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Pluralism and Complexity Without Integration? A Critical Appraisal of Mitchell's Integrative Pluralism

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Pluralism and complexity without integration? A critical appraisal of Mitchell's integrative pluralism[1]

(¿Pluralismo y complejidad sin integración? Una aproximación crítica a la noción de pluralismo integrativo de Mitchell)

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ABSTRACT: This paper critically examines Mitchell's integrative pluralism. Integrative pluralism is the view that scientific explanations should primarily aim to integrate descriptions from different ontological levels. We contend that, while integrative pluralism is a fundamental strategy in contemporary science, there are specific reasons why one should not expect integration in the sense developed by Mitchell to be the optimal strategy and the one that scientists should always aim for. Drawing on some examples from contemporary biology, we argue that integration is sometimes neither epistemically desirable, nor ontologically achievable. We conclude that integrative pluralism should thus be limited to a specific class of complex systems but cannot be generalised as the preferable research strategy without further information about the epistemic practices of the scientific community or the ontology of the system under investigation.

KEYWORDS: Biological Complexity; Mechanism; Philosophy of the Life Sciences; Scientific Integration; Scientific Explanation

RESUMEN: *Este artículo examina de manera crítica la noción de pluralismo integrativo de Sandra Mitchell. Según el pluralismo integrativo, las explicaciones científicas deben integrar descripciones de diferentes niveles ontológicos para ser científicamente sólidas. En este artículo argumentamos que, si bien el pluralismo integrador es una estrategia fundamental de la ciencia contemporánea, existen razones específicas por las cuales no se debe esperar que la integración en el sentido articulado por Mitchell sea la estrategia óptima y aquella a la que los científicos deban apuntar siempre. Utilizando ejemplos de la biología contemporánea, argumentamos que la integración a veces no es ni epistémicamente deseable ni ontológicamente alcanzable. Concluimos que el pluralismo integrador debería limitarse a una clase específica de sistemas complejos, pero no puede generalizarse como la estrategia de investigación preferible sin obtener más información sobre las prácticas epistémicas de la comunidad científica o la ontología del sistema bajo investigación.*

PALABRAS CLAVE: Complejidad biológica; mecanismo; Filosofía de las ciencias de la vida; Integración científica; Explicación científica.

Short summary: This paper critically examines the notion of integrative pluralism introduced by Sandra Mitchell. Integrative pluralism is the view that in order to provide good explanations of complex phenomena, scientists appeal to different levels of analysis and integrate them into a complete story. We claim that there are cases in contemporary biology in which integration is neither epistemically desirable nor ontologically achievable.

[1] This work is fully collaborative. The authors are listed in alphabetical order.

1. Introduction

Sandra Mitchell is one of the most influential contemporary philosophers of science. She has contributed to debates in epistemology, metaphysics of science, and philosophy of the special sciences, particularly philosophy of the life sciences. Her work has proven fundamental in each of these fields, helping to foster our understanding of how contemporary science is practised and has developed over the last half century. Particularly salient is Mitchell's contribution to our understanding of how complexity works, how it should be studied scientifically, and how its scientific study should in turn constrain our own philosophical theories about how the world is and how science develops. Mitchell is well-known for having coined very important concepts in fostering the philosophical study of complexity. These include, most prominently, the concept of "pragmatic laws" (Mitchell, 1997, 2000), developed to better comprehend what scientific laws have in common and how they differ across different scientific fields; and the concept of "integrative pluralism" (Mitchell, 2002, 2003), coined to understand how different levels of descriptions across scientific fields can collaborate to generate better explanations of the natural world. These two concepts have played a pivotal role in the intellectual development of many philosophers of science, as well as of the discipline as a whole. Additionally, they have been especially influential in our own research and intellectual development (Deulofeu et al., 2021). We have applied Mitchell's conception of pragmatic laws and integrative pluralism to our own investigation of biological complexity, helping us illuminate many aspects of contemporary scientific practice in the life sciences that would have been much less clear if these concepts had not been available to us.

Despite the relevance and importance of these concepts in understanding contemporary research in the life sciences, in this paper we aim to explore the limits of the concept of "integrative pluralism" in some specific areas of biology. Particularly, we argue that *integration, in the way conceived by Mitchell, is sometimes impossible to reach due to internal ontological constraints of the systems being studied, or undesirable from an epistemological point of view*. This is in no way a criticism to the notion of integrative pluralism or to its relevance in several scientific enterprises exploring complexity, but rather a reflection on its limits in understanding contemporary research on complexity as this is expressed in the biological world. In this vein, our paper will provide an important critical appraisal of Mitchell's ideas that will reinforce and further clarify the concept of "integrative pluralism" by exploring its own underlying assumptions and limitations.

Our agenda will be as follows. In section 2, we present Mitchell's characterization of integrative pluralism as an epistemological project to study complexity in the life sciences. In section 3, we present a criticism of this epistemological project, and argue that it is grounded on the alignment of epistemic goals in scientific (sub)communities and the desirability of integration, both of which are insufficient for integrative pluralism to be the case. In section 4, we present a potential rebuttal by Mitchell, which would be based on the appeal to the existence of different types of complexity and the different ontological features that these distinct forms of complexity may impose on the empirical cases. In section 5, we present a criticism to this latter view, arguing that it is grounded on an incorrect assumption about the ontological achievability of integration. Finally, in section 6, we present our conclusions.

2. Integrative Pluralism

Integrative pluralism is characterised as "a view of the diversity of scientific explanations that endorses close study and modelling of different causes and different levels of organisation but calls for integrations of the multiple accounts in the explanation of concrete phenomena" (Mitchell & Dietrich, 2006, p. S76). Integrative pluralism is the way in which Mitchell develop her own conception of pluralism, consisting in a form of pluralism about causes, about levels of analysis/explanation and about integration in which: a) it is accepted that a plurality of theories or models is the basis of scientific practice, due to the complexity of the world; b) it is accepted that theories or models may compete for an explanation both intra and inter level; c) it is assumed that mutually constraining (i.e., competing and complementary) explanations or descriptions about the same phenomenon at different levels can be integrated with each other, as they either directly contribute to explaining it or they affect the range of the explanations across levels. For c) to occur, it is enough that the explanations or descriptions at different levels are compatible with one another, but this is not necessary as the relationship between incompatible models can also be refined via joint refinement (Mitchell 2020). Joint refinement is used as a method of mutual error correction used in cases where multiple models explaining features about the same phenomenon conflict with one another, for example by diverging in the generation of predictions about the same phenomenon. Joint refinement assists in evaluating the compatibility of data produced by different methods and, if there are some incompatibilities, those are attributed to differences due to systematic biases derived from the instruments being used.

For Mitchell, the necessity of integrative pluralism in scientific practice has at least three sources. Firstly, it is due to the different dimensions in which biological systems are complex (Mitchell, 2003)—namely: constitutively (referring to the synchronic relationships between the properties of the parts and the potentially emergent properties of the whole), dynamically (referring to the development of a biological system from a single-celled zygote to a multicellular organism) and evolutionary (referring to the history of the lineage that an organism belongs to). In Mitchell's view, a biological system is complex in all these dimensions and they all need to be accounted for and sometimes they are explained in terms of competing explanations. Secondly, it is driven by pragmatic interests of the scientists, particularly centred in answering specific questions that are interrelated. Finally, it is based on different types of complex systems that exist—namely: aggregate and composite—because "the dual complexity [aggregate and composite] of the phenomena studied by scientists and the diverse interests and pragmatic constraints on the representations scientists devise to explain the phenomena conspire against simple pictures of scientific knowledge (…). Correspondingly, the strategy for integrating diverse theories and explanations will not be algorithmic" (Mitchell, 2003, p. 189). We will explain the two first reasons here and delay the explanation of the third reason to section 4.

Concerning the different dimensions of complexity, Mitchell believes that complex biological phenomena are (almost) never accountable in terms of a single causal factor, nor are they explainable in terms of many causal factors that account for all cases in every context, given that compositional, dynamic and evolutionary complexity require different theories and contribute different causal factors.[2] Her view is hence that any phenomenon will need

[2] It is important not to conflate the ways in which a system is complex, from the types of complexity. In Mitchell's account, the ways in which *every* system is complex determine the type of questions scientists need to address, whereas the type of complex system that a specific system is determines the research strategy that is available to study the system (see section 4).

to be explained in different ways, and what matters is whether these different explanations compete with each other or they are compatible. In the latter case, integration is possible, whereas in the former it is likely that competing explanations may clarify each other by constraining potential explananda. In any of these cases, though, Mitchell believes that more adequate descriptions of complex phenomena will always demand the integration of different models, as each will provide relevant features to account for the explanandum. Dynamic mechanistic explanations (Brigandt, 2010, 2013; Brigandt et al., 2017) constitute a canonical case of integration between compositional and dynamic complexity (but cf. Isaad & Malaterre, 2015; Deulofeu et al., 2021). This leads her to conclude that integration of diverse approaches is a hallmark of better science (Mitchell, 2003).

Pragmatism is a second fundamental source of integrative pluralism. While Mitchell's pluralism avoids Dupré's permissibility about what counts as a good theory (Dupré, 1993) by appealing to the idea of "levels of analysis" (Sherman, 1988), she does not renounce to the pragmatic dimension that characterises theory choice. The idea of levels of analysis consists in accepting that different questions about the same phenomenon require different explananda, and all these answers provide information about the phenomenon. For instance, why and how questions about the behaviour of a specific biological species demand different explananda, the latter appealing to a proximate mechanism while the former appealing to the ultimate evolutionary cause of the behaviour. In Mitchell's view, these different questions will set limits on pluralism by limiting what can and cannot be answered, and what must and does not need to be integrated.

This said, she contends that pragmatic considerations back up decisions about the truths of the world that count as scientific knowledge for a specific phenomenon (Mitchell, 2009). That is to say, pragmatism drives the representation that will be used for a specific explanation out of the many accepted representations for a phenomenon. This is because scientists will be interested in highlighting different aspects of its causal structure in different contexts. For example, to reduce or eliminate malaria from a population, it might be enough to drain the swamps and remove the mosquito that spread the illness. If that is the scientific goal, then it is not necessary to appeal to genetics to focus on the role of sickle cells in the infection of malaria in humans (Mitchell, 2009). In other contexts, however, scientists might need to produce more fine-grained analyses, for example, "if one's purpose is to produce an effect that is the result of a complex set of individually insufficient but necessary parts of a causal complex that may be itself unnecessary but locally sufficient to produce the effect (…), then one requires all the contributions to be represented and realized" (Mitchell, 2009, p. 16).

Let us now illustrate how integrative pluralism works by analysing two examples. First, a case in which explanations at different levels of analysis are compatible, and second, a case where different levels of analysis are not compatible. Let us start with the case of major depressive disorders (Mitchell, 2008) as an example of compatibility. According to the DSM-IV (American Psychiatric Association, 2000), major depressive disorders may result from several sources. These include failures in the neurotransmitter system, hormonal changes, cerebral blood flow, metabolic alterations, changes in the brain structure and/or family background—these latter suggesting a genetic basis, and stress/anxiety. This is thus a complex disorder acting on different levels and grounded on multiple causal factors, as psychiatrists themselves acknowledge (Kendler et al., 2006), apparently involving both bottom-up and top-down causes. In principle, any scientist interested in knowing how major depressive disorders work would need to pay attention to its components, its dynamics and even its evolutionary origins. All these three elements need to be taken seriously when

considering whether a person suffers from this type of disorder, thus adding an important layer of complexity in need of analysis.

Secondly, major depressive disorders are inter level, and causes at different levels frequently interact in complex manners. This is important because depending on the specific level that a scientist is interested in, her pragmatic decisions will determine the potential causes that she will focus on. Empirical studies have shown that major depressive disorders involve alterations at the genetic (*5-HTT* gene), neurological (changes in the amygdala structure), biochemical (serotonin deficit), and physiological (anxiety-related response in blood pressure) levels, as well as alterations in the learning process (learned helplessness), social behaviour (lack of social skills and low self-esteem) and expressed biological traits (via the expression of the major depressive disorder). But the problem in analysing major depressive disorders is that none of the alterations in each of these levels is itself necessary for a patient to suffer a major depressive disorder. On the contrary, it is well-documented that a patient may show an alteration in some of the levels and still fail to manifest a major depression disorder. Because of this, scientists can pragmatically focus on one subset of causes to uncover the complex connections between the levels, even though these different causes may be later integrated into a unified whole. The most salient case probably derives from genetic studies on the *5-HTT* gene. Hariri et al. (2005), for instance, showed that the gene is related to changes in the human amygdala that are usually related to major depression. However, the relationship is not consistent for every individual, suggesting that the *5-HTT* gene is related but not necessarily connected to these types of episodes. In another study, Kendler et al. (2005) investigated the relationship between stressful events, major depressive disorders and the *5-HTT* gene. They showed that there was a clear correlation between the susceptibility to major depressive disorders—measured by a decrease in serotonin levels—when the individuals experienced a stressful event and the allele variants of the *5-HTT* gene that they bear. However, Mitchell (2008) interprets—correctly, in our view—the study as showing that allele variants interact with the life effects of the individuals to cause depressive disorders.

Mitchell thus concludes that major depressive disorders must then be analysed as integrative systems in which there are multiple pathways to generate the same effect, making integrative pluralism the only possible strategy to follow in order to get a deep understanding of this psychiatric disorder. The integrative pluralism results from the facts that major depressive disorders are a complex phenomenon of the component integrative type (more in section 4). Thus, different types of explanations at different levels need to be integrated to obtain a comprehensive picture of what is going on when a person is affected by a major depression.

Let's now turn to a case of incompatibility. Mitchell (2020) introduces a scenario in which two different experimental methods provide incompatible data about the same target phenomenon. There are two main experimental methods to predict at the atomic level the structure of a protein, x-ray crystallography and nuclear magnetic resonance (NMR). The first one throws a beam of x-ray into a crystallised protein so that it gets diffracted by the electron clouds of the atoms of the protein. Measuring the angles and intensities of the diffracted beams an electron density map is built and from there the mean positions of the atoms found in the crystal can be predicted. Conversely, in the NMR method, a protein is prepared into a solution and introduced into a large magnet. As a consequence, the normal spin of the atom's nuclei in the protein is realigned according to the new magnetic current.

After that, a perturbation is introduced in order to modify the previous spin and scientists then observe how atoms return to the equilibrium state. Measurements there

provide means to build a map of how the different atoms are chemically linked, telling how close they are from each other, and thus, the predicted structure (Mitchell 2020). It turns out that on several occasions these two methods yield divergent predictions, and this supposes a challenge for integration, namely, how to interpret information coming from two models that diverge. However, Mitchell would claim that none of the models is superior to the other, but she would appeal to joint refinement. As introduced above, joint refinement is a "method of mutual error correction" (Mitchell, 2020, p. 190), in which the compatibility of data produced by both methods is analysed and if there is incompatible data, it is attributed to instrumental biases. For instance, the fact that the two methods investigate proteins at different physical levels (crystallisation with different solutions) might lead to some of the incompatible data. Different degrees of error rates could be another source of divergence. If known systematic biases can be resolved, a better picture of protein structure can be given using data from both methods. Thus, "when you have data from a plurality of perspectives, it can provide stronger justification for a predictive structure" (Mitchell, 2020, p. 191).[3]

Note that these examples clearly highlight that a defining feature of integrative pluralism is the epistemic and ontological necessity of integrating information at different levels of explanation. This requirement constitutes probably the most salient element of Mitchell's integrative pluralism and, in our view, her most important contribution to contemporary philosophy of science. Instead of defending an incompatibilism of explanations across levels, a monism about explanation, or a reductionistic picture of science in which every phenomenon should be explained by detailing the bottom-up causes, Mitchell realises that the biological world requires the combination of tools, descriptions and information across different levels.[4] This position is grounded on her conception of complexity and the different types of complex systems, which we will further discuss in section 4. We strongly agree with Mitchell that integration is an essential component of contemporary science, being particularly relevant in today's biological research. But the question that we now aim to address is whether her optimism about integration is always justified and, if not, when integration is not the best epistemic strategy.

3. Integration is Not Always Epistemically Desirable

There are several reasons why integration is not epistemically desirable for every complex biological system. By "being epistemically not desirable" we mean that trying to integrate explanations at different levels may lead to scientific failure. Importantly, we concentrate only on these cases where integration is not desirable because the bottom-up details are discarded, as these are the cases that suggest the existence of a different type of complex system than the three types isolated by Mitchell (aggregative, composite component and composite integrative, see section 4).[5] In this vein, we distinguish two types of cases where integrative pluralism is not epistemically desirable. First, cases where an integrated explanation would be rejected by the scientific (sub)community because it is at odds with its scientific goals, or the epistemic virtues they seek for in an explanation (values issue). Second,

[3] For a more detailed description of the X-ray example, see Mitchell & Gronenborn (2017)

[4] By reduction and reductionism, Mitchell means explanatory reductionism, according to which it would be enough knowing the internal components of a system and their spatial arrangement to explain its behaviour.

[5] Note that, if the argument were grounded on cases where only a bottom-up explanation is required, Mitchell could argue that the system is a composite system.

cases where the integrated explanation is less parsimonious than a non-integrated one, and only higher-level details matter (pragmatic consideration).

For the first example, let us consider Fagan's (2016) study of the use of clashing modes of explanation in stem cell research as an example in which the scientific (sub)community would reject an integrated explanation due to the contrasting scientific goals and epistemic virtues that two (sub)communities require from a scientific explanation. Particularly, Fagan focuses on stem cell research. Stem cells are a subset of cells in multicellular organisms with the capacity to self-renew and differentiate into other cell types. Stem cell scientists investigate the source(s) of these capacities. Stem cell research is a highly experimental field grounded in molecular biology, where the biologists are interested in discovering the molecules and the interactions underlying these capacities—constitutive complexity—as well as understanding the relationship between these capacities and cancer, regeneration, ageing and development more generally. As such, it is a field that seeks something akin to what has been recently characterised as mechanistic explanations, i.e., the discovery of the entities, their organisation and their interactions that jointly produce the phenomenon of interest (Bechtel & Richardson, 1993; Machamer et al., 2000; Fagan, 2012; Glennan & Illari, 2018). In stem cell research, the entities are specific molecules that serve as markers of stemness, and the activities refer to the functions that genetic regulatory networks activated in stem cells play. Importantly, an essential component of stem cell research is that experimentalists engage in cell level phenomena to investigate these elements. In a nutshell, thus, it could be argued that stem cell research is a part of molecular biology seeking to mechanistically understand how certain specific molecules and their interactions give rise to stem cell capacities in certain cells of multicellular organisms. We could claim, with Fagan, that these research practices define the explanatory norms that this scientific (sub)community take as necessary for considering a scientific explanation satisfactory. These norms are in turn simultaneously linked to the goal of using molecular knowledge to manipulate stem cells in relation to human health.

In addition to this research strand, Fagan (2016) describes a second (minority) approach in the study of stem cell biology emerging from systems biology (Green, 2022). Instead of focusing on the experimental and molecular sides of stem cell research, scientists in this community focus on mathematical modelling, in the tradition of dynamic systems theory. Their purpose is to discover how genetic regulatory networks in stem cells vary over time in such a way that stem cell capacities are feasible—dynamic complexity—so that they can uncover the general principles underlying these capacities. To study this, they build mathematical random networks identified with the cell, whose nodes represent genes and products of gene expression. The pattern of gene expression values for each node in the network at a time *t* is defined as the state of the cell. The pattern of gene expression in the network can show two possible structures: a robust network structure (in which the stem cell state is taken to be self-renewal), or a stochastic state (in which the stem cell state is interpreted as generating a specialised cell). Note that this approach is merely abstract, as the mathematical structures are taken to stand for genetic regulatory networks, but the method is purely theoretical, not experimental. This type of modelling allows uncovering the general conditions and the probabilities with which a stem cell will transition between a self-renewal and a differentiation state. Secondly, it also allows the modellers to make predictions based on some general principles: for instance, they can discover when pluripotency will be irreversibly lost. Thirdly, it is claimed that these models provide universal patterns about stem cells, on the basis that if the initial conditions of the model are ever empirically satisfied, then the predictions concerning differentiation or self-renewal will necessarily follow. Finally, the

models do not include any molecular details: they only include abstract knowledge about genetic regulatory networks that allows identifying a typical dynamic behaviour under certain initial conditions; this task does not require the networks to be identified with any real molecular network in stem cells[6].

Fagan (2016) claims that the model theoretic approach to stem cells behaviour conceives explanations in Hempelian terms (Hempel, 1965): scientists thus assume that a good explanation consists in building a general model, grounded on universal generalisations that allow yielding predictions about the system. Note that, as such, it clashes directly with mechanistic approaches to explanation, which renounce generality in their pursuit of the specific molecular details allowing manipulation. This has consequences with regards stem cell research, leading to an epistemic incompatibility that causes that both approaches cannot be integrated: on the one hand, the experimentalists claim that the model theoretic approach should be rejected because it fails to describe the molecular details of the system, and because it fails to associate the abstract networks of their models to any real genetic network in stem cells. On the other, modellers criticise experimentalists due to their failure to uncover any general principles that could be applied to different systems. The dispute cannot be solved unless one of the (sub)communities give up to its preferred view of explanations, as well as to their specific goals, and take each other as significant contributors to the conversation about stemness. But, in the meantime, the two approaches are impossible to integrate *in any sense*, and this is so even if one of the approaches is more concerned with the investigation of constitutive complexity and the dynamic complexity of the same phenomenon.

Our second example derives from Batterman & Green's study of multi-scale modelling (Batterman & Green, 2021; Green & Batterman, 2021). Multi-scale modelling consists in applying different mathematical models to capture the behaviours of different temporal and spatial scales of the same system. It usually encompasses three levels: the micro-scale, the macro-scale and the meso-scale. Multi-scale modelling is abundant in physics and engineering, although it has lately been used in the biomedical sciences to study diseases beyond the molecular level, particularly those affecting the cardiovascular and musculoskeletal systems, proving useful to gain knowledge about problems such as heart failure and osteoporosis. Batterman & Green (2021) make two points that are extremely relevant for assessing the universality of integrative pluralism. Firstly, drawing on Wilson (2012), they contend that mathematical models at different scales are often incompatible, because they rest on different theoretical assumptions, which restricts the differential equations being used to the specific scale where they are applied. As a result, "in many contexts, the difficulty of bridging between scales makes modellers focus only on a specific scale of analysis" (Batterman & Green, 2021, p. 1162). Secondly, drawing on Stoneham & Harding (2003), they claim that, epistemologically, it is more practical to choose a scale of analysis and remain there than trying to connect "atomic and continuum scale models" (Batterman & Green, 2021, p. 1162). This second point suggests that there are pragmatic reasons to avoid integration in the first place.

To illustrate this case against integration, let us consider their example of how meso-scale modelling is preferable than, and even incompatible with, micro-scale and macro-scale modelling of bone fracture (Batterman & Green, 2021). In bone fracture research, modellers identify three length scales (micro, meso and macro), being bones homogeneous at the macro-scale but formed by many different and complex structures at the meso and micro-scale. At the meso-scale level, researchers identify two tissues: trabecular and cortical bones.

[6] See Winther (2006) for a proposal of different ways of biological theorizing.

These tissues have "important implications for the physiological properties of bones" and, particularly, they are the ones that need to be studied to explain the relevance of the network structure of the bones and its connection to bone fracture and osteoporosis (Batterman & Green, 2021, p. 1171). The cortical bone is made out of osteons, concentric cylinders embedded in the bone, and it contributes greatly to the stiffness of the material, while trabecular bone "fills the interior and end of long bones" (Batterman & Green, 2021, p. 1171) and it is made of trabeculae, a type of strut that forms a three-dimensional network, known to resist compression. The combination of these two types of bone—the cortical as a more rigid part, and the spongy structure of trabecular as the flexible one—makes the bone resistant to fractures. This is because the meso-scale provides the information about the bone material density of the cortical and the trabecular bones, which in turn allows the obtention of the parameters that are required to plug in the model equations. Knowledge of this bone material density allows generating models that discriminate between young and elderly people, or people with osteoporosis or any other disease affecting the susceptibility to bone fracture. This is a result of the fact that the topology of the network structure changing the susceptibility to bone fracture is sited at the meso-level. Therefore, the meso-scale provides the relevant information to explain the bone susceptibility to fracture.

However, if one zooms in and studies the micro-level (nano level to be precise), it turns out that the information about the meso-scale is conceptually lost, and the components at that level fail to account for the resistance to fracture. Particularly, at the micro-level, the bone consists in an array of sheets called *lamellas*, which are made out of apatite crystals, collagen and water (Batterman & Green, 2021). The geometrical structure at this nano level turns out to be irrelevant to account for the stiffness of bones because the complex geometries displayed at the meso-scale are not visible at the micro-scale. Concretely, models of the micro-scale suggest a bone material density that does not allow distinguishing between the bone structure of young and elderly people, or people with osteoporosis and people without it. Instead, it suggests the same bone material density measure for everyone. Thus, micro-level modelling is epistemologically irrelevant for predicting and explaining bone susceptibility to fracture. Finally, given that the models at the meso-scale and the micro-scale might be theoretically incompatible, it follows that the micro-level is not just unnecessary for an explanation of bone fracture, but would even turn a meso-level explanation into an integrated unexplanatory picture of bone fracture.[7]

This example shows that, in some cases of multi-scale systems, modelling at a meso-scale is enough to capture the behaviour of the system and to answer the specific questions that scientists are addressing.[8] This shows that an integration may be either theoretically impossible (in cases when the mathematical models are theoretically incompatible) or, if

[7] Here we are assuming that the introduction of irrelevant information into the explanans makes it unexplanatory. This is a common position in philosophy of science, well-known in the debate about explanation, so we will not discuss it here. See e.g., Díez (2014), Woodward & Ross (2021).

[8] Some, but not necessarily all cases of multi-scale modelling. As a reviewer has pointed out, there are examples in which the scientists developing a multi-scale model claim that integration is required to explain the phenomenon. A case at point could be the explanation of cardiac electrophysiology, as studied by Carusi et al. (2012). The driving idea is that cardiac electrophysiology can only be explained by building a system that simultaneously considers and integrates information from a wide range of spatiotemporal scales, including both ionic and whole organ level information. In their view, the multi-scale system of cardiac electrophysiology can only be validated holistically, by analysing all the levels simultaneously. While this is what the scientists claim, though, it may be worth investigating whether integration in that case works as they claim, or the same kind of objections raised by Green & Battermann (2021) could also apply. We leave the exploration of these issues for future work.

potentially possible, integration is not epistemologically preferable, questioning the core assumptions underlying Mitchell's integrative pluralism.

Despite the limitations about the scope of integrative pluralism that we have highlighted here, Mitchell could reply by appealing both to pragmatism and the method of joint refinement (Mitchell, 2020). Concerning the former, she could claim that the fact that scientists *decide to focus* only at one of the levels does not in fact challenge integration, because their choice could be the result of a specific pragmatic consideration. If focusing on more than a level does not provide better means to reply to a scientific question or a scientific goal, then integration should not be pursued. Concerning the latter, Mitchell could claim that joint refinement would allow reconciling explanations across levels in a scenario in which the mathematical models at lower and meso-levels conflict with one another. The method of joint refinement could in fact show that there are ways of making the inconsistent predictions compatible and at the same time identifying biases causing the divergent predictions. This would show that the impossibility of integration is only apparent, and a better picture of the system that integrated both levels could be provided, understanding both models as partial representations (Mitchell, 2020).

While none of these answers would be incorrect, we still think the two cases we have discussed so far show that the epistemic purposes and standards of the scientific (sub)community strongly constrain the feasibility of integration. Another way of looking at this is understanding these two critical points as unveiling grounding epistemic assumptions of Mitchell's integrative pluralism. Particularly, integrative pluralism is based on the assumption that the epistemic aims of the researchers in a scientific (sub)community are always the same, and the same is the case for what the (sub)community considers epistemic virtues. But a closer look at certain dimensions of contemporary scientific practice suggests that a misalignment between these aims or shared values among the members of a (sub)community strongly compromises the feasibility of integration.

4. Complexity as the Sources of Integration in the Life Sciences

The two examples we have considered in section 3 are however prone to a response from defenders of integrative pluralism. A defender of integrative pluralism may object that even if the details of the lower-level do not directly matter for the higher-level explanation (more noticeably, in the case of stem cell research), the complex world is so that it ontologically integrates elements of both levels. For recall that the integrative pluralist only requires that explanations at different levels are compatible and/or mutually constraining to speak of integration. Thus, one potential response to our objection could go like this: while information about the lower-level system is not necessary to build a higher-level model, at least of the causal type, it is minimally required at a descriptive level to know the type of empirical system that the scientists are dealing with. This is because higher-level models are usually mathematical models, and without information about the lower-level components, the mathematical model could be applied to almost anything that follows the specific higher-level dynamics. Therefore, our argument in the previous section does not prove that integration isn't happening. It simply proves that integration does not occur at the causal level, but it will likely occur at the level of the descriptions.

Note that this argument can be easily applied to Fagan's (2016) and Batterman & Green's (2021) points. In the case of stem cell research, it is correct that any mathematical modelling aiming to explain stem cell states does not require engagement with experimental

methods. Yet, every element in the mathematical models needs to be interpreted as if they corresponded to certain lower-level entities or activities. For instance, as Fagan acknowledges, nodes correspond to genes or gene products, and networks are interpreted as gene regulatory networks. On the other hand, in the case of bone fracture one could argue that even if the relevant topologies instantiate at the meso-level, it is necessary to know the specific composition of the bones to realise that the models are models of bone fracture. Alternatively, this may lead to confusions with regards to the interpretation of the model, and the types of empirical system that it is intended to apply to. Thus, it would seem as if Mitchell's integrative pluralism were a good account of the epistemic situation, because despite the difficulties, scientists are in fact integrating information across levels.

There are however two ways of interpreting this argument, and how it supports Mitchell's integrative pluralism. First, a pragmatic interpretation, which simply suggests that scientists interpret their higher-level equations *as if* they were talking about lower-level entities, activities and their organisation. We think this interpretation is at odds with how Mitchell conceives integrative pluralism, as it is incoherent with her view that integrative pluralism is necessary for the specific way in which some systems are complex (reason 3 in section 2). For even if pragmatic elements also play a role in her account, she is also convinced that this pragmatic choice results from how the biological word is ultimately complex. This leaves room to a second, ontological interpretation of the argument, according to which integration is required because each level provides causally relevant information. Note that this would be coherent with the notion of integration via levels of analysis that she developed as a way to set limits on her pluralism. If different levels provide both distinct but jointly necessary information of the phenomenon, it must be because these levels are part of the complex system itself, and thus our models only provide partial combinable representations of these systems.

We take Mitchell's position to be more closely aligned to this second choice, especially given that she is presenting integrative pluralism as a theory to explain complexity which is coherent with the partiality of representation. What follows from this argument is therefore that, regardless of whether scientists epistemically decide to integrate or not their explanations, *for pragmatic reasons*, the existence of an ontological integration is a fact of how the complex world ultimately is: a world in which potential properties at the higher-level always need to result from the composition of elements at the lower-level, and thus integration is itself necessary in most systems. While Mitchell does not explicitly develop this argument—at least to our knowledge—we believe this argument coheres well with her own view of complexity in the biological world. So, a more coherent response to Mitchell will require arguing why Mitchell's view of the complexity of the biological world is, at least, incomplete. Let us present her view here, delaying why we believe it is incomplete to the next section.

Mitchell (2008) addresses the problem of biological complexity, with special emphasis on the features that make the complexity that is found in the biological world distinctive and different from the complexity one may find in other sciences. This leads her to differentiate three types of complex systems: *aggregative*, composite *component* and composite *integrative* systems. Aggregate complex systems are those whose properties are simply aggregates of the properties of the parts, and thus its behaviour is captured by investigating the behaviour of the parts. Mitchell (2008) illustrates the case with the sitting behaviour of *Caenorhabditis elegans*, which is an outcome of bearing the mutant allele egl-4. Composite component complex systems are those whose behaviour is determined by the behaviour of the parts plus their organisation. An example is lactose metabolism, which

depends on both the bearing the gene *LCT* as well as all the regulatory genes involved in the genetic network of lactose metabolism. Finally, composite integrative complex systems are those whose properties are emergent (Mitchell, 2012), and thus the properties of the higher-level partially determine the properties or behaviours of the parts. She illustrates her case with honeybees, where the specific needs of the colony determine the genetic expressions of individual bees (see also Triviño & Suárez, 2020). To explain the behaviour of an integrative complex system thus it is not possible to follow a reductive strategy and appeal to its parts and their organisation, but an integrative strategy must be followed (more in section 5). It must be noted, although in passing, that the type of complex system that a specific empirical system is excludes the possibility that it can be of any other type. In other words, if a system is a composite system, then it cannot be an integrative system, and the other way around.

Mitchell (2008) believes that the type of complex system that is being analysed will determine what the best research strategy for explaining certain phenomena will be, thus suggesting an ontological primacy when it comes to choosing between competing research strategies. Generally, she starts acknowledging, following mechanistic philosophy, that the best research strategies to analyse complex systems are decomposition and localization (Mitchell, 2008; Bechtel & Richardson, 1993; Machamer et al., 2000; Glennan & Illari, 2018). Scientists will start their research by decomposing a complex system into its functional parts, studying the behaviour of each of these parts and explaining the phenomena by appealing to the function of these parts and the way in which they are organised. However, the way in which these mechanistic strategies are used and/or integrated with other explanatory strategies will depend on the type of complex system that the scientists are investigating. If the system is an aggregate system, then reductionistic strategies will be optimal, and it may be enough to decompose the system in its component parts and study the behaviour of one or more of these parts, to understand the phenomena. This strategy is applicable to phenomena where there is a high degree of biological determinism, because simply knowing how one specific part is—e.g., a mutated gene—will be enough to explain the phenomena—e.g., a disease (see Suárez, under review). If the system is a component composite system, a direct reductionist strategy will not work, although a partial reductionistic strategy will do. Partial reductionistic strategies are based on the independence of the parts and the near decomposability of the system. To explain the phenomena produced in these systems it is thus necessary to know both the parts that compose the system—and the behaviour of these parts—and the organisation of the system. This is because "higher-levels of organisation (…) will set the constraints of the behaviour of the single component" (Mitchell, 2008, p. 28). Finally, Mitchell thinks that in component integrative systems, reductionistic bottom-up strategies do not work because higher-level properties affect lower-levels, so top-down approaches are needed. This does not mean that knowledge of the parts is not required: it is. Rather, it means that it needs to be combined with knowledge about downward causation in the system[9].

Mitchell (2008) applies her analysis about the types of complex system to her study of major depressive disorders which we discussed in section 2. This leads her to interpret all the evidence about the case as evidence showing that the complexity of the interacting systems makes it impossible to reduce the higher-level feature—major depressive disorder—to lower-level causes. Additionally, she thinks that this shows how higher-level features—

[9] Following Green and Batterman (2021) top-down causation occurs when specific dynamic behaviours describable at the higher-level can potentially be instantiated by a broad range of possible lower-level entities or states. This is what occurs in the example of major depressive disorders that we described in section 2.

like stressful episodes—can have top-down effects—serotonin alteration—in interaction with lower-level causes—specific genetic variants. This illustrates how multilevel causes and multiple components must interact to provide a deeper analysis of this type of disorder. This is consistent with Mitchell's view that the type of complex system that produces a specific phenomenon *determines* the type of research strategies available to the scientists. Given that the study of major depressive disorders must be assisted by top-down knowledge explaining how some social influences affect the expression of the trait, it seems clear that the system is what Mitchell calls a component integrative system, being the latter the main type of system for which she conceived her views about integrative pluralism.

While we do not necessarily disagree with most of the points raised by Mitchell about complexity, the different types of complex systems that exist and the research strategies needed to investigate, we suspect that her taxonomy of complexity does not capture every dimension in which a complex system *can* be complex. Our claim will be grounded on the existence of complex systems where top-down, *but not bottom-up*, causation occurs due to the structure of the system, and thus interlevel integration is ontologically unachievable for that specific phenomenon.[10] The existence of this type of system is at odds with Mitchell's view of complexity, setting some limits to it.

5. Integration is Not Always Ontologically Achievable

Our argument here will be based on the type of causality imposed by the higher-level, and how this ontologically affects the lower-level in systems that exhibit a network structure, and exert it via downward causation (Emmeche et al., 2000; Green, 2018, 2020; Suárez & Triviño, 2019; Moreno & Suárez, 2020). We contend that in these systems that there are no bottom-up causes, but simply a relation of constitution between levels. That is, the relationship between the lower-level and the higher-level is non-necessitated by the higher-system to exhibit its characteristic causal profile, but rather a contingent matter.

Downward causation is a relationship between levels in which the higher-level is assumed to synchronically depend on the lower-level in terms of composition (i.e., there is no any other material structure in the higher-level different from the components of the lower-level), but to retain a causal autonomy with respect to it that manifests diachronically. When a system exhibits downward causality, the system reduces the degree of freedom of its component parts and in doing so it creates the potential for the appearance of new structures and functions that would be unlikely if there were not downward causation acting on the system. So, in a sense, downward causation harnesses the possibilities for the parts involved in the relationship while simultaneously generating a new possible space of possibilities. Green (2018), drawing on Emmeche et al. (2000), builds the concept on the notion of boundary conditions, "conditions under which a given mathematical model or equation holds (e.g., by specifying a value interval for the possible solution)" (Green, 2018, p. 1000). These boundary conditions thus ontologically characterise how the higher-level causally constrains the behaviour of the lower-level parts, so that their range of behaviours is always restricted to those delimited by the mathematical model defining the boundary conditions—which, by definition, must be narrower than the possibilities offered by the laws governing

[10] One may wonder why we concentrate on the case where the information comes from the higher-level and ignores the lower-level, rather than in cases where the explanation comes exclusively from the lower-level and its aggregated properties. The reason is that Mitchell acknowledges the existence of the latter cases, and argues that they are characteristic of systems that show aggregate complexity. However, she does not seem to admit systems that *only* respond to higher-level causation, and hence our criticism.

the behaviour of the lower-level parts. Note that this claim about the mathematical model must be understood here ontologically: it is not that the mathematical model itself constraints the behaviours of the lower-level parts, but rather that the instantiation of the specific mathematical structure represented by the mathematical model, due to the specific form in which the system is organised, constraint these behaviours. This suggests a stronger, ontological understanding of the concept of downward causation and of the way in which a system structure causally affects the actions of its lower-level parts.

Downward causation—through boundary conditions, or differently—is not unknown for the defender of integrative pluralism, and in fact is frequently adduced as an argument for it (Mitchell, 2003). However, it is defended in the context of an integrative view, in which downward causation *also* causes the system's behaviour, together with the behaviour of the lower-level causes. But the peculiarity of some network models when it comes to downward causation, though, is precisely that *their universality prevents attributing any genuine causal role in the production of the phenomenon to the lower-level parts*. Moreno & Suárez (2020, p. 157) have expressed the idea as follows:

> [Some network models look] for the establishment of similitudes between different empirical systems that have the same mathematical structure (e.g., computers, social networks, genetic networks, and metabolic networks).

The point we are making here is that these network models are empirically feasible because there are some underlying structures universally shared by a very heterogeneous set of empirical systems which are ultimately responsible for the systems' behaviours. The similarities between different empirical systems that Moreno and Suárez point out would simply be a way of explaining what ontologically occurs, especially since the discovery of these structures strongly depends on empirical manipulation, given the number of variables, algorithms and simulations that are required. Once these discoveries are made and the network is built, the properties that the network describes, as well as the global behaviour that the network entails, could and should be conceived as a feature of the world, i.e., as an ontological consequence of the organisation of parts.

The existence of this type of system provides a solid reason to think that the causation is merely top-down, and there is no real bottom-up relationship. This is due to the fact that once the organisation is instantiated, the parts that are related in a way such that the organisation instantiates will act following the rules of behaviour of the organisation, as the latter is epistemically captured by the mathematical model describing it.[11] Once this occurs, the parts can have *any* nature, being this the main reason why things as different as ecosystems, tornados or the World Wide Web, work the same way. This is manifested in the fact that the mathematical model describing these systems simply represent the component parts as nodes, and their relations as edges, without any consideration about the specific components of the system (see Deulofeu et al. (2021) for an analysis in the case of ecosystems). Mathematically speaking, this is reflected in the fact that researchers directly attribute properties and establish predictions on the basis of the algorithms that the mathematical system implements, or on the simulations run by a computer. These predictions are later attributed to empirical systems of very different types and are attributed on the basis of the ontological higher-level organisation of the systems, not their lower-level natures (Huneman, 2010). The ontological peculiarity of the systems described by this type

[11] This point about the epistemic role of the mathematical model does not mean that our argument is ontological, i.e., about how the system is ontologically built.

of mathematical models is that they bear properties that do not depend on the properties that the lower-level elements bear.[12] Instead, network properties are strongly independent from the lower-level and, at most, they constrain how the latter behave and, in this sense, they causally govern their behaviour.

The ontological possibility of integration in systems realising a network structure is in most cases ruled out, because no specific part of the empirical system can be causally mapped with a concrete functional role accounting for the global behaviour of the system (Moreno & Suárez, 2020). The latter is an essential aspect for attributing causal properties to the lower-level, at least when it comes to the ontology of mechanisms, which Mitchell embraces as the best explanatory strategy in the life sciences. In some of the systems realising a network structure, the behaviour of each part (lower-level) is causally produced by the whole (higher-level), and no specific part can be causally mapped with a functional role in the network. Deulofeu et al. (2021) express this idea by saying that the (lower-level) causal story is "lost", and Moreno & Suárez (2020) reinforce the idea by arguing that some systems are such that the parts simply lack these functional roles. Particularly, Moreno & Suárez (2020) refer to cases in the boundary between psycho-chemistry and the life sciences in which the interacting organic elements have not yet evolved to create the necessary conditions to guarantee that each part plays a specific causal role. In these cases, the parts associate and act following the governing rules of the network, lacking any specific causal role in isolation. The point we want to emphasise in this paper, and which complements the previous accounts, is that this may reflect a peculiarity about the ontological structure of the world, and the way in which certain higher-level properties may govern certain aspects of it. The properties exhibited by the networks would govern many different types of particles across many different fields, and thus should be taken to have an ontological priority over the properties of the (heterogeneous) components of the network. In these cases, we contend, neither aggregate nor compositional complexity (section 2) would apply, as we will be facing a new type of complexity in which only the higher-level properties act causally and downwardly. When this occurs, integration is not ontologically achievable, even though scientists pragmatically claim that the nodes of their networks correspond to specific components. The relationship between levels in this case would be merely compositional, but the lower-level would play no causal role on the higher-level. Therefore, integrative pluralism is faced here with a limitation in its study of complexity, as it is a case where integration is not feasible and where integration in a strong sense would not be a feature of better science[13].

In conclusion, either the defender of integrative pluralism defends that integration is all a question of desirability; or they argue that the type of ontological impossibility of integration that we have described as an "in principle" situation is a mischaracterization of the empirical scenarios. Regardless of their choice, the existence of the second alternative in turn reveals another underlying assumption of Mitchell's integrative pluralism, namely: that there are no complex systems where the higher-level properties account for everything that happens, with no necessity of including knowledge of what's going on at the lower-level.

[12] This does not mean that the system has "something additional" (i.e., a different substance) to lower-level components. The point is that these lower-level components play a compositional role but play no causal role in the system itself.

[13] We are conscious that the ideas expressed in this section are rather schematic and need more development. However, we wanted to present it here because we genuinely believe that it allows identifying an underlying assumption in Mitchell's work.

6. Conclusion

Mitchell's account of integrative pluralism is an essential contribution to the study of complexity in contemporary philosophy of science, which has helped to clarify many scientific practices, has inspired scientists to do better science, and will definitely endure over time. However, it would be illegitimate to conclude from this that integrative pluralism is the way of carrying out scientific research that scientists should always aim for in dealing with complexity. In this vein, in this paper we have argued that there are some scientific practices in which integration is not epistemically desirable or ontologically achievable. These practices include two sets of cases: one, in which models across levels are either epistemically incompatible or scientists pragmatically prefer explanations at one level instead of integrative explanations; another, in which causation only runs at the higher-level and the lower-level is ontologically irrelevant. The specification of these two conditions in which integrative pluralism is not applicable serve to better frame the position and allow discovering some underlying assumptions embedded in it which had been previously unnoticed by other researchers. Particularly, we have shown that integrative pluralism requires, epistemically, that scientists agree on their epistemic goals and their conceptions of explanation, and ontologically, that complex systems are either aggregate or component.

Overall, our paper shows that while integrative pluralism may be an excellent strategy for dealing with certain forms of complexity, there may be some forms beyond the ones originally distinguished by Mitchell which are incompatible with the integrative strategy that she has put forward. In any case, integrative pluralism still remains an extremely valuable tool for philosophers of science, which should be studied with attention and applied across disciplinary fields. Our contribution only shows that some caution not previously envisioned by other researchers should be taken into account when applying it to new research areas.

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