Foundations for a Realism-Based Ontology of Protein Aggregates

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Abstract. The objective of this paper is to propose formal definitions for the terms 'protein aggregate' and 'protein-containing complex' such that the descriptions and usages of these terms in biomedical literature are unified and that those portions of reality are correctly represented. To this end, we surveyed the literature to assess the need for a distinction between these entities, then compared the features of usages and definitions found in the literature to the definitions for those terms found in Bioportal ontologies. Based on the results of this comparison, we propose updated definitions for the terms 'protein aggregate' and 'protein-containing complex'. Thus far, we propose the following distinguishing factors: first, that one important difference lies in whether an entity is disposed to change type in response to certain structural alterations, such as dissociation of a continuant part, and second that an important difference lies in the ability of the entity to realize its function after such an event occurs. These distinctions are reflected in the proposed definitions.

Keywords. Protein aggregates, protein complexes, realism-based ontology

1. Introduction

Researchers in biomedical ontology have thus far not addressed carefully enough how biological entities known as 'protein aggregates' should be represented faithfully to reality. They are not represented at all in any large biomedical ontology, and the two smaller ontologies in which they are represented provide incomplete definitions which lack unity and do not include all defining characteristics which differentiate them from protein complexes [1,2]. Other ontologies refer to these entities only indirectly through definitions for other terms such as 'protein aggregation'. This is consistent with the fact that definitions as provided in the biomedical literature are scarce and lack unity. These definitions also do not accurately represent the scope of protein aggregate types that exist. Protein aggregates (PAs) are participants in several clinically relevant pathological bodily processes, most notably neurodegeneration [3–5] and biological processes like cell migration [6].

In light of this, the existing definitions should be updated in such a way that the portion of reality, in this case protein aggregates, is accurately represented. The goal of the work presented here is to unify the descriptions and usages of multiple specific objective truths concerning PAs in a way that allows deduction of objective truth from the references. To accomplish this, we created a minimal set of terms, along with ontological definitions for those terms, which will serve to describe the unified objective

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truth concerning the characteristics of PAs. The terms that are contained in this set can then be used as contextual templates for discerning specific instances of these terms in the literature. The ontology which will be constructed based upon these new definitions will be specific to the domain of the biomedical sciences—the realm of PRO and GO.

2. Background

The term 'protein aggregate' is used loosely, and is employed as an informal term for entities which have as continuant parts proteins which are not in their 'native state.' As such, the use of 'protein aggregate' is in some cases a stylistic choice, rather than a semantically intentional choice. For clarity, this term should be reformulated.

2.1. Protein Aggregates in Neurodegenerative Disease

Protein aggregates are referenced in terms of their role in neurodegenerative diseases in a substantial portion of biomedical literature. For example, the presence of PAs, along with the death of specific types of neurons, are diagnostic criteria in Parkinson's disease (PD) patients [7]. In fact, the bodily process of protein aggregation in PD may be influenced by impairments in the ability of neurons to degrade damaged, mutated, or misfolded instances of the protein α-synuclein, which form unstructured clumps, instances of which are commonly referred to as protein aggregates [8].

2.2. Protein Aggregates in Non-Neurodegenerative Disease Contexts

The antibody—antigen complexes which form as part of the immune response process are also better understood as a type of PA. In these complexes, antibodies aggregate around and facilitate destruction of antigens. The term 'immune complex' is widely used, but we argue that the characteristics of immune complexes do not meet the criteria of yet other entities which are currently called 'protein complexes' or 'protein-containing complexes'. Through the process of 'immune complex formation', specific subtypes of antibodies cause agglutination of particulate antigens or precipitation of soluble antigens [9]. In particular, multivalent antigens induce a process of cross-linking of antigen particles with antibodies as the links, resulting in a 'clump' of antigen particles interspersed with antibodies [9]. This clump of antibodies and antigens is referred to as the 'antibody—antigen complex', although not all antigens an antibody may act upon are necessarily macromolecules, and not all constituent parts necessarily function together.

2.3. Protein Aggregates in Non-Disease Contexts

'Protein aggregate' as a category also includes entity types of which not all instances are participants in disease processes, but rather are participants in normal physiological processes. One example is the cytoskeletal actin filaments which form aggregates as part of the processes of cell growth, division, and motility. Actin filaments form a network wherein they polymerize and depolymerize to form a pseudopod so the cell can migrate, or of membrane protrusions called 'microvilli' which facilitate nutrient absorption [10]. During polymerization, individual actin proteins self-assemble around an actin trimer,

elongating and shrinking the filament via addition or loss of actin subunits on either end [11]. The rates of association and dissociation of actin subunits depends upon which nucleotide is bound to the subunit in question [6]. This allows for the relatively tight control of filament length. While the nucleation step of actin polymerization does require an actin trimer, the size of individual actin filaments themselves vary between instances, depending on what specific process is taking place.

3. Methods

We first reviewed the literature to assess the need for a distinct term for entities which form via physical associations of proteins and other molecules, but which did not suit the criteria for 'protein-containing complex'. A search of the MeSH headings in PubMed was performed to assess the numbers of papers concerning protein aggregates and protein complexes found in all MeSH categories (Table 1). Each MeSH heading was added to the search, followed by either "protein aggregate*" or "protein complex*". We then assessed the existing definitions of 'protein aggregate' in the literature (Table 2). For this assessment, we performed a PubMed search for the phrase "protein aggregate", using the filters: 'free full text', 'books and documents, 'reviews', 'systematic reviews'. These filters were selected on the basis that these particular source types, because they are syntheses of information, are more likely to contain an explicit definition for a term than, for example, a clinical trial. These publications were assessed to determine if they contained a definition for 'protein aggregate.' This process was repeated for the search term 'protein complex' with the same filters.

From this literature search, we collected examples of contextual usages and definitions of the terms 'protein aggregate' and 'protein complex' and identified key features contained within them, which were then compared with the contents of current ontological definitions (Table 4). Using the information obtained from these literature assessments, we propose definitions for the term 'protein aggregate', as well as changes to the definition of 'protein-containing complex', both based following the principles underlying the Basic Formal Ontology [12].

4. Results

Table 1 shows the prevalence of the phrases 'protein aggregate' and 'protein complex' in the literature. The search term 'protein aggregate' yields barely 70 percent of the number of results for the search term 'protein complex(es)'. Interestingly, 'protein aggregate' appears most frequently in the biomedical literature under MeSH subheadings 'Nervous System Diseases'', while 'protein complex' appears most frequently under 'Neoplasms'. Both terms are abundant under the subheading 'Pathological Conditions, Signs and Symptoms'.

Table 2 lists the definitions for the terms 'protein aggregate', 'protein complex', and 'protein-containing complex' as found in the literature. 'Protein aggregate' seems to be used when referring to an entity which is composed of component proteins as its continuant parts, which are noncanonical (e.g., misfolded) in some way. Protein complexes seem to be understood as consisting only of molecules in their native states as constituent parts. Those constituent parts function together and thus allow the complex to bear a specific role in a specific biochemical process.

Table 1. Results of search for the term 'protein aggregate' under the listed MeSH subheadings.

MeSH Disease Subheading	**'protein aggregate*'**	**'protein complex*'**
Disorders of Environmental Origin	0	0
Occupational Diseases	0	17
Otorhinolaryngologic Diseases	3	75
Stomatognathic Diseases	8	64
Wounds and Injuries	23	79
Skin and Connective Tissue Diseases	35	679
Chemically-Induced Disorders	39	72
Respiratory Tract Diseases	41	277
Hemic and Lymphatic Diseases	42	486
Male Urogenital Diseases	43	371
Female Urogenital Diseases and Pregnancy Complications	49	391
Immune System Diseases	70	650
Digestive System Diseases	86	597
Endocrine System Diseases	88	305
Eye Diseases	152	250
Musculoskeletal Diseases	158	412
Cardiovascular Diseases	176	303
Infections	204	850
Neoplasms	252	2352
Congenital, Hereditary, and Neonatal Diseases and Abnormalities	404	967
Animal Diseases	425	433
Nutritional and Metabolic Diseases	591	711
Pathological Conditions, Signs and Symptoms	1191	1902
Nervous System Diseases	2242	1198

The definitions of the terms in question are informed by their usage, and vice versa. Thus it is important to assess the ways in which the terms are used in the literature even when a definition is not provided. Examining common uses of prospective ontology terms allows us to differentiate between a term's formal definition and the ways in which it is used practically. 'Protein aggregate' seems typically used when referring to entities which participate in a disease process of some type and which do not appear to participate in normal biological processes. 'Protein complex' is indeed used when referring to entities which are participants in a specific biological process (Table 3).

Table 2. Definitions for 'protein aggregate' and 'protein-containing complex' in the literature.

Protein aggregate	• "Protein aggregates are oligomeric complexes of non-native conformers that arise from non-native interactions among structured, kinetically trapped intermediates in protein folding or assembly."[13] • "[…] Protein aggregates be defined as any protein species in non-native states and whose sizes are at least twice as that of the native protein. Dimers, trimers, which maintain the native-like state will not fall under the definition of aggregates."[14]
Protein complex	• "Protein complexes are molecular machines that perform many of the key biochemical activities essential to the cell e.g. replication, transcription, translation, cell signalling, cell-cycle regulation and oxidative phosphorylation." [15] • "[…] a collection of proteins that copurify together in a high-throughput proteomics experiment or through the analysis of patterns within pairwise interaction data." [16]
Protein-containing complex	• "A stable assembly of two or more macromolecules, i.e. proteins, nucleic acids, carbohydrates or lipids, in which at least one component is a protein and the constituent parts function together." [17,18]

Table 3. Examples of ways in which the terms 'protein aggregate', 'protein complex', 'protein-containing complex', and 'macromolecular complex' are used in the literature.

Term	Usage examples
Protein aggregate	• "[…] highly-ordered, β-sheet rich, insoluble aggregates are implicated in a diverse group of neurodegenerative diseases, including prion, Alzheimer, Parkinson and Huntington disease. In aged patients, often different aggregated proteins coexist." [19] • "Ordered aggregates are nm-long (un)branched amyloid fibrils, arranged in a cross β-sheet structure [3]. Disordered aggregates […] are the result of acute cellular stimuli (i.e., stress-caused denaturation, lack of assembly partners)." [20]
Protein complex	• "Independent evidence from global quantification of both protein production and decay using ribosome profiling and metabolic pulse labeling experiments has culminated in a conserved principle that the proportion of complex components is indeed carefully maintained." [21]

The definitions from the NIF Standard Ontology, the Neurodegenerative Disease Data Ontology, the EDAM Ontology, and the Semantic Science Integrated Ontology overall tend to track with common usages and informal definitions in the literature. Across these representations, the term 'protein aggregate' refers to an entity which has as constituent parts non-native proteins (Table 4).

Table 4 reflects the heterogeneity of the terms 'protein aggregate' and 'protein complex' amongst the ontologies in which they are represented. The class hierarchies for the two Bioportal ontologies containing the term 'protein aggregate' are distinct from one another, save that the hierarchies are claimed to be rooted in the Basic Formal Ontology. The hierarchies for those ontologies in Bioportal which contain the term 'protein complex' are also distinct The Semantic Science Integrated Ontology is inspired by the BFO and classifies 'protein complex' as an object, while the 'logic' of the EDAM Ontology hierarchy represents protein complexes as structures which are of type 'data'. Table 4 shows features from the literature definitions and usages to show common themes, as well as gaps between these and what is represented in the listed ontologies. These features were added to a column if they appeared in that definition. It is clear from examining these features that across usage and definition, protein complexes are

understood to at the very least have native-state proteins as their constituent parts. Usages and definitions in the literature indicate an understanding that within protein complexes, continuant parts of different types appear in consistent proportion to one another between instances in protein complexes and that those constituent parts function together, but the SIO definition does not reflect this (Table 2, Table 3). Assessment of usages and definitions for 'protein aggregate' indicate that they are widely understood as rigid and insoluble, having as constituent parts proteins which are not in their native state. Specific structural features like β-sheets appear frequently in usages, but do not appear in definitions.

Table 4. Representational characteristics of 'protein aggregate' and 'protein complex' **in Bioportal ontologies .**

	NIF Standard Ontology	**Neurodegenerative Disease Data Ontology**	**EDAM Ontology**	**Semantic Science Integrated Ontology**
Term	protein aggregate	protein aggregate	protein complex	protein complex
Definitions	A grouping of misfolded proteins that is often rigid and insoluble [1]	An insoluble mass of misfolded proteins [2]	3D coordinate and associated data for a multi-protein complex; two or more polypeptides chains in a stable, functional association with one another [22]	A protein complex is a molecular complex composed of at least two polypeptide chains.
Features of Usage Examples & Literature Definitions	Component proteins in non-native state	Insoluble Component proteins in non-native state	Constituent parts of the protein complex function together Comprised of two or more polypeptides	Comprised of two or more polypeptides
1st Parent	Aggregate object	Material entity	Protein structure	Molecular complex
2nd Parent	Object aggregate	Independent continuant	Structure	Chemical entity
3rd Parent	Material entity	Continuant	Data	Material entity
4th Parent	Independent continuant	Entity	Thing	Object
5th Parent	Continuant			Entity
6th Parent	Entity			

Based on these results we argue that PAs meet the definition of 'object' according to the BFO [12]**.** An *object* is a maximal causally unified material entity**.** PAs are causally unified via internal physical forces: if a continuant part *c* of a protein aggregate *p1* at *t1* (i.e. a portion of the aggregate on its interior) is moved in space at *t2* to be at a location on the exterior of the spatial region that was previously occupied by *p1* at *t1*, then *p1* is

either damaged or its other parts are also moved [12]. The important part to notice here is that to meet the criteria for an object, *c* must move in space to a location already occupied by *p1*, not in a different direction from the central axis of *p1* itself. Put another way, an instance of a PA of some type can be understood as a bound system which requires an intervention of a sufficient magnitude to overcome the bonds between its constituent parts and result in damage to the aggregate [23]. Bearing this in mind, the proposed definition – using the GO-term 'cellular component' which despite what the name might suggest does include entities which exist outside the cell such as the extracellular matrix – is as follows:

Protein aggregate= def. an BFO:*Object* of a type instances and some parts of these instances are, or once were, cellular components and have as primary constituents at least two instances of PROTEIN which comprise the majority of instances of macromolecules contained within the aggregate.

Axiom 1: An instance *pa1* of PROTEIN AGGREGATE at *t1* remains an instance of PROTEIN AGGREGATE at *t2* when a continuant part is added or removed as long as there are at least two instances of PROTEIN in *pa1* at *t2* and as long as the part added is of the same type as any of the continuant parts of *pa1* prior to the change.

Axiom 2: As long as an instance *pa1* of PROTEIN AGGREGATE remains an instance of PROTEIN AGGREGATE, it remains an instance of the same subtype of protein aggregate as long as any part added is of the same type as any of the continuant parts of *pa1* prior to the change

We also propose to change the GO definition of 'protein-containing complex' as PCCs have causal unity for the same reasons as protein aggregates do [12]. The proposed definition is as follows:

Protein-containing complex= def. an BFO:*Object* which is a cellular component, of a type instances of which have two or more macromolecules, i.e. proteins, nucleic acids, carbohydrates or lipids, in which at least one component is a protein and the constituent parts are disposed to function together only when all constituent parts are present within the complex.

Elucidation 1: An instance of a particular protein-containing complex at *t1* becomes of a different type of BFO:*Object* at *t2* when a continuant part is removed.

5. Discussion

An assessment of the available literature concerning PAs, compared with literature concerning protein complexes, yields some interesting observations. The first is that protein complexes are likely a more widespread topic of research and review than are protein aggregates. It also seems that the term 'protein complex' is used outside of the scope of its definition, and that sometimes, the more appropriate term to use is 'protein aggregate'. Additionally, when PAs are discussed in the literature, it is most often in the context of neurodegenerative disease and general pathological conditions. The examples of usages and definitions further point to a specific discrepancy in how these terms are used: 'protein aggregate' is used more commonly in a disease-specific context, while

'protein complex' is used with greater versatility and more frequently under a broader range of MeSH subheadings.

Protein-containing complexes are fundamental participants in bodily processes. Among types of PCCs, there is diversity and specificity in the disposition of the individual proteins to form a stable, correctly-folded secondary and tertiary structure [25]. It appears that some PCCs are comprised, at least in part, of constituent parts which are proteins that are disposed to do this, while others have as constituent parts individual proteins which do not. Specific instances of proteins within these PCCs may serve as stabilizers of the other proteins within the complex, while other types of PCCs do not need these support proteins [26].

An important distinction between aggregates and complexes is that an instance of a particular aggregate can have a component protein dissociate or detach with no change in type at that level. This is because PAs as types are not restricted to a specific number of individual continuant parts in the same way PCCs are. This matters in the context of the size of a specific instance of the entity, as PAs have fewer constraints on maximum area and mass than do PCCs and thus possess fewer spatial restrictions. Another key distinction lies in the degree of regularity or order in the arrangement of the components. PCCs form 'molecular machinery' networks, which must be precisely structured and contain all instances of their components in order to perform their function correctly [27]. Conversely, PAs vary structurally from instance to instance, and are less restricted in terms of size and shape than PCCs, as seen in the antibody—antigen example. Our understanding of PCCs and PAs is consistent with Schulz and Jansen's work on grains, components, and mixtures [28]. In this view, PCCs meet the definition of strict compounds—for example, all components of a PCC need not be of the same type but their number is critical. PAs can be understood as a type of flexible compound in that they possess as continuant parts instances of collectives of individual proteins. Importantly, collectives as a type are flexible with regard to their number of grains, which is consistent with our understanding of PAs. From this knowledge, it can be extrapolated that components of a PA are capable of higher degrees of disorder than the components of a PCC.

Alterations in the ability of a protein complex to *realize* its function can be achieved through a few avenues. First, the cause of the change must be determined. It is well established that proteins can dissociate from one another and lose their tertiary and quaternary structures, thus losing the ability to perform their function, for example as a result of the pH of the environment differing from their pKa [29]. Thus it is often not a question of whether the change is functional or environmental, but which came first.

The relationship between components and realization of function seems to serve as a dividing line between PAs and PCCs. For example, an instance of PA which is comprised of 600 individual protein molecules will not cease to be a PA of that type if 1/3 of those protein molecules are removed. Further, if concentration is a factor in the formation of PAs, as the presence of chaperonins suggests [30], diluting the space in which the proteins interact lowers the rate of aggregation. In both scenarios, the change in type is related to a change in the ability of that instance of a particular PA or protein-containing complex to realize its function. An instance of a particular PCC at *t1* may change type at *t2* when a continuant part is added or removed, while altering the ability of the PCC to realize its function in either direction. Conversely, an instance of a particular protein aggregate *pa1* at t1 does not change type at *t2* when a continuant part is added or removed. Thus the ability of that instance of the particular PA to realize its function, if any at all, is not affected.

Function is determined by the structural organization of a material entity [12]. A basic example of this is the denaturation (loss of secondary and tertiary structure) of a fully folded protein *p1* of type *R* at *t1* so that it changes to an instance of polypeptide type *Q* at *t2*. Polypeptides lacking secondary and tertiary structure no longer are of type 'protein', and cannot realize their function. So, in this case, the change in ability of an instance of an entity to realize its function is accompanied by a change in type of that particular instance.

A second case, where an entity retains its type but cannot realize its function, is also possible. Post-translational modifications (PTMs) modulate the activity of proteins and protein-containing entities through induction of conformational changes in the structure of the entity [31]. While PTMs are an avenue through which conformational (structural) change occurs, they result in a temporary loss (or gain) of the ability of an instance of an entity of a particular type to realize its function but do not result in a change in the type of that instance. In addition to discrepancies in the level of fluidity of the arrangement of their components, it is along these functional lines that PAs and protein-containing complexes differentiate—in their respective tendency to change type in response to various structural alterations as well as changes in ability to realize function.

Our proposed definitions for the terms 'protein-containing complex' and 'protein aggregate' are not without issue. Currently, the primary distinguishing feature of the definition of 'protein-containing complex' is the disposal to change type upon dissociation of a continuant part. However, the current definitions do not address the differences in maximum possible number of continuant parts which can comprise protein aggregates versus protein complexes. This is an important distinction the true nature of which needs to be explored in future work.

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