Biomedical Ontologies: Toward Scientific Debate

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Keywords
Biomedical ontologies, biomedical informatics, spatial ontologies, artificial intelligence, mathematical morphology

Summary
Objectives: Biomedical ontologies have been very successful in structuring knowledge for many different applications, receiving widespread praise for their utility and potential. Yet, the role of computational ontologies in scientific research, as opposed to knowledge management applications, has not been extensively discussed. We aim to stimulate further discussion on the advantages and challenges presented by biomedical ontologies from a scientific perspective.

Methods: We review various aspects of biomedical ontologies going beyond their practical successes, and focus on some key scientific questions in two ways. First, we analyze and discuss current approaches to improve biomedical ontologies that are based largely on classical, Aristotelian ontological models of reality. Second, we raise various open questions about biomedical ontologies that require further research, analyzing in more detail those related to visual reasoning and spatial ontologies.

Results: We outline significant scientific issues that biomedical ontologies should consider, beyond current efforts of building practical consensus between them. For spatial ontologies, we suggest an approach for building “morphospatial” taxonomies, as an example that could stimulate research on fundamental open issues for biomedical ontologies. Conclusions: Analysis of a large number of problems with biomedical ontologies suggests that the field is very much open to alternative interpretations of current work, and in need of scientific debate and discussion that can lead to new ideas and research directions.

1. Introduction

What are computational ontologies? Developed within the field of artificial intelligence (AI) [1, 2], as a way of representing knowledge about some aspect of reality that is being reasoned about on the computer, they define: a) modelling primitives that include objects, and classes or categories of objects such as for instance, cells, organs, persons, b) semantic relationships between objects such as “virion” is a “cellular component” or “kidney” is part of “Upper urinary tract”, and c) properties associated with each class, which may be purely descriptive, such as, definition of “cell” → “Anatomical structure which has as its boundary the external surface of a maximally connected plasma membrane. Examples: lymphocyte, fibroblast, erythrocyte, neuron.” [3] or functional, such as: definition of “caspase regulator activity” → “modulates the activity of a caspase, any of a group of cysteine proteases involved in apoptosis” [4]. With the above one can define facets (properties of relationships), instances (individuals belonging to a class), formal axioms, rules, functions, procedures, ontology mappings and other means of manipulating the elements of an ontology. In addition, inheritance in computational ontologies allows properties associated with a higher level (more encompassing) class to be inherited by its subclasses. Over the past years, computational ontologies have been implemented using different ontology mark-up schemas and languages with the goal of transitioning the existing WWW into the Semantic Web [1]. These include RDF, RDF Schema, OIL, DAML+OIL or the Web Ontology Language (OWL) – a “de facto” current standard [5]. In addition, “upper ontologies” are used to describe general concepts that are shared across various knowledge domains, with the idea of supporting semantic interoperability between different ontologies at lower levels. There are several upper ontologies, each one differing greatly in terms of their users, topics, focus and ontological foundations [6]. Examples include the Basic Formal Ontology (BFO) [7], the Descriptive Ontology for Linguistic and Cognitive Engineering (DOLCE) [8], Generalized Upper Model (GUM) [9], OpenCyc [10], Process Specification Language (PSL) [11], Suggested Upper Merged Ontology (SUMO) [12] and others. The BFO is now widely used for biomedical ontologies. Regarding the use of the word “ontology”, proposed by Gruber, there was much debate at the early stages of computational ontologies [13], given the philosophical pedigree of the term. It was finally adopted. Øhrstrøm et al [14] contrast usage between classical philosophy and computer science. They question whether the two deal with the same problems, and discuss their complementarities.
Many computational biomedical ontologies have been developed over the past two decades, with notable examples like the Gene Ontology (GO), which has proven to be a practical tool for managing the vast amounts of gene data [15]. At the time of writing, a PubMed search has retrieved 4557 journal articles containing the word “ontology”. This number points to the great and increasing importance of the area of computational ontologies [16–19]. Figure 1 gives the distribution of these publications by major journal and search term categories, using the GoPubMed software [20].

The recent biomedical literature [21–24] seems to be in strong agreement about the advantages of computational ontologies for helping to standardize and structure knowledge, and for managing and exchanging data and information between professionals and machines. In our own very positive experience with computational ontologies, we have used them in ontology-based data integration [25–27], query homogenization [28], ontology-guided data cleaning and mining [29], new models and informatics tools for integrated clinical-genomic trials [30], information extraction [31], information retrieval and text mining [32–34], building biomedical vocabulary servers [35] as well as analyzing and linking ontologies – e.g., from the open biomedical ontology (OBO) Foundry and the nanoparticle ontology (NPO) – for research on nanoinformatics [36], among others. More recently, members of our group at the Universidad Politecnica de Madrid (UPM) have also contributed to developing cancer ontologies [37]. In all these areas we have greatly benefited from ontologies, compared to previous research where they were not available for such tasks. Extensive reviews of different applications of biomedical ontologies are available elsewhere [38–39].

As seen in Figure 1, biological contributions of these computational ontologies span a wide range of topics. Such broad practical uses explain the current overwhelming agreement about the positive role of ontologies in supporting biomedical research and practice. However, our experience with biomedical ontologies is that they raise challenging and open questions for advanced scientific research and inquiry that are either largely underestimated or ignored.

In this paper we analyze some of these challenging questions posed by biomedical ontologies, and point out limitations of their current definition and usage. We discuss different aspects of their current status, concerning, for instance, the recent introduction of philosophical assumptions into the field and other topics, such as challenges in addressing issues like biological emergence, the use of computational ontologies for scientific inquiry, their role in modern AI or how they deal with well-known difficult problems like uncertainty management or inheritance. Finally, we suggest an approach for handling the complex problems of defining and classifying biological shape and function, which is an unresolved challenge for today’s computational ontologies. A main objective of the paper is to assess the adequacy of Aristotelian ideas to fill gaps that computational ontologists displayed in their early days. Finally, we discuss the likely impact of the scientific challenges raised.

2. Philosophical Foundations and the Computational Applications of Ontologies

Philosophers such as Aristotle, Kant, Husserl, Frege and Lesniewski, defined and developed (philosophical) ontologies as formalisms aimed at providing systematic
ways of describing reality, long before either the computer or the biological revolutions of the second half of the 20th Century. Early versions of computational ontologies such as the Gene Ontology (GO), the Unified Medical Language System (UMLS) and the National Cancer Institute Thesaurus were criticized by some classical ontologists because of deficiencies in how they related to classical formalisms for representing reality in terms of categories and their instances [40–42]. In response, some computational ontology communities, such as the OBO Foundry [43, 44] adopted a conceptualist or realism-based philosophical approach, based on classical Aristotelian assumptions – the BFO – to solve some of these reported problems [43]. The OBO Foundry gathers a large number of biomedical ontologies, with representative examples such as GO or the Foundational Model of Anatomy, with share such formalisms.

Within BFO, entities can be of two types: continuants (things, objects), which endure or continue to exist and occur- rents (processes, events, activities, changes), which unfold over time [45]. An example proposed by BFO developers is shown below [46]:

You are a continuant. Your life is an occur- rent. You are 3-dimensional. Your life is 4dimensional.

These two types, continuants and occur- rents, had been originally proposed within two different philosophical frameworks – three- and four-dimensionality, respectiv- ely – which, while usually considered to be opposites by today’s philosophers [47], have at other times been considered as equivalent [48]. Such contradictory interpreta- tions have generated significant de- bate in philosophical journals and forums [49–50]. The BFO takes a “neutral” philo- sophical position, considering both views as neither opposite nor equivalent, but rather as complementary, so that they are both included in the approach [45]. This raises the issue of inconsistency or vague- ness that can arise from allowing for two very different yet opposite interpretations under one umbrella, or, if both positions were to be considered equivalent, the danger of redundancy. The BFO divides occur- rents into two types: instantaneous and extended (over time). And, it defines con- tinuants as falling into two categories: inde- pendent and dependent. Examples of inde- pendent are a cell, a bacterium, an organ- ism (or a person), whereas examples of de- pendent are functions, qualities, etc [46, 51]. There are other distinctions made in the BFO, also based on Aristotelian as- sumptions.

These philosophical specifications for ontological entities are, unfortunately, not necessarily consistent with scientific needs and practice. How can cells or viruses be entirely independent entities, even within a controlled laboratory environment? View- ing them as independent entities may serve as a practical simplification for philosophi- cal, cognitive or even computational pur- poses, but does not capture the interre- lationships essential for biological function and life. For example, the distinction be- tween continuants and occurrences does not account for the contrast between reversible and irreversible processes in biology, chem- istry, computation, or quantum mechanics.

A concrete example, related to visual processes, illustrates the above. Niggemann et al proposed a realist philosophical ontol- ogy model for neuro-anatomy, based on an example from the visual system in [52]. It analyses the reflex systems of the pupillary light reflex and the accommodation reflex, involving various groups of neurons. Follow- ing OBO conventions, the authors claimed that current representations used in the Foundational Model of Anatomy (FMA) [53] can be transformed into the more realistically formal, ontological repre- sentations proposed in this model. The authors say that this “common sense” model only addresses anatomical issues and it is not intended to address physiologi- cal issues. We consider this interesting example below, from two different perspec- tives.

First, from an informational and physiological perspective, it is known that in the first steps of the visual process, light falls on the eyes, which receive information coming from the external world through their sensors. From an informational perspective, this is a reversible process. Inform- ation is collected but not really processed and analyzed, leading later, after the image reaches the retina and follows the optic nerve towards the visual areas of the brain, to an irreversible process. In this step, infor- mation is selected, so that only a small per- centage of the original information that impinges on the eye is retained. These com- binations of reversible and irreversible pro- cesses – originally pointed to from a com- putational perspective, by scholars like Feynman [54] –, occur ubiquitously in na- ture. The Nobelist Prigogine described and analyzed similar processes in chemistry, for which the concept of “time” in biology proved essential in defining the reversibil- ity and irreversibility of processes [55]. Processes like homeostasis and neural feedback were defined and modeled by Wiener and other cybernetics, leading to pro- found changes in our understanding of physiology [56]. Including such models as part of scientific conceptualizations of na- ture is a requirement for any computerized model of biological processes.

Second, in their neuro-anatomical pro- posal, the authors defined various new con- cepts and categories, based on an approach that they define as rigorous and based on common sense at the same time [52]. Here is one example, from its contents: <<A Functional-Group is therefore a kind of “ObjectAggregate” as defined in the BFO as “An independent continuant that is a me- terological sum of separate objects and pos- sesses non-connected boundaries”. Simi- larly, the definition of Functional-Group is consistent with Simons’ notation of “group”>> [52]. If we analyze this short paragraph, we can find eleven terms whose meaning needs a concrete, restricted, onto- logical interpretation: “functional-group”, “objectAggregate”, “Basic Formal Ontol- ogy”, “independent”, “continuant”, “mero- logical”, “separate”, “objects”, “non-con- nected”, “boundaries” and “Simons’ no- tation of “group”. Although it may support ontological design criteria, one wonders if these kinds of statements are actually fully understood by the majority of scientists who use ontologies.

Ontological approaches also incor- porate ideas from other fields, as for example considering literary figures like synec- doque – taking the part as a whole – or metonymy – which takes the part by the
whole. The analysis and use of both as proposed in the framework of ontologies [57] look more like a rhetorical device and arbitrary exercise; scientifically irrelevant, as they depend on the specific criteria used, or the intention of the person producing a statement.

Differences of opinion, world-view, psychological and social disposition, vocabulary, language usage, and controversies between scientists and philosophers have been ongoing for centuries. As we have already mentioned, various biomedical ontologies have adopted Aristotelian constructs. It might help to recall that while Aristotle founded natural philosophy, his writings in science were qualitative, not quantitative nor empirical, and by Galileo's time were already considered inadequate. In connection with this lack of empirical perspective, we can recall Russell's comment: "Aristotle maintained that women have fewer teeth than men; although he was twice married, it never occurred to him to verify this statement by examining his wives' mouths" [58]. Galileo showed that Aristotelian ideas on gravitation were wrong by carrying out crucial experiments that challenged them as well as by a beautiful thought experiment [59]. One of the causes frequently cited by historians of science for the "dark age" aspects of medieval science, was the rigid, authoritative adherence to Aristotelian thought [59].

Bunge, a well-known ontologist and quantum physicist – and, among other distinctions, a Fellow of the American Association for the Advancement of Science (AAAS) – pointed out that classical philosophy has rarely addressed important biological concepts such as the ideas of "system," "emergence" – discussed in the next section – and others [60, p 26]. Therefore, strictly philosophically-motivated formalisms might not adequately describe some fundamental biological phenomena. And, while ontological philosophical formalisms have been in place for the more than hundred year span of "modern" biology, they have had minimal influence on its scientific developments despite many proposals and considerable discussion [60, 61]. An example involves mereology, a philosophical theory of wholes-and-parts, which has been recently used in computational ontologies [62], and whose impact on biological research has been minimal since its inception [60–61]. Bunge – who stated that "thanks to a bit of algebra, the entire rather esoteric discipline of mereology gets compressed into a single paragraph" [60] – also points out that philosophers themselves frequently disagree about ontological formalisms [60–61], which may also contribute to their being ignored by practical biologists.

Comments from two Nobel Prize winners support the above. Monod [63] stated that the cornerstone of the scientific method is objectivity about nature, since philosophers before Galileo lacked the rigor of objective criteria. Similarly, Lorenz [64] considered that classical, non-biologically-oriented philosophers are frequently wrong when they state that we are capable of moving towards objective descriptions of all our personal and subjective prejudices and criteria and in attempting to reach a level where judgments and evaluations have universal value.

In our own experience, using the kind of philosophical assumptions currently specified for computational ontologies from the OBO Foundry has considerably complicated some of our work on database integration, paradoxically mostly from a practical perspective [65]. We often found that modeling data under the BFO produced unexpectedly long and complicated expressions in order to refer to the data themselves, which translated into rather cumbersome queries to extract the data. From our point of view, what was gained in terms of generality was lost in terms of usability. Other researchers have reported the opposite experience, citing advantages of using BFO and related philosophical assumptions for improving ontological engineering [43]. Comparing and contrasting such different experiences in a scientific debate might prove productive in advancing the field.

We see substantial differences usage of the term "ontology" in classical philosophy and in computer science which affects the adequacy of the term for both. In this regard, Sandholm has reviewed ontological ideas from Aristotle, Quine and Carnap and concluded that they are extremely useful for systematic formalization and categorization for the ontologies used in computer science [66]. However, he states that “one should however treat the more theoretical philosophical discussions about the existence and reality of entities, or absolute truth of theories in relation to nature with scepticism, if considering them at all”. Goguen, a professor of computer science at UCSD takes an even more critical position, considering that philosophical ontology is a step backwards in computer science, embracing extreme forms of realism and reductionism [67]. Finally, one might wonder what might have happened differently if Gruber had proposed a different name than (computational) "ontologies" like, for instance, "conceptual constructs" or "semantic structures".

3. Ontological Problems with Levels of Organization and Emergence in Biology

As mentioned above, some ontologists like Bunge have stated that traditional ontological formalisms cannot adequately handle novel biological knowledge, especially as it includes data from multiple levels and scales of structure and function, involving phenomena such as emergence [60, 61]. Multi-level interactions lead to the emergence of new properties that are specific to the phenomena in question, and to each living species, and depend on the ordering and proportion of their components. A simpler example is that of water, which is composed of hydrogen and oxygen – yet one cannot deduce the physical, chemical or biologically-relevant properties of water based on the properties of its components alone.

Emergence and the impossibility of deducing structure at higher levels based solely on characteristics of functions at lower levels have been discussed extensively, under different names, in many scientific fields. They include, in biology, Lorenz [64] and Mayr [68]; in physics, Bohr [69], in intelligence and cognitive aspects of the brain, Minsky [70] and Simon [71]; in chemistry, Prigogine [55] and Lehn [72] and in philosophy itself, Hartman [73] and Bunge [60]. So, when one considers...
ontologies such as GO [15], primarily designed for the genomic level, scientists need to be cautious about how they define mappings to other ontologies that address different biological levels. Many usual terms such as, for instance, "life", "apoptosis", or "inflammation" will be interpreted quite differently by molecular biologists, physiologists and clinicians. In addition, different domain ontologies may be designed to model the same entity at different granularities and in different contexts, making alignment difficult.

A challenge for designers of biomedical ontologies is how to include the necessary representational power needed to represent biologically complex systems. BFO developers have recognized the granularity-related limits of their approach [74]. In this connection, the biological processes branch of GO [15] and pathway archives like KEGG aim to represent complex interaction systems emerging from the interplay of genes, hoping to address emerging phenomena [75]. Ontological efforts to solve granularity issues, including emergence, have been mainly focused on realistic assumptions [76]. However, as Mayr has pointed out, emergence is an empirical and not a metaphysical principle [68].

Currently GO includes a comprehensive set of relationships describing gene/protein activity. However, its choice of dividing the gene ontology into the three categories of molecular function, biological process and cellular component [15] may prove limiting. Comprehensive ontologies in larger biological domains could facilitate integrative efforts [77]. In this context, Noble suggests that Gene ontology might fail without higher-level insight [78, 79], needed to establish direct causal relations between genes and the phenotype. Noble reminds us that GO specifically excludes protein domains or structural features, protein–protein interactions, anatomical or histological features above the level of cellular components, including cell types as well as the environment, evolution and expression. From his perspective, since GO excludes physiology and most aspects of evolutionary biology, it cannot adequately address modeling phenomena across different biological levels. On the other hand, the "Physiome" project [80], designed to create models and simulations of components of the whole body and link them to specific clinical data does envision this. Without introducing quantitative approaches and the capacity to computationally interact with such empirical models and simulation tools at various biological levels, current computational ontologies cannot fully address the functionalities involved in biological processes and their ecologies.

4. Ontologies and Scientific Theories

Some computational ontologists have stated that ontologies “can be seen as analogous to scientific theories” [81] – with the Foundational Model of Anatomy (FMA) ontology, considered as “a theory of structural phenotype” [82] –, with many other references suggesting the importance of building ontological theories of various scientific problems. In this connection, a BFO manual [83] states that the document is written in the spirit of Aristotle’s Organon, an instrument for the proper conduct and representation of scientific research. According to this view, the BFO should be a step in this direction. As stated in this BFO manual, “scientific theories are intended to express the truth about reality in their respective domains, full stop”.

A related approach [84], also considers ontologies as scientific methods for theory formation, since “ontologies as substantive theories offer ways to model phenomena of interest, and in particular model theories that are cast in the form of a conceptual framework – common in social sciences – in a much more rigorous fashion” [84]. Similarly, Hogan has developed a theory of substance intolerance based on an ontological perspective [85]. As he states, “rather than in chemistry or physiology, the framework of the Ontology for General Medical Science – which uses BFO as its uppermost level – was a more-than–adequate foundation on which to build the theory”. Also, Johansson et al describe an ontological vision of physiology [86] without addressing various fundamental physiological scientific issues, whereas Gennari et al. [87] restructure some specific aspects of physiology from an ontological perspective. Together with other ontological proposals [88] they make the contention that ontologies describe fundamental theories. Also along these lines, Metzinger [89] argues that the brain can be viewed as a representational system aimed at interpreting our world, which implies that it possesses an ontology too, since it creates primitives and makes existential assumptions. Interestingly, the author explicitly states that this model can explain known facts, but he does not want to imply a solution to the problem of consciousness, which is still unknown. From our perspective, this kind of post-hoc explanation misses two fundamental characteristics of scientific theories: explanation and prediction. Many models can be built – and have been built – to propose how the brain works. The key scientific advance would be to propose a crucial experiment that will accurately test the validity of a model, as in predicting the brain’s many responses to specific inputs and to explain them. In this regard, ontological assumptions can be used to provide post-hoc explanations to many different problems in various fields, but the one fundamental benchmark of modern scientific theories, the prediction of unexpected facts, has yet to be supported by computational ontologies alone.

Contrary to such ontological visions, Kuhn suggested that it is only a scientific paradigm shift which enables changes in an underlying ontology [90]. For instance, Einstein’s theory of relativity changed the concepts of light and time in a way that no pre-relativistic ontologies could have anticipated [91]. In other words, it is a new theory that defines and explains new concepts, not vice-versa [92]. In this sense, an ontology, considered as a theory, would not be able to predict unexpected phenomena, which is one of the main characteristics of fundamental scientific theories [90]. Therefore, it is highly improbable that existing descriptive ontologies will enable us to discover or learn the ontology for a new theory. While the concept of “atom” arose in Ancient Greece, it took almost 2500 years to develop the theory that finally explained it. For many centuries philosophical discussions and ontological assumptions were made about atoms, but it
was scientists like Planck, Einstein, Thomson and Rutherford who definitively established the scientific foundations of the concept of “atom” and, incidentally, generated strong insights in the philosophical disciplines [93].

Finally, we can see how ontological reconsideration of scientific theories has also led to re-analyses of past scientific achievements in the light of ontological perspectives which reinterpret the history of science. For instance, Müller-Wille considers that the true revolution in nineteenth-century life sciences “consisted in a fundamental shift in ontology, which eroded the boundaries between individual and species, and allowed biologists to move up and down the scale of organic complexity” [94]. According to him, this mode of thinking led to Mendel’s discoveries and advances in biochemistry, microbiology, and “may require us to rethink the history of biology and displace Darwin’s theory of natural selection from that history’s centre”. Yet, we can only wonder why, if the shift was ontological, it was not an ontologist, but rather Darwin, a scientist, who achieved the changes he did, triggering all the scientific work that followed.

5. Artificial Intelligence and Ontologies

Biomedicine is arguably the field where computational ontologies have been reported to be most successful from both a scientific and practical perspective. Historically, DENDRAL was the first expert system, developed at Stanford by Feigenbaum, Buchanan and the Nobel laureate Lederberg [95], and was designed to elucidate the unknown molecular structure of chemical compounds using empirical data from mass spectrometry. The project aimed at “theory formation” although it was primarily focused on “hypothesis generation” [96]. DENDRAL was followed by many other expert systems, with particular emphasis on medical decision-making [97, 98] – an area where one of the authors, CK, also made early contributions. These pioneering AI expert systems, however, did not solve general, broad problems, e.g., acting as a Delphic oracle [99] or trying to learn how to demonstrate complex scientific laws [100], but succeeded when they addressed particular, narrower problems that modeled and complemented human expertise [96]. The difficulties they encountered can mainly be explained by the large amount of noisy and incomplete data to be interpreted, the expense and difficulty of maintaining and updating expert knowledge bases, and the dearth of predictive theories in biology and medicine, which still remain a mixture of science, technology and art.

Ontologies as they have been defined in many projects, are part of the continuing efforts to develop knowledge conceptualizations and representations for problems using AI [1, 2]. In this sense, they can be seen as a way of advancing computational representations of concepts and their relationships, very much like an advanced version of semantic nets and related early work in AI [101–103]. But, here we would argue that they should not be really considered as an AI breakthrough. They cannot resolve contradictions that arise in theoretical systems where past assumptions and results need to be reconsidered with the full deployment of modern sophisticated modeling, simulation, and inference methods at multiple levels.

Let us consider an example. An “Ontology of Physics for Biology” (OPB) has been proposed, based on ontological principles as defined by the OBO Foundry [104]. It is designed to be “orthogonal and complementary” to representations of biological structure such as the FMA, and an example is cited of how the semantic annotations for OPB will help in “aligning, integrating and even debugging complex biosimulation models” [104]. The major claim is that by merging maps of three different sources the authors were able to obtain (by hand) a merged model that can “repurpose the expected effects of increased arteriolar calcium uptake to increase blood pressure and to decrease heart rate – effects that can be reproduced in the separate source models”.

While the approach is surely interesting, it should be noted that earlier generations of researchers in physics-based computerized knowledge representations [105–108] achieved somewhat similar types of model aggregation, but with traditional physio-

6. Ontologies and Biological Taxonomies

Developing large and complex hierarchies of classes with their semantic relations and properties contributes to systematization and can produce substantial improvements for computerized tasks of information structuring and management. While essential to establish consistency among many specific facts and across a wide range of relationships among the facts, from a purely scientific perspective, this approach does not necessarily bring anything new to the central processes of scientific discovery. Biology in the 18th and 19th centuries built and extended taxonomies of plants and animals, incorporating biological properties and functionalities. Linnaeus began the construction of taxonomies for the different kingdoms of animals, plants and minerals by defining classes, grouped into phyla. Each class in turn was split into families, tribes, orders, genera and species. Each of these groups was defined by specific, distinctive features of their members [111]. In the 20th century biology moved from being almost purely descriptive to becoming a more explanatory and predictive science – enabled by Darwin’s insights into evolution and later, genetics. From this perspective, computational ontologies in their present form appear to recapitulate 18th and 19th century biology.
Ongoing taxonomical reorganization of the entities of a domain is typical of all sciences. For instance, new discoveries frequently lead to the reclassification of diseases. Genes are continuously reclassified when more information is available from research [39]. A-priori categorization of biological, chemical or physical elements, following an ontological approach, requires corrections and changes every time a new scientific discovery is made. Only empirical observations and evaluation can lead to such conclusions. In this sense, ontological reorganization of scientific knowledge in new taxonomical organizations will not introduce new scientific knowledge and will face continuous modification. This is a difficult and expensive task involving much human evaluation that will have to be justified by measurable benefits.

An additional issue of current computational ontologies is that building taxonomical hierarchies or sequences of events or components which combine different types of concepts might lead to building hybrid constructs with doubtful scientific meaning. These might involve philosophical and biological components that will be difficult to define and test empirically. Let us consider an example, showing a sequential link of entities, proposed for one of the OBO ontologies, the Sequence Ontology [112].

Figure 2 illustrates a “philosophical-biological” proposal for the integration of concepts within the Sequence Ontology, described by their authors as having the practical objective of improving the structure of a specific ontology – but one which we argue, raises fundamental problems. Specifically we observe in such kinds of sequences abrupt transitions such as, for instance, RNA molecule → molecular entity → independent continuant, at the boundary between classical ontology and biology. They introduce direct links between rather different dimensions, which can be difficult to evaluate from a purely scientific perspective. While such “hybrid” constructs might have some practical ontological usefulness – and surely helped the authors to implement their approach –, they are difficult to test scientifically, since, being under-constrained, they can be fitted to very many different empirical data. Other similar examples can be found in the literature, given the combination of philosophical and biological classes that are in use in various biomedical ontologies [85, 113, 114].

7. Other Aspects of Biomedical Ontologies

As seen above, we have focused our attention on various significant aspects that we consider particularly relevant in the area of biomedical ontologies. However, there are others that should be mentioned. For instance, among them, issues such as inheritance, uncertainty management or the importance of consensus for ontology alignment.

To our knowledge, no current standard ontology markup language can efficiently represent the variability and variety of biological inheritance or the emergence of biological properties without introducing exceptions and additional approaches for inference. Top-down vs bottom-up vs. same-level causal interpretations suggest that properties emerge in multiple directions. With this in mind, in order to avoid knowledge engineering problems that have been reported with multiple inheritance, the BFO proposes the principle of a single “is-a” inheritance. Following logico-philosophical assumptions, inheritance has been proposed to obey concrete, simple rules, avoiding complex or multiple inheritance [115]. For instance, the creators of Cell Ontology have eliminated multiple inheritance in the asserted hierarchy to facilitate cross links with external ontologies, such as the Protein Ontology and the Gene Ontology [116]. Other researchers have proposed models for multiple inheritance in the BFO [117]. Again, while it can be argued that,
from a software engineering perspective, biological systems need to be simplified in order to be modeled by means of informatics techniques, including ontologies, the problem of inadequacy in representing current biological knowledge must be addressed.

While formalizing uncertainty has been addressed in statistics with probability and other measures [118], as well as in knowledge engineering with various heuristics, like Zadeh’s fuzzy possibilistic logic [119] or Shortliffe’s confidence measures [98] — these efforts have only yielded partial success in characterizing the uncertainty and unpredictability present in nature and in our models of it. As models of reality, ontologies have to deal with uncertainty — which they so far can do by using or building Bayesian models [120] — and models of imprecision [121] — by constructing, for instance, “fuzzy” ontologies. Schemes to represent uncertainty are under development in recent OBO ontologies such as PATO [122]. From a methodological perspective, they have been the subject of intense development during the last decade [39, 123]. However, these efforts to incorporate uncertainty have yet to demonstrate their impact in enhancing the practical application of computational ontologies to address complex biomedical problems. This issue proved quite difficult for earlier research on medical expert systems and data mining. Ironically, it may well turn out that the Achilles heel of ontologies could be the same one that has plagued knowledge-based AI systems: uncertainty and incompleteness in the basic science underlying biomedicine.

Regarding consensus, there has emerged a widely-held view that ontologies should be based on broad agreement that facilitate interoperability and knowledge reuse [124]. However, in science, consensus is rarely achieved until a paradigm or established theory with strong exemplars are accepted by the large majority of scientists in a field. And, as Planck stated with great irony, a new theory is not widely accepted until the defenders of the previous one die [125]. We argue that consensus by small groups analyzing scientific issues from an exclusively ontological perspective must also be subject to testable, empirical science. There has been discussion about whether consensus on ontological design should be based on purely “democratic” assessments or on assessments restricted to highly specialized authorities, like peer-review scientific processes in the literature [126]. Any kind of consensus has some practical, engineering usefulness, of course, but from a scientific perspective, a strictly democratic process can never ensure scientific consistency and sometimes combined forces of authority are used to resist the introduction of improved theories, like the history of science amply illustrates [90].

Finally, in the next section we suggest ideas for how future biomedical ontologies can address visual and graphical information.

8. An Approach for Creating Taxonomies of Shapes and Graphical Forms

There are many fundamental scientific questions that arise from efforts to develop computational ontologies. An important set of issues arises from trying to build ontologies that will help in the management and taxonomic classification of images and shapes, to include not only qualitative, but also quantitative information.

Returning to the experience with the first expert system, DENDRAL’s developers needed to represent organic molecular structures as graphs, so as to be able to split them into sub-graphs corresponding to the molecular fragments produced by the mass spectrometer [96]. Processing these taxonomies in graphical form was not done until the first knowledge-based rule system was built and successfully tested, opening up a whole new subfield within AI [96, 98]. Some indirect, qualitatively related efforts for managing shapes and forms have been carried out in the area of computational ontologies. More recently, and directly related to shape characterization, Spatial Ontology (part of the OBO Foundry) [127], was designed for anatomical spatial references, but expressed with qualitative terms such as “dorsal”, “ventral”, “axis”, and so forth. In this regard, there is an active sub-group in the ontology community, with their own Annual Workshop (SOCoP) [128] – the Spatial Ontology Community of Practice.

The BFO designers have also addressed issues linked to spatial topics such as granularity, adjacency, connectivity and others. As some ontologists have stated [129], the definition of those particular classes in BFO was dependent on the notion of physical concepts — e.g., connectedness. Nigge mann et al [52] have outlined a perspective with respect to neuro-anatomy, from the point of view of knowledge representation. They argued that the spatial dimension is not even necessary in order to define a “functional object”. Similarly, Borgo and Guarino [130] present granularity boundaries “avoiding to rely on their classical mathematical definition”. They adopt “a definition more akin to commonsense intuition, where surfaces and edges are thought of as concrete entities, and granularity considerations are invoked” [130]. Bittner et al. [131] define spatial characteristics like connectedness and adjacency in their qualitative approach to represent spatial relations of biological structures. In their proposal they also adopt the perspective of the FMA, considering the idea of “canonical anatomy” and express that “it is impossible to quantitatively describe aspects of shape and spatial arrangement of canonical anatomy. There is too much variation between the actual shapes and metric arrangements of particular structures among particular human beings”. For us, such a concept can serve for building ontological constructions — and, in fact, the use of categorization through prototypes has been used in classical philosophy and also recently adapted for fields such as anatomy or genomics [3, 39] —, but it does not seem to be precisely defined from a scientific perspective. What is canonical anatomy in scientific terms? Is there, for instance, a canonical nose? Can we consider, similarly, a “canonical” genome? In connection to the above, we believe that it is equally difficult — though maybe not impossible — to represent spatial information as purely qualitative or quantitative descriptions and make it effective for computation and for scientific applications.

When considering shapes, some fundamental concepts that arise are connectedness and adjacency. Such concepts have
been addressed from a qualitative perspective in the ontological literature, sometimes claiming them to be rigorous and formal [52, 129]. We argue that such proposals cannot disregard basic scientific knowledge about these spatially related issues, which goes back at least two centuries, from the works of Gauss, Euler and Riemann, among others. We suggest that the formalization of these spatially-related concepts needs to draw on the extensive work in the area of image processing and analysis. Concepts like connectivity or adjacency can be precisely, mathematically defined, as presented in Appendix I⁶.

Current ontologies use the “part-of” and “is-a” relations at their core. While the “is-a” relationship has been extensively used in purely semantic ways, it can encompass geometrical and morphological properties of shapes and can be embodied by classes of shapes. For example, a very simplified, high-level taxonomy of geometrical shapes is the following:

Shapes:

➢ 1-D Shapes
➢ 2-D Shapes
  ○ 2-D Geometrical shapes
    ▾ 2-D Geometrical shapes with genus 0
    ★ Circles
    ★ Polygons
    ○ Convex polygons
      ▾ Squares
      ▾ Triangles
      ▾ …
    ○ Non-convex polygons
      ▾ 2-D Geometrical shapes with genus 1
    ○ 2-D Non-geometrical shapes
➢ 3-D Shapes

In this example, we illustrate a simplified taxonomy with a hierarchy of the equivalence of classes representing shapes (Appendix II⁶). Shape subclasses inherit morphological properties of the class they belong to. To program computers to reliably perform such tasks is not trivial, although there are computational means to “detect” shapes that satisfy certain properties, as well as to measure the similarity degrees that exist among some shapes. Image processing and analysis methods [132–135] and pattern classification techniques [136] can be used in this regard. Other related proposals aiming to create shape ontologies, following different directions to ours, have been recently published [137, 138]. Different approaches include qualitative spatial reasoning [139, 140]. In our case, we are currently carrying out specific research on these problems, developing a prototype of a system designed to detect specific geometrical structures.

Of course, “ideal” shapes corresponding to geometrical figures are much easier to define and decompose than the shapes found in nature or even in engineered artifacts and systems. Yet, even in complex biological models, such as of human anatomy, a hand can be divided into several parts, such as a palm and fingers. At a finer level of granularity, the palm and fingers can be further decomposed into bones and muscles, veins and arteries, nerves, etc. Following this approach, future realistic ontologies of a domain must include also graphical representations of those visual characteristics that may not be fully captured in language, and semantically represented. Such graphical approaches might have an additional interest for topics like the functionality of proteins or viruses, for example, where their physiological or pathological activities can be greatly influenced by their shapes, facilitating, for instance, their matching with specific targets [141]. Different structures, like proteins and viruses, have some interactions such as e.g., agent-receptor, which might be analyzed also from a (mathematical) morphological perspective. For instance, each virus has characteristic size and shape. Transmission and virulence of some viruses have been reported to be influenced, at least in part, by virus morphology [141]. Such analyses could add useful information to traditional molecular biology research. Research on such “morphospatial” taxonomies or ontologies might shed light on current descriptive and functional classifications of viruses and their properties.

Let us consider an example. Figure 3 displays examples of viruses. On the left, there is an example of a small virus with an icosahedral capsid, whereas in the center we display a larger virus whose capsid presents a similar icosahedral shape. Both display different internal representations of symmetry, as shown by the letters included in their interior. On the right is a classical X-ray picture of a virus. Such a graphical representation presents potential opportunities for developing taxonomical representations of different shapes like, in the present case, viruses.

We present below a glimpse of an example of the kinds of components that could be used to develop what could be called a “morphospatial” taxonomy of a virus⁷:

Class properties of visual categories could be used to characterize common features or requirements that must be fulfilled by all instances of a given visual category. Examples of class or category properties would include the number and configuration of vertices and faces (in a 3-D shape) or line segments (in a 2-D shape).

Instance properties of a visual category could be used to express the dissimilarities among different instances of a visual class. For example, as the capsid of different icosahedron-shaped capsid viruses may have different sizes, each capsid could be represented as an instance of the “icosahedron” visual category with its corresponding value for the “size” property.

⁶ Additional material published on our website www.methods-online.com

⁷ In this paper, we use the “morphospatial” term to consider issues that concern both shapes and the spatial relations among those shapes.
Meronymy (part-whole) relationships present in regular ontologies could be used to represent complex viruses by interrelating the different visual categories that correspond to different parts of their anatomy. For instance, the virus depicted in Figure 4 could be represented as a whole by “connecting” the instance of the “regular icosahedron” class representing the virus’ capsid to the instance of the class “cylinder” representing the virus’ neck using a connectivity relationship – e.g. connecting the X vertex of the regular icosahedron to the upper basis of the cylinder. The rest of the anatomical parts of the virus would be “connected” in a similar manner. Besides, it would be possible applying rotation and translation operations to the instances representing the different anatomical parts of the virus if required.

In addition, similarly to current formal ontologies, additional operations or modifiers can be included, adapted to the requirements of such kind of “morphospatial” taxonomical approach, such as operators – like translation or rotation, in this case –, axioms, restrictions, procedures for inferences and operations – like comparison or analogy, for instance –, etc.

These are clearly topics that raise many open questions, which cannot be resolved here. However, we consider them as examples of the kind of scientific research which can be carried out in the future by BMI researchers investigating scientific discovery prospects for ontologies, and illustrating only a few of the possible directions that research can take in this area.

9. Discussion

We have raised critical questions about current computational ontologies, pointing out some of their specific limitations and challenges. To our knowledge, such a critical analysis is not currently available in the BMI literature. Interestingly, a criticism of examples of such ontological ideas, also applied to biomedical ontologies, has been made by a philosopher in a review published about a book on applied ontologies [142]. In this review [143], Simons comments about an ontological proposal reported in the book, related to the idea of “occurrents” which we mention earlier. He labels the proposal – related to a concrete medical application – as “absurd”, wondering how the author “managed to paint himself into such a corner”. For us, it is surprising how philosophers – as in this case and the early criticism of GO and other ontologies and terminologies [40–42] – seem to have been more willing than scientists to engage in critical comment, and initiate a debate on this topic. A possible answer is that trying to understand how ontologies can achieve so many different goals from scientific, engineering and philosophical perspectives is a truly demanding task, one which we have experienced ourselves. On the other hand, scientists might consider
these philosophical aspects and discussions to be placed outside of their scientific interests and fields. However, as mentioned above, since philosophical assumptions are currently used in biomedical ontologies and applications, they must be subject to scientific analysis—and debate, if necessary.

In this complex context, philosophical formalisms used today in current computational ontologies have to deal with deep scientific issues. This is shown, for instance, by the efforts to adapt the BFO to handle many of the tasks and address the issues we have mentioned in this paper as well as others related to, for instance, classical and modern physics. However, ontological proposals must fit in with our current scientific knowledge, and not vice versa. In this regard, Lord, a former BFO contributor, has publicly stated—in his blog—how “it makes little sense to create distinctions in our physical model of the world that physics does not make. We are creating work for ourselves and confusion for everyone else” [144]. He also stresses the divergence between aspects of the BFO and current scientific knowledge on various issues. While this statement obviously presents a partial, subjective and maybe circumstantial view, it supports our opinion regarding the need for more critical and objective evaluation, based on scientific terms, of the role and contents of the modifications being introduced in current computational ontologies. As Feynman noted [145], “whatever we are allowed to imagine in science must be consistent with everything else we know; that the electric fields and the waves we talk about are not just some happy thoughts which we are free to make as we wish, but ideas which must be consistent with all the laws of physics we know. We can’t allow ourselves to seriously imagine things which are obviously in contradiction to the known laws of nature”.

In this regard, it is possible to observe, even in the recent scientific literature not directly related to ontological engineering, a growing use of ontological terms and assumptions. In some cases, such use can lead to controversies. Let us consider one example. In a recent paper [146], Ackerman et al describe various experiments highlighting the importance of tactile experiences in decision making. While, taken in its most limited sense, this hypothesis appears to be supported by the reported experimental results, the authors make the following statement in the second line of the abstract: “physical touch experiences may create an ontological scaffold for the development of intrapersonal and interpersonal conceptual and metaphorical knowledge”. Just as in ancient Greek dramas, where a “Deus ex machina” is frequently used to resolve everything in a play, introducing generic ontological assumptions like the above may be used to justify almost anything that follows, as universal justifications which cannot be scientifically tested. These kinds of statements might consciously or unconsciously introduce biases that implicitly affect the scope and validity of a hypothesis without including these explicitly in the experimental design itself. In this connection, many recent BMI papers include ontological statements—like those quoted in this paper—that can be discussed from an ontological perspective, but might not be scientifically testable. In this regard, we believe that an excessive focus of computational ontologies on philosophical, linguistic or other non-scientific issues will detract from the scientific focus that ontologies must be anchored to.

In connection with the proposal for more work on “morphospatial” ontologies, we note that throughout history, eminent scientists like Leonardo da Vinci, Einstein and Feynman explicitly stated how they visualized their ideas through visual representations [147]. The field of visual cognition and creativity is a major concern of cognitive science [148]. Such a “visual” division of the components of a domain or a broader universe could help in enriching current approaches to ontologies, introducing morphological categorizations and relations. In fact, both approaches—qualitative and quantitative—could be complementary. Such a perspective ought to be especially useful for biomedicine, given that across the scales and levels of anatomy, physiology, molecular biology and all their medicinal and surgical applications involve critical visual anchoring and relative visualization to understand function and its modifications under different medical interventions.

In modern clinical practice, qualitative descriptions of human anatomy, for instance, are augmented with functional and quantitative data such as, e.g., fluid flow, volume, resistivity, diffusion, etc., which are needed to evaluate the clinical status of a patient. In addition, morphological structures of biological entities condition their function. Many examples, like, for instance, proteins, viruses, immunological entities, organs, cells, nanoparticles, suggest that shapes, forms, and spatial locations and distributions are fundamental determinants of biological processes and, thus, also of scientific discovery and the human perception and cognition underlying it. Thus, we can guess that future approaches to ontological or taxonomical scientific conceptualizations must incorporate visual components like volumes, shapes, graphics and quantitative information, in addition to the typical mostly semantic and qualitative information included in current biomedical ontologies. Such information is absolutely necessary for our understanding of the world or a domain.

Finally, in addition to the arguments previously presented, various reviews [38, 149] have pointed out specific limitations in the use of ontologies in connection to topics such as their availability, integration, discoverability, implementation, quality of annotations, noise, problems of creating automatic approaches or information dissemination, among others. McCray also reminds us about the biases that are inherent in every conceptualization of the world, which we have to recognize in developing ontologies [150]. Yet, the literature also includes many publications discussing the advantages of ontologies, from a wide range of perspectives, as already stated [16, 17, 21, 151–153]. More details can be found in these references.

10. Conclusions

In this paper we have analyzed various aspects of current computational biomedical ontologies, particularly those related to the recent introduction of classical philosophical assumptions to solve earlier problems found in the field. It seems to us that a fundamental issue is that despite a great research effort, as mentioned above, current biomedical computational ontologies—or
particularly those based on philosophical assumptions – are not yet deeply based on empirical knowledge. Similarly, some of their components cannot be fully tested using empirical approaches. Although many ontologies are solely coherent in their closed, ontological context, they can present inconsistencies with current scientific knowledge involved in a large number of issues. While we have focused our comments on some concrete examples of ontologies – and particularly the BFO, given its predominance in the biomedical domain and its Aristotelian foundations – a similar analysis could be made of other related ontological approaches.

Finally, we realize that we have stressed issues regarding biomedical ontologies that can be controversial. We could have carried out a formal analysis of the area, emphasizing our own positive experiences, and presented them in a comprehensive “review” manuscript. But, as mentioned throughout the paper, many such papers addressing the field of computational ontologies are already available elsewhere. In contrast, we felt that a different – though not necessarily opposite, but rather complementary – view was necessary. The many open issues involving current biomedical ontologies that we have presented need further scientific discussion. They hopefully can lead to new ideas and research directions and will need time to be resolved, like it has happened in all scientific fields before. However, no shortcuts should be taken by invoking the practical usefulness of current biomedical ontologies and ignoring their scientific limitations and challenges. In this regard, we encourage others to present their own arguments, perspectives, and suggestions on these topics.

Acknowledgments

The present work has been funded, in part, by the European Commission through the ACTION-Grid support action (FP7-ICT-2007-2-224176) and the DICODE project (FP7-ICT-2009-5-257184), the Spanish Ministry of Science and Innovation through the ImGraSec project (ref. TIN2007-61768), FIS/AES PS09/00069 and COMBIOMED-RETICS, and the Comunidad de Madrid, Spain.

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