;\&\; \forall\, t \in T \text{ such that } \forall\, j\sigma(o,t)_j = \langle \phi, \phi, \phi \rangle [1 \leq j \leq \rho(O)] : \quad \eta(o,\tau,t) << \eta(o,r,t)$$

With these additional constraints, it follows that the biological activity δ has the following value:

$$\delta(t) = \frac{\varepsilon_{S\tau t}}{S_t}$$

This is the form in which GL1 appears in (Monod *et al.* 1965, p. 92) for Michaelis-Menten systems, and the biological activity profile is the one previously shown in Figure 1 (grey dotted line).

(aii) Allosteric systems (AL)

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

$$SL2 \quad \kappa_{S\tau} << \kappa_{Sr} \;\&\; \forall\, t \in T \text{ such that } \forall\, j\sigma(o,t)_j = \langle \phi, \phi, \phi \rangle \quad [1 \leq j \leq \rho(O)] : \quad \eta(o,\tau,t) > \eta(o,r,t)$$

With these restrictions the activity has the following form

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1+\varepsilon_{Srt})^{\rho_0 - 1}}{\iota_0 \dfrac{(1+\varepsilon_{I\tau t})^{\rho_0}}{(1+\varepsilon_{Art})^{\rho_0}}(1+\varepsilon_{S\tau t})^{\rho_0} + (1+\varepsilon_{Srt})^{\rho_0}}$$

This corresponds to sigmoidal curves in Monod *et al.* 1965, p. 93 (shown in Figure 1 with a black continuous line), where the greater the difference in affinities, the more sigmoidal the curve is.

Allosteric systems 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 (HO)

These systems satisfy SL2 and another constraint that states that no oligomer is bound to activators or inhibitors in any protomer:

$SL3 \quad \forall\, o \in O, \forall\, t \in T[1 \leq j \leq \rho(O)] : \forall\, j\sigma(o,t)_j = \langle s, a, i\rangle$ such that $a = \phi \;\&\; i = \phi$

In homotropic systems, i.e., satisfying SL2 and SL3, the activity is this (note that when s is also empty, activity is null):

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1 + \varepsilon_{Srt})^{\rho_0 - 1}}{\iota_0 + (1 + \varepsilon_{Srt})^{\rho_0}}$$

(bii) Non-cooperative heterotropic systems (NCHE)

These systems also satisfy SL2, but instead of SL3, they satisfy a different constraint: oligomers are bound to activators in addition to the substrate, the affinity for activator is much higher in r than in τ.

$$SL4 \quad \kappa_{A\tau} << \kappa_{Ar} \;\&\; \forall\, o \in O, \forall\, t \in T[1 \leq j \leq \rho(O)] : \forall\, j\sigma(o,t)_j = \langle s, a, i\rangle \text{ such that } a \neq \phi \;\&\; i = \phi$$

In these cases the implied activity is

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1 + \varepsilon_{Srt})^{\rho_0 - 1}}{\iota_0 \dfrac{1}{(1 + \varepsilon_{I\tau t})^{\rho_0}} + (1 + \varepsilon_{Srt})^{\rho}}$$

(biii) Cooperative heterotropic systems (CHE)

In these systems the oligomers are bound to inhibitors, in addition to their substrate and the affinity for inhibitors is much lower in r than in τ:

$$SL5 \quad \kappa_{I\tau} >> \kappa_{Ir} \;\&\; \forall\, o \in O, \forall\, t \in T[1 \leq j \leq \rho(O)] : \forall\, j\sigma(o,t)_j = \langle s, a, i\rangle \text{ con } i \neq \phi \;\&\; a = \phi$$

In these systems the activity is:

$$\delta(t) = \frac{(\varepsilon_{S\tau t})(1 + \varepsilon_{Srt})^{\rho_0 - 1}}{\iota_0 (1 + \varepsilon_{I\tau t})^{\rho_0} + (1 + \varepsilon_{Srt})^{\rho_0}}$$

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

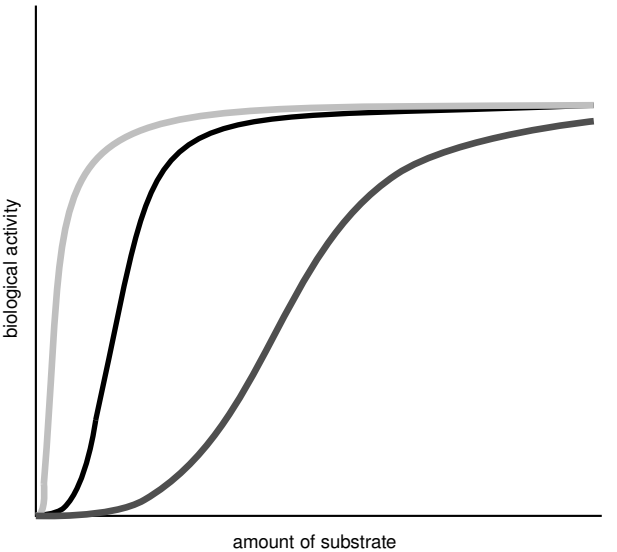

FIGURE 5. The figure shows schematically three possible biological activity profiles: in light grey, the non-cooperative heterotropic (NCHE) effect, in black the homotropic effect (HO), and dark grey the cooperative heterotropic (CHE) effect.

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

5. *Application: Theories, Laws and Mechanisms*

The new mechanist philosophy was developed focusing mainly on molecular biology, biochemistry and neuroscience, highlighting important aspects of scientific practice insufficiently emphasized, when not completely ignored, by traditional philosophy of science, both the statement and the model-theoretic accounts. Taking some paradigmatic case studies in these fields, prominent mechanists have not seen the new account as merely complementing the traditional ones, but rather as challenging traditional accounts in essential respects. Among others, two such aspects criticized are the usefulness of the notion of theory as a helpful conceptual tool to account for relevant features of scientific practice in these fields, and the existence and use of laws in relevant explanatory practice.

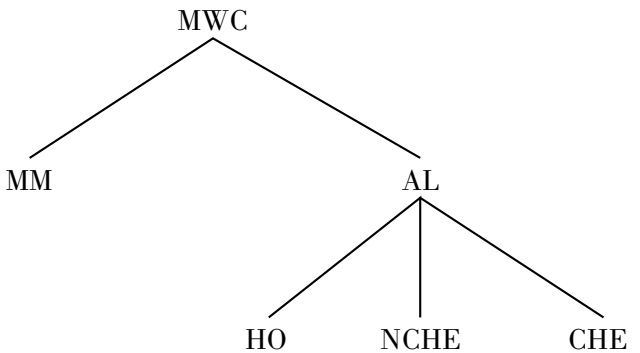

FIGURE 6. MWC tree theory-net. MM: Michaelis-Menten systems, AL: allosteric systems, HO: homotropic systems, NCHE: non-cooperative heterotropic systems, CHE: cooperative heterotropic systems.

Our goal here is to show that the formal analysis and reconstruction of MWC as a unified theory-net proves useful to shed light on these meta-theoretical controversies and serves to vindicate that these two elements of traditional philosophy of science are still meta-theoretically valuable and at the same time compatible with the main tenets of the new mechanist philosophy. We claim that our analysis shows: (a) that the unified aspects of allosteric explanations, essential for a correct understanding of such practice, cannot be accounted for merely in a mechanistic manner and are well explicated by the structuralist notion of *theory-net*; and (b) that laws, in the weak sense of non-accidental (and possibly domain-specific) generalizations, as they appear in the allosteric theory-net, are essential for allosteric explanations.

Although mechanicism is not a homogeneous program, and authors diverge in some respects (cf., e.g., Machamer, Darden and Craver (henceforth, MDC) 2000, Bechtel and Abrahamsen 2005, and Craver 2007a for a survey), most mechanist philosophers share certain tenets with regard to theorization, explanation and lawfulness. Many also defend that putting the focus on mechanisms reveals that some concerns considered relevant in traditional philosophy of science are not so for a proper understanding of scientific practices, at least in the fields in which the presence of mechanisms is dominant. With regard to theories, prominent mechanists raise doubts whether the (or any?) notion of theory is of useful application in 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 and Tabery 2009, Section 3.2, referring to Machamer, Darden, Craver 2000, and Craver 2001.)

Craver, for instance, accepts that a certain, broad notion of theory is applicable across all disciplines and useful for understanding scientific practice:

> Scientists use theories to control, describe, design, explain, explore, organize, and predict the items in that domain. Mastering a field of science requires understanding its theories, and many contributions to science are evaluated by their implications for constructing, testing, and revising theories. Understanding scientific theories is prerequisite for understanding science. (Craver 2001, p. 55)

But he doubts that the two dominant accounts of theories, the syntactic or axiomatic and the semantic or model-theoretic, provide any useful notion of theory of general application —much less in mechanistic theories:

> The two dominant philosophical analyses of theories have sought an abstract formal structure common to all scientific theories. While these analyses have advanced our understanding of some formal aspects of theories and their uses, they have neglected or obscured those aspects dependent upon nonformal patterns in theories. Progress can be made in understanding scientific theories by attending to their diverse nonformal patterns and by identifying the axes along which such patterns might differ from one another. (Craver 2001, p. 55)

When Craver refers to "the two dominant philosophical analyses of theories" he considers the syntactic/axiomatic and the semantic/model-theoretic accounts, and it must be emphasized that, regarding the latter, he only refers to Suppe's analysis. Craver does not deny that there is a general notion of theory applicable, but confines it to what he calls the *formal aspects/patterns*, the most important issues being neglected or excluded.

With regard to laws and explanation, 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 questioned 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, Darden and Craver 2000, p. 7)

Similar claims have been made by other mechanist philosophers.[9]

There is a strong tradition against the existence of laws in biology (cf., e.g., Smart 1963, Beatty 1995, Rosenberg 2001), and in this line mechanisms would provide further examples; the main arguments are based, as in the above quote, on the failure of *universality*, and also of *exceptionlessness*, since in biology regularities are not universal and exceptionless but domain-restricted and with 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, Lange 1999, Dorato 2005, 2012, Craver and Kaiser 2013). Although some mechanists have accepted the talk of non-accidental (and domain-specific) regularities in the description of mechanisms and their activities (Machamer, Darden and Craver 2000, Glennan 1996, Bechtel 2011, Craver and Kaiser 2013), the role they usually concede to them in explanations is very little, or subsidiary. On the other hand, regarding functional laws and explanation, some relevant mechanists claim, mainly referring to biochemistry, that mechanistic explanations are fully causal, and that functional, but not fully mechanistically specified explanations are somehow "defective" (provisional, incomplete, elliptical) (e.g., Craver 2006, 2007, 2008, Piccinini and Craver 2011). Our case study aims also at showing that the presence of, non-accidental, functional generalizations is *central* and *non-provisional* in allosteric biochemical explanations.

[9] Cf. Glennan 1996, 2002, Bechtel and Abrahamsen 2005, Craver 2007; cf. also Leuridan 2010, and Craver and Kaiser 2013 for a recent debate.

It seems then that prominent mechanists challenge the usefulness of some traditional meta-theoretical notions, in particular in fields where mechanisms are the rule such as molecular biology, biochemistry and neuroscience. We vindicate a more moderate, conciliatory/complementary position claiming that, at least in our MWC paradigmatic biochemistry case, the unified aspects of allosteric explanations —essential for a correct understanding of such practice— cannot be accounted for merely in a mechanistic manner but are nevertheless well explicated by the structuralist notion of *theory-net*; and also that laws, in the sense of non-accidental and possibly domain-specific generalization, are essential components of the allosteric theory-net and play a central role in allosteric explanations. To conclude, let us briefly see how our analysis and reconstruction of MWC support these claims.[10]

To start with the applicability of the notion of theory, we agree that there are important traits of theories that are not expressible by any (general) notion of theory in the market. For example, the mechanistic (or non-mechanistic) nature of a theory cannot be expressed by any (general) notion of theory; nor can it be expressed whether a theory is, or is not, causal; or whether it is, or is not, materialist; and so forth. But the problem has not to do with formal *vs* non-formal aspects, but with generality: no *general* notion of theory, actual or possible, can express these facts for, if the notion is really general, it should apply to both mechanistic (causal/materialist/. . .) and non-mechanistic (non-causal/non-materialists/non-. . .) theories. Since these are very important things to know about theories, there are many important things that are not expressible by any general notion of theory but need other more restricted notions that apply only to a specific family of theories. Unless one can conceptually exclude the existence of, for instance, non-mechanistic theories (and nobody does), no general concept of theory can express the mechanistic aspects, but this does not mean that a general notion of theory is of little interest in molecular biology, biochemistry and neuroscience —the paradigmatically mechanistic scientific fields. 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 are other aspects, even in mechanistic theories, that are general and are of equal or complemen-

[10] For a more detailed discussion of some of these issues, and other related topics, see Alleva, Díez and Federico 2017.

tary importance, and deserve to be analyzed by a broader concept of theory.

Our case study shows this with regard to an important feature that a theory may have, namely its unified, hierarchized nature. The semi-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 witnesses. MWC possesses the main traits that highly unified theories such as Classical Mechanics, Thermodynamics, or Natural Selection have: a hierarchized structure with a general guiding principle at the top that specializes downwards in different branches ending in bottom elements that explain different, yet similar, phenomena.

We believe that this is an important feature that is not expressible if we confine the analysis to mechanist features. Paying attention to this unified character and its corresponding net-like structure, one understands better (i) relevant similarities of different MWC explanations in different MWC branches (*across-branches* similarities), and (ii) strict similarities between mechanistically different yet MWC identical explananda (*same-branch* similarities). With regard to (i), the reconstruction shows that explanations of the biological activity of different proteins by means of differential ligand binging and modification of conformational states, have a common allosteric part and, each one, a specific allosteric component. The common part is due to the common nomological constraints that the explanans of these different explananda share, namely the allosteric equilibria. The specific part corresponds in each case to the specific parametrical relation: affinity of the ligands for the conformational states to explicate the kind of interaction between protomers (allosteric vs Michaelis-Menten modes) and the kind of ligand that binds to the protein to distinguish the effect of substrates, activators and inhibitor on biological activity. These communalities and differences are essential features of MWC explanatory practice and a proper understanding of such practice remains incomplete without explicating it. As for (ii), it is also a crucial feature of MWC explanations that the same allosteric models, e.g. the "heterotropic allosteric" branch above, applies to what are, materially/causally, very different kinds of systems: enzymes, hemoglobin, membrane channels or receptors. All these systems are proteins but mechanistically very different ones (for example, while membrane channels function by the opening and closing of a pore crossing

the membrane to allow or prevent the transport of a molecule from one side to the other of that membrane, enzymes take a molecule and transform it into another different molecule); nevertheless they are explained by a similar MWC explanans. This feature cannot then be explicated in mechanistic terms, but is well expressed by our theory-net analysis.

We take it that our analysis, and the notion of theory on which it relies, is irreducible to mechanist notions (on pain of trivializing the notion of mechanism), and sheds light on important aspects of MWC explanatory practice. We think that these conceptual tools are both meta-theoretically valuable and complement the mechanist approach providing together a better understanding of MWC, a paradigmatic mechanistic biochemical theory. Although lack of space does not allow us to argue for it here, we also claim that this point about the notion of theory in our case study generalizes to other cases in molecular biology, biochemistry and neuroscience with a similar unified character.[11]

The point made in (ii) is related to the second issue we announced, namely the role of laws, in the sense of non-accidental, nomological generalizations, in MWC (and other mechanistic) explanations, for the sense in which mechanists accept the presence of non-accidental regularities in mechanisms is not clearly compatible with functional laws such as the ones we find in MWC (and other theories).

Although many mechanists deny the presence of universal laws in mechanistic explanations, they accept that such explanations involve the existence of (non-universal) non-accidental, i.e., counterfactual supporting, regularities:

> Nonetheless, the notion of activity carries with it some of the characteristic features associated with laws. Laws are taken to be determinate regularities. They describe something that acts in the same way under the same conditions, i.e., same cause, same effect. [...] This is the same

[11] The notion of theory-net is very general, thus applicable to many theoretical/explanatory practices. In an *adequately modified* version, it could also apply to non-empirical systems (legal? political? philosophical?, ...). But this does not make it an empty notion that trivially applies to everything. It applies only to the kind of unified, guiding-principle driven systems exemplified here. Of course this still has a very wide scope, but what else may a *general* meta-theoretical concept be? If it has a wide application it is because, fortunately, theoretical practice often generates unified hierarchized systems. What matters for its value is not how wide its range of application is, but how useful it is for explicating relevant scientific features, and it is our claim, based on this and other case studies from biology, but also from physics and other fields, that it actually helps in substantive epistemological issues.

> way we talk about mechanisms and their activities. A mechanism is the series of activities of entities that bring about the finish or termination conditions in a regular way. These regularities are non-accidental and support counterfactuals to the extent that they describe activities. For example, if this single base in DNA were changed and the protein synthesis mechanism operated as usual, then the protein produced would have an active site that binds more tightly. This counterfactual justifies talking about mechanisms and their activities with some sort of necessity. No philosophical work is done by positing some further thing, a law, that underwrites the productivity of activities. (Machamer, Darden and Craver 2000, p. 8)

One can find similar claims in other mechanists (e.g., Glennan 1996, Bechtel 2011, Craver and Kaiser 2013). This may make them committed to the, or at least some, notion of law as useful in conceptualizing mechanistic explanations, but we do not want to enter into terminological debates here. What matters to us is that the only sense in which they seem to accept some notion of law is restricted to the physical/material specificities of the mechanism in point, the regularities corresponding to the *activities* of the specific mechanism. The focus on mechanisms works better than on laws, and the accompanying restrictions to materially specified regularities at the very bottom, characterizes the mechanist "gestalt-shift" made explicit by Craver and Kaiser in their reply to Leuridan (2010):

> 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 material structures that scientists endeavour 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, centered in laws, has become mired in debates that are inconsequential and, as a result, have stopped generating new questions and producing new results. (Craver and Kaiser 2013, p. 143)

Mechanists deserve recognition for the benefits that this gestalt-shift has brought to our better understanding of many aspects of scientific practice in biology and neuroscience. Important as this is, we believe, though, that their emphasis on (in some extreme cases, restriction to) the material specific concretization of the laws/regularities involved in mechanisms, makes them divert attention from more abstract features/regularities that are nevertheless of equal, or complementary, importance in explanatory practice in these fields. In particular, our reconstruction shows that (conservative or not) the explanatory relevant regularities in MWC are not so materially tied, but have a more abstract/functional character (cf. section 4). Moreover, not all the components of the "allosteric mechanism" are fully mechanistically specifiable. Some are, such as the "sites" in protomers that may or may not be bound to certain substances (ligands). But other elements are not fully mechanistically specifiable in the above material sense. Some are described partially in functional terms and are multiply realizable; for instance, the same allosteric models, e.g., the "heterotropic allosteric" branch above, apply, materially/causally, to very different kinds of systems, as explained above: enzymes, hemoglobin, membrane channels or receptors. And still others, equally essential for MWC explanations, are hardly mechanistically characterizable (on pain of trivialization) and are better described in purely functional terms. The affinity of protomers for ligands is a case in point, which is not simply a functional/abstract characterization of a mechanistic element that could eventually be made mechanistically more concrete; affinities are purely functional. Mechanists might respond that functional elements/explanations are provisional, incomplete or elliptical (e.g., Piccinini and Craver 2011). This may very well be the case sometimes, but to claim that they are always so is quite implausible (what incompleteness do we find in affinities?). Abstraction, functionality and multiple realizability may be explanatorily essential, not only in cognitive science but also in biological sciences and even at molecular level (Aizawa 2007). To conclude: (in Craver and Kaiser's terms) "conservative" (yet non-universal) laws are of great, non-provisional importance in explanatory practice in our paradigmatic biochemical case. And we also think that this point generalizes to other cases in molecular biology, biochemistry and neuroscience.

6. *Conclusion*

To summarize, we believe that our reconstruction of the MWC explanatory set-up theory has shown (a) that the unified aspects of al-

losteric explanations, which are essential for a correct understanding of such practice, cannot be accounted for merely in mechanistic terms and are well explicated by the notion of *theory-net*; and (b) that laws —in the weak sense of non-accidental, and possibly domain specific, generalizations— with essential functional aspects not fully expressible in mechanistic terms, as they appear in the MWC theory-net, are essential for allosteric explanations. We also believe —though this needs additional case studies— that both aspects of our study generalize to other theories in molecular biology, biochemistry and neuroscience. In this regard, we take it that mechanicism and the approach we have followed here are not rivals but complementary; both can, and must, collaborate for a better understanding of scientific practice in these fields.

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