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ORIGINAL RESEARCH

A Monist Proposal: Against Integrative Pluralism About Protein Structure

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Abstract
Mitchell & Gronenborn (2017) propose that we account for the presence of multiple models of protein structure, each produced in different contexts, through the framework of integrative pluralism. I argue that two interpretations of this framework are available, neither of which captures the relationship between a model and the protein structure it represents or between multiple models of protein structure. Further, it inclines us toward concluding prematurely that models of protein structure are right in their contexts and makes extrapolation of findings from one context to another seem unwarranted. Instead, protein structure determination ought to be understood as *modestly monistic*. There is one model for every protein in each physicochemical context, and models of the same protein produced in different contexts are compatible with one another. 'Integrating' multiple models amounts to extrapolating from one context to another; this is possible because the effect of context on protein folding is relatively weak and predictable. Modest monism better describes the practice of protein structure determination than integrative pluralism and enables greater attention to how context affects protein folding.

1 Introduction

Proteins are complex macromolecules. Polypeptide chains typically contain between 50 and 2,000 amino acid residues and can adopt one of a staggering number of folded states.[1] Experimental techniques give us some information about this folding, reduc-

[1] For instance, there might be 3^{100} possible states for a polypeptide chain of just 100 amino acids, and this is on the conservative assumption that each amino acid can adopt only three conformations (Levinthal, 1968, 1969).

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ing the number of prima facie possible structures. But structural biologists ultimately want to know how proteins fold in their functional environments, which differ substantially from experimental conditions. In their functional environments, proteins interact with other molecules and undergo post-translational modifications. In contrast, experimental techniques require proteins to be purified and placed under different physicochemical conditions, specific to each technique. For instance, X-ray crystallography relies on crystallized proteins, whereas solution nuclear magnetic resonance (NMR) spectroscopy uses proteins in solution; each experimental context subjects a protein to temperatures and *p*H values that differ from those of its native environment. Computational techniques for determining protein structure similarly do not take features of a protein's functional environment into account; moreover, they generally rely on input from experimental data to help reduce the large number of in-principle possible structures compatible with an amino acid sequence. How, then, do biologists determine the structure of proteins in their native environments from data produced under different conditions?

According to Sandra Mitchell and Angela Gronenborn (2017), they do so by integrating multiple models, each of which constitutes a partial representation of protein structure.[2] Nevertheless, the relationship between multiple models is "one of integration that maintains pluralism, rather than unification that eliminates all but one fundamental, complete model" (Mitchell & Gronenborn, 2017, 705). Mitchell and Gronenborn thus take protein science to provide a new example of *integrative pluralism*, a middle-ground position between strong pluralism and unificationism or monism.[3]

In this paper, I argue that integrative pluralism mischaracterizes protein structure determination. Although biologists do indeed produce multiple models of protein structure, each such model corresponds to a particular protein in a given experimental context. That is, each experimental or computational technique produces one model per protein structure-in-context, rather than many models that cannot be combined without information loss. The "integration" of multiple models produced using different techniques is best understood as the *extrapolation* of knowledge about a protein structure-in-context to knowledge about the structure of another (possibly different) protein in another context. Such extrapolation is possible because although context affects protein folding, sufficient similarities between proteins in different contexts are maintained. Further, different experimental techniques are based on theories that do not contradict one another; the models computed from data produced by such techniques are compatible.

This paper thus defends a view of protein structure determination that I call *modest monism*. Modest monism has ontological and epistemological dimensions. A protein exists as a single structure in a given context at each point in time; although context affects how proteins fold, its effect is not so significant as to preclude extrapolation of findings from one context to another. Knowledge about each protein structure-in-context can be captured in a single model, and multiple models of structures-in-

[2] Similarly, Mitchell (2020) argues that different models constitute different perspectives on protein structure.

[3] See also Mitchell (2002, 2003, 2009, 2020) and Mitchell & Dietrich (2006).

context can be unified when they are integrated via extrapolation between contexts. That is, multiple models are necessary, but only because each represents a particular protein in a given context at a particular time; a plurality of models is not needed for knowledge about a single such structure.

The paper proceeds as follows. I begin in Sect.2 by considering pluralism more generally, explicating what integrative pluralism might entail, and introducing modest monism against this backdrop. Then, in Sect. 3, I show that, although information from multiple models is indeed used in protein structure determination, the relationship between these models is not a sort of integration that maintains pluralism. In Sect. 4, I consider the consequences of viewing protein structure determination through the lens of integrative pluralism. I show that doing so encourages too-hasty inferences to the validity of models in their contexts and makes it difficult to justify the extrapolation of findings from one context to another. In Sect. 5, I present a positive case for modest monism. I argue that the common causes responsible for protein folding in different contexts justify monism, which further enables us to pay closer attention to how, precisely, context affects protein folding. Finally, I conclude in Sect. 6 by explaining why the monism defended in this paper is modest.

2 Pluralism, Integrative Pluralism, and Modest Monism

What is scientific pluralism, and how is it related to monism? This section begins by charting the landscape on which these views lie (Sect. 2.1). Then, it considers what integrative pluralism might entail by examining Mitchell's (2002, 2003) discussion of this view in the context of understanding the development of cooperative behavior in social insect colonies (Sect. 2.2). Finally, it introduces modest monism as an alternative to integrative pluralism in the protein structure case (Sect. 2.3).

2.1 Varieties of Pluralism

Scientists have many aims and rely upon a variety of methods in pursuing them. The result is a multiplicity of models, theories, and explanations. Scientific pluralism is the view that this multiplicity does not constitute a deficiency in scientific practice, to be eliminated at some ideal end of inquiry in favor of a single, unified understanding of all natural phenomena. Rather, it is necessitated by the fact that these phenomena are complex, and indeed, may simply be such that multiple methods, models, theories, and explanations are necessary to characterize them (Kellert et al., 2006). Further, the scientists who study these phenomena have limited perceptual and cognitive capacities. It is thus a mistake to hope that we can bridge the gap between the complexity of natural phenomena and our limited capacity to perceive and comprehend them. Scientific monism, in contrast, acknowledges the multiplicity of models, theories, and explanations in science, but nonetheless takes the ultimate aim of any given science to be "a single, complete, and comprehensive account of the natural

world (or the part of the world investigated by [it]) based on a set of fundamental principles" (Kellert et al., 2006, x).[4]

Although scientific pluralism is commonly presented as a methodological and epistemological thesis, it is compatible with a monistic ontology, one that posits a single underlying reality.[5] Mitchell (2009, 23), for instance, does not deny that although "scientists [from different fields] study different aspects of the one world, […] they are all studying the *same* world."[6] Instead, her pluralism opposes the view that there is a single, privileged description of that world. This compatibility illustrates a general point: pluralism (or monism) in one sense does not entail pluralism (or monism) in another. In particular, and importantly for our purposes, methodological pluralism leaves open the possibility that multiple models in some domain will ultimately converge on a single model, or that multiple explanations can be unified.

One goal of Mitchell and Gronenborn's paper is to argue that methodological pluralism will persist in protein science, given the complexity of a protein's functional environment and the partiality of information provided by any computational or experimental technique. They are certainly right about this, and I will take methodological pluralism for granted in what follows.[7] I will further take for granted ontological monism. A second goal of their paper, however, is to argue for epistemic pluralism. Accordingly, the present paper will primarily be concerned with pluralism about models. Along the way, we will also address the related issue of explanatory pluralism.

2.2 What Might Integrative Pluralism Entail?

Mitchell's integrative pluralism seeks a middle road between pluralism and monism. Before turning to the case of protein structure, it will be instructive to examine another example of how she characterizes this view. Mitchell (2002, 2003) argues that explanations of the development of cooperative behavior in social insect colonies require multiple idealized models, each of which targets a subset of relevant causal factors. These models are integrated only upon application to a particular insect colony. For instance, a model that explains division of labor by appealing to genetic diversity represents an insect colony as genetically diverse, but otherwise uniform; a model that accounts for division of labor via learning diversity represents

[4] This is the first of five tenets of monism that Kellert et al., (2006) list, and is the most relevant for the foregoing discussion.

[5] The idea of a single reality is compatible with the view that we can have multiple, equally good taxonomies of the entities in that reality (see, for instance, Craver 2009, Dupré, 1993, Ereshefsky & Reydon, 2015, Mitchell, 2009, and Slater 2009).

[6] See also Mitchell & Gronenborn (2017, 707).

[7] In fact, John Kendrew's Nobel Prize lecture, which serves as a foil for Mitchell and Gronenborn, might be interpreted as sharing this view. Kendrew thought that protein structure prediction from amino acid sequence alone "will not come soon," but should be possible only "in the very long run" (1963, 1266)—certainly not within fifty years, as the title of Mitchell and Gronenborn's paper suggests. Recognizing the complexity of the structure of myoglobin—which itself is simpler than most proteins—Kendrew could not "even hazard a guess as to why the helix content of myoglobin is so high, let alone see how to predict its structure in detail [from its amino acid sequence alone]" (ibid.). Instead, he thought, experimental techniques would continue to be indispensable for determining protein structure.

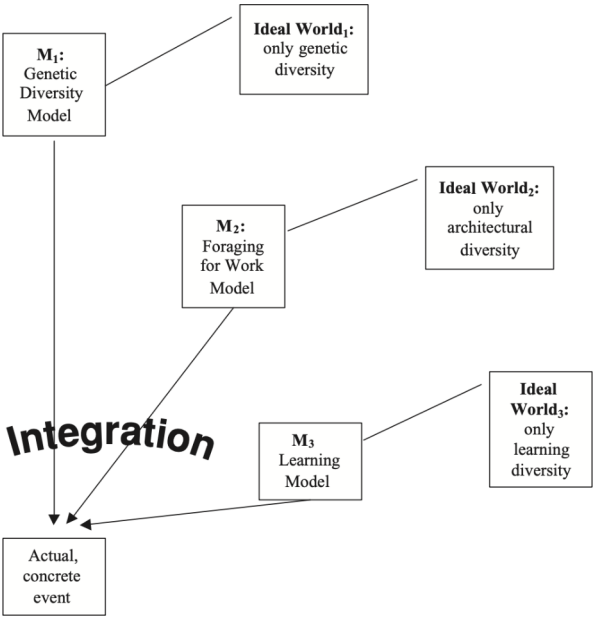

Fig. 1 Integrative pluralism in the case of the development of cooperative behavior in social insect colonies. Multiple models of social insect colonies are integrated upon application to a concrete event. Reproduced from Mitchell (2003, 215).

the colony as exhibiting only learning diversity among its members, which are otherwise identical; and so on for models isolating different causal factors. Multiple such models are integrated to explain an actual, concrete phenomenon—cooperative behavior in a *particular* insect colony—rather than the development of cooperative behavior *in general*. A multiplicity of models necessarily exists at the theoretical level, which is best understood pluralistically. Integration takes place only at the level of explaining a concrete phenomenon, where "there is only one causal history that, in fact, has generated [that] phenomenon" (Mitchell, 2003, 216) (Fig. 1). Multiple models at the theoretical level provide a menu from which models might be selected for integration in any particular instance, where different causal factors may be more or less significant.

Integrative pluralism has been criticized on the grounds that it ultimately reduces to monism, since pluralism is an appropriate description only at the theoretical level, and not in the explanation of concrete phenomena (Fehr, 2006; Kellert et al., 2006; Plutynski, 2004). Mitchell & Gronenborn (2017) do not address these criticisms, nor do they spell out precisely how the integration of multiple models in the case of protein science is a form of genuinely pluralistic integration.[8] So let us consider another proposal for what integrative pluralism might amount to in the social insect colonies case. I will show that this proposal can equally be applied to the protein structure case, permitting an alternative interpretation of that case, and of what integrative pluralism might entail more generally. This will enable us to interpret Mitchell and

[8] Rather, they illustrate this thesis using examples, which I consider in the next section. Here, I am interested in understanding what integrative pluralism might entail in more general terms.

Gronenborn's (2017) position in a way that addresses the criticism that integrative pluralism collapses into monism.[9]

Fehr (2006) argues that explaining the evolution of sex by simply integrating multiple explanatory models would result in an impoverished understanding of how sex evolved. Different explanatory models are developed within different biological subdisciplines. These models propose different kinds of mechanisms for the evolution of sex, and operate at different levels of selection, referring to different evolutionary benefits of sex. For instance, Muller's Ratchet (MR) describes a process whereby deleterious mutations accumulate within an asexual population. In sexually reproducing populations, it is possible for offspring to have fewer mutations than either parent, since each parent contributes only half of its genetic material to its offspring. MR thus explains why there are few ancient asexual species. It offers a group selection mechanism that works best when populations are small and the rate of deleterious mutations is high. In contrast, the DNA repair model explains the evolution of sex by reference to sexually reproducing organisms' ability to repair damage to the genome during meiosis. This model operates at the individual level of selection, targeting the molecular and cellular levels of organization, giving a mechanistic explanation of the biochemistry of meiosis. No model makes sense outside of its particular epistemic framework, the disciplinary and explanatory context in which it was constructed. And because different explanatory models refer to different organizational levels, each abstracts away certain aspects of sex and highlights others. We cannot integrate these models without losing some bits of information—information that each model is designed to showcase.

Fehr's explanatory pluralism is explicitly opposed to Mitchell's integrative pluralism. However, taking Fehr's criticism on board, Mitchell might plausibly amend her view to suggest that pluralism is necessary both at the theoretical *and* the concrete, phenomenal levels. This is consonant with an aim of integrative pluralism: to answer the question, "How can a diverse, well-confirmed, but irreducible set of theories be used collectively to achieve a more complete understanding than any of the theories taken in isolation?" (Mitchell, 2003, 186). Mitchell might acknowledge that, just as multiple explanatory models of the evolution of sex are each constructed in particular epistemic contexts, abstracting away certain features but not others, so too are the different models of social insect colonies. She could then agree with Fehr that each of these models is in fact required for a complete understanding of a concrete particular, some actual insect colony.

What we have, then, on this amended view, is the following. Multiple idealized models are integrated to explain the development of cooperative behavior in a particular insect colony. But because such integration merges different causal factors, it obfuscates the role each plays in the production of cooperative behavior in the insect colony in question. So, in order to maintain an understanding of the contribution of each causal factor—a crucial part of our understanding of cooperative insect behavior—we must retain a plurality of models after integration. Doing so might enable

[9] Mitchell proposes three other kinds of integration—mechanical rules integration, local theoretical integration, and explanatory, concrete integration—but these are less relevant to the protein structure case than the insect colonies case (Mitchell, 2003, 192–94; see also Mitchell 1992 and Mitchell et al., 1997).

us, for instance, to ask questions about the relative contributions of different causal factors, or to compare different insect colonies with respect to one causal factor or another.

Retaining a multiplicity of models after their integration, on this view, increases explanatory power. We end up with an integrated model, alongside multiple individual idealized models; all these models are necessary for a complete understanding of the development of cooperative behavior in that colony. Discarding the multiple idealized models after integrating them in the service of explaining the development of cooperative behavior in a *particular* insect colony would detract from our understanding *of that colony*. The retention of multiple models, and their necessity for understanding the phenomenon of interest, is what makes integrative pluralism a variety of pluralism: we should not expect to have that same understanding without the plurality of models, even at some ideal end of inquiry. Adopting this position would enable Mitchell to avoid the critique that her view collapses into monism. I therefore proceed by considering this reformulation alongside Mitchell's own account of integrative pluralism, showing that the escape from monism it could offer is not available in the case of protein structure.

2.3 Modest Monism About Models of Protein Structure

With this picture of integrative pluralism in hand, let us examine what a monistic framework for protein structure determination to which this view is opposed might look like. Recall that monism can be characterized as understanding the aim of any given science to be "a single, complete, and comprehensive account of the natural world (or the part of the world investigated by [it]) based on a set of fundamental principles" (Kellert et al., 2006, x). What might a single, comprehensive account of protein structure consist in? Notice, first, that monism need not require that there be a single model equally suited to describing the structures of all folding protein sequences. The fact that different proteins have different structures, each requiring different models to characterize them, is compatible with monism: the single, complete *account* distinctive of monism might include a multiplicity of *models*, one per protein. In other words, it would be absurd to demand of a monistic account of protein structure that it posit a homogeneous reality, wherein all proteins have the same structure. Instead, such an account can be heterogeneous and complex.

Further, as noted above (and as Mitchell and Gronenborn emphasize), a protein's structure is contingent upon its environment. A purified and crystallized protein subjected to X-ray crystallography, for instance, tends not to adopt the same folded structure it would in its native environment, where it interacts with other molecules in performing its function, moving more freely instead of being confined to a solid state. A monist could acknowledge the need for different models to describe the protein's structure in each of these contexts, again maintaining that different instances of protein folding can be explained by reference to a common set of factors, including the identities of the amino acid residues in the polypeptide chain and interactions with other components of the protein's environment. Having one model for each protein structure-in-context—that is, a protein adopting a particular conformation in a particular environment at a given time—is also compatible with monism.

This is especially important because structural biologists are not typically interested in investigating a protein structure *tout court*; it is not even clear what that would amount to, given that proteins always exist in some concrete in vivo or in vitro environment. The structure-in-context is the phenomenon that every model of protein structure represents. This does not preclude multiple models' use in *making inferences* about the protein's structure in its functional environment; but this is different from claiming that they are all models *of* that structure—a point we revisit in Sect. 4.2. Thus, the existence of multiple models, each representing different proteins in different environments, in particular conformations at particular times, does not by itself entail pluralism. It is compatible with protein structure determination being oriented toward the end goal of a single unified account based on a set of fundamental principles. We can have different models for each protein-in-context, unified by being explainable in terms of the same causal factors.

I will argue that protein structure determination is better understood as modestly monistic than as an example of integrative pluralism. Modest monism says that each protein molecule has a single structure at a given point in time. It does not deny that at any given time, a bulk protein sample used for techniques such as X-ray crystallography and solution NMR includes many molecules, each of which is in a slightly different conformation; nor does it deny that protein structure is dynamic, so each molecule's conformation changes over time. But the complexity of the underlying reality should not be taken to necessitate epistemic pluralism, especially when a more parsimonious explanation is available. Modest monism posits a common set of causal factors between various (in vitro and in vivo) contexts: the protein's primary sequence, together with factors particular to a given environment, such as temperature, *p*H, and the presence of other molecules, determine how it folds. Differences between protein structures in different contexts are thus attributable to differences between those contexts. Accordingly, the proximate aim of protein structure determination is a single valid model for each protein structure-in-context. Each experimental model of protein structure represents a snapshot of a protein molecule in a given context at a given time.[10]

In contrast to the social insect colonies or the evolution of sex cases, I will argue that multiple models are *not* required for understanding the structure of a protein-in-context. My argument proceeds via an extended critique of Mitchell and Gronenborn's characterization of the relationship between multiple models as one of "integration that maintains pluralism" (2017, 705). I show that such a characterization neither adequately describes protein structure determination nor helps to improve this practice. The framework of modest monism better captures the role that multiple models play and can offer normative guidance.

[10] The model of protein structure in the case of solution NMR or X-ray crystallography also reflects the uncertainty in the data, which is a result of relative lack of information and imperfection in the modeling method, including the inability to accurately model heterogeneous samples. In NMR, this uncertainty is conveyed by presenting an ensemble of 20–100 structures, each of which satisfies the data and stereochemistry sufficiently (and equally) well. In X-ray crystallography, atomic coordinates represent the average atomic coordinates in the sample, with their standard deviations given by the isotropic temperature factors.

3 What Is the Relationship Between Multiple Models of Protein Structure?

To show that the relationship between multiple models of protein structure is one of integration that maintains pluralism, Mitchell and Gronenborn would need to demonstrate that something akin to the social insect colonies case is also going on in the protein structure case, either on the original or amended interpretations of integrative pluralism: that multiple models from the theoretical level are integrated when they are applied to a particular protein structure in a given context (original interpretation), or that multiple models must be retained for a complete understanding of that structure-in-context (amended interpretation). In this section, I argue that the protein structure case differs significantly from the social insect colonies case on either of these interpretations. I show that, unlike in the insect colonies case, the models of protein structure that get integrated are not taken from the theoretical level. Rather, they are models of concrete phenomena, *viz.*, of protein structures-in-context.[11] Further, multiple models need not be retained for a complete understanding of a protein structure-in-context.

3.1 The Case for Integrative Pluralism

Mitchell and Gronenborn promote integrative pluralism as the relationship between multiple experimental models of protein structure, as well as between experimental and computational models.[12] Let us examine their arguments for such an understanding of each of these relationships in turn.

When possible, scientists investigate the structure of a protein using more than one experimental technique. No technique produces a model of the structure directly, but instead generates data that must be interpreted to construct a model. For instance, a crystallographic structure determination uses a diffraction pattern of X-rays scattered by the protein to produce an electron density map, charting how electrons are distributed in the molecule, which must be interpreted to yield atomic coordinates for the structure. An NMR structure determination generates a set of internuclear distances, which must also be interpreted in terms of structure; NMR models are presented as multiple superimposed structures, each of which is compatible with the data. Because interpretations rely on certain assumptions and approximations, they can contain errors; thus, data from a second experimental technique can help narrow down which of several interpretations (of data produced by a given technique) is correct.

Methods that combine information from multiple sources are known as *hybrid methods* or *integrative approaches* (Rout & Sali, 2019).[13] Mitchell and Gronenborn

[11] I will further argue that, strictly speaking, they are not even integrated; instead, inferences are drawn between them. I reserve this discussion for Sect. 4.2 and will continue to refer to the 'integration' of multiple models as shorthand.

[12] I call 'computational models' (and methods) what Mitchell and Gronenborn refer to as 'ab initio models' (methods). I prefer this terminology because it is broader: ab initio methods are a subset of computational methods for protein structure prediction (Dill & MacCallum, 2012).

[13] In fact, even traditional methods such as X-ray crystallography are best understood as integrative, since they consider X-ray diffraction data together with other information, for instance about chemical composi-

list several such methods: using an NMR structure to solve a crystal structure via a technique called molecular replacement; using a crystal structure as an input for an NMR model; or adopting a joint refinement approach, which enables the combination of X-ray and NMR data (2017, 718). Their function, according to Mitchell and Gronenborn, is to improve accuracy: because different experimental models are causally dependent on some of the same features, one model can correct for error or bias in another (see also Mitchell 2020). They consider the application of these methods to be an example of integrative pluralism between multiple experimental models in protein science.

Another such example, according to Mitchell and Gronenborn, comes from computational modeling, the aim of which is to predict folded structure from amino acid sequence. Computational models cannot do this in a purely theoretical way, that is, without relying on input from experimentally derived models. Mitchell and Gronenborn discuss the reasons why. Most significantly, computational modeling faces a pragmatic challenge. To predict structure from primary sequence, computational algorithms sample possible conformations and calculate their potential energies with the aim of identifying those in which potential energy is minimized. These conformations, in turn, are taken to be among the ones that the protein adopts in its native environment. But the number of possible conformations is colossal, making it difficult to generate the lowest free-energy conformations in the first place, given limitations in computational power.

One role for experimental models is therefore to help reduce the size of the space of conformations for an algorithm to sample. They offer clues as to which structures are most likely to be correct, and which region of the possibility space can be ruled out definitively, so that the algorithm need not run through the vast number of prima facie possible structures—a task that would be prohibitively time-consuming. Even if we could, in principle, predict protein structure from amino acid sequence, experimental models would still play a crucial role in such predictions. In this sense, their function is like that of extant experimental models in experimental protein structure determination, which aid in the interpretation of data from a particular experimental technique by eliminating a portion of the space of prima facie possible structures.

3.2 Why the Case for Integrative Pluralism Fails

Although both hybrid methods and computational modeling certainly enable the use of data from multiple sources in conjunction, it is not clear that they exemplify "integration that maintains pluralism" (Mitchell & Gronenborn, 2017, 705), no matter which interpretation of integrative pluralism we adopt. Recall that according to Mitchell's (2003) proposal, integration takes place at the level of explaining a concrete phenomenon, whereas the theoretical level is pluralistic. But in these cases, the theoretical level does not even enter the equation. As I emphasized in Sect. 2.3, each experimental model is instead a model of a concrete phenomenon, a protein in a particular context. Because computational models rely heavily on input from empirical models, they, too, do not constitute models at the theoretical level. If we amend

tion, stoichiometry, and geometry of a molecule (Rout & Sali, 2019).

Mitchell's (2003) position along the lines that Fehr (2006) suggests, these models are still best understood monistically: combining data from experimental structure determinations or using extant experimental models to narrow down the size of the space of conformations from which a computational algorithm can sample yields a single, unified model of protein structure—*of a particular protein, in a particular context*.

Mitchell and Gronenborn correctly point out that each of the models that is integrated is retained in the Protein Data Bank (PDB), a database holding experimentally derived structural information about proteins and other large biological molecules (Berman et al., 2000). But the cataloging of protein structures in the PDB is not by itself a sufficient argument for pluralism: the retention of a model does not entail its necessity for understanding the protein structure-in-context whose determination it was used to aid. When a model M_1 of a protein structure S_1 in the PDB is used to aid the solution of a novel protein structure S_2, yielding a model of that structure M_2, M_1's retention in the PDB does not facilitate continued understanding of S_2. Rather, M_1 is necessary for understanding S_1—again, in the experimental context in which its determination took place. Retaining M_1 in the PDB is a record of *that* experimental protein structure determination and a useful resource for information about S_1. Moreover, it has heuristic value for aiding the prediction of further protein structures S_n (for all $n > 2$). This is not a case of pluralism wherein multiple models are required to describe or represent a particular protein structure S_2 in a particular context.

Hybrid methods instead proceed by using data from different experimental or computational techniques to generate restraints on the structure being investigated. A scoring function assigns a degree of confidence to each restraint, indicating how well it accommodates the data. A sampling algorithm then finds the structural models that satisfy the restraints sufficiently well. Those models are subsequently validated using a set of data that had been left out of the original procedure. This process proceeds iteratively to narrow down the models that best fit the data from each technique, taking care not to overinterpret the data (Politis & Borysik, 2015; Rout & Sali, 2019; Srivastava et al., 2020).

The goal of this process is to incorporate data from multiple sources into a model of the protein's structure in its native environment, rendering that data obsolete once the model has been obtained.[14] This is unlike the development of social insect colonies or the evolution of sex, wherein there may be cases in which multiple models cannot be combined without the loss of some information, necessitating the retention of each for the fullest possible understanding of the phenomenon in question. Data from multiple techniques probing protein structure are not only compatible with one another; they are in fact often successfully combined.[15] Integrative pluralism therefore fails to capture the relationship between multiple models of protein structure.

[14] This is not to suggest that they have no epistemic value whatsoever. They are certainly indispensable in the context of justifying the particular choice of model for the functional protein structure, for arguing for its validity, and for enabling others to check the work that has gone into this process.

[15] Though not always; a failure to integrate data from multiple techniques might indicate poorer data quality than initially expected or radically different structures in different states. Nonetheless, the point here is that when integration is successful, the multiple models that are integrated need not be retained for a full understanding of the structure in question.

4 Integrative Pluralism, Model Validity, and Extrapolation

I have shown that Mitchell and Gronenborn fail to establish integrative pluralism as the relationship between multiple models of protein structure. Neither the integration of multiple experimental models nor the use of experimentally derived models in computational modeling are therefore clear cases of pluralism, either in the sense of having a plurality of models at the theoretical level or in the sense of requiring multiple models to adequately represent or describe a particular phenomenon. But what is at stake in misdescribing this relationship? In this section, I argue that viewing the practice of protein structure determination through the lens of integrative pluralism can be misleading. The 'pluralism' part of integrative pluralism inclines us to conclude too quickly that models are right in their contexts, and that they can never ground inferences to other protein structures in other contexts. And conceiving of protein structure determination as 'integrating' multiple models is not, strictly speaking, correct; rather, findings from one experimental context are *extrapolated* to another. Instead of making blanket statements about the context-sensitivity of models, we therefore ought to pay attention to the *ways in which* models are context-sensitive. Such attention can help us to determine when such extrapolation is warranted and when it is not.

4.1 Integrative Pluralism Encourages Premature Conclusions About Model Validity

In Sect. 3, we saw that a model produced by a particular experimental technique can guide the interpretation of data produced by another. But a model can only be used this way when it and new data converge on the same structure. Mitchell and Gronenborn note that sometimes extant experimental models and new data instead diverge, each suggesting different structures for a particular protein. What ought we to conclude about such cases? Alluding to a case wherein X-ray and NMR studies produced divergent models of the protein A2, Mitchell and Gronenborn claim that "[t]he disagreement of models of the same protein generated by X-ray and NMR protocols does not mean that one or the other method produced flawed results. Each got the 'right' model of its prepared sample of the A2 protein" (2017, 719; see also Mitchell 2020, 189). That is, the X-ray model got the 'right' structure for crystallized A2, while the NMR model got the 'right' model of A2 in solution.

Given the significance of a protein's environment for how it folds and given that X-ray and NMR experiments place proteins in different environments, Mitchell and Gronenborn correctly claim that we ought not to infer that either of them is wrong when they give divergent results. However, their conclusion that each got the right model for A2 does not follow. Even if we are not warranted in *concluding* that one of the models is wrong, this still leaves open the *possibility* that it is, even in its context.[16] As we have seen, neither X-ray crystallography nor solution NMR produce a model of a protein structure-in-context directly; rather, each generates data that are subject to interpretation, and interpretations can be mistaken. It will be worthwhile to

[16] Indeed, it also leaves open the possibility that both models are wrong.

say more at this juncture about why we ought to take the possibility of misinterpretation seriously.

Constructing a structural model from experimental data is a multi-stage process; each stage of that process involves assumptions and approximations, which are subject to error. For instance, the product of an X-ray crystallography experiment is a diffraction pattern, which is used to automatically generate an electron density map. This map can in turn be used to construct an atomic model, which is subsequently refined by varying model parameters (the x, y, and z coordinates of each atom, as well as a mobility parameter known as the B-factor) to find the best agreement between observed reflection amplitudes and those calculated by the model. This is typically an iterative process, alternating between automated optimization and manual correction (Wlodawer et al., 2008).

Errors of interpretation become more likely the lower the resolution of the experimental structure determination, since the lower the resolution, the less information a set of data contains, and the greater the number of structures compatible with it.[17] The resolution is limited by how much data an experimenter can gather, with more data generating a higher-resolution structure. Often, pragmatic constraints, such as the impossibility of crystallizing some proteins, prohibit obtaining anything but low-resolution data (Deller et al., 2016). Resolution is also limited by how much of the protein is ordered: many proteins contain disordered regions, which do not have a fixed three-dimensional structure, making their experimental determination challenging.[18]

Given the variety of assumptions going into experimental protein structure determinations and the limitations imposed by experimental techniques, there are many ways to go wrong in the interpretation of data. For instance, Lawrence Bragg, John Kendrew, and Max Perutz, in an early attempt to determine how the protein keratin folds, identified twenty possible structures, selecting from among them the structure they deemed to be most compatible with X-ray diffraction data (Bragg et al., 1950). The structure they chose was later found to be mistaken, a consequence of their having misinterpreted the data.[19] A more recent example of an NMR structure that was subsequently revealed to have misinterpreted the data comes from Gronenborn's own work, wherein a subsequent NMR study of a particular domain of the protein ETS1 revealed an error in the original interpretation of NMR data (Werner et al., 1997).

Thus, we ought to exercise caution when inferring that divergent experimental protein structure determinations each got the 'correct' structure—even for a particular protein in a particular experimental context.[20] In Sect. 5, I will argue that mod-

[17] In X-ray crystallography, resolution is expressed in terms of interatomic distance. For instance, a resolution of 2 Å indicates that atoms separated by less than 2 Å will appear fused together in the electron density map. In NMR spectroscopy, resolution is expressed as a function of how close the ensemble of models compatible with the data are to one another, expressed as a root-mean-square deviation (RMSD) of their atomic coordinates.

[18] Although advances continue to be made. See Tompa (2012).

[19] It turned out that one of the eliminated structural possibilities was fairly similar to the correct structure, determined a few years later by Linus Pauling (Olby, 1974, 289–90).

[20] Mitchell and Gronenborn acknowledge that "noise, error and incompleteness are all present" at various stages in experimental and computational protein structure determination (2017, 717). But this point is not readily squared with their unqualified assertion that both A2 models were right in their contexts. For

est monism better enables such caution than integrative pluralism does. But first, in Sect. 4.2, I turn to a related worry: that integrative pluralism can undermine the justification for extrapolating findings from one context to another.

4.2 Integrative Pluralism Can Undermine the Justification for Extrapolation

Much scientific knowledge, particularly in the biological sciences, relies on the possibility of extrapolating findings from a simpler or more manageable experimental setup, or one that makes the phenomenon of interest more readily accessible or salient, to another more complex but physiologically relevant setup (Steel, 2007; Bolker, 2009; Baetu, 2016). This is the case, for instance, when model organisms such as yeast or the common mouse are used for studying processes or mechanisms in higher beings (Ankeny & Leonelli, 2011). Whenever findings are extrapolated in this way, we run the risk of error, and we must address questions about whether the experimental and target contexts are sufficiently similar to warrant extrapolation. The practice of extrapolating results from simpler to more complex systems is also common in basic research (Baetu, 2016).

Importantly, protein structure determination involves extrapolating findings from one experimental context to another, or to the protein in its native environment. But understanding this practice through the framework of integrative pluralism obscures the fact that this is taking place, with both the 'integration' and 'pluralism' components of integrative pluralism contributing to the problem. Consider hybrid methods for using extant models to guide the interpretation of new experimental data or computational modeling. By regarding the relationship between multiple models in these cases to be one of 'integration', we are encouraged to imagine them to be merged or incorporated, like a migrant family becoming integrated into their new community or bike lanes being integrated into public transport infrastructure. But, strictly speaking, the integration of multiple models of protein structure is not tantamount to combining them in this or any other way. Rather, it involves extrapolating a finding about protein folding in a particular experimental context to another. That is, it involves *inferring* that (part of) one protein, in a particular context, folds in the same way as (part of) another—the homologous region—in a different context. Conceiving of this process as an inference highlights the fact that it, like all inferences, is prone to error (Guala, 2003; Mayo, 1996). We might find that we were mistaken, for instance, to think that differences between the experimental contexts of X-ray diffraction crystallography and solution NMR would not be significant enough to affect protein folding, when in fact they are. Further, discovering this error would allow us to learn more about which causal factors affect protein folding, and how they do so.

The 'pluralism' component of integrative pluralism can be misleading, too, making it seem as though extrapolation from one experimental context to another is never warranted. To see why, consider another case that Mitchell and Gronenborn discuss. Sometimes, a single protein cannot be subjected to multiple experimental techniques. In such a case, scientists can compare models of one protein constructed using a

there is an alternative explanation of the case of the divergent A2 models that Mitchell and Gronenborn do not consider: that one of the models was mistaken, perhaps due to an error of interpretation of noisy data.

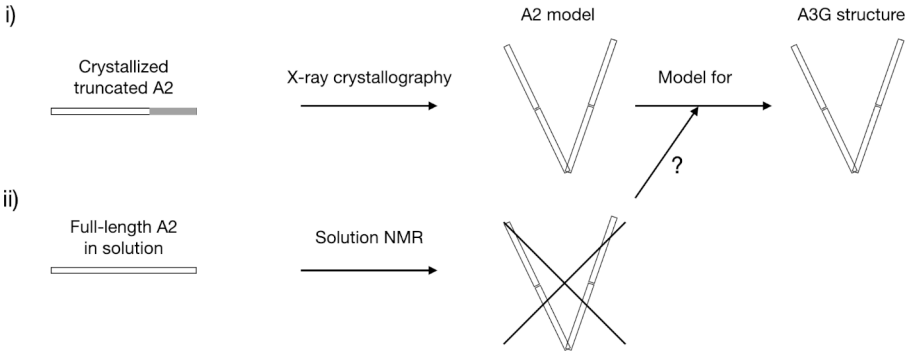

Fig. 2 Schematic diagram of Mitchell & Gronenborn's characterization of integration between A2 and A3G models of protein structure. (i) Truncated A2 was crystallized, and a model of A2 structure was determined by X-ray crystallography. A2 was found to be a V-shaped homotetramer. This A2 crystal model was then used as a model for A3G. (ii) Subsequently, full-length A2 was placed in solution and an NMR model was determined. A2 was found *not* to be a V-shaped homotetramer in solution. Mitchell and Gronenborn conclude that the original inference from the V-shaped model to the A3G structure had to be questioned.

particular experimental technique to models of another protein from the same family built using a different technique. Mitchell and Gronenborn discuss an example in which two different experimental models of A2 were used to investigate the structure of a related protein, A3G,[21] in its native environment. At first, only an X-ray model of a truncated form of A2 was available. It was used as a basis for drawing inferences about the structure of A3G: A3G was taken to have the same structure as A2. But later, an NMR model of full-length A2 was produced. This model diverged significantly from the X-ray model of truncated A2. According to Mitchell and Gronenborn, the new NMR model showed that the initial inference from the X-ray model of A2 to the structure of A3G was wrong (Fig. 2). The function of multiple experimental models of protein structure, as in the case of multiple convergent experimental models, is a sort of mutual correction: "[r]elying on a single method can lead to erroneous inferences that can be exposed by comparison with another method" (Mitchell & Gronenborn, 2017, 718).

This claim is puzzling, given the emphasis Mitchell and Gronenborn place on the effect of experimental context on structure, necessitating the plurality of models discussed in the case of divergent experimental models of a single protein, in which both models of A2 got the 'right' structure for their respective experimental contexts. Mitchell and Gronenborn write, "given the variation in the different [A2] in vitro contexts, there was *no longer* warrant for inferring that the homologous A3G protein has features similar to the X-ray model of A2" (2017, 719; my emphasis). But, on their account, it's not clear what warrant there could have been for drawing inferences from the X-ray model of A2 to the in vivo A3G structure in the first place. There is always variation between different in vitro contexts, and between in vitro and in vivo

[21] A2 and A3G are both members of the APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like") family of cytidine deaminases, proteins that play diverse functions in health and disease (Prochnow et al., 2007; Salter et al., 2016).

contexts; so why think we are ever justified in drawing inferences from in vitro to in vivo contexts?

Indeed, Mitchell and Gronenborn seem to suggest that we are not in fact warranted in drawing conclusions from either X-ray or NMR models of A2 to A3G. Given that (on their view) we cannot make inferences about A3G based on the X-ray model of A2, they conclude that A3G "may instead be closer to the NMR A2 model, or unlike either" (2017, 719). As in the case of divergent experimental models of A2 discussed in Sect. 4.1, here we are neither warranted in integrating either of the A2 models with A3G, nor in assuming a kind of pluralism according to which both A2 models are the 'right' models for A3G. That is, we seem to be unwarranted in extrapolating the findings of one experimental protein structure determination to another protein's structure in a different context.

But scientists do in fact draw inferences from one protein's structure in a particular in vitro context to the structure and function of another in vivo; this is, in fact, a central aim of protein structure determination. Indeed, the re-examination of NMR data in Gronenborn's work on ETS1 mentioned in Sect. 4.1 was prompted by a disagreement between the original NMR model of ETS1 and a subsequent crystal model (Werner et al., 1997). Had scientists simply assumed that both models were right in their contexts, they would have had no reason to re-examine the original NMR data. Although context is certainly important, we ought not to conclude that it is so important that we are never justified in drawing conclusions about a protein's structure between different in vitro or in vivo contexts.[22]

5 A Monist Proposal

Let us take stock of where we have gotten so far. I began in Sect. 2 by considering two interpretations of what integrative pluralism might entail. On the original interpretation, multiple models are necessary at the theoretical level, and become integrated once they are applied to a concrete phenomenon. On an alternative interpretation, multiple models must be retained for a complete understanding of a concrete phenomenon, even once they have been integrated. In Sect. 3, I showed that, on either interpretation, integrative pluralism inadequately describes the relationship between multiple models of protein structure. Models of protein structure are all models of concrete phenomena, rather than phenomena at a theoretical level, and a plurality of them is not necessary for understanding a protein structure-in-context. Then, in Sect. 4, I further argued that integrative pluralism can lead to premature conclusions about model validity and preclude extrapolation of findings to protein structure between contexts—which would be inconsistent with their joint use in the interpretation of data.

[22] Mitchell and Gronenborn clearly would not accept that context is so important that drawing conclusions about a protein's structure from one in vivo or in vitro context to another is *never* warranted, as the case of convergent experimental models discussed in Sect. 3.1 illustrates. But their discussion of the case of divergent models is inconsistent with this, and the only support they give for their claim that each A2 and A3G model was right is that the models were produced in different contexts.

I now turn to the virtues of modest monism as an alternative framework within which to understand protein structure determination. Recall that, according to modest monism, each protein molecule adopts one conformation at each point in time in a given in vivo or in vitro context. Although context affects protein folding, it does so in predictable ways and generally not enough to preclude learning about how it folds in one context from how it does in another. And protein structure determination is possible precisely because extrapolation of knowledge about a structure in one context to an understanding of its structure in another is warranted. Modest monism says that only one model is required for each protein structure-in-context; different models do not contradict one another and are unified by virtue of relying on the same causal factors.

In this section, I argue that modest monism provides a more accurate description of protein structure determination than integrative pluralism and offers normative guidance. I begin with a defense of modest monism as the appropriate framework for making sense of the kind of complexity particular to protein structure determination (Sect. 5.1). Then, I argue that modest monism facilitates a more rigorous approach to the context-sensitivity of protein structure (Sect. 5.2).

5.1 Modest Monism About Protein Structure Models

The epistemology of integrative pluralism was motivated by the aim of capturing the inherent complexity of biological phenomena such as cooperative behavior in social insect colonies (Mitchell, 2003) or major depressive disorder (Mitchell, 2009). Mitchell characterizes the complexity she has in mind as "the messy, murky causal relations displayed by genes and phenotypes, human interventions on the global climate, or the multilevel, feedback-laden phenomena in modern psychiatry" (2009, 3). That is, complexity here has to do with causes operating at different levels, such that it would be difficult, if not impossible, to put them together into a single explanation of these phenomena. For instance, although genetic factors are associated with the likelihood that someone develops depression, they alone are not sufficient to predict its onset. Environmental factors, such as the presence of childhood trauma or difficult life events, are also relevant. Studies have found that different causal factors interact with one another: having a particular genetic makeup makes one less resilient in the face of challenging circumstances, and thus more susceptible to depression (Kendler et al., 2005). Nonetheless, these causal factors are not readily combinable into a single model.

A key takeaway for Mitchell (2009) is that reductionist strategies are unlikely to be successful in cases like these. Because different causes of depression operate at vastly different levels—from the chemical and biological through to the psychological and social—we should not hope that these can all be subsumed under a single, all-encompassing explanation for depression. As we have seen, a similar point can be made about explanations of cooperative behavior in social insect colonies: each explanation depends on isolating a different factor (evolutionary, genetic, etc.), and it is not clear how these different levels of explanation interact—and, indeed, whether they do.

Protein structure, albeit complex in one sense, is not complex in this sense. The central difficulty facing protein structure determination, as we have seen, is that the protein's *functional environment* is extremely complex, with a great many factors affecting how it folds in myriad ways. In the 1960s, Christian Anfinsen demonstrated that proteins spontaneously fold into their native conformations in a test tube after denaturation (Anfinsen et al., 1961). This result was initially taken to indicate that protein folding inside the cellular environment was dictated solely by a protein's amino acid sequence. However, the conditions of the protein's native environment are very different from those under which Anfinsen observed protein folding. The cellular environment is crowded; rather than folding spontaneously after exiting ribosomes, proteins fold with the aid of chaperonins, which prevent misfolding and can also help proteins to stay folded in their native states, a process known as *proteostasis* (Balch et al., 2008). The necessity of chaperonins for stabilizing protein structure does not negate Anfinsen's findings, but is compatible with them. Indeed, some chaperone proteins function by creating what has become known as an Anfinsen cage, a shielded environment in which a protein can fold into its native conformation without disruption (Ellis, 2003).

Nevertheless, the complexity of protein folding is not the same as what we find in social insect colonies or major depressive disorder. In these latter cases, there are multiple kinds of causes, operating at different levels, neither reducible to a common cause nor easily combined into a single, very complex cause. In contrast, the causes of protein folding are all biochemical. Protein folding is partially determined by amino acid sequence because different amino acids have different chemical properties, preferentially folding into certain conformations rather than others. Some conformations are prohibited because they would result in steric clashes between amino acid residues. Different amino acids have different propensities for alpha helical and beta sheet conformations. Further, folded protein structure is stabilized by, *inter alia*, hydrogen bonds and disulphide bridges, which also depend upon chemical properties of amino acids. When contextual factors of a protein's environment like its *p*H or the binding of a metal ion affect protein folding, they do so by interacting with these properties.

This is not to deny that we can investigate proteins at different levels, for instance, at the cellular and molecular levels. Rather, it's to stress that there is a compatibility between explanations at these levels which does not seem to exist between the different levels of explanation in depression or social insect colonies. It might not be obvious how genetic and environmental factors that figure in separate models in those cases could be combined; in contrast, models of protein structure have the same causal factors operating in them. We should not conflate context and complexity with incompatibility between different causal factors.

According to modest monism, we can explain the structure of a protein in a given context with just one model (for that structure in that context). Ultimately, investigators often seek to determine a protein's functional structure, which is bound to differ from its structure in experimental and computational contexts, since factors that affect its function, such as *p*H, temperature, post-translational modifications and binding other molecules, are absent from them. Rather than requiring multiple models to fully explain a protein's structure in its functional environment, those models

can instead be used to make inferences about that structure. Once inferences have been made, the individual models need not be retained for knowledge about it. Modest monism is thus a descriptively adequate framework for understanding protein structure determination. In the next section, I argue that it can also offer normative guidance for investigating how context affects protein folding.

5.2 The Context-Sensitivity of Context-Sensitivity

The problem with how Mitchell and Gronenborn characterize the A2/A3G case (Sect. 4), given their emphasis on the joint use of multiple experimental models, is that they give us no way to distinguish between when models can legitimately be used for mutual correction and when they cannot. That is, the framework of integrative pluralism does not tell us when we ought to accept divergent models as each being right in their contexts, and when their divergence indicates that an error has been made. By adopting modest monism, we instead accept (at most) one correct model for each protein structure-in-context. We may then ask whether we can extrapolate from one model of a protein structure-in-context to the structure of another (possibly different) protein in another (possibly different) context. The answer will depend upon our assessment of similarities and differences between the proteins and contexts.

In the A2/A3G case, we can ask: What is responsible for the divergence between different experimental models of A2? A partial answer to this question lies in the fact that the A2 molecule in the crystallography experimental context was truncated, whereas the molecule subjected to NMR was not. And it turns out that the truncated amino acid residues significantly affect protein folding. Assuming that those same residues are also constituents of A3G would give us reason to be suspicious of any conclusions drawn from the *truncated* A2 crystal model to A3G; however, it would not provide a case against the NMR model of (full-length) A2 as a basis for conclusions about A3G. We therefore ought not to conclude simply that A3G could be like the X-ray A2 model, the NMR A2 model, or neither, as Mitchell and Gronenborn do. We should instead ask *how* the truncation of A2 affects our ability to draw inferences from any model of this protein to A3G, or how the experimental context of NMR might do so.

Indeed, in order to apply hybrid methods to determine protein structure experimentally, one must *assume* that the contextual factors particular to each experimental setup are not sufficiently significant to undermine the joint use of the data from each. That is, the techniques that Mitchell and Gronenborn identify as enabling mutual correction between experimental models (Sect. 3.1) presuppose at least a modest monism. This is related to what Chang (2001, 2004), in the context of measurement, calls the principle of single value: using one measurement device to corroborate or correct the output of another is possible only on the assumption that there is a single value that both measure. Similarly, we may only use a model generated by a particular experimental technique to aid in the interpretation of data generated by another if we assume that the structure is essentially the same in both contexts—something not readily accommodated within Mitchell and Gronenborn's framework.

Similarly, computational protein structure prediction is possible only on the assumption that protein sequence largely determines folded structure (Dill & MacCallum, 2012), so contextual factors specific to the protein's (experimental or native) environment can be set aside. This is a reasonable assumption to make for many proteins, which is what makes computational methods successful. But there are exceptions. Some amino acid sequences, called chameleon sequences, can fold differently in different proteins: for instance, a sequence of amino acid residues that folds into an alpha helix in one protein might form a beta strand in another (Mezei, 2018; Minor & Kim, 1996). Thus, if we are attempting to predict the structure of a protein that contains such a sequence, we should be especially cautious about extending conclusions based on experimental models of different proteins containing that same sequence. Other structures are *metastable*: they are capable of changing conformation into one or more different structures, each of which is stable. For example, globular proteins such as lysozyme and transthyretin can re-fold into aggregates known as amyloid fibrils, which are associated with diseases such as Alzheimer's and Parkinson's. Moreover, amyloid fibrils from proteins whose native states differ significantly from one another can be remarkably similar (Dobson, 1999). Gaining insight into what is responsible for the metastability of these proteins would mark a step toward better understanding and treating these diseases.

Rather than simply stating that models of protein structure are context-sensitive, we ought to look more closely at the different ways in which context affects protein folding. As we have seen, many factors can significantly alter the higher-order structure a protein adopts. But just because there are many such factors does not mean that we must stop at listing them and stating *that* they affect protein folding. For many (albeit not all) of these factors have predictable effects on protein folding. For instance, an aqueous environment tends to drive hydrophobic amino acid residues into a protein's core, and heating a protein denatures it. Thus, we may examine *how* they do so, with the aim of assessing the possibility of extrapolating experimental results with respect to further (computational or experimental) protein structure determinations. In short, we should heed the context-sensitivity of context-sensitivity, and a modestly monistic perspective can help us to do so.

6 Conclusion: Why *Modest* Monism?

Scientific monism has gotten a bad rap. It's been depicted as naive in its monolithic depiction of science, overly optimistic about the prospects of a grand unified theory, and divorced from scientific practice. Whereas pluralist philosophies of science are proliferating, monism has thus fallen out of favor. I conclude by reflecting on monism's disrepute and explain why the monist position I advocate for is a modest one.

Pluralism can be a recourse for tolerating equally good models—for example, in cases where these models contradict one another or are incommensurable (Dickson, 2006) or inconsistent (Morrison, 2011, 2015; Weisberg, 2007). In these cases, a pluralistic perspective may promote a better understanding of that practice and indeed move it forward (Cartwright, 1999; Chang, 2012). In the case of protein structure

determination, however, pluralism distracts us from the most philosophically salient features of scientific practice. It primes us to conclude too quickly that experiments produce models that are correct in their contexts and makes it difficult to see how findings can be extrapolated from one context to another.

I've argued that a complex reality, together with our limited cognitive and perceptual capacities, does not by itself entail pluralism. We should understand models of protein structure as each representing one protein in a given physicochemical context at a given time. Because differences between contexts do not typically radically alter how a protein folds, scientists can extrapolate findings from one context to another. The result is multiple models of protein structure, each with a different target. These models are neither contradictory nor incommensurable or inconsistent. Further, they are unified by their common appeal to the same set of biochemical causes of protein folding. A monist understanding of protein structure determination therefore more accurately describes what scientists do when they construct models of protein structure. And it offers a path toward better understanding the various ways in which contextual factors affect protein folding.

A further aim of this paper is to think more carefully about what monism might look like. The monist picture of protein structure determination I advocate for is a modest one because it does not commit to the strong unificationist, monolithic view of science to which pluralists are opposed. By arguing that different models of protein structure are unified by virtue of their appeal to a common set of causes, I am not proposing a grand unified theory of protein folding. I am not sure I know what such a theory would look like. Nor am I suggesting that such a theory is attainable in the long run. Such a claim (like its negation) would in any case be difficult to support. I am also not taking the additional step of claiming that all of biology or all of science is or will become unified. Moreover, my argument in this paper has been restricted to structural biology; whether it applies to other areas of science would require further investigation.

This monism is modest also by virtue of being informed by scientific practice. I have shown that protein structure determination supports a monistic ontology and epistemology. Scientists know, based on the best available theories and empirical evidence, about how context affects folding, and how to use data from different experiments to construct models. They find that they do not require multiple models to represent each protein structure-in-context. But should they eventually determine that multiple models are in fact required for a complete understanding of a protein structure-in-context, that would be reason to reevaluate monism's descriptive adequacy. Thus, modest monism's modesty arises from an acknowledgement of the fact that, as science evolves, so too should our philosophical views.

I hope, therefore, to have shown that a monistic picture of science, appropriately qualified, can share some of the putative virtues of pluralism—acknowledgement of complexity and our human limitations, resistance to strong unificationism, and sensitivity to scientific practice—while furnishing a better understanding of central elements of that practice, such as interpretation and extrapolation.

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