Examining Part–Part Interactions toward Improving Mechanistic Explanations in Cell Biology

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Abstract

Mechanistic explanations are a mainstay of causal accounts in cell biology. Such explanations are underpinned in large part by a network of part–part interactions, e.g. protein–protein or protein–nucleic-acid interactions. These interactions have traditionally either been discovered in a focused, experiment-by-experiment manner or via so-called 'hypothesis-free' large-scale interactome studies, which require subsequent verifications of the individual interactions of interest. In all such studies, regardless of the scale and mode of experimentation, there is a tacit assumption that an 'interaction' is constituted simply by the proximity between and/or enzymatic changes imparted on the two parts (of note, multipart interactions can still be thought of as being composed of a number of two-part interactions). However, very few substantive theoretical accounts of what may actually constitute an 'interaction' in the context of the cell have been put forth. Starting with the example of a mechanistic explanation of an important cellular phenomenon (the mitochondrial respiratory chain), I develop a two-part account of protein–protein interactions, with implications for other types of cellular part–part interactions. First, I map out four aspects relevant to the sequence of events taking place in protein–protein interactions, and, second, propose (i) interaction-enabling properties of proteins and (ii) interaction-enabling properties of the proteins' environment as elements that could be explained by relevant lawlike generalizations. These generalization-based explanations could answer contrastive *why-this-and-not-that* types of questions pertaining to different aspects of a protein–protein interaction of interest in a mechanistic explanation.

Keywords

Biological Generalizations; Interactions; Mechanistic Explanation; Philosophy of Cell Biology; Scientific Explanation; Scientific Laws

Introduction

Explanations in the current practice of molecular and cellular biology ('cell biology' for short), despite enormous success in providing mechanistic descriptions of various phenomena, face problems of accounting for *why* the processes and elements of the explanations happen in the way that they do, and not in some plausible other ways (Deulofeu & Suárez, 2018; Ehsani, 2020). As will be argued for in this paper, one way to increase the fruitfulness[1] of such explanations is to develop a philosophical framework to aid in crystallizing what is entailed by notions of part–part (i.e. biomolecule–biomolecule) 'interactions' that are so prevalent in cell biological explanations.

The paper is organized into four main sections. In **Section 1**, I introduce the mechanistic explanation of the mitochondrial respiratory chain (henceforth, 'MRC') to be used as a running example, and argue that it can be considered a paradigmatic mechanistic explanation in cell biology. In **Section 2**, I use a normative framework from contemporary work in the philosophy of mechanisms to assess the MRC explanation, arguing that one (but certainly not the only) puzzling aspect emerging from such an assessment is the uncertainty surrounding the notion of 'interactions' in the explanation. In **Section 3**, I develop an account of 'interactions' between parts (and in particular *proteins*) in a mechanistic explanation, and discuss how it might augment the MRC explanation as a case in point. Finally, in **Section 4**, I argue that one of the distinct explanatory contributions of lawlike generalizations is in providing answers to contrastive *why-this-and-not-that* types of questions that may arise from the earlier developed account of part–part interactions. This is against the backdrop of the existence of very few *sui generis* generalizations in cell biology, thus hinting at the need for the discovery of such generalizations. Overall, the philosophical framework on interactions introduced in this paper can bridge mechanistic and nomological explanations, producing an overall explanation that may be more fruitful.

1. The MRC as a paradigmatic cell biological mechanistic explanation

Throughout this paper, I will refer to the mitochondrial respiratory chain ('MRC') that takes place in various types of cells as a running example to illustrate certain points. However, I will also sparingly use other examples, particularly from physics, where generalizations are integral parts of explanatory practice. But first, what is the MRC, and why should it be a running example?

1.1. The MRC is a time-honored and fundamental-to-the-cell mechanistic explanation.

Most eukaryotic cells have an organelle called the mitochondrion, on the inner membrane of which lie five protein complexes which together produce adenosine triphosphate (ATP), the energy 'currency' of the cell. These proteins form what is called the mitochondrial 'respiratory chain' (MRC). The mechanistic explanation of their production of ATP is probably one of the most fundamental explanations when it

[1] I am referring to the Kuhnian notion of 'fruitfulness' in a scientific explanation, as analyzed more recently in (de Regt, 2009; Ivani, 2019), where scientists hope to expand their domain of inquiry and understanding of a given phenomenon by using an explanation to pose new questions and puzzles to investigate, eventually reaching a more nuanced or 'complete' explanation, in a manner of speaking.

comes to the workings of eukaryotic cells, and aspects of the MRC explanation were the subject of a Nobel Prize in 1978. Philosophers such as James Tabery have also focused on this explanation in some of their writings on mechanisms (Tabery, 2004).[2]

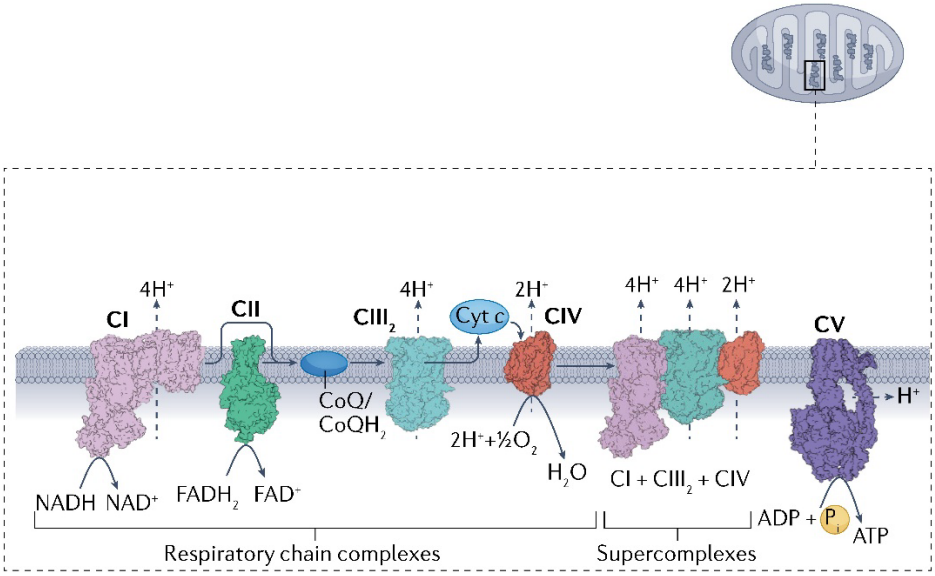

Figure 1. Schematic of the five protein complexes involved in the mitochondrial 'respiratory chain' (MRC). Adapted from (Bennett, Latorre-Muro, & Puigserver, 2022), and reproduced with permission from Springer Nature.

In the schematic above, the five large proteins, labelled 'CI' (complex I) to 'CV', are depicted sitting on the inner mitochondrial membrane along with a number of other smaller molecules that are present in the 'respiratory chain'. Why is it called 'respiration'? As Judy Hirst explains, "in the chain, three major respiratory complexes, complexes I, III and IV, catalyze the step-wise transfer of electrons from NADH (generated from the food we eat) to O_2 (from the air we breathe). The oxidation of NADH by O_2 releases a lot of energy, which is trapped by the complexes in transporting protons [shown as H^+ on the figure] across the inner mitochondrial membrane, charging it up like a biological battery. The battery is discharged as protons flow back across the membrane through the ATP synthase rotor, turning it to generate ATP" (Hirst, 2018, p. 1). In short, the current mechanistic explanation can be thought of as stating that "complex I converts energy stored in chemical bonds into a proton gradient across the membrane that drives the synthesis of [ATP via complex V]" (Kampjut & Sazanov, 2020, p. 1). I have skipped many details, but this is the nub of the explanation.

1.2. The MRC can be counted as a paradigmatic explanation in cell biology.

Even if one agrees that the MRC explanation is well-accepted, can it be used to make more general observations about explanatory practices in cell biology? I argue that it can, in so far as the mechanistic

[2] Tabery discusses the example of electron transport in photosynthesis taking place in chloroplast organelles. For organellar similarities between mitochondria and chloroplasts, and their respective respiratory and photosynthetic electron transport chains, see (Allen, 2015).

component of explanatory practices is concerned. Let us examine this from at least three perspectives. First, Lindley Darden and Carl Craver note that "in reasoning in the discovery of mechanisms, one proceeds with the goal of eliminating gaps in the description of the mechanism's productive continuity" (Darden & Craver, 2002, p. 19). While there are always more details to be added, no obvious gaps seem apparent in the MRC explanation and its step-wise 'chain' of electron transfer. In other words, there is spatiotemporal contiguity, as far as one can tell, in the transfer of electrons from the beginning to the end of the MRC explanation. Second, taking another angle on the issue, Caleb Trujillo and colleagues performed a thematic analysis of the explanations of seven biologists of a cellular mechanism of their choice, and have proposed a consensus model of mechanistic explanations that is informative in evaluating an explanation such as the MRC because it helpfully synthesizes intuitions in cell biological practice (Trujillo, Anderson, & Pelaez, 2015). Their model rests on four components: the methods of research, or the tools, data or procedures "used to generate evidence that informs the explanation and qualifies or limits the generalizability of interpretations" (p. 10); the explanation's analogies and stories; the social or biological context; and, finally, how the mechanism works: "how the component entities of a biological phenomenon interact at the molecular, microscopic, and macroscopic levels to produce detectable changes in state, activities, and spatial and temporal organization" (p. 10). Acknowledging this full spectrum of features that an explanation may possess, I take the MRC explanation to be paradigmatic of the 'how the mechanism works' component.

Finally, we can count the MRC explanation as a 'successful explanation'. These explanations, as pointed out by Craver (who was not commenting on the MRC specifically), "embody the collective wisdom [in the field] about what constitutes an acceptable explanation" (Craver, 2007, p. x), and "paradigmatically successful explanations reveal features of successful explanations" (p. x). Being successful, however, does not imply there are no more important open questions left; quite the contrary (Vercellino & Sazanov, 2022), as would be expected from any active and evolving subfield of research. I will return to these open questions in the next section, and also later.

2. Assessing the MRC using normative accounts of mechanisms

Despite being time-honored and widely-accepted, as just noted, the MRC explanation continues to pose questions for the biologist as to, e.g., how the structure and dynamics of each protein contribute to the sequential biochemical activities that end in the production of ATP (Bennett et al., 2022; Hirst, 2018). But can these and other open questions be identified theoretically? In fact, how would the MRC fare under the light of contemporary philosophy of mechanism? In this section I will argue that if one assesses a cell biological phenomenon such as the MRC using normative frameworks that have been developed over many years in mechanistic philosophy, a number of puzzles or problems can be theoretically identified. I take one of these puzzles, i.e. concerning part–part 'interactions' in the MRC explanation, and develop it further in the remainder of the discussion in this paper.

To begin with, here I will build on Stuart Glennan and Phyllis Illari's concept of 'minimal mechanism', whereby "a mechanism for a phenomenon consists of entities (or parts) whose activities and interactions are organized so as to be responsible for the phenomenon" (Glennan & Illari, 2017a, p. 2).[3] As Glennan and Illari set out to synthesize the previous decade of philosophical work on mechanisms, we can use this to help lay out several criteria that could be thought of as normative requirements (in the sense of (Craver, 2007)) for good mechanistic explanations. For ease of assessment, I will present them here in the format of a series of 'tests'. These five tests are meant to help determine whether an explanation meets the normative criteria:

- TEST #1: *The phenomenon to be explained is set out as unambiguously as possible*. (The phenomenon is a part of all accounts of mechanisms, from (Bechtel & Richardson, 2010/1993) to (Glennan & Illari, 2017b).) For our case, the phenomenon of mitochondrial respiration and ATP production is the target of the MRC explanation. Of course, there is always room for more detailed description, but the MRC phenomenon seems reasonably well-described at least compared to other cellular phenomena.

- TEST #2: *The explanation sets out an environment to situate the mechanism leading to the phenomenon and refers to some decomposable and detectable parts that constitute the mechanism (the environment itself might be constituted by decomposable and detectable parts as well)*. (Decomposition and localization have been regarded as key mechanism discovery heuristics at least since (Bechtel & Richardson, 2010/1993), following Stuart Kauffman (Kauffman, 1970) and even Herbert Simon (Simon, 1956, 1962).[4]) The MRC phenomenon is taking place at a specific locale in a cellular organelle, and the important protein and other molecular players seem to be known, at least based on publications in the field. Of note, as parts (e.g. proteins) and environments (e.g. the cell's cytosol) are inextricably linked and influence each other, these criteria have been grouped together in one test. This is because, for example, a protein's structure only takes its final and functional shape when situated in a cytosolic environment, revealing the deep causal dependencies between the part and its environment.

- TEST #3: *The parts represented in the mechanistic model on which the explanation relies are organized in some way.* (Organization is also part of all mechanism accounts from (Bechtel & Richardson, 2010/1993) to (Glennan & Illari, 2017b). It is discussed extensively by (Craver, 2007).[5] While it is not controversial, understanding it is not straightforward.) For our case, the protein complexes the MRC explanation accounts for are arranged in an assembly-line-like

[3] For a thorough account of different minimal conditions for mechanistic explanations, see (Fagan, 2015). See also (Ratcliffe, 2015) for a three-part ontology for mechanisms consisting of entities, dispositional properties and processes, which will be beyond the scope here to discuss further.
[4] I am grateful to Phyllis Illari for pointing out the scope of work relevant to mechanism discovery heuristics.
[5] Craver writes that organization "is not merely a matter of being describable in terms of a box-and-arrow diagram or a program. Instead, it involves the active, spatial, and temporal organization of different components. This addition is required to distinguish mechanistic explanations from aggregate explanations, morphological explanations, and taxonomies" (Craver, 2007, p. 162). Nevertheless, organization leaves many open puzzles from minute questions in cell biology to network-based phenomena in systems biology.

chain, i.e. their organization seems to have spatial, temporal and enzymatic-activity-based dimensions.

- TEST #4: *The parts described in the explanation causally 'interact' and the features and consequences of key interactions are specified.* (Interactions are always present, but under different guises, from 'component operations' (Bechtel & Richardson, 2010/1993), 'activities' (Machamer, Darden, & Craver, 2000), to 'activities and interactions' (Glennan & Illari, 2017a). However, as I will argue below, interactions in cell biology need more attention.) In the MRC, the dependence of biochemical tasks upstream and downstream of the chain on each other seems to be clear, but the exact 'interactions' between parts seem tenuous: how does each protein complex 'interact' with the protein complex sitting next to it, or with the lipid molecules around it, or with the intracellular small molecules in the fluid medium surrounding it? How do each of these interactions compare, and what are the consequences of each interaction?

- TEST #5: *The explanation can account, without any gaps, for the sequence of changes leading to detectable variation in the phenomenon or the maintenance of said phenomenon if it is a homeostatic one.* (This is not explicitly mentioned in minimal mechanism, but appears in various forms elsewhere. (Machamer et al., 2000) wish for 'productive continuity' without gaps, an idea developed by (Bogen & Machamer, 2011). (Craver & Darden, 2013, p. 19; Darden & Craver, 2002) develop this idea in a more practice-oriented way attending to e.g. the history of the discovery of the mechanism of protein synthesis.) This test is dependent on the previous criteria. In the MRC, although the sequence of biochemical changes (the movement of protons across the membrane, the creation of new molecules such as ATP, etc.) is clear, the sequence of protein-to-protein changes is not as clear.

In each of the five tests, if one delves deeper into any of the issues, or persists in asking more detailed follow-on questions, open problems and puzzles will most likely emerge. That being said, even at this cursory level of inspection, it is evident that at least as far as the features in Tests #3 to #5 are concerned, what would improve the quality of the MRC explanation is if a clear conception of what constitutes *protein–protein interaction* existed. Again, this is not the only problematic issue emerging from the tests. Puzzles surrounding the delineation of parts in the MRC, e.g. what constitutes a protein 'complex', or how exactly the explanation accounts for the organization of the chain reaction within the mitochondrial lipid membrane but also the passage of molecules across it, are other interesting and puzzling questions. However, I am choosing to continue the discussion with the puzzle of interactions particularly because of the potentially crucial role of generalizations, as I will get to later.

I should note that the shortcoming with the notion of protein–protein interactions is also hinted at in the relevant MRC literature. For example, although protein complexes I, III and IV "can each function perfectly well in isolation", Hirst explains that "it is now well established that, in mitochondria, they are organized into weakly associated supramolecular assemblies known as supercomplexes" (Hirst, 2018, p. 1). However, "the complexes do not need to associate into supercomplexes in order to catalyze

effectively: the reason (or reasons) why they do so remains enigmatic" (p. 1). In the next section, I will first start with how one can approach defining interactions between molecules in the cell.

3. Defining part–part interactions with a focus on proteins in cell biology

In developing an account of interactions between parts in a cell, my aim for the outcome is to be applicable to the interaction of any two biomolecules (proteins, nucleic acids, lipids, small-molecule compounds, etc.).[6] However, for simplicity and also because proteins are generally taken to be the 'workhorses' of the cell, I will focus mainly on protein–protein interactions. Therefore, some details of my account will not be pertinent to other molecular interactions in the cell.[7] But first, is such an account of interactions really needed? Surely, doesn't cell biology already have a working account of interactions? As I will now discuss, the answer is surprising.

3.1. Cell biology lacks a cogent concept for an 'interaction' between biomolecules.

As I have already hinted at, cell biological mechanistic explanations are underpinned in large part by a network of part–part (biomolecule–biomolecule) *interactions*, e.g. protein–protein or protein–nucleic-acid interactions. Work on protein–protein interactions picked up in earnest in the 1950s before the advent of molecular biology (Linderstrøm-Lang, 1952; Waugh, 1954). At present, 'interaction' is supposedly a term of art in biological practice but, surprisingly, without a proper theoretical framework to be understood in, and hence lacks a precise and consensus definition. This is not to say that the importance of such interactions is not recognized; quite the contrary. For example, Thuy-Lan Lite and colleagues note their place in biology as follows: "protein-protein interactions underlie most cellular processes and are the basis of established and emerging therapies such as monoclonal antibodies, chimeric antigen receptor T cells, and stapled peptide drugs. To prevent non-specific and potentially detrimental interactions, proteins must discriminate between cognate and non-cognate interaction partners" (Lite et al., 2020, p. 1). Clara Bodner and Mario Brameshuber put this into an even broader context: "life is all about interactions: from a simple handshake or a meaningful eye contact between humans, down to complex interactions between single cells and organelles, further down to the interactions of individual (bio)molecules, and even further down to nucleonic interactions between the smallest building blocks of life" (Bodner & Brameshuber, 2023, p. 278).

The scientific community has indeed rewarded much work on interactions, particularly in the field of physics. Taking Nobel prizes as an indication, there have been five prizes for interactions in physics (1969: classification of elementary particles and their interactions; 1979: theory of the unified weak and electromagnetic interaction between elementary particles; 1984: weak interaction; 1999:

[6] Of note, multipart interactions can still be thought of as being composed of a number of two-part interactions. Indeed, in analyzing the interaction between two proteins, one could also look at domain–domain interactions (Alborzi, Ahmed Nacer, Najjar, Ritchie, & Devignes, 2021; Deng, Mehta, Sun, & Chen, 2002).

[7] There is increased attention recently in the cell biology literature toward cell–cell interactions (Armingol, Baghdassarian, & Lewis, 2024; Nakandakari-Higa et al., 2024). Because interactions between cells can involve many different molecules and hence many different part–part interactions, accounting for interactions between molecular parts can also go some way in also helping to study cell–cell interactions.

electroweak interactions; 2004: theory of the strong interaction), one in chemistry (1987: molecules with structure-specific interactions of high selectivity), and one in physiology or medicine (1975: interaction between tumor viruses and the genetic material of the cell).[8]

Narrowing in on protein–protein interactions, at a broad level, these are generally taken to be some structural and/or functional change exerted by one protein onto another in its close proximity, and are considered crucial to arguably any mechanistic explanation in cell biology that involves proteins, which basically means almost all cell biological explanations. However, much of the current picture of protein–protein interaction has been obtained through empirical routes, and the focus continues to be on the technical aspects. A recent important paper, for example, points out that "most proteins function by interacting with other proteins, yet we lack tools to study these potentially transient interactions at single-molecule resolution in live cells" (Graham, Ferrie, Dailey, Tjian, & Darzacq, 2022, p. 1). In experiments that lead to large datasets, interactions might be defined in terms of the enrichment of pairs of proteins compared to some control conditions: e.g. "positive interactions were defined as enriched or filtered protein pairs occurring significantly more often than expected in the enriched library" (Yang et al., 2023, p. 9). But what exactly constitutes an interaction? When one digs a bit deeper, it seems that most accounts, for practical purposes, simply rely on proximity to define an interaction,[9] which cannot be the full picture. As a case in point, in statistical modelling of protein-protein interactions, an approach is to say that "if paths of interacting proteins come within distance ε of each other, then these proteins are considered to have interacted (ε is about a protein diameter)" (Batada, Shepp, & Siegmund, 2004, p. 6446). That being said, a scenario-based account of protein–protein interactions by Ilana Kotliar and colleagues is a helpful step toward a more thorough theoretical picture: "(i) formation of a relatively stable and long-lasting physical bimolecular complex; (ii) a transient physical complex formation that has some functional consequence; or (iii) indirect effects mediated by complex formation, either stable and long-lasting, or transient with another relevant regulatory protein" (Kotliar, Lorenzen, Schwenk, Hay, & Sakmar, 2023, p. 7).

I will build on Kotliar *et al.*'s scenario-based account while also emphasizing that the parameters, aspects and scope of 'interaction' need thorough theoretical development in their own right. Moreover, the philosophical challenge, I argue, is to ask: *what aspects do interactions in cell biology have in common*? (Although this challenge pertains in particular to the philosophy of cell biology, it is relevant to problems in the philosophy of chemistry and physics as well.[10]) Before putting forth my proposal, I will look at a number of important extant philosophical work on interactions.

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[8] The citations are from the Nobel Prize Outreach website (https://www.nobelprize.org/prizes/lists/all-nobel-prizes/).

[9] This proximity may be in the 1–10nm range (Larijani & Miles, 2022).

[10] When it comes to interactions between two macromolecules like proteins, the problem is both a cell biological and a chemical one. This discussion therefore may be of direct interest to philosophers of chemistry as well. The topic of 'interaction' is additionally germane in the philosophy of physics. Indeed, the 2022 Nobel prize in physics was awarded on this very notion: "The three physicists' work has focused on exploring how two particles interact, behaving like a single unit, even when they are far apart. The phenomenon, known as quantum entanglement, was dubbed 'spooky action at a distance' by Albert Einstein, and is expected to play an important role in quantum computing" (Davis, 2022, par. 4). Having said this, the current paper's discussion

3.2. The few existing philosophical works on interactions can only weakly account for biomolecular interactions.

If one interprets interactions in the context of causal relations, there is certainly a great wealth of material that is well beyond any form of review here. However, looking strictly for accounts of 'interactions' per se, the extant contemporary philosophical works can only apply faintly in the cell biology context. In the 1960s, Jerry Fodor (1935–2017) made an explicit connection between causal and interaction talk, writing: "the class of mechanical interactions is specified precisely by providing a general, abstract characterization of the necessary and sufficient conditions for a change of trajectory, for example, in terms of such abstract theoretical constructs as force, mass, and momentum. This characterization, together with relevant information about initial states, allows one, in principle, to compute the trajectory of any given physical object" (Fodor, 1968, p. 42).

In the same causal context, perhaps more in line with our target of biomolecular interactions are the 'production' accounts of causality. These are usually associated with the works of Hans Reichenbach, Wesley Salmon and Phil Dowe (Dowe, 2000; Salmon, 1997), and especially the 'mark transmission' theory that emphasizes local structural modifications: "for Salmon and Dowe, a process is causal if it transmits a conserved quantity, such as energy mass, charge or momentum. An interaction between two processes is causal if they exchange a conserved quantity" (P. M. Illari, 2011, p. 98) (see also (Vineis, Illari, & Russo, 2017)). The transmission of a conserved quantity can indeed track well with the way one interacting protein might influence or modify another: sugar molecules could be added/removed from the interacting protein (glycosylation), other chemical groups could be added/removed (phosphorylation, acetylation, etc.), small peptides could be added/removed, or parts of the protein could even be cleaved (Y. C. Wang, Peterson, & Loring, 2014). The broader consequence of these physical changes imparted on proteins within a certain mechanism in the cell could be that, for example, a signal is passed from the outside to the inside of the cell. For instance, a protein 'receptor' on the surface of an immune T cell can sense an antigen outside the cell, and this is followed by a 'signal' that is passed to the nucleus of the cell through successive protein–protein (and other) interactions (Gaud, Lesourne, & Love, 2018).

But what if we want an account of interactions that might not be captured by production accounts, such as cases in which two proteins might simply 'stick' to each other and thereby make the interacting partner unavailable elsewhere in the cell? It would be a stretch to apply the conserved quantity transmission account to these cases as well. In the contemporary mechanist literature, Stuart Glennan has paid particular attention to the general concept of an interaction, defining it as "an occasion on which a change in a property of one part brings about a change in a property of another part" (Glennan, 2002, p. S344). He has also noted that "all interactions will have some effects—that is part of what it is to be an interaction" (Glennan, 2017, p. 150), but the difficulty is that at times the nature of

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is focused on macro-level common features of interactions. How such features relate to more fundamental quantum-level phenomena present in each protein molecule is a matter of research and debate.

some effects may not even be known. Consider, for example, that in the case of the MRC, not only would a protein complex be interacting with another protein in close proximity and perhaps exerting a structural and hence functional change, but concomitantly it may be interacting with water and other small molecules, interacting with lipids in the mitochondrial membrane, experiencing intra-protein interactions amongst *its own* amino acid residues,[11] and also perhaps interacting non-locally, through the charge gradient that it is helping to create across the membrane, with a protein that is situated further downstream on the same membrane. This mind-boggling picture is still most likely a simplification of the actual reality of the given protein complex's interactions. We are therefore in need of a framework that could potentially capture a bigger slice of the spectrum of part–part interactions in the cell.

Given that 'action' and activities are part and parcel of 'inter*action*', a look at the New Mechanist focus on activities can be insightful. Lindley Darden defines activities as "producers of change" and as being "constitutive of the transformations that yield new states of affairs" (Darden, 2008, p. 962): in the biological domain, we can think of activities such as "molecules *bond*, helices *unwind*, ion channels *open*, chromosomes *pair* and *separate*" (p. 962). Tabery, in the same paper referenced in **§1.1** (Tabery, 2004), attempted to synthesize the 'activity' and 'interaction' concepts into the notion of 'interactivity' (first suggested by Peter Machamer (1942–2023)), noting that "the concept of an activity captures […verbs such as binding, breaking, transporting, pushing, etc.] in this basic form, but the minute one starts to examine in what sense these activities are to be productive in a mechanism, then some notion of Glennan's interaction as an occasion whereby a property change in one entity brings about a property change in another entity is required alongside of the concept of an activity" (Tabery, 2004, p. 11). Machamer, responding to Tabery, agreed that "it may have been unclear that activity is meant to include activities that are mutually effective and affected. There is no dispute about interaction if the 'action' part is taken to refer to activities (so they'll be interactivities), and not as is usually done to refer to relations that exist among static states" (Machamer, 2004, p. 37). In the account that I will now develop of interactions, and as I will explain in **§3.4**, I propose to consider an interaction as a specialized 'activity'.

3.3. An account proposing four aspects to protein–protein interactions.

To develop my account of protein–protein interactions, I propose to make use of an existing structural classification of such interactions (Scott, Bayly, Abell, & Skidmore, 2016) and also an account of a human handshake (Lenders, 2022) as a working analogy of our intuitive conception of an 'interaction'.[12] Let's start with the latter. Luuk Lenders has provided a useful stepwise definition of a handshake analogy (Lenders, 2022, p. 20): (i) "moving open right hands towards each other, the thumb is on the normal plane of the other fingers and creates a U-shape with the index finger";[13] (ii) "when the hands are close

[11] We might, for example, think of these intra-protein interactions in terms of 'bandwidths': "one discerns components within a complex system on the basis of interaction bandwidth profiles in accord with the principle that there is much more interaction *within* components than *between* components" (Grush, 2003, p. 62).
[12] In the protein biology literature, one may also come across other handshake-related analogies, such as the notion of 'handholds' in the context of protein–protein binding (Service, 2022).
[13] An interesting topic that the analogy to handshakes conjures up is the issue of chirality or handedness in proteins (Inaki, Liu, & Matsuno, 2016). Amino acids that form proteins can be left-handed or right-handed (L- or D-amino acids), where left-handed amino acids are the kind that is overwhelmingly found in cellular life on Earth. D-amino acids can still be synthesized in the laboratory (Harrison, Mackay, Kambanis, Maxwell, &

to each other, proceed moving till the purlicue (the somewhat web-like skin between the index finger and thumb) of both hands touch"; (iii) "after this initial contact, close the fingers into a (somewhat) firm grasp of the other hand"; (iv) "(usually) shake up and down"; (v) "release the grasp and return the hand towards a resting position".

I find this helpful for two reasons. First, a handshake is intimately tied with our notion of an interaction (recall the earlier quote by Bodner and Brameshuber). But more so I find interesting parallels with what is known about protein–protein interactions. In the aforementioned structural classification of protein interactions (Scott et al., 2016), the authors note that when two proteins come together, their interacting surfaces could either be 'preformed' or induced upon some proximity (see **Figure 2**). We can just as well imagine that in a handshake, one of the hands could, just for the sake of argument, take the shape of a shaking hand before even reaching the other hand (this is perhaps the case in a fist bump), or, more commonly, the shaking hands assume their 'interacting' shapes when they have actually reached each other.

Analyzing the handshake and protein structure frameworks, I suggest four aspects that could capture the key features of both protein–protein interactions and a human handshake: (i) preformed or induced interacting surfaces, (ii) 'contact' and 'binding', (iii) proximate/ultimate interaction consequence(s), and (iv) duration and end of interaction.

Starting with the first aspect, i.e. preformed or induced interacting surfaces, we can ask: what exactly is happening at the structural *interface* between two interacting proteins? Pablo Gainza and colleagues invoke the notion of a 'fingerprint', writing that "a high-level representation of protein structure, the molecular surface, displays patterns of chemical and geometric features that fingerprint a protein's modes of interactions with other biomolecules" (Gainza et al., 2020, p. 184). Indeed, conjuring up the image of a handshake, two interacting proteins must have compatible geometric surfaces accompanied by suitable electrostatic forces, hydrogen bonds, van der Waals forces, cation–π non-covalent bonding (Gallivan & Dougherty, 1999; Xie et al., 2024), etc. at some proximity, and for some time, for the consequences of their interaction to manifest themselves.

The contact and binding terms are in quotation marks because of their vagueness: as alluded to earlier, how close should two proteins be (and for how long) for there to be contact, for instance? Moreover, when it comes to the functional consequence of the interaction, there might be one or more immediate effects on one or both proteins, but proximate or local effects play a role in the ultimate function of the cellular mechanism of which those proteins are a part. Take, for example, the protein complexes of the MRC. The functional consequence of the interaction of complexes IV and V is, evidently, dependent on the interaction of the first two complexes in the chain, and so on.

Payne, 2023), and it is an important question to find out if, for example, the right-handed forms of two proteins that are known to interact naturally have the same interaction features as their left-handed counterparts.

Two proteins would normally interact for an amount of time and then dissociate, making them available for other functions in the cell. The duration might have something to do with how strongly the two interacting molecules have made contact (hence the arrow on **Figure 2**). However, these 'transient' interactions are not necessarily the rule when it comes to protein interactions as a whole. As discussed elsewhere, in cases such as Alzheimer's disease where protein aggregates are formed, proteins within such aggregates are in a kind of a permanent 'interaction', making them unavailable in other parts of the cell (Ehsani, 2022). Indeed, interacting molecules in the cell can continuously associate and dissociate (Marklund et al., 2022), but if two proteins permanently associate, such as proteins in a bigger protein complex (e.g. in the case of the MRC), or in a protein aggregate (e.g. in the case of amyloid plaques in Alzheimer's disease), the question then becomes whether an 'interaction' is still really taking place.

Each one of these aspects, as will be discussed in the next section, might be amenable to explanation by one or more generalizations. Nevertheless, a salient feature of all four aspects is that the parts/entities (i.e. the proteins or the hands) and their immediate environment (i.e. the viscous cytosolic liquid around a protein or a glove on an interacting hand) can shape the overall interaction.

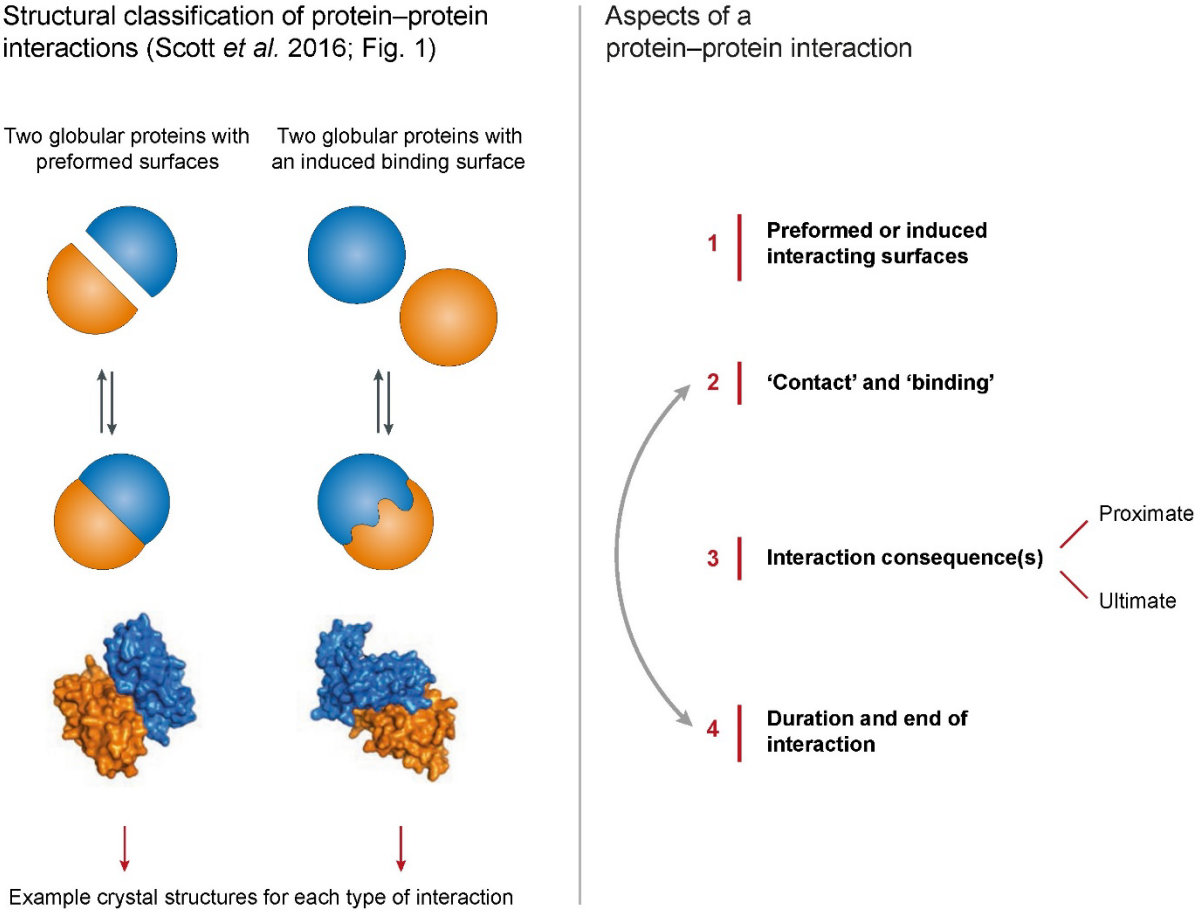

Figure 2. Schematic of two modes of protein–protein interaction, adapted from (Scott et al., 2016), followed by the four proposed aspects of such interactions. Left panel adaptation reproduced with permission from Springer Nature.

3.4. Interaction-enabling properties figure in each aspect of an interaction.

Recall that our intention was to shed some light on the puzzling nature of protein–protein interactions in mechanistic explanations. Having an account of some aspects of such interactions is a first step. But what can explain each of these aspects? To move some way in answering this question, we could consider an interaction as a specialized 'activity' that proteins engage in. Why an activity? Phyllis Illari and Jon Williamson, responding to Machamer, Darden and Craver's entities-activities ontology (in contrast to an entities-capacities ontology), suggest that activities "have two distinctive features not present in some other ontologies: they are extended in time, and they have unrestricted arity", in other words "an activity need not be a monadic property of some single entity, but can relate any number of entities" (P. Illari & Williamson, 2013, p. 72).[14] This, as may be apparent, is true for interactions as well: protein–protein interactions must have some duration, and proteins can interact with various other proteins.

If that is so, why not just call an 'interaction' an 'activity'? In protein biology, the term 'activity' is almost universally taken to imply the enzymatic/catalytic activities of proteins: some interaction consequences may not necessarily be related to enzymatic activities, but rather to the change of location or availability of the interacting partner. Therefore, keeping the term 'interaction' is true to practice and avoids confusion.

Now, taking a cue from Lindley Darden and Carl Craver's concept of the "activity-enabling properties" of entities (Craver & Darden, 2013, p. 78; Darden & Craver, 2002), one could analogously define two interaction-specific properties: *interaction-enabling properties of the entity* and *interaction-enabling properties of the environment*. Recall from the previous section that a salient feature of the four aspects of protein–protein interactions is that the parts/entities and their immediate environment can shape the overall interaction. Craver and Darden note that "entities engage in activities by virtue of the fact that they have the right properties", and they "call the properties that make such activities possible the *activity-enabling properties* of an entity. […] Such activity-enabling properties include three-dimensional structure and size, as well as location and orientation" (Craver & Darden, 2013, p. 78). In our case, when it comes to the *interaction-enabling properties of proteins*, the many biophysical and biochemical properties of proteins could be stipulated. Relatedly, the *interaction-enabling properties of*

[14] There are other takes on the notion of 'activity' in the mechanisms literature. Craver, for instance, has this view: "I use the term 'activity' […] merely as a filler term for productive behaviors (such as opening), causal interactions (such as attracting), omissions (as occurs in cases of inhibition), preventions (such as blocking), and so on. In saying that activities are productive, I mean that they are not mere correlations, that they are not mere temporal sequences, and, most fundamentally, that they can potentially be exploited for the purposes of manipulation and control" (Craver, 2007, p. 6). By this definition, an interaction could still be considered a specialized case of an activity.

the proteins' environment could include the many biophysical and biochemical properties of lipid membranes and water and ionic molecules.

Each one of the biophysical and biochemical properties can be explained by one or more generalizations (that already exist or await discovery). In the next section, I will show how known generalizations can explain a sample of such properties (it is not possible here to do an exhaustive survey of all such potential properties). In doing so, I hope that the two main aims of the paper could be fulfilled: (i) how having the interaction-enabling properties of the entity and the environment framework in hand, and a subsequent appeal to relevant generalizations, could move us some way in better explaining the puzzle of protein–protein interactions, and (ii) why this is a distinct achievement by generalizations that cannot be made redundant using only a mechanistic explanation.

4. Explaining interactions using generalizations

Having identified interactions as a niche in cellular mechanistic explanations with various puzzling features, I now move to the topic of how exactly generalizations could explain the interactions of parts in a way that cannot be achieved mechanistically. It will hopefully become clear by the end of this section how generalizations can address (or help to pose) the many potential questions of the type: *why did this aspect of the interaction happen this way and not some other way*. But first, in the following subsection (**§4.1**), I will concentrate on why the explanatory work provided by generalizations is genuinely distinct from that of mechanisms.

4.1. A mechanistic explanation and a generalization-based explanation can each do distinct explanatory work but still be mutually informed in the overall explanation.

Zooming out from cell biology for an instant, we can already see the coexistence of mechanistic and generalization-based explanations in other fields of current scientific practice. In organic chemistry, for instance, the provision of explanations can consist of reaction mechanisms and appeals to the laws of thermodynamics (Flynn & Ogilvie, 2015) or to mathematical generalizations such as the Michaelis–Menten kinetics (Holdgate, Meek, & Grimley, 2018). In ecology, mechanistic accounts of predator–prey interactions can be augmented by mathematical generalizations that explain population dynamics such as the Lotka–Volterra equations (O'Dwyer, 2020).

While I have worked based on the premise that in cell biology generalizations could augment mechanistic explanations, notice that this augmentation could be a two-way street. Take, say, the Hodgkin–Huxley mathematical generalization accounting for the initiation and propagation of neuronal action potentials dating back to 1952. The generalization has had, amongst other impacts, a lasting effect on understanding the protein-level mechanisms of action potential, whereby it "established a framework in which to describe the structural and functional properties of ion channels, including the mechanisms of ion permeation, selectivity, and gating" (Catterall, Raman, Robinson, Sejnowski, & Paulsen, 2012, p. 14064). But what is more is that mechanistic understanding of the protein ion channels

has more recently led to "efforts to capture channel fluctuations with noise terms added to the equations of Hodgkin-Huxley type" (Goldwyn & Shea-Brown, 2011, p. 1). A mechanistic explanation of a particular phenomenon has thus augmented a complementary generalization-based explanation of the same phenomenon. The augmentation, or the two types of explanations mutually informing each other, could go either way.

4.1.1. Contrastive explanation: why this way and not some other way

Now, while one might potentially find disparate examples from different fields of science of various unique explanatory contributions of generalizations, as I have gestured at thus far in this paper, one particularly significant such contribution of generalizations that is applicable to our case is to discover, pose and answer why-this-and-not-that questions. These types of questions are often posed in discussions of new mechanistic discoveries in cell biology. Take the case of the MRC itself; a recent commentary on how the assembly of the multiprotein structures in the MRC is regulated states: "the structure of complex IV […in kidney cells] was shown to contain COX7A isoform COX7A2, *and not* SCAF1, and our results consistently show that complex IV […from heart muscle cells] harbours the muscle-specific isoform COX7A1" (Vercellino & Sazanov, 2022, p. 155). In other words, the contrastive question is why protein complex IV associates with one isoform of the COX7A protein and not the other.

Discussions of contrastive explanations are particularly rich in the field of psychology. In 1990, for example, Denis Hilton wrote that "one does not explain events per se, but […] one explains why the puzzling event occurred in the target case but not in some counterfactual contrast case" (Hilton, 1990, p. 67).[15] Some years later, Jeroen Van Bouwel and Erik Weber added some helpful granularity to contrast cases. Compared to a plain-fact question such as "why does object *a* have property P?", they spelled out three different contrastive questions, namely: "why does object *a* have property P, rather than property P'?"; "Why does object *a* have property P, while object *b* has property P'?"; and "Why does object *a* have property P at time t, but property P' at time t'?" (Van Bouwel & Weber, 2002, p. 438).

As may be obvious, the earlier-mentioned notions of interaction-enabling properties of the entity and interaction-enabling properties of the environment, inspired by Darden and Craver's work, connect well with Van Bouwel and Weber's framework. Indeed, one can pose quite complicated contrastive questions in need of explanation: e.g. why does one of the proteins in the MRC complex IV have a certain lipid-interacting property *t*-minutes after cell division but a different lipid-interacting property *t'*-minutes after cell division? This type of question, I hope, really illustrates how we need a thorough mechanistic description, fulfilling the various tests stated previously, to lead to the point where such a hypothetical contrastive question could be posed, ready to be handed over to explanatory clarification using one or more generalizations.

[15] Christopher Pincock, for instance, proposes that one consider all explanations to be contrastive (Pincock, 2018). For a recent summary of various views on contrastive explanations, see (T. Miller, 2019, p. §2.3).

The discussion will delve deeper into this in the next subsection (**§4.2**). However, I feel that a quick detour might be necessary at this point in this section because some readers may still have reservations about the distinctness of generalization- and mechanism-based explanations, and specifically about questions of 'reduction' of generalizations to mechanisms.

4.1.2. The question of 'mechanism all the way down'

When one talks about explaining a certain contrastive question about some interaction-enabling property of a protein, generalizations that one could appeal to might be high-level generalizations, i.e. generalizations at the level of a cell or protein, and not at the fundamental quantum level, say. But a high-level generalization, one could argue, might be reducible to mechanisms (a metaphysical question), or barring that, at least be explainable mechanistically. For the sake of completeness of our discussion, I will try to address these in some brief comments.

First, notice that generalizations do their explanatory work aided by, to use Travis McKenna's phrase, a "supporting cast of helpers" including "things like boundary conditions, material parameters, interfacial stipulations [and] rigidity constraints" (McKenna, 2023, p. 2). One might indeed find a handpicked example of a generalization where either the generalization or one of its supporting cast of helpers is in fact explainable using some other means. For instance, researching cell size scaling laws, Romain Rollin and colleagues have found that "these laws can be explained quantitatively by a single model of size regulation based on three simple, yet generic, physical constraints" (Rollin, Joanny, & Sens, 2023, p. 1). But my question here is broader: can generalizations, as a rule, be explained using other means, and in particular mechanistically?

My contention is that most established scientific generalizations are, as the evidence reviewed here shows, refractory to further reduction or downward explanation. For one, if scientifically-relevant generalizations could be reduced to equally-explanatory mechanistic alternatives, would one not expect this to have happened eventually over a certain amount of time, given a general keenness in the natural sciences for parsimony and simplicity of explanations (if possible)? Evidently, however, this has not happened. Take physics; while generalizations such as Kepler's laws of planetary motion can be deduced from Newtonian laws of motion and the law of universal gravitation, the Newtonian laws have remained stubbornly irreducible to mechanistic explanations at the subatomic particle level. In chemistry, thermodynamic laws have not been reduced to some mechanistic alternative. The utility of thermodynamics, by functioning in guises such as the Gibbs free energy, is in its current non-reduced form, even if reduction was somehow possible in principle. Indeed, it is not clear what a mechanistic reduction of thermodynamics would entail. Thermodynamics might be explainable using statistical mechanics, and also involve probability distributions on phase space;[16] but this is still not mechanistic, for the 'parts' or 'entities' are not readily stipulable.

[16] I am grateful to Luke Fenton-Glynn for pointing these elements out to me.

This lack of obvious ‘parts’ or ‘entities’ for a mechanistic explanation is an important point. As I will mention again later, Coulomb’s law is a generalization that can explain the contact and binding properties of interacting proteins. The law states that “the magnitude, or absolute value, of the attractive or repulsive electrostatic force between two point charges is directly proportional to the product of the magnitudes of their charges and inversely proportional to the squared distance between them”[17]. (This law is similar in structure to Newton’s law of universal gravitation but deals with charge rather than mass.) What entities should one take into account to mechanistically explain the attractive or repulsive electrostatic force? Put differently, what entities or parts is the ‘force’ itself (i.e. not the point charges) actually made of? There is no clear answer to this. We are hence ‘stuck with’ the generalization. One finds a similar strand of argumentation in Craver’s defence of an ontic account of scientific explanation. He calls what I take to be generalizations ‘phenomenal models’. Having this caveat as context, he writes that “to mark the difference between a phenomenal model and a mechanistic model […] one must appeal to the (quasi-mereological) structures of the world that relate the *explanans* to the *explanandum*” (Craver, 2014, p. 43). Reduction to mechanisms stops when we can no longer, at a minimum, posit ‘entities’ that would have activities and some organization.

Now let us take an example specific to cell biology and proteins. Suppose we had an empirically-tested generalization about the induced shapes of a family of proteins’ interacting domains. (I say empirically-tested to suggest that we can take the generalization to have some validity over repeated experimentation.) In this example I also say the generalization applies to a family of proteins, and not all proteins, to avoid contentions about the generalization’s overly broad scope. This generalization, for the sake of our discussion here, appeals to such things as the geometric shape of the various protein domains, the viscosity of the cytosolic liquid around the interacting proteins, the movement hindrances of the domains within the interacting proteins themselves, and other aspects relating to the specific cellular locale of the proteins.

Next, suppose one could explain the same induced shapes of the protein family’s interacting domains by appealing to the infinitesimal quantum chemical details of every single atom that makes up the interacting protein domains. In doing so, one may be able to provide a detailed mechanistic explanation whereby some change in the quantum chemistry of certain atoms leads to other atomic changes elsewhere in the protein domain, leading to an overall change in the shape and chemical properties of the domain as a whole. But such a mechanistic explanation, if it were indeed possible, cannot ignore the chemical forces amongst the protein’s atoms, or chemical forces between the surrounding water molecules and those atoms. For those, some law of chemistry would be needed. Therefore, we have substituted a generalization at the level of the protein with two explanations: a mechanistic and a generalization-based one, but at the chemical level. And it is not at all clear whether this trade-off of the simplicity of a single generalization would return any explanatory benefit.

[17] This is from the Wikipedia entry on the law, referencing Charles-Augustin de Coulomb’s 1785 exposition on the subject (https://en.wikipedia.org/wiki/Coulomb%27s_law).

In their classic paper referenced earlier, Machamer, Darden and Craver call these apparent irreducibilities 'bottoming out': "in molecular biology and molecular neurobiology, hierarchies of mechanisms bottom out in descriptions of the activities of macromolecules, smaller molecules, and ions" (Machamer et al., 2000, p. 14). They then categorize four types of 'bottom out activities': "geometrico-mechanical", "electro-chemical", "energetic" and "electro-magnetic" (Machamer et al., 2000, p. 14). We are thus in the domain of phenomena explainable by the laws of chemistry and physics. Bechtel also points to this bottoming out to chemistry in explanations in neuroscience: "in the context of reductionistic accounts of cognitive information processing I argue that this requires going down to a level that is largely overlooked in these discussions, that of chemistry" (Bechtel, 2022, p. 1).

I will not belabor this strand of discussion further; but I hope it is now sufficiently evident that generalizations can provide distinct explanatory work, and one important way they could do so is through contrastive explanation.

4.2. Generalizations can contrastively explain the interaction-enabling properties of biomolecules.

Taking up the issue of how generalizations could explain interactions, first some context is necessary. Herbert Simon (1916–2001), whose work was cited earlier in reference to mechanism discovery heuristics, might have been sympathetic to what I am going to say in this section. He wrote, for instance, that "by a complex system I mean one made up of a large number of parts that interact in a nonsimple way" and that "in such systems, the whole is more than the sum of the parts, not in an ultimate, metaphysical sense, but in the important pragmatic sense that, given the properties of the parts and the *laws of their interaction*, it is not a trivial matter to infer the properties of the whole" (Simon, 1962, p. 468) [my italics]. Glennan, in the same 2002 paper in which he provided a definition of interactions, wrote that "a mechanism for a behavior is a complex system that produces that behavior by the interaction of a number of parts, where the interactions between parts can be characterized by direct, invariant, change-relating generalizations" (Glennan, 2002, p. S344). He further explained his word choice between generalizations and laws as follows: "in earlier papers (Glennan 1992, 1996) I have called generalizations describing interactions between parts 'laws.' I did so with the caveat that these laws must be understood in a more homely way than philosophers typically understand them. Woodward and others have convinced me that, given that many philosophers think laws must be exceptionless, my use of the term 'law' was liable to lead to misunderstanding" (Glennan, 2002, p. S345). Therefore, his use of generalizations is similar to mine in this paper.

At the conclusion of **§3**, we were left with four aspects pertaining to protein–protein interactions, and two interaction-enabling properties: interaction-enabling properties of proteins (*protein properties* for short), and interaction-enabling properties of the proteins' environment (*environment properties* for short). The two property types play into each of the four aspects. Below I provide some examples of how such interplays could manifest themselves:

- ASPECT 1 (preformed/induced interacting surfaces): The three-dimensional structures of proteins need complementary surfaces for interacting. Here protein properties of interest could include geometric properties, size properties, protein shape dynamics properties, etc. Environment properties of interest include cytosolic viscosity properties and thermal properties.
- ASPECT 2 ('contact' and 'binding'): Proteins need to come within a certain distance of each other and bind using electrostatic and other forces. A protein property of interest could be protein residue charge properties, and an environment property of interest could be cytosolic ionic charge properties.
- ASPECT 3 (proximate/ultimate interaction consequences): Proteins can be considered enzymatic catalysts: they perform some enzymatic function on each other, be it the addition/removal of a chemical group or cleaving a domain of their interacting molecule. But they may also transport their interacting partner to another location, or reduce their presence somewhere by binding to them. A protein property of interest could be protein catalytic properties, and some environment properties of interest could again be cytosolic ionic charge properties, viscosity properties and thermal properties.
- ASPECT 4 (duration and end of interaction): Proteins dissociate after some time, but some may form much longer interactions, such as in amyloids. This aspect of the interaction is so dependent on known and unknown factors, particularly the environment surrounding the proteins, that it is difficult to say which property of the protein is directly contributing to it. But, of course, a protein property of interest that is certain to play a part is protein residue charge properties, because a very strong binding between two interacting protein domains may guarantee a longer interaction. Environment properties of interest could include membrane lipid vibrational and fluidity properties, for example if the proteins are sitting on a plasma membrane, as is the case for the MRC protein complexes.

For the rest of the current discussion, I will take Aspect 4 above (duration and end of interaction) and create a hypothetical scenario. Suppose it was discovered that proteins interacting with each other on plasma membranes in the cell (including those in the MRC) interacted for durations in multiples of 10 ns: i.e. 10 ns, 20 ns, 30 ns, etc., but not e.g. 15 ns or 27 ns. Suppose further that this occurrence was not the case for proteins interacting elsewhere in the cell, i.e. the duration of their interaction did not take place in any particular timing multiples or patterns. Then a contrastive question could be asked: *why are protein interaction durations in multiples of 10 ns on the plasma membrane but not elsewhere in the cell?* Now suppose that a generalization was discovered that pertained to this very problem; here I call it the principle of quantized membrane protein interaction:

> ***Principle of Quantized Membrane Protein Interaction (QMPI)****: proteins on plasma membranes can only associate/dissociate in line with the vibrational frequency of lipids in the plasma membrane.*[18]

The QMPI principle, which I consider a form of generalization,[19] can explain the vibrational property of the lipid environment of membrane proteins. It can thus answer the question of why protein interaction durations happen in multiples of 10 ns on the plasma membrane but not elsewhere in the cell by stating that the vibrational frequency of plasma membranes only affects proteins sitting on membranes and not elsewhere in the cell, for example.

But the QMPI principle could also do a few more things. First, if more evidence is gathered from studies so that the principle becomes more precise, e.g. what exactly the vibrational frequency range is, or how the type of lipid affects this frequency, one could make certain *predictions*. If one knows the type of lipid membrane, for example, perhaps the interaction duration of two unknown proteins could be predicted (not even knowing their identity). Prediction has also been variously expounded in the literature under topics such as quantification, possibility generation (Ward, 2007) and expectability (Díez, 2014; Hempel, 1968). On prediction and possibility generation, Barry Ward writes that "when we predict and explain we use laws to *generate* descriptions of particular cases. When I say the laws generate a description of a particular case, I mean that the law statements, along with statements of the relevant boundary or initial conditions, are (non-redundant) assumptions in a derivation that yields a specification or model of the behavior of the system in question" (Ward, 2007, p. 545).[20] And in fact new routes of investigation are opened up when there are deviations from what a generalization predicts to be possible.[21]

The flipside of the coin of possibility generation is that of constraints: when we say a generalization such as the QMPI delimits what is possible, that is another way of saying it imposes constraints on our explanatory domain of interest. Here the recent works of Sara Green and Nicholaos Jones (Green & Jones, 2016) and that of Lauren Ross (Ross, 2023) are of particular relevance. Ross notes that constraints imposed by generalizations can be considered "external to the system of interest and [viewed] as providing a guiding, regulatory force on it" (p. 7), and such constraints are "fixed in the sense that they are not viewed as manipulable" (p. 7). In all, Ross suggests that a generalization can be "an ever-present background condition that structures the outcome as opposed to initiating it" (p. 7).

[18] While there may be some evidence in the literature as inspiration for this principle and the preceding timing regime examples, consider these purely hypothetical and for illustrative purposes only.
[19] On the choice of the term 'principle', see (Ehsani, 2023) for a proposed framework to distinguish scientific generalizations according to a law–principle taxonomy.
[20] Here Ward adds that "while *governing* is a putative feature of the metaphysics of laws, *generation* is primarily an aspect of how law statements are, or might be, used in scientific practice" (Ward, 2007, p. 545).
[21] See these two recent examples from different subfields in physics: (Marder, 2023; K. Miller, 2023; M. Wang, Shi, & Fineberg, 2023).

The second explanatory route is that of *counterfactual dependency* and *intervention*, to help answer *what-if-things-had-been-different* questions (Woodward, 2003). First let's take a non-cell-biology example: using the case of the ideal gas law, Gabriel Siegel and Carl Craver write in a recent article that this generalization is explanatory "because it provides counterfactual dependency information, answering *what-if-things-had-been-different questions*", and it "indicates roughly how volume would have been different given ideal interventions on temperature, namely, in accordance with pV = nRT" (Siegel & Craver, 2024, p. 8). Now while these types of counterfactual questions are contrastive, they should not be considered the same as *why-this-and-not-that* questions. When it comes to counterfactual dependency and intervention, specific parameters of the generalization need to be known to answer a specific *what-if-things-had-been-different* query. However, *why-this-and-not-that* questions are concerned with specific aspects of the target phenomenon as described by a mechanistic description. There is more to say here, but such connections and differences between these two types of contrastive questions are an area of investigation that seems ready for interesting new philosophical work. That being said, a more specified version of the QMPI principle could answer a counterfactual question such as: what if the sizes of the membrane proteins were such that the vibrational frequency of the lipid membrane was affected? Or, what if the composition of the lipids in the membrane was changed, etc.

The third potential mode of explanation that needs to be highlighted is that of *unification* (Bhogal, 2020; Kitcher, 1989). Tracing back to Michael Friedman's discussion of explanatory unification (Friedman, 1974), Harjit Bhogal writes that "we gain unification by reducing the number of phenomena that we need to accept independently" (Bhogal, 2020, p. 176).[22] Now, ideally, a nomological-mechanistic explanation making use of one or more generalizations could provide a unified explanation of different interacting proteins in different cellular environments. That is the ultimate goal; but what of the QMPI principle? How can it provide unificatory explanatory work? The most obvious way is that regardless of the cellular mechanism in which two proteins are a part, as long as they happen to be located in a similarly situated environment on the plasma membrane, they will have the same interaction duration timing regime. As such, different mechanistic descriptions could be cross-connected temporally if they happen to utilize proteins in similar cellular milieus.

Finally, I should note that the overall explanation can get even more enriched when multiple generalizations, some explaining protein properties and others explaining environment properties, are all brought together to answer the same *why-this-and-not-that* question about a particular aspect of a cell biological mechanistic description. That being said, the dynamics of such multifaceted explanations are certainly beyond the present paper.

[22] Bhogal explains this citing the kinetic theory of gases: "the development of the kinetic theory of gases allowed us to give a single explanation of phenomena that we previously had to accept independently, like phenomenon to do with the relationship between the heat and pressure of gases, and to do with gaseous diffusion. In this way we reduce the number of phenomena that we need to accept independently" (Bhogal, 2020, p. 176).

5. Conclusions

I have attempted to point out a particular niche within cell biological mechanistic explanations that could be prone to further explanatory work by scientifically-relevant generalizations, namely the niche of protein–protein interactions, with implications for other biomolecular interactions as well.[23] I then mapped out four aspects relevant to the sequence of events taking place in protein–protein interactions, and proposed (i) interaction-enabling properties of proteins and (ii) interaction-enabling properties of the proteins' environment as elements that could be explained by relevant generalizations. These generalization-based explanations could answer contrastive *why-this-and-not-that* types of questions pertaining to different aspects of a protein–protein interaction of interest.

The picture provided here is a simple one. While one can always make a mechanistic explanation more detailed and complicated, the framework here proposes that biomolecular interactions could be an element of a mechanistic explanation that connects it with one or more generalization-based explanations. The generalizations answer *why-this-and-not-that* types of questions that would be difficult to achieve otherwise. It remains to be seen whether and how this picture might pan out in practice, but I should note that the framework might be amenable to improvement by even further simplification, such as by providing an account of how the augmentation of a mechanistic description would work when multiple generalizations, and not just one, are at play.

Simplicity is not just one of many explanatory virtues, but quite an important one for that matter. Albert Einstein, reflecting on his life's scientific work in a 1950 *Scientific American* article, wrote that a motivation for positing new theories of puzzling phenomena is "the striving toward unification and simplification of the premises of the theory as a whole" (Einstein, 1950, p. 13). He continued that a theoretician or scientist (or a "tamed metaphysicist" in his terms), "believes that not all that is logically simple is embodied in experienced reality, but that the totality of all sensory experience can be 'comprehended' on the basis of a conceptual system built on premises of great simplicity. The skeptic will say that this is a 'miracle creed.' Admittedly so, but it is a miracle creed which has been borne out to an amazing extent by the development of science" (p. 13).[24] While the discovery of new generalizations in cell biology is certainly no easy task, once discovered and empirically validated, their explanatory contribution can lead to unification, simplicity and an overall greater fruitfulness of the explanatory task at hand.

[23] An account of other biomolecular interactions, e.g. between proteins and nucleic acids (Lukauskas et al., 2024), would still need to take into account the nuances associated with the properties of the particular parts involved. That said, there might be features common to all biomolecular interactions; if such features are eventually identified, a further question of interest would be to determine how, for example, they might compare with features common to interactions at a species level (Krishnadas, 2023; Lebrija-Trejos, Hernandez, & Wright, 2023), or even interactions studied in non-living objects (Huber & Huhtinen, 2024; Veenstra et al., 2024).

[24] For more on this concept in a non-cell-biology context, see (Chomsky, 2022, 2023).

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