*Running Title: Building Blocks and Domain Granularity Framework*

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# Levels and Building Blocks—Towards a Domain Granularity Framework for the Life Sciences

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# ABSTRACT

The use of online data repositories and the establishment of new data standards that require data to be computer-parsable so that algorithms can reason over them have become increasingly important with the emergence of high-throughput technologies, Big Data and eScience. As a consequence, there is an increasing need for new approaches for organizing and structuring data from various sources into integrated hierarchies of levels of entities that facilitate algorithm-based approaches for data exploration, data comparison and analysis. In this paper I contrast various accounts of the level idea and resulting hierarchies published by philosophers and natural scientists with the more formal approaches of theories of granularity published by information scientists and ontology researchers. I discuss the shortcomings of the former and argue that the general theory of granularity proposed by Keet circumvents these problems and allows the integration of various different hierarchies into a domain granularity framework. I introduce the concept of general building blocks, which gives rise to a hierarchy of levels that can be formally characterized by Keet's theory. This hierarchy functions as an organizational backbone for integrating various other hierarchies that I briefly discuss, resulting in a general domain granularity framework for the life sciences. I also discuss the implicit consequences of this granularity framework for the structure of top-level categories of *'material entity'* of the Basic Formal Ontology. The here suggested domain granularity framework is meant to provide the basis on which a more comprehensive information framework for the life sciences can be developed.

# INTRODUCTION

In biology, the question of how molecules make up cells and cells make up organisms resulted in the publication of various compositional hierarchies of different levels of biological organization of living systems and their component parts (e.g., Woodger, 1929; Novikoff, 1945; Wimsatt, 1976, 1994; MacMahon et al., 1978; Mayr, 1982; *genealogical hierarchy*, Eldredge & Salthe, 1984; *somatic hierarchy*, Eldredge, 1985; *scalar hierarchy*, Salthe, 1985, 1993; *Theorie des Schichtenbaus der Welt*, Riedl, 1985, 1997, 2000; *ecological hierarchy*, Levinton, 1988; *homological hierarchy*, Striedter & Northcutt, 1991; *cumulative constitutive hierarchy*, *genetic hierarchy*, Valentine & May, 1996; *building block systems*, Jagers op Akkerhuis & van Straalen, 1998; Heylighen, 2000; McShea, 2001; Valentine, 2003; Korn, 2005). Interestingly, depending on the respective frame of reference, different scientific disciplines have different compositional hierarchies. Whereas morphologists talk about the ultra-structural level, the cellular level, the tissue level and the organ level, psychologists and cognitive scientists talk about the neuronal level, the brain level, the psychological level, and the behavioral level. Evolutionary biologists, on the other hand, talk about the genetic level, the cellular level, the level of the organism, the level of the species, and ecologists about the population level, the community level, the ecosystem level, and the biome level. Arranging a heterogeneous collection of entities into a set of different levels (layers or strata) that are organized and linearly ordered in a hierarchy from a fundamental level at the bottom to some higher level at the top is a general ordering scheme that dates back at least as far as to ancient times (Wilson, 1969).

The underlying **levels idea** is simple and elegant and can be flexibly used in many different contexts (see *levels metaphor*, Craver, 2015), ranging from descriptions to explanations and ontological inventorying (List, 2016). It is not only frequently used in school and academic textbooks (e.g., Raven & Bergh, 2001; Solomon et al., 2002; Reece et al., 2014), but provides an important basic conceptual framework in various scientific and philosophical debates, including debates on downward causation, mechanistic explanation, complexity, reduction, and emergence (e.g., Morgan, 1927; Simon, 1962; Schaffer, 2003; Craver & Bechtel, 2007; Eronen, 2013).

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Various particular applications of the levels idea have been proposed in science and philosophy (e.g., *levels of sciences, theories, and explanation*, Oppenheim & Putnam, 1958; *levels of complexity*, Simon, 1962; *levels of processing*, Craik & Lockhart, 1972; *levels of sizes/composition*, Wimsatt, 1976; *levels of implementation*, Marr, 1982; *levels of organization*, Churchland & Sejnowski, 1992; *levels of analysis*, Churchland & Sejnowski, 1992; Sheperd, 1994; *levels of aggregation*, Wimsatt, 1986, 1997; *levels of causation and explanation*, Kim, 1998; *levels of realization*, Gillett, 2002; *levels of abstraction*, Floridi, 2008; *levels of parts and wholes*, Winther, 2011). Although distinct from each other, many of these applications of the levels idea at the same time relate to one another, take subtly different forms when applied in neighboring contexts, thereby often resulting in conceptual problems (Craver, 2015)[1].

In their seminal paper about the unity of science, Oppenheim and Putnam suggested six conditions of adequacy for their reductive levels approach (Oppenheim and Putnam, 1958, p.9):

1. there must be several levels;
2. the number of levels must be finite;
3. there must be a unique lowest level;
4. any entity of any level except the lowest level must possess a decomposition of entities belonging to the next lower level;
5. no entity of any level should have a part on any higher level; and
6. the levels must be selected in a way that is natural and scientifically justifiable.

Philosophers have made several similar attempts to establish criteria for the validity or usefulness of the levels idea, but they are usually not expressed in form of necessary and sufficient formal criteria, and no commonly accepted consensus has been reached for any set of criteria (Eronen, 2013; Craver, 2015). Instead of having to decide and stick with a specific account of levels, Craver therefore (2015, p.2) suggests **descriptive pluralism** about the levels idea, claiming that "the world contains many

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[1] See, for instance, Oppenheim and Putnam's (1958) theory of reduction, according to which the **unity of science** would be achieved by explaining phenomena of a higher-level science in its theories by referring to the entities and theories from the more fundamental science. Oppenheim and Putnam associate levels of material entities with levels of broad scientific disciplines (e.g., physical, chemical, etc.) and levels of their corresponding theories. Bechtel and Hamilton's (2007) criticize that this approach results in material entities of physics, which range from sub-atomic particles to planets and the entire universe, to reside in a single physical level.

distinct, legitimate applications of the levels metaphor that are either unrelated or that have only indirect relations with one another."

Irrespective the lack of commonly accepted formal criteria, the different accounts of the levels idea proposed by philosophers usually have in common that each level must represent an increase in organizational complexity, with each entity of a higher level being directly composed of entities belonging to the next lower level (Pavé, 2006), and they usually result in a **linear hierarchy of levels** from a bottom level to a top level. Moreover, the idea presupposes that entities exist for which it makes sense to understand them as being at the same level.

However, the levels idea and the idea of hierarchies based on levels have not only been discussed in philosophy and the life sciences, but also in information science and ontology research. Here, they have become increasingly important due to the increased need of researchers to manage ever increasing amounts of data with the help of computers and software applications. In times of **high-throughput technologies** and **Big Data** becoming increasingly important in the life sciences, a **data exploration/eScience** approach to science becomes increasingly important as well. This brings about an increasing necessity for researchers to communicate biological data via the World Wide Web and to use databases and online repositories (Gray, 2009). Moreover, it brings about the need for data comparability and data integration across various data providers, which requires a new way to standardize data and metadata, and the necessity to make data computer-parsable, but also to organize knowledge and all relevant types of entities into hierarchies of distinct and unambiguously defined levels that can be reasoned over, all of which can be facilitated by the use of ontologies (e.g., Stevens et al., 2000; Bard, 2003; Bard & Rhee, 2004; Vogt, 2009, 2013; Vogt et al., 2013). As a consequence, in order to meet these special demands, ontology researchers have developed their own approaches to levels, which they call **granularity levels**, and to different types of hierarchies based on levels, which they call **granular perspectives**. Due to the need of computer-parsability, ontology researchers necessarily had to provide explicit criteria for identifying and demarcating different levels and hierarchies. These criteria specify what is called a **granularity framework**.

In the following, I attempt to develop a domain granularity framework for the life sciences that reflects the hierarchical anatomical organization of organisms, marking an important step towards developing a general overarching information framework for the life sciences. I focus on morphology, because morphology takes a central role in all attempts of developing a hierarchical system of levels of biological entities, as it is "... one of the covering disciplines that spans every single entity in any biological organism" (Gupta et al., 2007, p. 65). Morphology provides essential diagnostic structural knowledge and data for almost all disciplines within the life sciences (Masci et al., 2009; Vogt et al., 2010). Morphological terminology thus provides the **basic reference system and descriptive framework for the supra-molecular domain in the life sciences**. It is central to all efforts of biological inventorying and to biological knowledge representation in general, and it provides a common backbone for the integration of all kinds of different biological information (Stevens et al., 2000; Bard, 2003; Rosse & Mejino, 2007; Smith et al., 2007; Vogt, 2010).

The paper is divided into two parts. In the first part I briefly discuss four different examples of specific accounts of the levels idea that are relevant in the life sciences and that have been proposed by philosophers and scientists. Each hierarchy is based on its own specific account of levels. I discuss their shortcomings and contrast them with a formal approach that is based on granular partitions that has been proposed by ontology researchers. I contrast the notion of a cumulative organization, which most theories of granularity assume for the anatomical organization of biological entities, with the more realistic cumulative-constitutive organization and discuss some of the conceptual problems that the latter brings about. Before I introduce the **general theory of granularity** proposed by Keet (2008a, 2006a,b), which allows the integration of various different granular perspectives (=hierarchies), with each employing its own specific application of the levels idea, I take a brief look at the granularity scheme implicit in the Basic Formal Ontology (BFO). In the second part I continue with discussing BFO's characterization of bona fide objects based on the identification of different types of causal unity and argue for the addition of two more types of causal unity for characterizing functional and historical/evolutionary bona fide entities. I also introduce the concept of **general building blocks**, which gives rise to a hierarchy of levels of building blocks that specifies its own granular perspective, which is intended to function as an **organizational backbone** for integrating various additional granular perspectives that are relevant in the life sciences, resulting in a **general domain granularity framework for the life sciences**. I briefly discuss some of these additional perspectives and the implicit consequences of this approach for the structure of top-level categories of 'material entity' of BFO. The here suggested domain granularity framework is meant to provide the initial basis on which a desperately required overarching and more comprehensive **information framework for the life sciences** (Larson & Martone, 2009) can be developed.

## FOUR ACCOUNTS OF LEVELS FROM PHILOSOPHY AND NATURAL SCIENCE

### *The Compositional Account of Levels*

Several authors have interpreted the levels idea taking a **mereological perspective** in which part-whole relations are fundamental for distinguishing levels, resulting in **compositional levels**. According to this perspective, wholes are composed of parts and the wholes are at a higher level, whereas their parts are at lower levels (see, e.g., Alexander, 1920/2013; Oppenheim & Putnam, 1958; Simon, 1962; Wimsatt, 1976, 1994; Kim, 1999). The philosophical literature about parts and the part-whole relation is not extensive (e.g., Nagel, 1961; Simon, 1962; Kauffman, 1971; Wimsatt, 1972, 1994), but the topic gained considerable attention in biology (e.g., Raff, 1996; Wagner & Altenberg, 1996; Wagner, 1996, 2001; Bolker, 2000; McShea, 2000; McShea & Venit, 2001; Rieppel, 2005; Winther, 2001, 2006, 2011), and even more so in ontology research (e.g., Smith, 1996; Bard & Winter, 2001; Mejino et al., 2003; Aitken et al., 2004; Bittner, 2004; Burger et al., 2004; Donnelly, 2004; Donnelly et al., 2006; Schulz et al., 2006; Keet & Artale, 2007; Varzi, 2007; Jansen & Schulz, 2014). Winther (2006) argues that there is an entire style of biological theorizing that he calls *compositional biology* that is based on relations of parts and wholes and their functions and capacities. Compositional biology is for instance employed by comparative morphology, functional morphology, developmental biology, and cellular biology. Winther (2006) contrasts it with *formal biology*, which is another style of theorizing that focuses on mathematical laws and models and that is for instance employed by theoretical population genetics and theoretical ecology.

When comparing an exemplary compilation of references to compositional hierarchies from biomedical literature (see table 1), we see considerable overlap regarding levels that refer to key concepts of morphology, i.e. *'cell'*, *'tissue'*, *'organ'*, *'organism'*. However, many of the schemes are problematic because they include fundamentally different types of entities within the same hierarchical system, resulting in comparing apples and oranges. For instance Eldredge's **somatic hierarchy** (see table 1; Eldredge, 1985; see also McMahon et al., 1978; Levinton, 1988) comprises spatio-structurally individuated entities, such as *'atom'*, *'molecule'*, and *'cell'*, alongside primarily functionally individuated entities, such as *'organ'* and *'individual organism'*. A hierarchy of levels of organization implies that any real entity can be unambiguously assigned to exactly one level, and that entities belonging to a higher level are composed of entities from lower levels. The mixing of spatio-structurally defined entities with functionally defined entities, however, results in a system in which some real entities belong to more than one level of the same hierarchy. If entities of a lower level are defined in reference to a specific spatio-structural or qualitative property *X* and the entities of the next higher level in reference to a specific type of function *Y* that its entities bear, it cannot be ruled out that some entity exists that has the property *X* and bears the function *Y*. This is exactly the case with mono-cellular organisms, like for instance protozoa such as *Paramecium* or *Euglena*, that belong to both the *'cell'* and the *'individual organism'* level, but do not contain any tissue, organ or organ system. Obviously, by attempting to accommodate fundamentally different categories of entities, these systems make category mistakes, which at their turn limit their potential applicability within analyses. Moreover, Eldredge's somatic hierarchy also includes a *'tissue'* level. A tissue, however, is a cluster of cells. If a cluster of cells is included, why not also include a cluster of atoms, a cluster of molecules, a cluster of organelles, etc.?

**Table 1:** Parthood-based compositional applications of the levels metaphor. '<' stands for *'lower/finer level than'*

| **authors** | **atom** | | **molecule** | | **cell part** | | **cell** | **supra-cellular** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **general hierarchy** | | | | | | | | | | | | | |
| Oppenheim & Putnam, 1958 | *elementary particle* | *atom* | *molecule* | | *cell* | | | *(multicellular) living thing*[2] | | | | | |
| Wimsatt, 1976 | *atom* | | *molecule* | *macro-molecule* | *(unicellular) cell* | | | *smaller metazoan* | | *larger metazoan*[3] | | | |
| Eldredge &Salthe, 1984 | *codon* | | *gene* | | - | | - | - | | - | | | *organism*[4] |
| Eldredge, 1985 | *subatomic particle* | *atom* | *molecule* | | *organelle* | | *cell* | *tissue* | | *organ* | | *organ system* | *individual organism* |
| Riedl, 1985, 1997, 2000 | *quantum* | *atom* | *molecule* | *biomolecule* | *cell organelle* | | *cell* | *tissue* | | *organ* | | | *individual*[5] |
| Levinton, 1988 | - | | *molecule* | | *cell organelle* | | *cell* | *tissue* | | *organ* | | | *organism*[6] |
| Streidter & Northcutt, 1991 | - | | *gene* | | *development* | | - | *morphology* | | *functions* | | | *behavior* |
| Valentine & May, 1996 | - | | *gene* | | - | | *genome* | - | | - | | | -[7] |
| Raven & Berg, 2001 | *atom* | | *molecule* | | *cell* | | | *tissue* | | *organ* | | *body system* | *organism*[8] |
| Solomon et al., 2002 | *atom* | | *molecule* | *biomolecular complex* | *organelle* | | *cell* | *tissue* | | *organ* | | *organ system* | *organism*[9] |
| Smith et al., 2005 | - | | *molecule* | | *sub cellular* | | *cell* | *tissue* | | *organ* | | *organ system* | *whole organism* |
| Keet, 2006b | - | | *molecule* | | *cell part* | | *cell* | *tissue part* | *tissue* | *organ part* | *organ* | *organ system / subdivision of principle body part / principle body part* | *body* |
| Common Anatomy Reference Ontology | *acellular anatomical structure* | | | | *cell component structure* | *multi-cell-component* | *cell* | *portion of tissue* | | *multi-tissue structure* | *compound organ* | *organism subdivision* | *multicellular organism* |

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[2] further level: social group

[3] further level: socio-cultural / ecological entity

[4] further level: deme < species < monophyletic taxon < all life

[5] further levels: action < group < civilization < culture < environment < biosphere < planet < solar system < galaxy < cosmos

[6] further levels: population < community < biotic province < biosphere

[7] further levels: gene pool < collection of gene pools < collection of collected gene pools < etc.

[8] further levels: population < community < ecosystem < biosphere

[9] further levels: population < community/biocoenosis < ecosystem < biome < biosphere/ecosphere

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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reece et al., 2014 | *atom* | *(complex biological)molecule* | *sub-cellular organelle* | | *cell* | *tissue* | | | *organ* | | *organ system* | | *complex organism*[10] |
| **model organism hierarchy - vertebrate taxa** | | | | | | | | | | | | | |
| Zebrafish anatomy and development ontology | *(acellular anatomical structure)* | | *cell* | | | *portion of tissue* | | | *multi-tissue structure* | *compound organ* | *organism subdivision* | | *whole organism* |
| Xenopus anatomy and development ontology | *(acellular anatomical structure)* | | *cell part* | | *cell* | *multicellular anatomical structure*<br>*cell condensation* | | | | *organ part* | | | *whole organism* |
| Teleost anatomy ontology | *(acellular anatomical structure)* | | *cell component*<br>*multi-cell-component structure* | | *cell* | *tissue*<br>*cell condensation* | | | *multi-tissue structure* | *compound organ* | *organism subdivision* | | *multi-cellular organism*<br>*body* |
| Drosophila gross anatomy ontology | *gene*<br>*(acellular anatomical structure)* | | *cell partt*<br>*cell component* | *multi-cell-component structure* | *cell* | *multicellular structure* | | | | | | | |
| Hymenoptera anatomy ontology | *(acellular anatomical structure)* | | *cell component* | | *cell* | *portion of tissue* | | | *multi-tissue structure* | *compound organ* | *organ system* | *organism subdivision* | *multi-cellular organism* |
| **model organism hierarchy - *Homo sapiens*** | | | | | | | | | | | | | |
| Grizzi & Chiriva-Internati, 2005 | - | *molecule* | *sub-cellular entity* | | *cell* | *tissue* | | | *organ* | | *apparatus* | | *organism* |
| Kumar et al., 2004 | - | *biological macromolecule* | *subcellular organelle* | *collection of subcellular organelles* | *cell* | *collection of cells* | *tissue subdivision* | *tissue* | *organ part* | *organ* | *cardinal body part* | *organ system* | *organism* |
| Kumar et al., 2006 | - | *sub-cellular* | | | *cell* | *tissue* | | | *organ part* | *organ* | *organ system* | | |
| FMA, Rosse & Mejino, 2003 | - | *biological macromolecule* | *cell part* | | *cell* | *tissue* | | | *organ part* | *organ* | *organ system* | *body part* | *human body* |
| FMA, Rosse & Mejino, 2007 | - | *biological macromolecule* | | | *cell* | *portion of tissue* | | | *organ* | | *organ system* | *cardinal body part* | *body* |
| **model organism hierarchy - human central nervous system** | | | | | | | | | | | | | |
| Churchland & Sejnowski, 1992 | - | *molecule* | *synapse* | | *neuron* | *network* | | | *map* | | *system* | *CNS* | - |

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[10] further levels: population < community < ecosystem < biome < biosphere

Whereas the compositional account of levels is very intuitive and seems to be widely spread, many philosophers have criticized it for its lack of usefulness and coherence (Kim, 2002; Bechtel & Hamilton, 2007; Rueger & McGivern, 2010; Love, 2012; Potochnik & McGill, 2012), mainly criticizing that the world is too complex to be described with a single globally applicable scheme of levels of composition. Moreover, this compositional account of levels has the limitation that it does not allow the ordering of entities that are not part of the same part-whole hierarchy (Bechtel & Hamilton, 2007).

### *Wimsatt's Prototypical Account of Levels of Organization*

Another approach, which has been derived from the compositional account of levels, has been suggested by Wimsatt (1976, 2007). Wimsatt contrasts his account of levels with what he calls **aggregativity**. According to Wimsatt (1986), an aggregate, like for instance a pile of sand, is a collective of entities that are simply amassed together **without any specific organization**. The behavior of the component parts is the same as when they are outside of the aggregate—no specific dependencies seem to exist between the component parts, and the behavior of the aggregate depends simply on the number of parts present. Therefore, aggregates neither built entities of higher levels nor do they require new ways of inquiry.

If, however, some parts depend on the prior operation of other parts in order to perform their own operations, the resulting system can accomplish more than any aggregate of components (Wimsatt, 1986). Wimsatt therefore contrasts aggregativity with his **prototypical account of levels of organization** (Wimsatt, 1976, 2007). According to Wimsatt (2007, p.209), "levels of organization can be thought of as local maxima of regularity and predictability in the phase space of alternative modes of organization of matter". In other words, when mapping a measure of regularity and predictability against a sequence of different types of material entities that is ordered by their size-scale, the resulting graph will show significant peaks which are indicative of different levels of organization. Wimsatt described a set of core characteristics that levels of organization typically, but not necessarily, have in common (Wimsatt, 1976; cf. Craver, 2015):

- *Size*: a level is constituted by a family of entities of comparable size, with higher-level entities being larger than lower-level entities.

- *Composition*: higher-level entities have lower-level entities as their parts.
- *Laws*: laws hold mostly between entities of the same level.
- *Forces*: each level has distinct forces operating between its entities.
- *Predictability*: levels are local maxima of regularity and predictability that appear at different size-scales.
- *Detection*: entities of a given level are detectable primarily by other entities of that level.
- *Causes*: causal relationships hold predominantly between entities of the same level.
- *Theories*: scientific theories describe phenomena that are mostly limited to a single level.
- *Techniques*: techniques and instruments used for detecting entities usually detect entities of the same level.
- *Disciplines*: disciplines of science usually direct and limit their attention to entities belonging to the same level.

Wimsatt argues that his prototypcial account yields a complex branching structure of levels rather than a simple linear hierarchy. Moreover, as Wimsatt (1994, 2007) points out, the layering into levels according to interactions often breaks down at higher levels, and in these cases it would be more accurate to talk about **perspectives** rather than levels. In case it is impossible to determine what is composed of what and to which perspective a problem belongs, because things are increasingly interconnected, the boundaries of perspectives break down and perspectives degenerate into **causal thickets** (Wimsatt, 2007). The psychological and social realms are examples for causal thickets. Unfortunately, however, the notions of perspectives and causal thickets remain vague and unclear (Walter & Eronon, 2011).

Wimsatt embraces descriptive pluralism regarding the levels idea, but the different applications share sufficiently strong family resemblance due to the prototypical approach, which is why they seem to integrate well. However, as Craver (2015) argues, the different characteristics in this list are best indirectly related and fail to map to one another in any tidy way. We know for instance from interdisciplinary (or better: cross-level) research programs in the life sciences that causal chains can extend from a specific genetic composition and its accompanying molecular machinery through developmental pathways to the anatomical organization of major bodyplans and even to the social structure of populations. In an evolutionary time scale, through natural selection, the direction of influence can even be reversed from phenotype to genotype (e.g., Wagner, 2014). Moreover, we also know that specific research questions often involve the study of a diverse set of entities that span multiple levels of size, composition, theories, techniques, disciplines, etc., and we know that entities interact independent of their differences in size-scale and level affiliation (Bechtel & Hamilton, 2007; Craver, 2015). However, Wimsatt's list of characteristics nevertheless gives a good account on how complex the idea of levels actually can be.

## *Mechanism-Based Account of Levels*

An alternative approach to the levels idea, which does not aim at developing a globally and universally applicable scheme of compositional levels, understands levels as locally applicable schemes. It claims that the compositional levels approach must go beyond being solely based on formal parthood relations, "because spatial, temporal, and causal organization are relevant to (make a difference to, partly constitute) the property of the whole" (Craver, 2015, p. 16).

According to this account of levels, different levels of organization can be identified in relation to a given **mechanism**, with mechanisms being organized collections of entities and activities that relate to a mechanistic explanation that spans multiple levels (Craver & Bechtel, 2007). In other words, the term 'mechanism' describes "non-aggregative compositional systems in which the parts interact and collectively realize the behavior or property of the whole" (Craver, 2015, p. 16). This approach to levels is based on component-mechanism relations (Bechtel, 1994, 2008; Craver, 2001, 2002, 2007) and is obviously intended to reflect and represent causally grounded features of the organization of reality (see *levels of nature*, Craver, 2007).

A mechanism always involves entities of at least two levels, i.e. the mechanism itself and its component parts. The component parts of a mechanism constitute entities of a finer level that perform their operations in sub-mechanisms, constituting the next finer level of mechanisms (Bechtel & Hamilton, 2007). In other words, a mechanism at a higher level performs a specific function, and its working parts at the next lower level contribute to the operation of that mechanism, with each working part being a mechanism itself (Bechtel, 2008), resulting in a nested hierarchy of mechanisms and their sub-mechanisms. Since this approach defines levels in dependence of a given mechanism, it is a local and case-specific rather than a universal and globally applicable scheme (Bechtel, 2008). Moreover, entities belonging to the same level do not necessarily have to belong to the same size-scale; they only have to be working parts of the same mechanism.

This mechanism-based account depends on the compositional account of levels. In fact, one could characterize the mechanism-based account as an account of **mechanistic composition** (Eronen, 2013), because it combines a hierarchical organization of material entities (i.e. components) based on their structural part-whole relations, but restricts the infinite set of all possible mereological partitions of a component entity into its parts to the particular partition that also reflects the functional partition of the corresponding mechanism into its sub-mechanisms. The number of levels that must be distinguished cannot be determined *a priori*, but must be determined for each pair of **mechanism-component entity** on a case-by-case basis by discovering, which of its component parts are explanatorily relevant (Craver, 2015).

Contrary to the compositional account of levels, in which the properties of the parts of simple aggregates of entities are summed, in the mechanism-based account lower-level entities are organized together in such a way that they make up some behavior or property of the whole that is not present in its parts (Craver, 2015). Obviously, the mechanism-based account is also influenced by Wimsatt's prototypical account of levels of organization, but focuses on component-mechanism relations.

The mechanism-based account has gained broad acceptance and is considered to be the currently most coherent and promising account of levels (Eronen, 2013). Unfortunately, however, it gives no unique answer to the question of when two component parts are at the same mechanistic level, because levels of mechanisms are only defined by relations between components and mechanisms at higher and lower levels. If a given component part *b* is not part of another component part *c*, then *b* and *c* are not at different levels and if they belong to the same mechanism, they are at the same level (Craver, 2015). This results in the unfortunate situation that if one compares a component part $b_1$ and all its sub-parts $b_{2\text{-}n}$ of a given mechanism with other component parts $c_{1\text{-}n}$ that are not sub-parts of $b_{2\text{-}n}$, $b_1$ and $b_{2\text{-}n}$ share the same level with $c_{1\text{-}n}$, because $b_1$ and $b_{2\text{-}n}$ are not part of any of $c_{1\text{-}n}$. However, component parts $b_{2\text{-}n}$ cannot be at the same level as component part $b_1$, because they are component parts of $b_1$. This is obviously contradictory, because we have a set of entities ($b_{1\text{-}n}$) that are in relation to another set of entities ($c_{1\text{-}n}$) at the same level, but the entities belonging to this set ($b_{1\text{-}n}$) cannot share the same level amongst themselves[11]. This, and other inconsistencies (see, e.g., Eronen, 2013), make the mechanism-based account of levels not suitable as a basis for developing a general information framework for the life sciences.

## *Operator-Based Account of Levels: an Evolutionary Systems-Theoretical Perspective*

Are hierarchies artifactual and thus mind-dependent constructs? If we use the levels idea merely because it takes a central role in our representations of reality, why should we bother to ask nature which hierarchy is most realistic? Whereas these questions are legitimate, evidence exists that suggests that evolution*[12] leads to modularization. If evolution$^*$ has the tendency to aggregate material entities to larger compositions with a significant increase in complexity, robustness, and stability, resulting in a modularization of matter, then hierarchy is a necessary consequence of evolution$^*$. If **building block systems** evolve, which become parts of larger building block systems, then a hierarchical composition of building block systems must result that has lower-level building block systems as its parts. The resulting compositional hierarchy of building block systems is the product of natural processes and thus exists independent of any human partitioning activities.

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[11] Craver himself provides this example and responds: "The appearance of circularity, I believe, results from the fact that most people assume that the notion of "same level" must be primitive relative to the notion of "different level", and I have reversed that assumed order" (Craver, 2015, p.19, fn23). "Indeed, it is of central importance that the idea of levels of mechanisms articulated here entails no positive story about what it means to be at a level, only a negative story about when things are not at different levels" (Craver, 2015, p.3)

[12] From here on throughout the remainder of this paper, evolution$^*$ refers to evolution in a broad sense, including cosmic evolution (e.g., Hawking, 1988).

The idea that evolution* has the tendency to evolve such building block systems is not new. Simon (1962) argued for the evolution* of complex systems on grounds of his **Parable of the Watchmaker** (Simon, 1962, p. 470):

> "There once were two watchmakers, named Hora and Tempus, who manufactured very fine watches. ... [T]he phones in their workshops rang frequently—new customers were constantly calling them. However, Hora prospered, while Tempus became poorer and poorer and finally lost his shop. What was the reason? The watches the men made consisted of about 1,000 parts each. Tempus has so constructed his that if he had one partly assembled and had to put it down ... it immediately fell to pieces and had to be reassembled from the elements. ... The watches that Hora made were no less complex than those of Tempus. But he had designed them so that he could put together subassemblies of about ten elements each. Ten of these subassemblies, again, could be put together into a larger subassembly; and a system of ten of the latter subassemblies constituted the whole watch. Hence, when Hora had to put down a partly assembled watch ..., he lost only a small part of his work, and he assembled his watches in only a fraction of the man-hours it took Tempus."

Simon argued that the evolution* of complex forms from simple ones results from purely random processes, with the direction towards complex forms being provided by their stability[13]. The lesson we can learn from Simon's parable is that "[t]he time required for the evolution of a complex form from simple elements depends critically on the numbers and distribution of potential intermediate stable forms" (Simon, 1962, p. 471). Simon therefore concluded that hierarchy emerges almost inevitably through evolutionary* processes for the simple reason that hierarchical structures are stable (Simon, 1962).

We have gained a lot of knowledge since the time Simon has proposed his *Parable of the Watchmaker*, and improved our understanding of how morphological structures evolve and how they develop during morphogenesis. Especially with the newly emerged field of evo-devo and the discovery of hox genes, we started to understand how regulatory gene networks function like modular structures (Wagner, 1996; Abouheif, 1999; Wake, 1999) that can recombine with other modules in the course of evolution to form new networks (Gerhard & Kirschner, 1997), and how they strongly affect development of morphological structures, their evolutionary stability, and their

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[13] "survival of the fittest—i.e., of the stable" (Simon, 1962, p. 471).

evolvability (e.g., Müller & Wagner, 1996; Wagner & Altenberg, 1996; Schlosser & Wagner, 2004; Wagner, 2014). Some gene regulatory networks have been identified that have the role of individualizing parts of the body during development, and it seems to be the case that these "candidate gene regulatory networks for character identity determination, called Character Identity Networks (ChINs), ... are more conserved than are other aspects of character development" (Wagner, 2014, p. 417).

Based on the idea of building block systems, interpreted as lego-brick-like entities that evolve, diversify, and provide reality's inventory of basic categories of material entities, another account of levels has been suggested. According to this account, various types of building block systems emerged during evolution[*], starting when there were only elementary particles present, to a universe that has gradually evolved with the emergence of more and more new building block systems (e.g., Feibleman, 1949; Simon, 1962; von Bertalanffy, 1968; Heylighen, 1995; Close, 1996; Jagers op Akkerhuis & Van Straalen, 1998; Jagers op Akkerhuis, 2001).

Jagers op Akkerhuis and Van Straalen (1998; see also Jagers op Akkerhuis, 2001, 2008) have suggested criteria for the identification of different levels of building block systems and the transitions from a building block system of a lower level to a building block system of a higher level. According to Jagers op Akkerhuis and Van Straalen (1998), a special type of building block system, which they call **'operator'**, possesses a hypercycle set of elements that is contained by a layer they call **'interface'**, which mediates the interactions between the elements of the hypercycle and the environment of the building block system. A hypercycle is a cyclic process that creates a secondary reaction cycle (Eigen & Schuster, 1979; Kauffman, 1993). For example, the evolution of a new type of catalytic interaction, in which enzymes transform substrate molecules with the resulting product of the catalytic process being the catalyst of a next catalytic process, represents a new (catalytic) hypercycle that performs a newly emerged property, an autocatalysis. If now a boundary (i.e., interface) evolves that contains this catalytic hypercycle, a new operator emerges. A cell membrane represents such an interface. The evolution of cells as a building block system thus required the simultaneous occurrence of two emergent properties: (i) hypercyclicity and (ii) containment by a bio-membrane (Jagers op Akkerhuis & Van Straalen, 1998). Jagers op Akkerhuis and Van Straalen

(1998) argued that one can derive an unambiguous hierarchy of building block systems from studying such mechanisms of **hypercycle formation** and subsequent **compartmentation** through an interface.

According to Jagers op Akkerhuis and Van Straalen (1998), two additional similar construction pathways can be recognized: the sequence from (i) quarks to atoms and (ii) cells to neural networks. As a consequence, the following hypercycles with their different possibilities of containment through corresponding interfaces result in a hierarchy of different operators (Jagers op Akkerhuis & Van Straalen, 1998; Jagers op Akkerhuis, 2001, 2008):

1. Particle-like quarks (Dirac-fermions) are the hypercycles and the force carrying gluons (bosons) the interface. Together they directly form **hadron operators** (mesons and baryons).
2. The nuclear hypercycle together with the electron shell as corresponding interface form the **atom operator**. Electron shells can bind to form molecules, which are multiplets of atom operators.
3. The autocatalytic hypercycle and the cell membrane as corresponding interface form the **prokaryotic cell operator**. These can aggregate to form simple multicellular stages, which are multiplets of prokaryotic cell operators. However, they can also differentiate further to **eukaryotic cell operators**, by adding a nuclear envelope that provides an internal compartment that separates the basis of RNA production inside from the cell's protein production outside of the nucleus. These eukaryotic cell operators can also aggregate to form multiplets of eukaryotic cell operators.
4. Groups of neural cells that interact cyclically (**C**ategorising **A**nd **L**earning **M**odules hypercycle), together with an interface of sense organs and activation organs, forms the **memon operator**. Memons show auto-evolution as emergent property and are capable of constructing an internal representation of their environment and themselves in it.

This hierarchy of operators ranks complexity solely in a strict layer-by-layer fashion—it is a robust hierarchy that does not allow for bypasses, such as the sequence *'sand'* < *'stone'* < *'planet'* allows bypassing the *'stone'* level by constructing a planet from sand alone (Jagers op Akkerhuis & Van Straalen, 1998, p.331)[14]. It provides what Craver (2015) would call **monolithic levels** and a **hierarchy that is globally and universally applicable**. This hierarchy also explains the increase in diversity and variability of different types of operators from lower levels to higher levels. Whereas the number of elementary particles is very limited, the number of possible atomic nuclei is already much higher and becomes exponentially higher when considering all possible combinations of atoms to form molecules. The diversity continuously increases with each operator level, and the possibilities of combining them to form multiplets of operators even more (Jagers op Akkerhuis & Van Straalen, 1998).

This evolutionary* systems-theoretical account of levels picks up some aspects from the mechanism-based account discussed above, but limits these to a focus on hypercycle dynamics. By understanding the levels of complexity as a result of evolution* and that with higher building block levels the complexity and diversity exponentially increases, it also reflects some ideas of Wimsatt's prototypical account of levels of organization. However, with their definition of an operator, Jagers op Akkerhuis and Van Straalen (1998) are more specific about how levels are distinguished and what is required for a new level to evolve*.

## FORMAL THEORIES OF GRANULARITY AND GRANULARITY LEVELS

### *Ontologies and Granularity*

Besides the level ideas discussed by philosophers and scientists above, information scientists and ontology researchers came up with their own account of levels of different granularity of entities by following a formal approach that allows for computer-parsability and automated reasoning over hierarchies of different levels of granularity, with each hierarchy (=granularity tree) being understood as a distinct granular perspective. Ontologies play an essential role in this approach, as they also do in combination with techniques of the Semantic Web in reliably communicating and

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[14] Levels in an aggregate hierarchy allow such bypassing (see also distinction of aggregates and levels of organization in Wimsatt, 1986).

managing data within and between databases and online repositories, and online repositories and the data exploration/eScience approach in general.

An **ontology** consists of a set of terms with commonly accepted definitions that are formulated in a highly formalized canonical syntax and standardized format, with the goal to yield a lexical or taxonomical framework for knowledge representation (Smith, 2003). An ontology is like a dictionary that can be used for describing a certain reality, consisting of a set of terms that is organized into a nested hierarchy of classes and subclasses, forming a tree of increasingly specialized terms that is called a **taxonomy** (see *taxonomic inclusion*, Bittner et al., 2004). Every term defined in an ontology represents a resource that can be unambiguously referenced through its own unique Uniform Resource Identifier (URI).

A taxonomy of terms/resources can be considered to be fundamental to any ontology, because it often represents the only formalized hierarchical system it contains. When ontology researchers need to refer to other hierarchies, as for instance a parthood-based hierarchy, they usually do that in reference to some (external) granularity framework. Some ontologies, however, include an additional hierarchical structure that is based on a part-whole relation, called a **partonomy**. This partonomy, however, is usually only expressed indirectly through formalized descriptions specifying specific parthood relations between resources within the taxonomy. Whereas the taxonomy relates all resources of the ontology in a single subsumption hierarchy, the formalized descriptions often result in several disconnected partonomies. These partonomies thus provide only locally applicable granularity schemes, as opposed to a single globally and universally applicable scheme of granularity levels, like for instance the abovementioned operator-based hierarchy of building block systems.

Whereas the number of biomedical ontologies is continuously increasing (e.g., BioPortal; http://bioportal.bioontology.org/), they often differ considerably, and their taxonomies as well as their implicit partonomies and even some of their term definitions are often inconsistent across each other (Rosse et al., 2005; Brinkley et al., 2006; Smith et al., 2006). As a consequence, if databases and online repositories differ with respect to the ontologies they use, their contents are likely to be incomparable, which significantly hampers data exploration and integration. A solution to this problem involves two distinct

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approaches that must be followed: using **formal top-level ontologies**[15], as for instance the Basic Formal Ontology (BFO; Arp et al., 2015; Smith et al., 2015), and applying a **general formal theory of granularity** for developing a **domain granularity framework** that is independent of any particular ontology.

## *Partial Order, Granular Partition, and Granularity Tree*

Key to the development of any general formal theory of granularity is the formal characterization of the relation that holds between entities belonging to different levels of granularity. A first step is to identify what is called partial order relations. In mathematics and logics, a **partial order** is a binary relation 'R' that is **transitive** (if *b* has relation R to *c* and *c* has relation R to *d*, than *b* has relation R to *d*: $(Rbc)(Rcd) \rightarrow Rbd$), **reflexive** (*b* has relation R to itself: $Rbb$), and **antisymmetric** (if *b* has relation R to *c* and *c* has relation R to *b*, than *b* and *c* are identical: $(Rbc)(Rcb) \rightarrow b=c$) (e.g., Varzi, 2016). An example of a partial order relation is the parthood relation.

**Granular partitions** are based on partial ordering relations (Bittner & Smith, 2001a,b, 2003a; Reitsma & Bittner, 2003). Granular partitions are involved in all kinds of listing, sorting, cataloging and mapping activities. A granular partition is a hierarchical partition that consists of cells*[16] that contain subcells*. It requires a specific theory of the relation between its cells* and subcells* that must meet the following conditions (Bittner & Smith, 2001a,b, 2003a; Reitsma & Bittner, 2003):

1. the subcell* relation is a partial ordering relation;
2. a unique maximal cell* exists that can be called the root cell*;
3. chains of nested cells* have a finite length; and
4. if two cells* overlap, then one is a subcell* of the other, therewith excluding partial overlap.

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[15] Formal top-level ontologies are supposed to provide domain- and purpose-independent theories within a formal framework of axioms and definitions for most general terms and concepts, which can be used as a top-level template and formal framework for developing domain reference ontologies and terminology-based application ontologies (Smith et al., 2004; Rosse et al., 2005).

[16] 'cell*' here used in the general non-biological meaning of cell

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Additionally, an empirically meaningful theory of granular partition requires a theory of the relations between cells* of the partition and entities in reality (i.e. *projective relation to reality*; Bittner & Smith, 2001a,b, 2003a).

Depending on what is partitioned and the ontological nature of the parts, one can distinguish a **bona fide granular partition**, which partitions a bona fide object[17] into its bona fide object parts, from a **fiat granular partition**, which partitions any material entity into its fiat entity parts[18] (for a distinction of bona fide and fiat entities see discussion below and Vogt et al., 2012b; see also Arp et al., 2015; Smith et al., 2015).

A granular partition can be represented as a **granularity tree** (Reitsma & Bittner, 2003; Kumar et al., 2004; Smith et al., 2004), because every finite granular partition can be represented as a rooted tree of finite length (Mark, 1978; Bittner & Smith, 2001b, 2003a,b), i.e. a rooted directed graph without cycles (Wilson & Watkins, 1990). In a granularity tree, a granularity level is a **cut** (*sensu* Rigaux & Scholl, 1995; see Fig.2B) in the tree structure (Bittner & Smith, 2003b). Within a granularity tree, different levels of granularity can be distinguished, with the root being a level itself and all immediate children of the root another level, etc. The elements forming a level of granularity are *pairwise disjoint*, and each level is *exhaustive*, because for every entity *b* of the partition exists some other entity *c* of the same partition, which belongs to another level of granularity, and *b* stands in a partial ordering relation to *c*, or vice versa (Reitsma & Bittner, 2003). If the partitioning relation is a mereological relation, such as the part-whole relation, all entities belonging to one level of granularity in a granularity tree exhaustively sum to the whole that is partitioned (=root cell*) (Reitsma & Bittner, 2003).

The partitioning relation constrains the type of entities that it partitions. The primitive part-whole relation, for instance, exists only between instances (e.g., Smith et al., 2005; Schulz et al, 2006; Craver, 2015; Varzi, 2016; for a translation to a class expression of parthood see Smith & Rosse, 2004; Schulz et al., 2006). As a consequence, parthood-based granular partitions can be represented as **instance granularity trees**. Subsumption relations, such as the class-subclass relation, on the other hand, are also

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[17] entities that are demarcated by a *bona fide* boundary and thus exist independent of any human partitioning activities

[18] entities that are demarcated by a *fiat* boundary and thus exist as a consequence of human partitioning activities

partial ordering relations. Contrary to the parthood relation, however, the class-subclass relation exists only between types (classes, universals). As a consequence, granular partitions based on a class-subclass relation can be represented as **type granularity trees**. The taxonomy of terms of an ontology represents a type granularity tree. (see also *instance* and *type granularity tree* in Vogt, 2010; Vogt et al., 2012a)

## *Biological Reality: The Problem with Cumulative Constitutive Granularity*

Hierarchies are based on **strict partial ordering** relations, which represent **irreflexive** (*b* cannot stand in relation R to itself: ¬R*bb*) partial ordering relations[19]. Hierarchies thus represent a specific case of granular partitions and granularity trees. The direct proper parthood relation is a strict partial ordering relation. This complies with any formal system of minimal mereology, including pure spatiotemporal parthood.

On grounds of this very basic characterization of hierarchies one can distinguish four basic types of hierarchical systems (Valentine & May, 1996; Valentine, 2003; Jagers op Akkerhuis, 2008): (i) constitutive hierarchy, (ii) cumulative constitutive hierarchy, (iii) aggregative hierarchy, and (iv) cumulative aggregative hierarchy (Fig. 1), of which only the former two hierarchies are of interest in the here discussed context. Interestingly, constitutive hierarchies are commonly used by philosophers and ontology researchers to model granularity, whereas biologists use cumulative constitutive hierarchies.

### ***Constitutive Granularity***

In a **constitutive granularity** (i.e. *constitutive hierarchy*, Mayr, 1982), all material entities of a given level of granularity constitute the entities of the next coarser level, as for instance aggregates of all atoms constituting all molecules and aggregates of all molecules constituting all cells (Valentine & May, 1996). In other words, coarser level entities consist of physically joined entities of the next finer level of granularity (Jagers op Akkerhuis, 2008). Constitutive granularity is thus based on partonomic inclusion resulting from a proper part-whole relation (i.e. *irreflexive* part-whole relation). Bona fide entities of different levels of granularity are mereologically nested within one another, thus representing a **mereological granularity tree** (Reitsma & Bittner, 2003). For any

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[19] The reflexive binary partial ordering relation represents a more general case of the stronger irreflexive binary relation of strict partial ordering (Varzi, 2016). Thus, the latter can be defined in terms of the former.

given constitutively organized complex whole holds that *all* its parts that belong to one level of granularity constitute *all* parts of the next coarser level and that the sum of all parts belonging to one level yields the maximal entity (Fig. 1A).

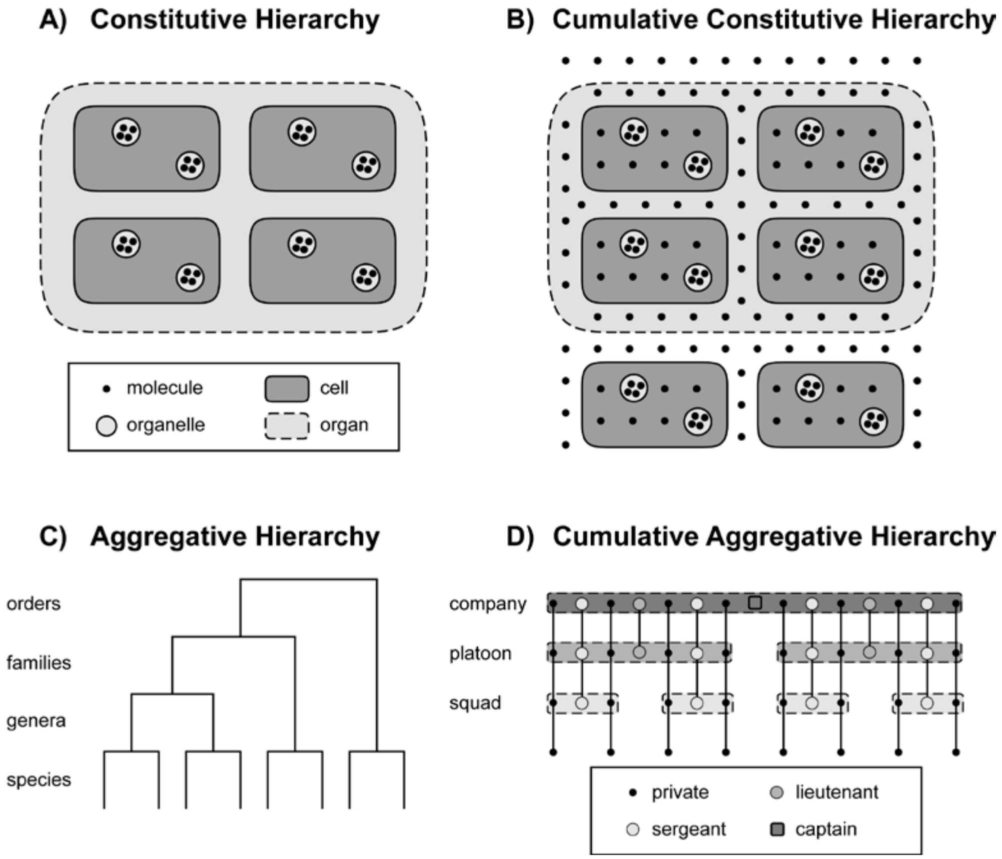

**Figure 1. Four different types of Hierarchies. A)** A constitutive hierarchy of molecules, organelles, cells, and organs of a multi-cellular organism. It can be represented as an encaptic hierarchy of types, with every molecule being part of some organelle, every organelle part of some cell and every cell part of some organ. **B)** The same set of entities as in A), organized in a cumulative constitutive hierarchy, which represents the more realistic model of the organization of biological material entities. Here, not every molecule that is part of an organism necessarily also is part of some organelle and not every cell necessarily part of some organ. **C)** An aggregative hierarchy is based on mereological/meronymic inclusion that results from a part-whole relation (e.g., ecological hierarchies; Levinton, 1988; Valentine & May, 1996) or it is based on taxonomic inclusion (Bittner et al., 2004) that results from a subsumption relation (e.g., Linnean taxonomy). In case of mereological inclusion, this hierarchy represents a mereological granularity tree and higher level entities consist of parts that are not physically connected, but only associated with each other. **D)** In a cumulative aggregative hierarchy, as it is used in the hierarchical organization of military stuff, individuals with higher ranks, such as sergeants, lieutenants, and captains, 'emerge' in aggregates of higher order, so that squads consist of privates and sergeants, in the next level platoons of privates, sergeants, and lieutenants, and companies of privates, sergeants, lieutenants, and captains. (*Figure modified from Vogt, 2010*).

Most granularity schemes suggested in the ontology literature so far presuppose a constitutive organization of material entities (e.g. Mejino et al., 2003; Kumar et al., 2004; for an exception see Vogt, 2010), and many bio-ontologies, although often not accompanied by an explicit representation of formally defined levels of granularity, also follow this scheme. This is insofar problematic, as constitutive granularities not only assume that coarser level entities always exclusively consist of aggregates of entities of the next finer level, but also that every entity belonging to one level of granularity is part of some entity of the next coarser level of granularity. Unfortunately, this is not the case for many material entities: ions or chlorine radicals demonstrate that not every atom necessarily is part of a molecule; in humans, extracellular matrix[20] and blood plasma (both not consisting of cells) demonstrate that not every molecule is part of a cell; protozoa, protophyta, erythrocytes, coelomocytes, or leukocytes demonstrate that not every cell necessarily is part of an organ (Vogt et al., 2012a). Obviously, in the biological realm *not all* the entities belonging to one level of granularity necessarily form parts of entities of the next coarser level.

Moreover, constitutive granularities also assume that all parts of any given level of granularity exhaustively sum to the complex whole. Regarding biological material entities this implies that the sum of all cells of a human individual would have to yield the human individual as a whole. The totality of cells of any given human being, however, does not sum to the body as a whole, since this mereological sum would not include the extracellular matrix in which the cells are embedded and which provides the topological grid that determines the relative position of the cells to one another. Without the extracellular matrix the aggregation of cells that belong to a human body would disintegrate and could not constitute the body as a bona fide whole. Moreover, since not all atoms are part of a molecule and not all subatomic particles are part of an atom, neither the sum of all molecules, nor the sum of all atoms existing in the universe exhaustively sum to the universe as a whole (Vogt et al., 2012a). As a consequence, not all parts that share the same granularity level exhaustively sum to the maximal whole (contradicting, e.g., Reitsma & Bittner, 2003; Kumar et al., 2004).

### *Cumulative Constitutive Granularity*

Instead of employing a constitutive hierarchy, biologists have argued that typical biological material entities, like for instance multi-cellular organisms, are organized

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[20] Extracellular matrix is a macromolecular formation that is not a component of cells, but a component of tissues and therefore also organs and multi-cellular organisms.

according to a **cumulative constitutive hierarchy** (Fig. 1B; Valentine & May, 1996; Valentine, 2003; Jagers Op Akkerhuis, 2008). When comparing the characteristics of constitutive granularity with the characteristics of cumulative constitutive granularity one can easily see why most approaches to granularity that are frequently used in ontologies, but also the formal theory of granularity of Kumar et al. (2004), model the bio-medical domain on the basis of the constitutive granularity. When partitioning an individual multi-cellular organism (=unpartitioned whole, Fig. 2B) into its direct proper bona fide parts according to the over-simplified constitutive granularity, *all* the parts belonging to a cut, and thus to an instance level, instantiate the same basic type of anatomical entity (Fig. 2B, left). Therefore, each cut in the **instance granularity tree** can be associated to a specific basic type of anatomical entity. As a consequence, instead of talking about *'Cut I'*, one could just as well talk about the *'organ'* granularity level. Translating or mapping the topology of an instance granularity tree to its corresponding **type granularity tree** is thus straight forward and poses no conceptual problems—***if*** one applies constitutive granularity for partitioning the multi-cellular organism that is (Fig. 2C, left). Regarding the levels idea one must also conclude that by comparing the type granularity trees of several multi-cellular organisms across various taxa, one *could* conveniently derive a general, globally applicable, linear compositional levels hierarchy for the life sciences—***if*** one applies the constitutive granularity model.

However, when applying the more realistic cumulative constitutive granularity model, the entire process becomes more complex and conceptually more challenging (Vogt, 2010; Vogt et al., 2012a). According to cumulative constitutive granularity, the parts of a multi-cellular organism that belong to a cut of an **instance granularity tree** do *not all* instantiate the same basic type of anatomical entity (Fig. 2B, right). For instance the parts that belong to the first cut in the example shown in Figure 2B, instantiate organs, cells, and molecules. As a consequence, and contrary to instance granularity trees based on constitutive granularity, the mereological sum of all entities belonging to one instance granularity level does *not necessarily* sum to the unpartitioned whole (see, e.g., *'Cut III'* in Fig. 2B, right). Thus, one must conclude that Kumar et al.'s (2004) theory of granularity and one of Reitsma and Bittner's (2003) criteria for mereological granularity trees are not conformant with anatomical reality (Vogt, 2010).

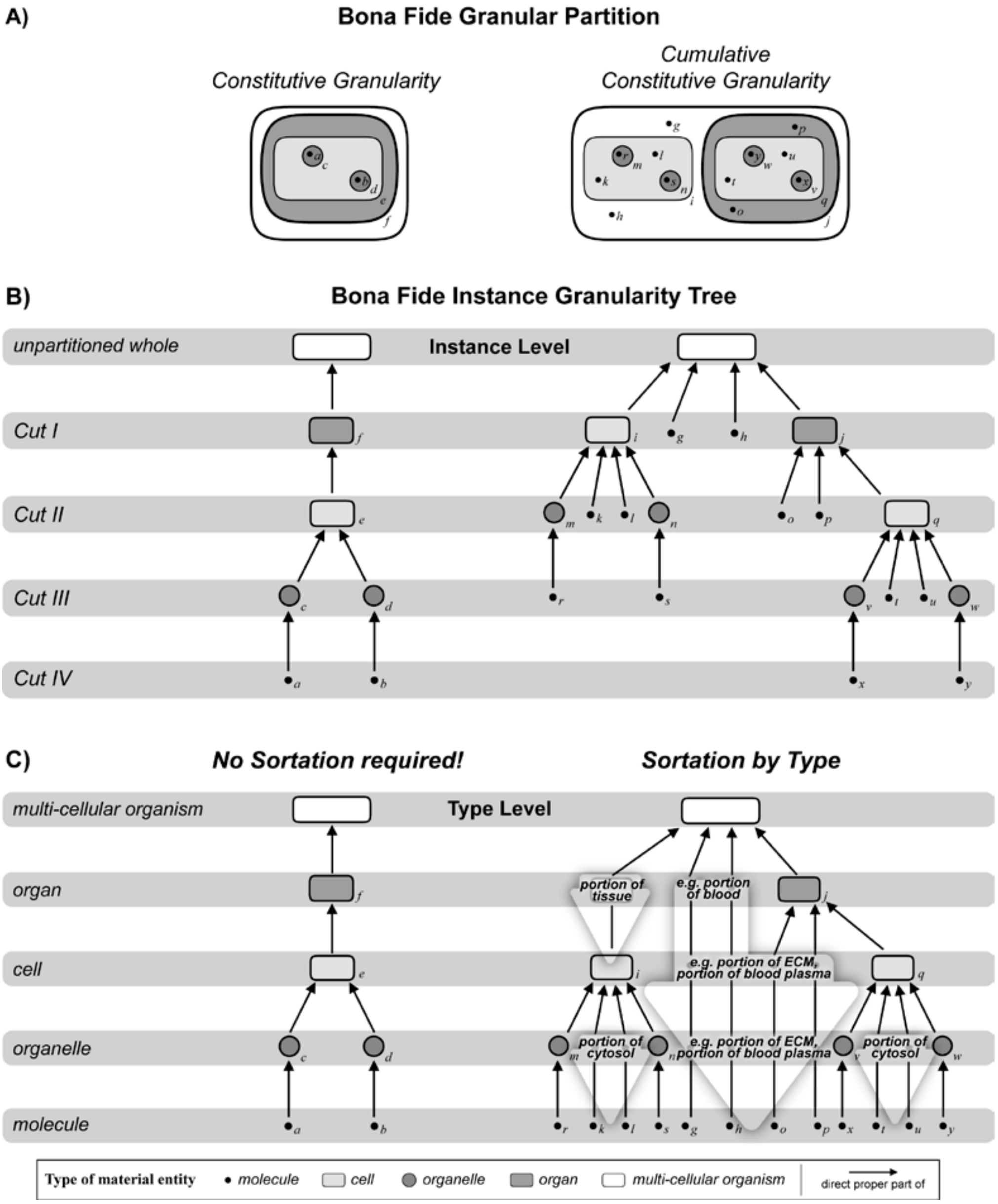

**Figure 2. Instance Granularity Tree and Type Granularity Tree for Constitutive and Cumulative Constitutive Granularity. A)** Compositional partitions of a constitutively and a cumulative-constitutively organized idealized multi-cellular organism into their constitutive bona fide object parts. Four corresponding partitions are shown. Left: into organs (f); cells (e); organelles (c,d); and molecules (a,b). Right: into organs with cells and extracellular molecules (i,j,g,h); cells with organelles and extracellular and cellular molecules (q,m,n,o,p,k,l); organelles and molecules (v,w,t,u,r,s); and molecules (x,y). **B)** The four compositional partitions from A) represented as a bona fide instance granularity tree. Each partition constitutes a cut in the instance granularity tree (Cut I–IV) and thus an instance granularity level. **Left**: Contrary to cumulative-constitutively organized material entities (see right side), instances of the same type of material entity do not belong to different cuts and thus are restricted to the same level of instance granularity. **Right**: Instances of the same type of material entity, like for instance of the type '*molecule*', belong to different cuts and therefore to different levels of the respective instance granularity tree. The extension of the type '*molecule*' thus transcends the boundaries between instance granularity levels. **C) Left**: The bona fide instance granularity tree can be directly transformed into the corresponding type granularity tree—no sortation of any parts across the boundaries of granularity levels required, because the topology of the bona fide instance granularity tree is identical with the bona fide type granularity tree.

**Right**: The bona fide instance granularity tree cannot be directly transformed into or mapped upon the corresponding type granularity tree. However, by following the simple and intuitive rule that a type must occupy the same granularity level as its finest grained instance (see *sortation-by-type*, Vogt, 2010) and by applying the concept of *granular representation* (see further below), one can transfer the instance granularity tree into a corresponding type granularity tree. (*Figure from Vogt et al., 2012a*)

Moreover, the topology of the resulting instance granularity tree cannot be easily translated into its corresponding **type granularity tree**, because each instance level comprises different types of entities (except for the root and the finest level). A consequence of cumulative constitutive granularity is that, when partitioning a multi-cellular organism, different instances of the same basic type of anatomical entity can belong to different instance granularity levels. In other words, when conceiving types of anatomical entities as classes, the extension of a class such as '*bio-molecule*' crosses the boundaries of different levels of instance granularity when applying the realistic cumulative constitutive granularity. Therefore, mapping types directly to instance levels would result in some types (e.g. '*bio-molecule*') to belong to more than one level.

This poses a fundamental problem, because ontologies are dealing with types (=classes) and not with individuals (=instances), and thus require a type-based granularity framework. I have proposed an intuitive solution, i.e. **sortation-by-type**, in which a type granularity tree is derived from an instance granularity tree by ranking types according to the lowest level of granularity of their corresponding instances (Vogt, 2010). Sortation-by-type can be seen as a sort of *granular sedimentation* of all instances of one type to the lowest level they occupy (see large transparent arrows in Fig. 2C, right). Whereas this approach seems to be intuitive, the downside is that in the type granularity tree, the entities belonging to a granularity level neither exhaustively sum to their respective whole (except for the lowest level), nor do all of them form parts of the entities belonging to the next higher granularity level (Vogt, 2010).

## *The Granularity Scheme implicit in the Basic Formal Ontology*

Formal top-level ontologies, such as the Basic Formal Ontology (BFO; Arp et al., 2015; Smith et al., 2015), play a key role in establishing standards across different ontologies. BFO provides a genuine upper ontology upon which all ontologies of the

Open Biomedical Ontologies Foundry[21] (OBO Foundry; Smith et al., 2007; http://www.obofoundry.org/) are built. Together with the OBO Relations Ontology it is one of the guarantors for the interoperability of the ontologies within the OBO Foundry.

Because BFO is an upper ontology, its taxonomy is comparably flat and does not include any distinction of different granularity levels of material entities. However, BFO's distinction of *'object'*, *'object aggregate'*, and *'fiat object part'* as top-level categories of *'material entity'* (see Arp et al., 2015; Smith et al., 2015) can be interpreted as a basic granularity scheme applied for modeling the granularity within a given level of object granularity. The underlying basic idea is that a certain domain first must be partitioned into its top-level object categories (e.g., *'bio-macromolecule'* < *'organelle'* < *'cell'* < *'organ'* < *'organism'*), resulting in a general domain-specific bona fide granularity tree[22]. According to BFO, in order to comprehensively cover the domain, each level of this bona fide granularity tree must be modeled by its own level-specific domain reference ontology, with cross-ontology relations managing the relationships between entities of different levels. Then, in a next step, the distinction of *'object'*, *'fiat object part'*, and *'object aggregate'* indicates within each such ontology a very simplified model for fiat partitions and fiat granularity trees (see Fig. 3). Of course, object aggregates can be parts of larger object aggregates and fiat object parts can be further partitioned to smaller fiat object parts, thereby extending the basic scheme shown in figure 3 with additional levels.

This approach of modularizing granularity, however, does not seem to be very practicable, because it implies that instead of developing a single anatomy ontology of a specific taxon of multi-cellular organisms, one would have to (i) develop several granularity-specific ontologies, ranging from an ontology for molecules, to an ontology for organelles, for cells, for tissues, for organs and an ontology body parts, and (ii) one would have to develop an additional layer of axioms and relationships to define the granularity relations between entities across these different ontologies.

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[21] The OBO Foundry represents one of the most important initiatives for standardizing biomedical ontologies. Its amount of accepted ontologies is continuously increasing and includes the well known Gene Ontology (GO) as well as the widely used phenotypic ontology (PATO).

[22] For the distinction between bona fide and fiat granularity trees see Reitsma and Bittner (2003). The former represent granular partitions of entities into their bona fide, the latter into their fiat parts.

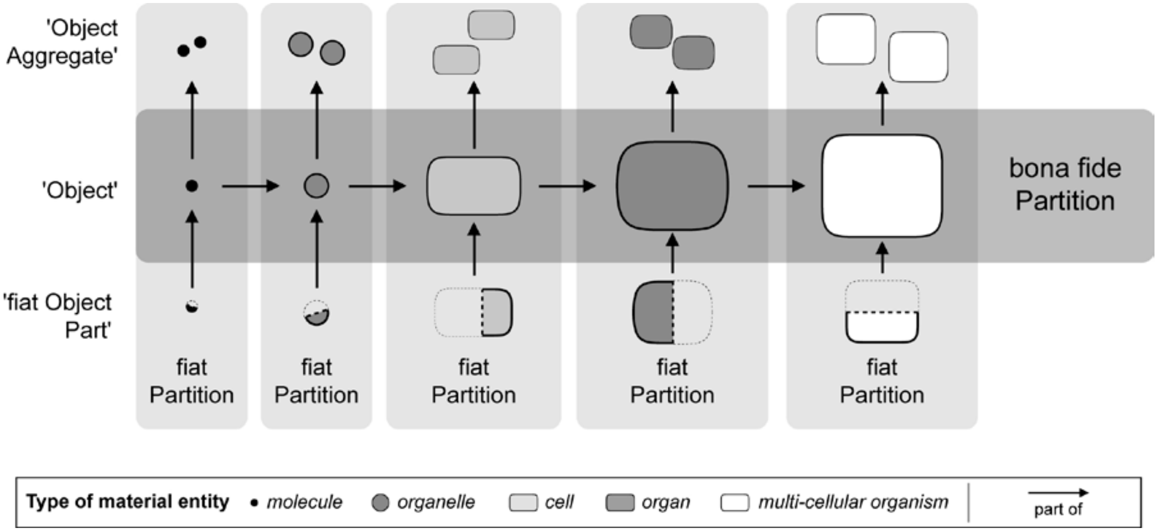

**Figure 3. BFO's Basic Granularity Framework.** A bona fide partition from *'molecule'* to *'multi-cellular organism'* represents the center of this granularity framework and reflects top-level categories of BFO's *'object'* for the biological domain. According to BFO, each level of the corresponding bona fide granularity tree must be modeled by its own domain reference ontology (e.g., a molecule ontology, a cell ontology, etc.). Within each such level-specific ontology, BFO's top-level distinction of *'object'*, *'fiat object part'*, and *'object aggregate'* indicates a basic fiat partition that orthogonally crosses the bona fide partition. The bona fide partition can therefore be understood as an integrating cross-granular backbone for the different ontologies of a given domain together with their implicit fiat partitions.

Because BFO does not provide a formal granularity framework, many of the currently available biomedical ontologies within the OBO Foundry significantly vary regarding their underlying granularity assumptions. This causes fundamental problems with the comparability of biomedical ontologies and substantially limits the comparability of data across databases and online repositories that reference these ontologies. The life sciences in general and comparative morphology in particular, but also the *compositional biology* style of biological theorizing (Winther, 2006), would substantially benefit from a consistent and realistic granularity framework that accounts for the organizational complexity of anatomy. In order to allow algorithm-based reasoning and inferencing, such a framework requires an underlying formal theory of granularity that explicitly states formal granularity relations and explicitly ranks levels of granularity. Unfortunately, most anatomy ontologies are only based on implicit assumptions regarding granularity.

## *Keet's Formal Theory of Granularity*

Keet (2008a, 2006a,b) has developed a general formal theory of granularity that is agnostic regarding cumulative or cumulative constitutive granularity and thus circumvents some of the problems of other published theories of granularity (see, for example, Kumar et al., 2004; problems discussed in Vogt, 2010). Keet (2008a) argues that granularity always involves modeling something according to certain criteria, with each model together with its criteria defining a **granular perspective**. Finer levels within a perspective contain knowledge or data that is more detailed than the next coarser level, and coarser levels of granularity simplify or make indistinguishable finer-grained details. A particular granularity level, however, must be contained in one and only one granular perspective, whereas a particular entity (individual or type) may reside in more than one level of granularity, but all levels in which it is contained must belong to distinct granular perspectives (Keet, 2008b). Moreover, a granular perspective has at least two levels of granularity and there has to be a strict total order between the entities of different levels of a given perspective. And if there is more than one granular perspective for a subject domain, then these perspectives must have some relation among each other. This way, several different perspectives of granularity, each with its specific levels of granularity and corresponding granularity tree, can coexist within the same granularity framework, like for instance a granular perspective of relative location that is based on fiat granular partitions along side with a granular perspective of structural composition that is based on bona fide partitions, a perspective of biological processes that is based on temporal partitions, a perspective of functional units that is based on functional partitions, and a granular perspective based on developmental relations (see also Vogt, 2010).

The idea that a domain can be modeled by different granular perspectives is not new (e.g., Rosse & Mejino, 2003; Burger et al., 2004; Smith et al., 2004; Jagers Op Akkerhuis, 2008; Winther, 2006), but Keet (2008a) provides the first general formal theory of granularity that incorporates different granular perspectives within a single **domain granularity framework**. Keet's theory can therefore be understood as the attempt to accept descriptive pluralism about the idea of levels (Craver, 2015), but nevertheless integrates the resulting set of diverse hierarchies within an integrated strictly formalized framework, her **general formal theory of granularity**.

A granular perspective can be specified by the combination of a **granulation criterion** (*what to granulate*) and a specific **type of granularity** (*how to granulate*) (Keet, 2008a). Each perspective has exactly one granulation criterion and exactly one type of granulation. This combination determines the uniqueness of each granular perspective (i.e. all granular perspectives contained in a domain are thus disjoint). Keet (2008a) presumes that a domain of reality can be granulated according to different **types of granularity** (mechanisms of granulation), requiring the existence of a certain type of **granulation relation** that must be specific to each particular granular perspective. The entities (individuals or types) granulated by a type of granularity are disjoint.

Various different types of granulation relations can be applied, which can be classified into (i) scale-dependent (e.g., resolution, size) and (ii) non-scale-dependent types of granularity (e.g., *mereological parthood*: structural parthood, functional parthood, spatial parthood, involvement; *meronymic parthood*: membership, constitution, sub-quality relations, participation) (Keet, 2008a, 2010). Within a given perspective, the granulation relation relates entities (individuals or types) of adjacent granularity levels with one another. If a granular perspective has more than two levels of granularity, the granulation relation must be *transitive*. If a granulation relation is intransitive, then the respective perspective has only 2 levels.

The **granulation criterion** delimits the kind or category of properties according to which the domain is partitioned, the levels identified, and the subject domain granulated (i.e., data, information, or knowledge). It specifies an aspect that all entities in a granular level must have in common, whereas the contents of a level can be either entity individuals (instances) or types (universals, classes), but not both. It comprises either (i) at least two properties, none of which is a quality property (for non-scale-dependent types of granularity) or (ii) at least one property that is not a quality property together with exactly one quality property that has a measurable region (for scale-dependent types of granularity) (Keet, 2008a).

Keet's (2008a) formal theory of granularity thus provides the respective formal definitions, axioms, and theorems that allow the formal representation of granular partitions based on parthood relations (i.e., mereology) as well as on taxonomic inclusion (i.e. class-subsumption hierarchies based on set theory) and other types of granulation relations (see also Keet, 2006b), and even accommodates both quantitative (i.e., arbitrary scale) and qualitative (i.e., non-scale-dependent) aspects of granularity. Moreover, it also provides a well suited framework for analyzing and identifying some of the problems of already published granularity schemes, taking Eldredge's somatic hierarchy (see table 1; Eldredge, 1985) as an example[23]. The somatic hierarchy comprises an *'atom'*, *'molecule'*, and *'cell'* level together with an *'organelle'*, *'organ'*, and *'individual organism'* level of granularity. An obvious problem of this hierarchy is that its underlying granulation criterion has been conflated between levels, because spatio-structural entities have been mixed with functional entities. As a consequence, the underlying granulation relation varies depending on the level an entity belongs to between spatio-structural parthood and functional parthood. Moreover, the *'tissue'* level seems to involve a scale-dependent granularity type, because it concerns resolution—a tissue is the representation of a cell aggregate at a coarser level of resolution, in which the finer-grained details of the cell aggregate that enable the individuation of individual cells are simplified or made indistinguishable. This mixing of criteria and types of granularity results in inconsistent granulation[24]: a mono-cellular organism is an entity that belongs to both the *'cell'* and the *'individual organism'* level of the same perspective, but according to Keet (2008a) an entity can only reside in more than one level if each of these levels belongs to a separate perspective.

## DEVELOPING A DOMAIN GRANULARITY FRAMEWORK FOR THE LIFE SCIENCES

The increase in formalism coupled with the increase in generality compared to other theories of granularity results in more flexibility and therefore a broader applicability of Keet's theory. Her theory allows a detailed and sophisticated modeling of

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[23] This criticism applies to many of the published levels schemes, even including Kumar et al.'s (2004) scheme.

[24] "... one should not mix different ways of granulating data within one perspective lest the hierarchy of levels will be inconsistent" (Keet, 2008a, p.61).

a domain by assigning specific types or individuals of entities to specific types of hierarchies (= granular perspectives) that are interconnected in a domain granularity framework. This framework can either be used (i) as a common template for the organization of top-level categories of different domain ontologies or (ii) to provide an independent overarching information framework that functions like an additional organizational layer, i.e. a meta-layer, to which terms/resources of different ontologies can be mapped. This meta-layer would provide a consistent and integrated system of well integrated granular perspectives that allows modeling not only parthood-based hierarchies, but all kinds of other relevant hierarchies, as for instance developmental or evolutionary hierarchies. It can be formally added onto an existent knowledge base to facilitate the construction of a more realistic and more detailed model of the biological domain (see also Vogt, 2010).

A domain granularity framework based on Keet's theory of granularity would not only provide a much needed conceptual framework for representing domains that cover multiple granularity levels, as for instance anatomy/morphology or the life sciences, but also a structure that can be utilized for providing users a more intuitive experience when navigating respective knowledge bases and content management systems. For instance, by using it for querying a given semantic graph in order to retrieve any partition expressed in the graph that corresponds with the perspective that the user is interested in. The framework can contain various such perspectives, each of which can be applied on a given semantic graph or knowledge base to the effect of filtering out all information irrelevant to this perspective, thereby substantially facilitating a desperately needed system that supports browsing and navigating through increasingly complex datasets.

If the hierarchical order of the various granular perspectives contained in a corresponding domain granularity framework reflects reality, the framework could provide a hierarchical structure that could be meaningfully employed for reasoning over different granularity levels and even different granular perspectives, thereby providing a framework in which comparability of terms/resources of different ontologies could be established effectively. This could, for instance, be used for automatic assessment and measurement of **semantic similarity** between different semantic graphs, which would provide new means for analyzing all kinds of data from the life sciences (e.g., Vogt 2016, 2017, *submitted* a).

In order to be broadly applicable throughout many existing bio-medical ontologies, such a domain granularity framework for the life sciences would have to be developed in reference to the Basic Formal Ontology (BFO) and its implicit granularity scheme that uses a **compositional bona fide 'object' granular perspective** that granulates bona fide *'object'* entities according to a **direct proper parthood** granulation relation (see Fig. 3). All additional granular perspectives can be directly or indirectly related to this compositional perspective, which functions as an **organizational backbone** for the entire framework, as each additional perspective possesses some level that shares entities with some level of this compositional perspective. The development of such a domain granularity framework, however, may result in new demands that BFO (or some intermediate domain reference ontology) must meet, which could result in the necessity to adapt or extend BFO accordingly.

## *Integrating BFO and Frames of Reference in the Basic Organization of a Domain Granularity Framework*

### ***BFO's 'object' Category of 'material entity'' and Frames of Reference***

Smith et al. (2015; see also Arp et al., 2015) characterize BFO's bona fide '*object*' category and thus natural units that exist independent of human partitioning activities as **causally relatively isolated** (Ingarden, 1983; Smith & Brogaard, 2003) entities that are both **structured through and maximal relative to a certain type of causal unity**. They distinguish three types of causal unity:

**1) Causal unity via internal physical forces**, which unifies an entity through physical forces (e.g., fundamental forces of strong and weak interaction, covalent bonds, ionic bonds, metallic bonding, etc) that are strong enough as to maintain the structural integrity of the entity against the strength of attractive or destructive forces from its ordinary neighborhood. Whereas Smith et al. (2015) mention only examples of physical forces that apply to the atomic and molecular scale (atoms, molecules, portions of solid matter, as for instance grains of sand, lumps of iron), I would explicitly include all kinds of physical connections between material component parts, independent of their scale, including cell-cell connections, but also screws, glues, and bolts. Ultimately, they all go back to the physical forces discussed in Smith et al. (2015).

**2) Causal unity via physical covering** unifies an entity through a common physical covering, as for instance a membrane. This covering may have holes, but must be completely connected[25] and must still serve as a barrier for entities from inside and entities from outside that are above a certain size threshold. Examples: organelles, cells, tissues, organs.

**3) Causal unity via engineered assembly of components** unifies an entity through screws, glues and other fasteners. Often, the parts are reciprocally engineered to fit together (e.g., dovetail joints, nuts and bolts). Examples: cars, ballpoint pens, houses, shoes, power grids

These three types of causal unity are ontologically not independent from one another, because the latter two **existentially depend** and thus supervene on causal unity via internal physical forces. Moreover, they do not cover all cases of causal unity relevant in the life sciences[26]. Functional units and historical/evolutionary units are not covered, although they are bona fide entities in their own right that exist independent of any human partitioning activities (Vogt et al., 2012b). Therefore, I suggest two additional types of causal unity that are suited to cover the missing cases:

**Causal unity via bearing a specific function** unifies an entity through the function that the entity bears, with its functional component parts bearing sub-functions (see Vogt, *submitted* b). This type of causal unity is more general than and thus includes causal unity via engineered assembly of components.

**Causal unity via common historical/evolutionary origin** unifies an entity through the common historical/evolutionary origin of the entities component parts. A historical/evolutionary unit is demarcated so that all of its component parts share the same historical/evolutionary origin, with no material entity not belonging to it sharing the same origin (see Vogt, *submitted* b).

Moreover, because a given material entity can depend on several different types

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[25] Connected in the sense that a continuous path can be traced between any two points on the surface and that path has no gaps and does not leave the surface.

[26] Note: BFO does not claim completeness regarding the list of cases of causal unity (Smith et al., 2015; Arp et al., 2015).

of causal unity at the same time, of which not all are relevant in every context, each type of causal unity is connected to a specific basic frame of reference (see Vogt, *submitted* b). Both causal unity via internal physical forces and causal unity via physical covering, at least as conceived by Smith et al. (2015; see also Arp et al., 2015), are associated with a **spatio-structural frame of reference**. One of the reasons for applying a spatio-structural frame of reference lies in inventorying ***what is given*** in a particular point in time by focusing on the spatio-structural properties of a given entity (see *spatio-structural perspective* in Vogt et al., 2012b). Causal unity via bearing a specific function, on the other hand, is associated with a **functional frame of reference**, which may be applied for making reliable predictions of ***what can happen*** in the future by focusing on dispositional/functional aspects of reality (see *predictive perspective* in Vogt et al., 2012b). And causal unity via common historical/evolutionary origin is associated with a **historical/evolutionary frame of reference**, which may be applied for making reliable retrodictions of ***what has happened*** in the past by focusing on using a set of known types of repeatable processes to reconstruct the sequence of events that may have lead to the currently observable situation (see *retrodictive (diachronic) perspective* in Vogt et al., 2012b).

Moreover, because BFO's general granularity scheme associates to each top-level category of *'object'* a corresponding *'fiat object part'* and *'object aggregate'* category and because we can distinguish different spatio-structural categories of *'object'*, we can differentiate additional spatio-structural sub-frames of reference, one for each spatio-structural top-level category of *'object'* that we can distinguish (e.g. atom, molecule, cell, etc.; see discussion below!). Each such frame of reference includes not only the entities of the respective *'object'* category, but all entities of corresponding *'fiat object part'* and *'object aggregate'* categories. One of the reasons for distinguishing different spatio-structural frames of reference lies in enabling the identification of ***what is comparable*** in a particular point in time by focusing on entities belonging to a particular top-level *'object'* category and its corresponding fiat object part and object aggregates entities. As a consequence, the number of spatio-structural frames of reference directly depends on the number of top-level spatio-structural *'object'* categories we can identify.

### *The Basic Organization of a Domain Granularity Framework for the Life Sciences*

As a consequence of the relevance of the different cases of causal unity for the life sciences, a domain granularity framework for the life sciences would have to cover three basic categories of granular perspectives: granular perspectives relating to (i) **spatio-structural**, (ii) to **functional**, and (iii) to **historical/evolutionary** material entities. In analogy to BFO's general granularity scheme discussed above, each such basic category will include one or more corresponding bona fide granular perspectives, with each granularity level of a bona fide perspective having associated *'fiat object part'* and *'object aggregate'* fiat perspectives. As a consequence, the number of granular perspectives for each such category depends on the number of granularity levels of its corresponding bona fide perspectives, with each bona fide level requiring some additional associated fiat perspectives.

However, since each of the three basic categories of perspectives corresponds with one of the three basic frames of reference relevant to the life sciences, any given material entity always belongs to *at least* three different granular perspectives—one for each basic frame of reference. Moreover, when considering that at least the basic spatio-structural frame of reference actually consists of a set of several distinct spatio-structural frames of reference, one for each identified spatio-structural top-level *'object'* category, any given material entity actually belongs to *more than three* granular perspectives. In other words, an entity belonging to some level of functional granular perspective will always also belong to some level of historical/evolutionary granular perspective and some level of each of the different spatio-structural granular perspectives, and vice versa. And because all the different granular perspectives of one category overlap in the sense that no granular perspective exists that does not overlap directly or indirectly with the bona fide perspective of this category, the perspectives of the three categories overlap each other as well, thus integrating all the different perspectives of the domain granularity framework. As a consequence, the bona fide perspectives function as the organizational backbone of the entire framework (at least, if only one such bona fide perspective exists for each category). Ideally, the organizational backbone perspectives of the three categories would directly overlap with each other, which would substantially increase the overall integration of the framework.

## *1st Step: Identifying the Organizational Backbone Granular Perspective for the Life Sciences based on Building Blocks*

### ***Building Blocks as Spatio-Structural bona fide Objects***

Whereas the evolutionary* systems-theoretical '*operator*' perspective that Jagers op Akkerhuis and Van Straalen (1998) have followed seems to provide a promising framework for developing a globally and universally applicable hierarchy of levels of material composition, their focus on hypercyclic dynamics and thus their account of an '*operator*' unnecessarily restricts its applicability. Therefore, I want to suggest the concept of a **general building block** that follows this evolutionary* systems-theoretical perspective, but only to a certain degree, leaving out the idea of an '*operator*'. This concept is insofar relevant to the development of a domain granularity framework for the life sciences, as I will argue that it gives rise to a compositional granular perspective of general building blocks that represents the abovementioned ideal bona fide spatio-structural granular perspective that functions as organizational backbone for the granularity framework.

A general building block can be characterized as follows:

- New types of general building blocks emerge as a result of evolution*.
- A general building block possesses a **physical covering** that is comparable to what Jagers op Akkerhuis and Van Straalen (1998) have referred to as an '*interface*'. It not only demarcates the building block from its environment, making it a **spatio-structurally bona fide entity**, but also functions as a **physical barrier** that protects a specific *inside milieu* from the *outside milieu* that surrounds the building block, establishing a micro-ecosystem within the building block that follows different functional vectors than the outside macro-ecosystem[27]. It is also comparable to Smith et al.'s (2015) account of causal unity via physical covering (see above), but on the one hand more general, because it treats electron shells as a physical covering, and on the other hand more specific,

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[27] In a certain sense, the physical covering of a general building block provides the kind of boundary that Wimsatt called the system-environment interface, which he discussed in the context of reductionist strategies (Wimsatt, 2006)—with the important difference, however, that it is a natural boundary as opposed to a fiat boundary that has been chosen based on various strategic reductionist considerations.

because it includes functional aspects of the physical covering. Moreover, contrary to the mathematical account of boundary followed by Smith et al. (cf. Smith, 1994, 1995, 2001; Smith & Varzi, 1997; Smith et al., 2015), the physical covering of a building block is itself a three-dimensional material entity and is therefore rather a **boundary region**. This is an important aspect, as it provides general building blocks with what Wimsatt called **robustness**[28] (Wimsatt, 1994; see also Levins, 1966). The physical covering itself is not only a boundary region, but also a bona fide functional unit that not only provides the surface of the boundary, but also bears the dispositions with which the building block interacts and communicates with its environment.

- A general building block is not only a spatio-structurally bona fide entity, but also a **bona fide functional unit** that possesses its own regulatory machinery with feedback mechanisms, so that to a certain degree it is self-organizing and self-maintaining. General building blocks represent localized islands of order that have a **stable internal organization** and maintain their integrity during typical interactions. A general building block usually lives/exists longer than its constituent parts and its behavior is predictable for the situations typically found in its environment.
- A general building block is able to interact with other building blocks to form aggregates and more complex building blocks (Simon's '*assemblies*', 1962). Building blocks of a coarser level are composed of building blocks of finer level(s). As a consequence, a building block of a coarser level is necessarily **existentially dependent** on some building block of a finer level, resulting in a **hierarchy of irreducible levels**. Building blocks of coarser levels can only evolve after finer level building blocks have evolved.

General building blocks thus provide Nature its universal inventory of matter, just like lego-bricks with which increasingly complex structures can be built. The emergence of a new level of building blocks always corresponds with a substantial increase in material diversity and adds a new dimension to the spatio-structural space for evolution*

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[28] "Things are robust if they are accessible (detectable, measurable, derivable, definable, producible, or the like) in a variety of independent ways" (Wimsatt, 1994, p. 210f).

to explore. General building blocks are spatio-structurally, functionally, developmentally and evolutionarily* both integrated and stable, but at the same time increase Nature's overall evolvability*.

### *Non-Biological Building Blocks*

In analogy to Jagers op Akkerhuis and Van Straalen's (1998) identification of the electron shell as an '*interface*' of an '*operator*', the **electron shell** is considered to be a unit of physical covering of a building block. There are two types of material entities that are covered by electron shells: atoms and molecules. In an **atom**, a cloud of electron 'waves' surrounds the nucleus. It physically covers the atom and also determines the interaction of the atom with the entities of its environment. Electromagnetically, one can clearly identify a stable inside milieu that is protected from an outside milieu via the electron shell.

Electron shells from several atoms can bind to form a **molecule**. In a **molecule**, several atoms thus share a common electron shell, forming the building blocks of the next coarser level of granularity. This also applies to lumps of metal, in which several atomic nuclei share a common electron shell[29]. As a consequence, causal unity via physical covering in the here proposed concept of general building blocks would include atoms, lumps of metal and molecules[30] as bona fide *objects* in the sense of Smith et al. (2015).

Molecules can further combine to form bona fide objects based on intermolecular (weak) forces, like for instance a portion of water that consists of several water molecules that aggregate due to hydrogen bonds. These objects, however, do not constitute building blocks themselves, because they lack a common physical covering. Instead, they are **bona fide aggregates of molecule building blocks**.

### *Biological Building Blocks delimited by a Plasma Membrane*

Biological building blocks are general building blocks that are biological material entities that can be found universally across a wide range of taxonomic groups. Their prototypical forms have evolved during biological evolution and have been very

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[29] In metals, however, the sharing of electrons is not localized between two atoms (i.e. covalent bond), but instead *free* electrons are shared among a lattice of positively charged ions (i.e. metallic bonding).

[30] For the sake of simplicity, from here on I include metals in molecules and also treat ionic compounds as molecules. In other words, I include all compositions of atoms in molecules that are based on intramolecular (strong) force.

successful in combining and recombining finer level building blocks to built building blocks of the next coarser level. Because biological building blocks continue to evolve, a variety of different forms exists, all of which, however, share some common characteristics so that they can be referred to as instances of the same set of prototypical building block categories. As a consequence, biological building blocks can considerably vary in size, in particular across different taxa. Correlating biological building block levels with scale levels across different taxa is therefore often impossible.

In order to identify a biological building block, we must identify, which types of biological physical coverings meet the criteria discussed above to be addressed as the physical covering of a biological building block. The **biological plasma membrane** qualifies as such a physical covering. Various biological material entities are surrounded and naturally demarcated by a biological plasma membrane, with its most important component being amphipathic molecules. Amphipathic molecules, like for instance phospholipids, and most of the proteins within membranes possess both a hydrophobic and a hydrophilic region. According to the fluid mosaic model, the membrane is a fluid structure that is arranged in a mosaic-like fashion with different kinds of proteins embedded in or attached to a phospholipid bilayer (Reece et al., 2014). This supramolecular structure is thus an **aggregate of molecules** that is primarily held together by hydrophobic interactions, which are significantly weaker than covalent bonds, but nevertheless strong enough to maintain its structural integrity. Therefore, following Smith et al.'s (2015) definition of bona fide objects, each bio-membrane as such is a molecule aggregate that is a bona fide object that is causally unified via internal physical forces, i.e. the hydrophobic interactions (see discussion above). A specific degree of fluidity is essential for the proper functioning of the membrane as a semi-permeable barrier and for its embedded enzymatic proteins, many of which require being able to move within the membrane for their activity (Reece et al., 2014).

Whereas the phospholipids provide the spatio-structural skeleton of the membrane, its various types of proteins determine most of its functions, ranging from for instance selective transport across the membrane, to various enzymatic activities, signal transduction, cell-cell recognition, intercellular joining, like for instance gap junctions or tight junctions, and attachment to the cytoskeleton and the extracellular matrix. Each type of plasma membrane can be characterized by its set of membrane proteins.

There are two types of biological material entities that are covered by biological plasma membranes: **cells** (prokaryotic as well as eukaryotic cells) and **organelles**, the latter of which are membrane-enclosed structures within eukaryotic cells, including nucleus, endoplasmatic reticulum, lysosome, mitochondrion, peroxisome, cisternae of the Golgi apparatus, central vacuole, chloroplast, and all vesicles and vacuoles. In the here suggested strict sense of *organelle* as a membrane-enclosed material entity within eukaryotic cells, the Golgi apparatus itself is not an organelle, but an aggregate of organelles, because its cisternae are physically disconnected organelles themselves.

Cells and organelles are thus biological building blocks and therefore spatio-structural as well as functional bona fide entities. When only considering the topology of the membranes, one must, however, distinguish a building block *'**single-membrane-enclosed entity**'* that comprises all organelles and prokaryotic cells, from a building block *'**membrane-within-membrane entity**'* that comprises eukaryotic cells, which are membrane-enclosed entities that have membrane-enclosed entities as their parts.

Several eukaryotic cells can fuse to form a syncytium[31], which is a multinucleated cell, or they can conduct multiple nuclear divisions without accompanying cytokinesis to form coenocytes. In both cases several nuclei share the same cell membrane, thus, forming mutliplets of eukaryotic cells. However, although topologically substantially different to eukaryotic cells with a single nucleus, syncytia and coenocytes are nevertheless membrane-within-membrane entities.

Prokaryotic cells as well as eukaryotic cells can aggregate, as for instance seen in bacterial colonies and epithelia of multi-cellular animals, forming bona fide objects in the sense of Smith et al. (2015) based on causal unity via internal physical forces. These objects, however, do not constitute building blocks themselves, because they lack a common physical covering. Instead, they are **bona fide aggregates of molecule and cell building blocks**.

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[31] E.g., skeletal muscles and cardiac muscle in humans and the syncytiotrophoblast in vertebrates, which is the epithelial covering of a placenta.

### *Biological Building Blocks delimited by an Epithelium*

An epithelium is another type of biological physical covering that qualifies as a covering of a general building block. An **epithelium** is composed of polarized cells that form a tightly packed continuous single-layered sheet of cells. Every epithelium has an apical surface and a lower basal surface, the latter of which is attached to a basal lamina that is a layer of extracellular matrix secreted by the epithelial cells. The basal lamina acts as a filter for any molecules attempting to pass into space covered by the epithelium. At the apical side, many epithelial cells possess microvilli that increase the surface area of the apical side of the epithelium, which is important for functions of secretion, absorption, and sensory functions. The apical side can also possess a motile cilium for pushing substances along the apical surface. Tight junctions in case of vertebrates and septate junctions in case of invertebrates connect the plasma membranes of adjacent epithelial cells through specific proteins in the membrane, forming a continuous semi-permeable seal around the epithelial cells that prevents fluids from moving through the intercellular spaces of the epithelial cells and thus across the epithelium. According to Smith et al.'s (2015) definition of bona fide objects (see above), each epithelium as such is thus a cell aggregate that forms a bona fide object that is causally unified via internal physical forces, i.e. the tight junctions or septate junctions respectively. The epithelium functions as a diffusion barrier, like for instance the hemato-encephalic barrier in humans. Epithelia can have various additional functions, ranging from selective absorption of water and nutrients, protection, elimination of waste products, secretion of enzymes and hormones, transcellular transport, and sensory functions. All animal glands, for instance, are made of epithelial cells.

There are two types of anatomical entities that are covered by epithelia: organisms with an epidermis, and epithelially-delimited compartments, the latter of which are epithelium-enclosed structures within multi-cellular animals, including for instance the circulatory system in humans, lungs in vertebrates, and the intestine in animals. Therefore, '***epithelially-delimited compartment***' and '***epithelially-delimited multi-cellular organism***' are both biological building blocks, the latter of which are epithelium-within-epithelium entities.

Epithelially-delimited compartments can aggregate, as for instance the gastrointestinal tract together with all accessory organs of digestion (tongue, salivary glands, pancreas, liver, and gallbladder) in humans forming the digestive system. Although one can argue that such an aggregate forms a functional bona fide unit, it does not constitute a building block, because it lacks a common physical covering. Instead, it is an **aggregate of molecules, cells and epithelially-delimited compartment building blocks** (see discussion below).

## *Results I: Spatio-Structural Granular Perspectives*

### *Compositional Building Block (CBB) Granular Perspective*

Based on the abovementioned characterization of general building blocks one thus can identify the following prototypical building blocks: *'atom'* < *'molecule'*[32] < *'single-membrane-enclosed entity'* (= most organelles and all prokaryotic cells) < *'membrane-within-membrane entity'* (= eukaryotic cell) < *'epithelially-delimited compartment'* (= some, but not all of the entities that are commonly referred to as organs) < *'epithelially-delimited multi-cellular organism'* (= organisms with an epidermis).

Comparable to the hierarchy proposed by Jagers op Akkerhuis and Van Straalen (1998), the resulting hierarchy of levels of building blocks ranks complexity solely in a strict layer-by-layer fashion that does not allow for bypasses. It provides **monolithic levels** that reach across all material domains of reality and that are **globally and universally applicable**. Because the concept of a general building block is based on an evolutionary* interpretation, it explicitly predicts the diversification of newly evolved* building blocks of a given level, with each higher level exhibiting the possibility of an exponentially larger number of different types of entities associated with a building block to be evolved*—the number of possible types of molecules is exponentially larger than the number of possible types of atoms. When considering that actual material entities can be composed of a multiplicity of different possible combinations (= aggregates) of those building blocks, comparable to constructions made from lego-bricks, the diversity of possible types of material entities increases even more with each newly evolved* general building block.

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[32] This includes also metals and ionic compounds (see footnote above).

Based on this concept of building blocks and the implicit hierarchy of building blocks, a granular perspective of levels of building blocks can be characterized using Keet's general formal theory of granularity (Keet, 2008a)[33]. The bona fide partition of a given biological material entity into its building block components represents a qualitative compositional partition[34]. This **compositional building block (CBB) granular perspective** is based on a **direct proper parthood** relation between instances of different top-level categories of building blocks (see discussion below), and thus has the **granulation criterion** (Fig. 4):

building block directProperPartOf building block;
building block hasDirectProperPart building block.

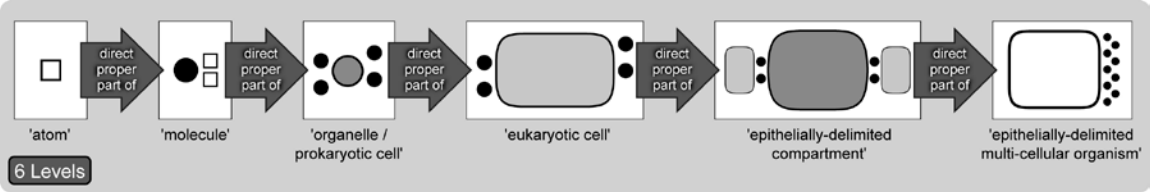

**Figure 4. Compositional Building Block (CBB) Granular Perspective.** The different building blocks are granulated according to the direct proper parthood granulation relation (the dark arrows). The granulation is of the non-scale dependent single-relation-type granularity type (*nrG*, Keet, 2008a), and uses the combination of the granulation relation together with the common properties of all categories of the building block type as its granulation criterion. Due to the cumulative constitutive organization, finer-level building block entities can be considered to be parts associated with coarser-level building block entities, as for instance ECM being an associated part of a eukaryotic cell.

Based on Keet, this perspective has a granulation of the non-scale dependent single-relation-type **granularity type** (*nrG*, Keet, 2008a; also called non-scale dependent primitive granularity type, *npG*, Keet, 2006b). It is based on the direct proper parthood relation as its **granulation relation**. Entities residing in adjacent CBB granularity levels are thus related through the direct proper parthood relation. In order to constitute a CBB granular perspective, instances of at least two different categories of the building block type must exist, of which instances of one category are direct proper parts of instances of the other. In other words, the levels of the CBB granular perspective are demarcated from one another according to the properties of the top-level categories of building block and they are ordered from finest to coarsest granularity level according to the direct proper parthood relation. The number of levels within the CBB granular perspective directly

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[33] The **subject domain** in all granularity perspectives discussed in the following is restricted to cumulative-constitutively organized material entities.
[34] As opposed to a qualitative regional partition or a quantitative resolution-based partition.

depends on the number of top level categories of building blocks identified (Fig. 4).

According to the underlying cumulative constitutive organization, for all instances of building block holds (see also *compositional object granularity perspective* in Vogt, 2010):

1. An instance of a building block is not necessarily a proper part of an instance of some building block of the adjacent coarser CBB granularity level.
2. Every instance of a building block, except for those belonging to the finest CBB granularity level, has at least two instances of building blocks of finer levels as its proper parts.
3. The instance of the building block that is granulated is the maximum entity that belongs to the coarsest CBB granularity level, and every other instance of a building block belonging to this granulation is a proper part of this maximum entity. However, because this maximum entity is cumulative-constitutively organized, its direct proper parts not necessarily all belong to the second coarsest CBB granularity level.

Because each entity belonging to a specific CBB granularity level represents a BFO *'object'*, we can distinguish six different spatio-structural frames of reference, which **can be ordered according to the associate CBB granularity levels from finer to coarser spatio-structural frames of reference**: an atom, a molecule, an organelle/prokaryotic cell, a eukaryotic cell, an epithelially-delimited compartment and an epithelially-delimited multi-cellular organism frame of reference. Each such spatio-structural frame of reference has its own set of granular perspectives. As a consequence, whereas any given material entity can belong to six different spatio-structural granular perspectives, it can belong to maximally one CBB granularity level.

Moreover, because a general building block is defined as a bona fide spatio-structural entity as well as a bona fide functional unit, the CBB granular perspective comes close to the ideal organizational backbone for the development of a domain granularity framework for the life sciences. Conceptually, it therefore takes in a central position within the domain granularity framework for the life sciences.

### Compositional Building Block Cluster (CBB-C) Granular Perspectives

As already mentioned above, building blocks can aggregate to form bona fide entities that are not building blocks themselves. Thus every spatio-structural frame of reference accommodates two distinct categories of bona fide entities. The eukaryotic frame of reference, for instance, includes *'eukaryotic cell'* as well as *'bona fide cluster of eukaryotic cells'*. Whereas the former belongs to the respective granularity level of the CBB granular perspective, the latter does not, because only the former is based on the more restrictive causal unity via physical covering as criterion for their bona fideness. The bona fideness of *'bona fide cluster of eukaryotic cells'*, on the other hand, is only based on the more general causal unity via internal physical forces. However, because they represent aggregates of building blocks that can be partitioned into their component object parts that belong to the same spatio-structural frame of reference one can characterize the corresponding qualitative compositional partitions as the compositional building block cluster (CBB-C) granular perspectives (see Fig. 5). Each CBB granularity level has its own corresponding CBB-C granular perspective. This CBB-C granular perspective is based on a direct proper parthood relation between instances of building blocks of a given spatio-structural frame of reference and their corresponding bona fide clusters, and thus has the building-block-level-specific **granulation criterion** (Fig. 5):

'building block' $^X$ directProperPartOf *'bona fide cluster of* [building block]*s'* $^X$;
*'bona fide cluster of* [building block]*s'* $^X$ hasDirectProperPart 'building block' $^X$;
X=a specific spatio-structural frame of reference.

Like the CBB granular perspective, the CBB-C perspective has a granulation of the non-scale dependent single-relation-type **granularity type** (*nrG*, Keet, 2008a) and is based on the direct proper parthood relation as its **granulation relation**. Because the domain and range of the granulation relation differ according to the granulation criterion, the granulation relation is *not* transitive and thus each of the CBB-C perspectives includes only two distinct granularity levels.

### Region-Based Granular Perspectives

Besides the two types of compositional granular perspectives, each spatio-structural frame of reference has its own set of seven different associated region-based granular perspectives (for an overview, see Fig. 5). The different perspectives, together with their specific granulation criterion, granulation type, and granulation relation are listed in table 2. They differ only with respect to their granulation type, but they all share the same non-scale dependent single-relation-type **granularity type** (*nrG*, Keet, 2008a) and are all based on the proper parthood relation as their **granulation relation**.

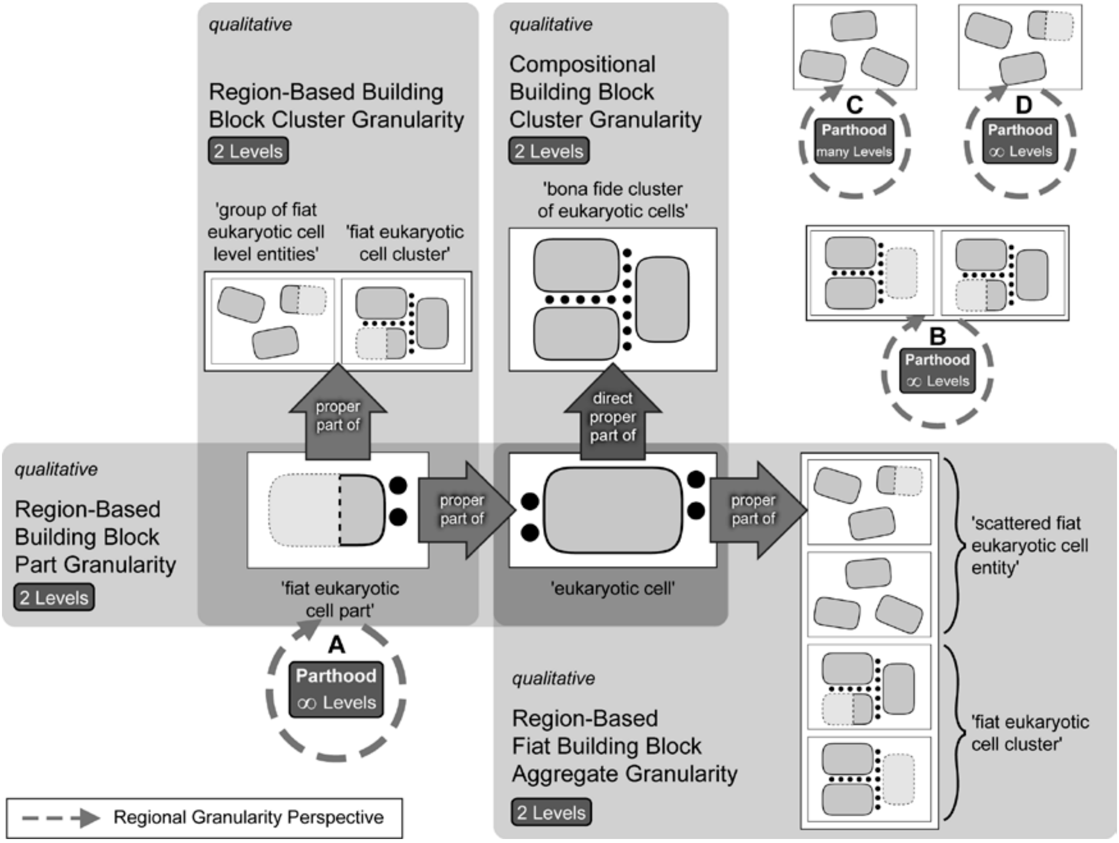

**Figure 5. Set of Granular Perspectives within a given spatio-structural Frame of Reference.** The figure shows all qualitative granular perspectives that the domain granularity framework for the life sciences distinguishes for any given spatio-structural frame of reference and thus any corresponding CBB granularity level (here, the set of perspectives for the eukaryotic cell level as an example). The dark arrows indicate the granulation relation and the white boxes contain the granulated entity types. **A** = Region-Based Fiat Building Block Part Granularity Perspective; **B** = Region-Based Fiat Building Block Cluster Granularity Perspective; **C** = Region-Based Group of Building Block Level Objects Granularity Perspective; **D** = Region-Based Group of Fiat Building Block Level Entities Granularity Perspective (see also Table 2).

These seven types of region-based granular perspectives result in a set of 49 different region-based granular perspectives within the domain granularity framework for the life sciences. This set is sufficient to model all possible region-based partition relations between any given pair of spatio-structural entities for a given spatio-structural frame of reference.

**Table 2:** List of Region-Based Granularity Perspectives for each given spatio-structural frame of reference (compare with Fig. 5); *nrG* = non-scale dependent single-relation granularity type, sgrG = scale-dependent grain size with respect to resolution (Keet, 2008a)

| **Level-Specific Granularity Perspective** | **Granulation Criterion** | **Granularity Type** | **Granulation Relation** | **# Levels** |
|---|---|---|---|---|
| **Region-Based Granularity Perspectives** | | | | |
| Region-Based Building Block Cluster Granularity Perspective | *'fiat* [building block] *part'* properPartOf *'group of fiat* [building block] *level entities'* **OR**<br>*'fiat* [building block] *part'* properPartOf *'fiat* [building block] *cluster'*;<br>*'group of fiat* [building block] *level entities'* hasProperPart *'fiat* [building block] *part'* **OR**<br>*'fiat* [building block]*cluster'* hasProperPart *'fiat* [building block] *part'* | *nrG* | *proper parthood* | 2 |
| Region-Based Building Block Part Granularity Perspective | *'fiat* [building block] *part'* properPartOf '[building block]';<br>'[building block]' hasProperPart *'fiat* [building block] *part'* | *nrG* | *proper parthood* | 2 |
| Region-Based Fiat Building Block Aggregate Granularity Perspective | '[building block]' properPartOf *'fiat* [building block] *cluster'* **OR**<br>'[building block]' properPartOf *'scattered fiat* [building block] *entity'*;<br>*'fiat* [building block] *cluster'* hasProperPart '[building block]' **OR**<br>*'scattered fiat* [building block] *entity'* hasProperPart '[building block]' | *nrG* | *proper parthood* | 2 |
| Region-Based Fiat Building Block Part Granularity Perspective | *'fiat* [building block] *part'* properPartOf *'fiat* [building block] *part'*;<br>*'fiat* [building block] *part'* hasProperPart *'fiat* [building block] *part'* | *nrG* | *proper parthood* | ∞ |
| Region-Based Fiat Building Block Cluster Granularity Perspective | *'fiat* [building block] *cluster'* properPartOf *'fiat* [building block] *cluster'*;<br>*'fiat* [building block] *cluster'* hasProperPart *'fiat* [building block] *cluster'* | *nrG* | *proper parthood* | ∞ |
| Region-Based Group of Building Block Level Objects Granularity Perspective | *'group of* [building block] *level objects'* properPartOf *'group of* [building block] *level objects'*;<br>*'group of* [building block] *level objects'* hasProperPart *'group of* [building block] *level objects'* | *nrG* | *proper parthood* | many |
| Region-Based Group of Fiat Building Block Level Entities Granularity Perspective | *'group of fiat* [building block] *level entities'* properPartOf *'group of fiat* [building block] *level entities'*;<br>*'group of fiat* [building block] *level entities'* hasProperPart *'group of fiat* [building block] *level entities'* | *nrG* | *proper parthood* | ∞ |

### *Function-Based and History/Evolution-Based Granular Perspectives*

In analogy to the distinction between the CBB and the region-based granular perspectives for spatio-structural entities, one can also distinguish between a compositional functional unit (CFU) granular perspective[35] and various region-based functional entity granular perspectives, as well as between a compositional historical/evolutionary unit (CH/EU) granular perspective and various region-based historical/evolutionary entity granular perspectives respectively.

The partition of a given functional unit or historical/evolutionary unit into components that themselves are functional units or historical/evolutionary units represents a qualitative compositional partition. The functional compositional partition is based on a direct proper functional parthood[36] relation between instances of different sub-categories of *'functional unit'* (see next chapter), which thus represents the **granulation relation** of the CFU granular perspective. Its **granulation criterion** is:

| | | |
|---|---|---|
| *'functional unit'* | directProperFunctionalPartOf | *'functional unit'*; |
| *'functional unit'* | hasDirectProperFunctionalPart | *'functional unit'*. |

The historical/evolutionary compositional partition, on the other hand, is based on a direct proper historical/evolutionary (DirPropHistEvol) parthood relation[37] between instances of different sub-categories of *'historical/evolutionary unit'* (see next chapter), which thus represents the **granulation relation** of the CH/EU granular perspective. Its **granulation criterion** is:

| | | |
|---|---|---|
| *'hist/evol unit'* | DirPropHistEvolPartOf | *'hist/evol unit'*; |
| *'hist/evol unit'* | hasDirPropHistEvolPart | *'hist/evol unit'*. |

Based on Keet, both perspectives have a granulation of the non-scale dependent single-relation-type **granularity type** (*nrG*, Keet, 2008a). Contrary to the CBB granular perspective, however, an underlying hierarchy of levels of functional or historical/evolutionary building blocks that defines the number of possible levels of a CFU or CH/EU granular perspective, like the CBB granular perspective does for spatio-

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[35] The CFU granularity perspective within the domain granularity framework for the life sciences corresponds with the mechanism-based levels metaphor discussed above.

[36] This direct proper functional parthood relation can be derived from the direct proper parthood relation by restricting its domain and range to instances of *'functional unit'*.

[37] This direct proper historical/evolutionary parthood relation can be derived from the direct proper parthood relation by restricting its domain and range to instances of *'historical/evolutionary unit'*.

structural entities, is missing. Neither the CFU nor the CH/EU granular perspective can be based on a hierarchy of monolithic levels of functional or historical/evolutionary units that are globally and universally applicable and reach across all domains of the life sciences[38]. Instead, representatives of different species, even different particular biological material entities, can substantially differ in the number and structure of their CFU and CH/EU granular perspectives.

Because we do not distinguish between different sub-types of functional and historical/evolutionary causal unity, like we do with causal unity via internal physical forces and via physical covering for spatio-structural entities, there is no analog for the CBB-C granular perspective for functional and historical/evolutionary entities. However, one can differentiate various region-based functional and region-based historical/evolutionary granular perspectives in analogy to the various region-based granular perspectives for spatio-structural entities, which I do not discuss here for lack of space.

## *2nd Step: Dealing with Specific Problems Resulting from the Cumulative Constitutive Organization of Reality*

### ***Extending and rearranging BFO's Top-Level Categories of 'material entity' to accommodate different Frames of Reference***

The frame-dependence of the relevance of different types of causal unity and the resulting differentiation of three basic categories of granular perspectives and their corresponding basic frames of reference, together with the differentiation of spatio-structural frames of reference in dependence on the number of granularity levels identified for the CBB granular perspective, reflect a basic distinction of foundational categories of *'material entity'*. I therefore suggest the following top-level categories for BFO's *'material entity'* (see Fig. 6). The classes *'functional entity'*, *'historical/evolutionary entity'*, and *'spatio-structural entity'* distinguish foundational types of material entity based on their underlying type of causal unity, which is causal unity via bearing a specific function, causal unity via common historical/evolutionary origin, and causal unity via

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[38] To stay within the metaphor: we do not know reality's inventory of functional and historical/evolutionary lego-bricks.

internal physical forces[39], respectively. Because of the frame-dependence of the relevance of these different types of causal unity, these three classes are **not disjoint**[40].

Based on the identification of different spatio-structural frames of reference, I can now suggest the following top-level categories for *'spatio-structural entity'*: *'atom level entity'*, *'molecule level entity'*, *'organelle/prokaryotic cell level entity'*, *'eukaryotic cell level entity'*, *'epithelially-delimited compartment level entity'*, *'epithelially-delimited multi-cellular organism level entity'* (see Fig. 6). **Each of these categories corresponds with one of the spatio-structural frames of reference.** Due to the frame-dependence, these six classes of *'spatio-structural entity'* are also **not disjoint**, because some given spatio-structural entity may be a molecule, but at the same time also a fiat organelle part and a fiat eukaryotic cell part.

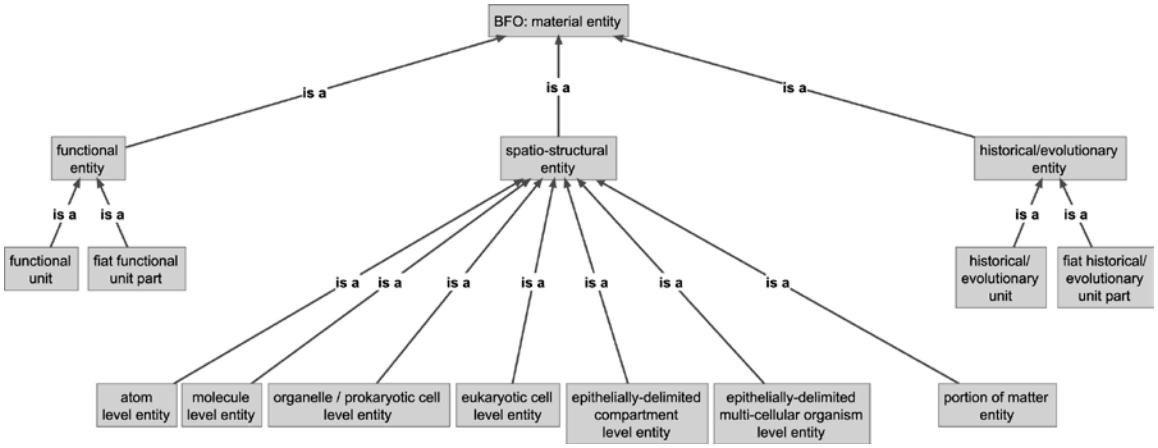

**Figure 6. Top-Level Categories of '*material entity*' and '*spatio-structural entity*'.** The grey boxes represent categories. The category *'spatio-structural entity'* is based on causal unity via internal physical forces, *'functional entity'* is based on causal unity via bearing a specific function, and *'historical/evolutionary entity'* is based on causal unity via common historical/evolutionary origin. As a consequence of the perspective-dependence of bona fideness, these three categories are not disjoint. The functional and historical/evolutionary entities are further differentiated according to disjoint categories of bona fide units and fiat unit parts. Spatio-structural entities are further differentiated in correspondence with the granularity levels of the compositional building block granular perspective (see discussion in text), ranging from *'atom level entity'* to *'epithelially-delimited multi-cellular organism level entity'*, but include not only the respective bona fide entities of that level, but also their corresponding object aggregate and fiat object part entities. Because bona fideness is not only perspective-dependent, but also granularity-dependent, and each building block level has its own spatio-structural frame of reference and thus its own perspective, and due to the cumulative-constitutive organization of biological entities, entities from finer spatio-structural frames of reference (e.g. molecules) must be represented in coarser frames of reference (e.g. eukaryotic cell) as fiat portions of matter. These representations are covered through the *'portion of matter entity'* category (see also Fig. 8).

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[39] Because causal unity via physical covering supervenes on causal unity via internal physical forces, the latter covers the former.

[40] As a consequence, some given material entity may instantiate *'functional entity'*, *'historical/evolutionary entity'*, and *'spatio-structural entity'* at the same time.

Based on (i) the identification of different spatio-structural frames of reference, (ii) the implications of a cumulative constitutive organization of biological material entities, and (iii) because bona fideness is granularity- and thus frame-dependent (see also discussion in Vogt et al., 2012b; Vogt, *submitted* b), I treat all bona fide and fiat entities from a given spatio-structural frame of reference in coarser frames of reference as **fiat entities**. As a consequence, the category *'portion of matter entity'* is introduced as another top level category of *'spatio-structural entity'* in addition to the set of building block level specific categories. It refers to the **representation** of entities from a finer spatio-structural frame of reference level at coarser frame-levels (see next chapter and Fig. 6, 8).

Regarding the functional and historical/evolutionary entities, one can only distinguish bona fide and fiat entities with respect to their corresponding frames of reference. Therefore, *'functional entity'* has the top-level categories *'functional unit'*, which comprises all bona fide functional entities, and *'fiat functional unit part'*, which comprises all fiat functional entities respectively. Accordingly, one can distinguish *'historical/evolutionary unit'* from *'fiat historical/evolutionary unit part'*. Because for functional and historical/evolutionary entities no backbone granularity scheme exists that is comparable to the building block levels hierarchy and the associated CBB granular perspective discussed above, no additional differentiation into further sub-categories is suggested. One could, of course, differentiate functional entities based on the type of functions they bear and thus the type of corresponding processes (=functionings), into functional units of locomotion, physiology, ecology, development, and functional units of reproduction and propagation, and historical/evolutionary entities into historical units of development, heredity, and of evolution and developmental, genealogical and evolutionary lineages (see Vogt et al., 2012b).

Because each spatio-structural frame of reference includes not only the corresponding building block and its bona fide aggregates[41], but also their corresponding fiat building block parts and fiat building block aggregates, each category of *'spatio-structural entity'* includes all corresponding fiat and bona fide entities. In other words, I interpret BFO's categories *'object'*, *'object aggregate'*, *'fiat object part'* as being

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[41] Whereas bona fide entities exist independent of human partitioning activities, fiat entities exist only due to them.

applicable to each spatio-structural frame of reference. Therefore, I consider the distinction between fiat and bona fide material entities to be foundational for spatio-structural frame of reference. In case of the *'eukaryotic cell level entity'* (i.e. membrane-within-membrane frame of reference) as an example, it results in the basic distinction of *'eukaryotic cell level object'* and *'fiat eukaryotic cell level entity'* (see Fig. 7).

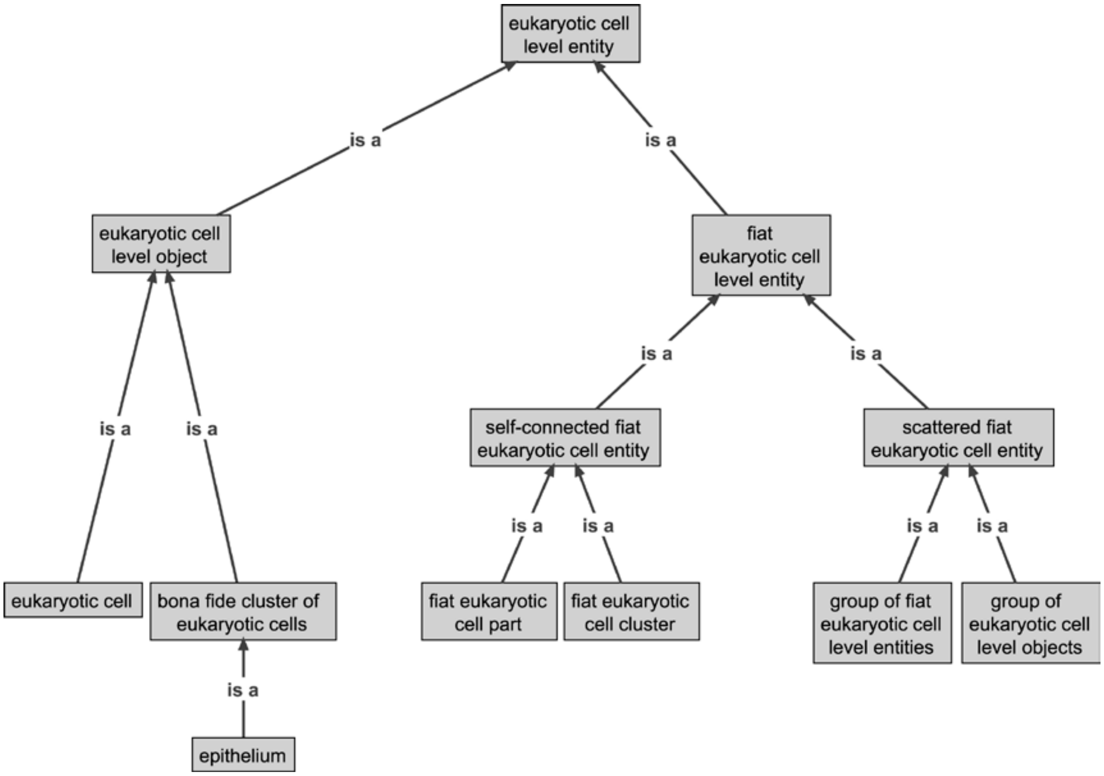

**Figure 7. Top-Level Categories of '*eukaryotic cell level entity*'.** Eukaryotic cell level entities are differentiated into a bona fide *'eukaryotic cell level object'* and a *'fiat eukaryotic cell level entity'* category, which are disjoint. The former is differentiated based on its underlying type of causal unity into *'eukaryotic cell'*, which is based on physical covering, and *'bona fide cluster of eukaryotic cells'*, which is based only on internal physical forces and not on physical covering. The fiat eukaryotic cell level entities are differentiated based on their self-connectedness into the disjoint categories of *'self-connected fiat eukaryotic cell entity'* and *'scattered fiat eukaryotic cell entity'*. See text for more details.

The *'eukaryotic cell level object'* corresponds with BFO's *'object'* category. Depending on which type of causal unity is relevant for the given object entity, I distinguish two types of objects for each spatio-structural frame of reference and thus each category of *'spatio-structural entity'*. On the one hand the entities that belong to the corresponding CBB granularity level, which are objects that are based on the more specific causal unity via physical covering. This would be *'eukaryotic cell'* in the case of *'eukaryotic cell level object'* (see Fig. 7) or *'molecule'* in the case of *'molecule level* *object'*. On the other hand, because building blocks can aggregate to form bona fide clusters based on the more general causal unity via internal physical forces, another object category is required to deal with these types of objects. Thus, *'eukaryotic cell level object'* would not only have *'eukaryotic cell'* as objects (=bona fide entities), but also *'bona fide cluster of eukaryotic cells'* as for instance those cells that together build an epithelium (which provides the physical covering of the building block entities of the next coarser spatio-structural frame of reference). Or, in case of *'molecule level object'*, *'bona fide cluster of molecules'* can form a bio-membrane or a chitin cuticula, both of which are bona fide objects that are based on causal unity via internal physical forces (as opposed to the building block itself, which is additionally based on causal unity via physical covering).

These building block level objects are contrasted with fiat building block level entities, which cover BFO's *'fiat object part'* and *'object aggregate'* and comprise all material entities that possess spatio-structurally no causal unity (neither via internal physical forces nor via physical covering)[42]. These fiat building block entities can be further distinguished based on whether they are spatio-structurally self-connected, giving rise to the two distinct sub-categories. In case of *'fiat eukaryotic cell level entity'* this results in the distinction of *'self-connected fiat eukaryotic cell entity'* and *'scattered fiat eukaryotic cell entity'* (Fig. 7). Self-connected fiat entities can be further differentiated into fiat building block parts and thus the building block level specific correlate to BFO's *'fiat object part'*, and fiat building block clusters. For the eukaryotic cell level, the former would translate into *'fiat eukaryotic cell part'* and the latter into *'fiat eukaryotic cell cluster'*, respectively. A scattered fiat entity, on the other hand, can be further differentiated based on the type of its scattered component parts. If all scattered component parts are building block level objects that correspond to the relevant spatio-structural frame of reference, the scattered entity is a group of building block level objects (e.g., *'group of eukaryotic cell level objects'*). However, if at least one of its component parts is a fiat building block level entity, the scattered entity is a group of

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[42] Note that this fiatness depends on the granularity level of the building block entity, which provides the relevant spatio-structural frame of reference in this context.

building block level entities (e.g. *'group of fiat eukaryotic cell level entities'*)[43] (see Fig. 7).

### *Consequence from the Cumulative Constitutive Organization and the Frame-Dependence of Biological Material Entities'*

The abovementioned categories of *'spatio-structural entity'* must accommodate all types of material entities found in cumulative-constitutively organized biological material entities. Therefore, its sub-categories always refer to the building block entity of the corresponding spatio-structural frame of reference, independent of whether finer-level entities are also involved. In other words, *'eukaryotic cell'* or *'fiat eukaryotic cell part'* comprise all types of eukaryotic cell or eukaryotic cell part entities, with and without associated portions of connected ECM, and *'epithelially-delimited compartment'* comprises all types of epithelially-delimited compartments, with and without associated portions of connected molecular matter and portions of connected tissue (see also Fig. 4, 5). Therefore, when we talk about a eukaryotic cell cluster, this can refer to a cluster of cells with surrounding ECM, but it could also refer to a cluster of cells without surrounding ECM.[44]

Because biological material entities are usually cumulative-constitutively organized (see discussion above), entities of finer building block levels can exist outside of building blocks of coarser levels, like for instance molecules outside of eukaryotic cells. Unfortunately, these finer level entities cannot be covered with the categories of the coarser level entities, since they are neither a bona fide objects nor fiat object parts entities of this object level—a molecule that exists outside of eukaryotic cells does neither represent a eukaryotic cell level object nor a fiat eukaryotic cell level entity. In other words, the adequate categories for referring to these entities belong to a different and finer spatio-structural frame of reference. However, respective entities still must be represented in the coarser frame of reference level (see *sortation-by-type* and *type granularity trees* problematic discussed in chapter *Cumulative Constitutive Granularity*,

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[43] For a distinction of (i) *groups* based on *metric proximity* as the relation between its parts versus (ii) *clusters* based on *topological adherence* as the relation between its parts see Vogt et al. (2011, 2012a).

[44] This is a rather pragmatic choice, as the alternative would require covering each possible combination of different levels of building block entities that can be found in a cumulative constitutive organization with its own category. This, however, would result in a tremendous increase in top-level categories (see Vogt et al., 2011, 2012a), which would neither be convenient and intuitive to use, nor really necessary.

see Fig. 2). As already mentioned above, I therefore introduce the category *'portion of matter entity'*. For instance, eukaryotic cell clusters and single eukaryotic cells, as well as molecule clusters and single molecules, can exist outside of epithelially-delimited compartments (see also Fig. 2). As a consequence, none of the sub-categories of *'epithelially-delimited compartment level entity'* can accommodate these material entities. They are therefore covered by the categories *'portion of molecule entity*' and *'portion of eukaryotic cell entity'* respectively, which are frame-of-reference-specific sub-categories of *'portion of matter entity'* (see Fig. 6, 8).

A **portion of matter** is a non-countable entity (c.f. *masses* Bittner, 2004; *amount of matter* Rector et al., 2006; *portion of unstructured stuff* Bittner & Donnelly, 2007; see also *body substance* Rosse et al., 1998; and *portion of body substance* Rosse & Mejino, 2007). In order to count the number of component parts a portion of matter, one would have to change the spatio-structural frame of reference from the current frame to a finer frame that corresponds with the component parts. Thus, a cluster of molecules, like for instance the chitin cuticula that forms the exoskeleton in insects, which is a bona fide cluster of chitin molecules and thus instantiates *'molecule level object'* at the molecular frame of reference, is represented as a self-connected (fiat) portion of molecular matter at all coarser spatio-structural frames of reference. The individual molecules that build the cluster cannot be individually differentiated anymore at reference levels coarser than the molecular level, because their bona fideness disintegrates at these coarser levels[45] (Vogt et al., 2012a). If a portion of matter consists of a mixture of building block entities of different spatio-structural frames of reference, as for instance a portion of connective tissue that is a group of cells embedded in a cluster of collagen molecules, the coarsest building block entity is used for classifying it, which in this case would be a portion of connective tissue[46].

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[45] This is why all portions of matter are treated as fiat entities.

[46] Portions of tissue always refer to cell aggregates. Most cells in multi-cellular organisms are surrounded by a complex cluster of molecules, called the extracellular matrix (ECM). In case of plant cells it mainly consists of cellulose, in bacteria of peptidoglycan, and in fungi of chitin, and it is referred to as cell wall. The ECM of animal cells, on the other hand, usually mainly consists of collagen. The exact composition of the ECM varies considerably and depends on the cell type it surrounds. But not only varies the composition, but also the amount of ECM surrounding a cell. In connective tissue, bone tissue, cartilage tissue, and in blood, the ECM is considerably rich, often accounting for the majority of the substance of the respective tissue, whereas in epithelia ECM accounts only for a small amount of the overall substance of the tissue.

Because entities belonging to a finer spatio-structural frame of reference are always represented as non-countable fiat portions of matter in coarser spatio-structural frames of reference, one can only distinguish between self-connected and scattered portions. In case of *'portion of eukaryotic cell entity'*, one can thus distinguish *'self-connected portion of eukaryotic cell tissue'* from *'scattered portions of eukaryotic cell tissue'* respectively (see Fig. 8).

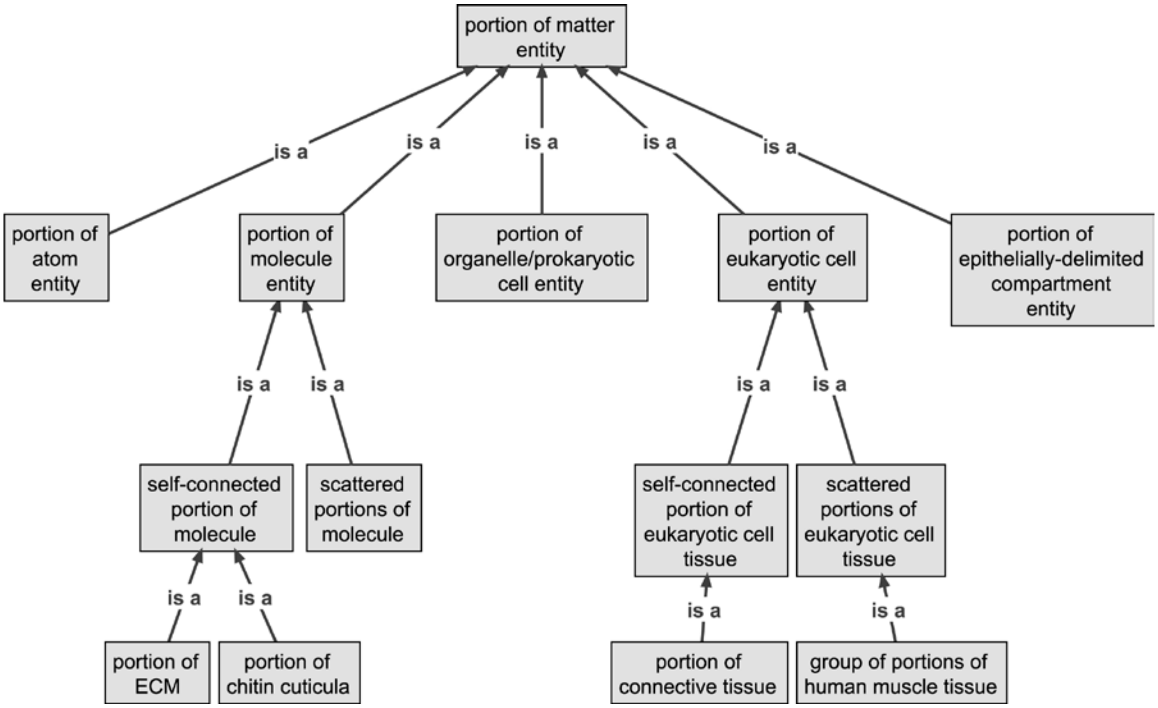

**Figure 8. Top-Level Categories of '*portion of matter entity*'.** The entities of each building block level, except for the coarsest level of epithelially-delimited multi-cellular organisms, can be represented as a respective portion of matter entity in coarser spatio-strutural frames of reference. Therefore, *'portion of matter entity'* is differentiated into building block level specific subcategories. Here, further differentiations are shown for the *'portion of molecule entity'* and the *'portion of eukaryotic cell entity'* category, which are based on whether the entity is a self-connected portion of matter, as for instance a portion of ECM or a portion of connective tissue, or a group of scattered portions, as for instance the group of muscle tissues in a human being.

### *Cross-Granular Multiple Instantiation*

Due to its granular nature, any given biological material entity always instantiates several different material entity categories at the same time, one for each spatio-structural frame of reference (Vogt et al., 2012a). For example, every instance of *'eukaryotic cell'* instantiates at finer frames of reference also *'bona fide cluster of molecules'* and *'bona fide cluster of atoms'*, because a eukaryotic cell is a bona fide composition of clustered molecules and at the same time also a bona fide composition of clustered atoms. At coarser frames of reference it instantiates frame-specific entity categories. However, which category is instantiated at those coarser frames depends on the particular eukaryotic cell. If it exists outside of any epithelially-delimited compartment, it is not covered by any level-specific subcategory of *'epithelially-delimited compartment entity'* and therefore instantiates some category of *'portion of eukaryotic cell entity'* (see discussion in previous chapter). If it is part of an epithelially-delimited compartment, however, then it instantiates *'fiat epithelially-delimited compartment part'*.

One could, of course, define a class *'eukaryotic cell'*, a class *'maximal cellular molecule cluster'*, and a class *'maximal cellular atom cluster'* and all these three classes would have the same extension, although they belong to different frames of reference; and according to the principle of extensionality of class logic, these classes would be identical from a logics point of view. However, from an epistemic point of view, due to the frame- and granularity-dependence of bona fideness, these classes cannot be strictly synonymized (Vogt et al., 2012a). Therefore, when dealing with biological material entities we necessarily have to deal with **multiple cross-granular instantiations**[47] (Vogt et al., 2012a) of subcategories of *'material entity'*, all of which do not stand in a subsumption relation to one another[48]. They are a necessary consequence of the fact that every building block level has its own associated spatio-structural frame of reference. In a knowledge base this is dealt with by assigning each granular instantiation that a user wants to reference its own individual resource, so that the corresponding real entity is represented in this knowledge base using several resources.

## *Results II: Additional Granular Perspectives*

### *Granular Representation and Resolution-Based Representation (RBR) Granular Perspectives*

Due to the abovementioned multiple cross-granular instantiation, each particular biological material entity necessarily instantiates multiple categories. This can be

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[47] One reason for introducing frame-of-reference-specific categories of *'portion of matter entity'* is to prevent that the extension of a class, like for instance *'eukaryotic cell'*, transcends the boundary between the cell level and the level of epithelially-delimited compartments, which would result in trans-granular multiple instantiations (Vogt et al., 2012a).

[48] As opposed to, for instance, a rhabdomeric light-sensory cell that not only instantiates *'rhabdomeric light-sensory cell'*, but necessarily also *'light-sensory cell'*, *'sensory cell'*, and *'eukaryotic cell'*, because all these classes stand in a class-subclass relation to each other.

modeled through providing a URI for each representation. In order to indicate that these URIs refer to the same concrete thing in reality, the resources must be adequately related to one another. Therefore, a specific strict partial ordering relation, i.e. **granular representation relation**, is introduced which can be differentiated into *has coarser granular representation* and its inverse relation, *has finer granular representation*. It has *'spatio-structural entity'* as its range and its domain. This relation gives rise to a granular partition, a **scale-based resolution granular partition**.[49]

As a consequence, the entities that belong to the same scale-based resolution granular partition are only different **granular representations** of the same particular concrete material entity, with each granular representation directly linked to a specific spatio-structural frame of reference (Vogt et al., 2012a).

Based on this granular representation relation, and in addition to the various qualitative granular perspectives discussed so far, one can differentiate several quantitative scale-based granular perspectives (cf. Vogt, 2010). This is required to formally model the specific relation between resources that refer to different granular representations of the same particular concrete material entity in various finer and coarser spatio-structural frames of reference.

All resolution-based representation (RBR) granular perspectives are based on the combination of the CBB granular perspective and a strict partial ordering granular representation relation between instances of different subcategories of *'spatio-structural entity'* that belong to different spatio-structural frames of reference. The possibilities for distinguishing different types of RBR granular perspectives is extensive and results from the different range and domain combinations for the granulation relation, with each unique combination resulting in a unique granulation criterion. Here, however, I will only discuss the most general and inclusive type of RBR granular perspective that has the **granulation criterion** (Fig. 9):

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[49] *Scale-based*, because the CBB granularity perspective can be interpreted to provide a scale that is based on the ordering of CBB granularity levels from the finest to the coarsest level. *Resolution*, because each individual resource refers to the same concrete material entity, but represents it in its level-specific resolution. This scale-based resolution granular partition also covers the non-countable *'portion of matter entity'* granular representations of a given particular material entity that can instantiate identical categories of *'portion of matter entity'* across several spatio-structural frames of reference (see Fig. 2, C).

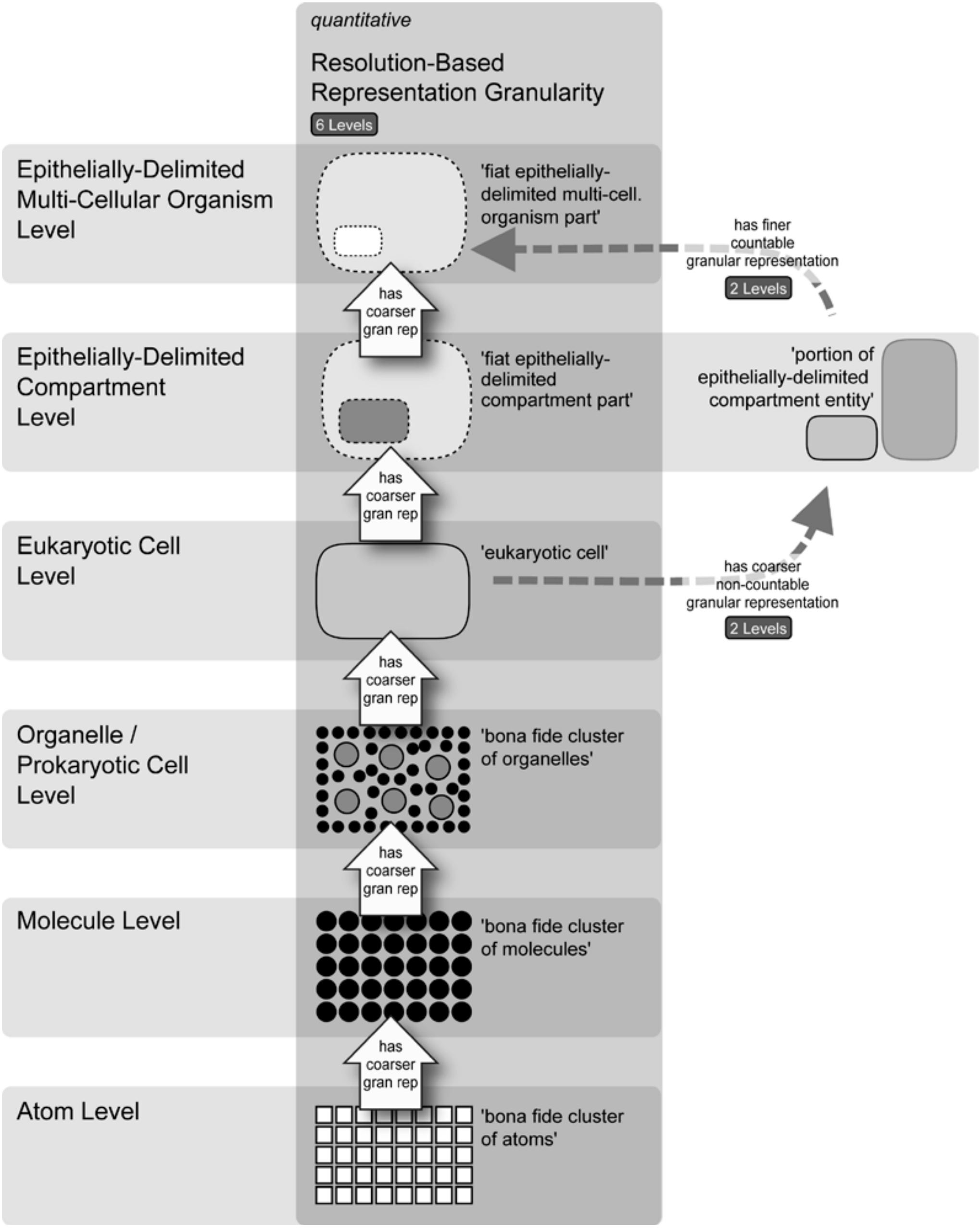

**Figure 9. Resolution-Based Representation (RBR) and Resolution-Based Countability Representation (RBCR) Granulary Perspective.** The different levels of the RBR granular perspective are granulated according to the *has coarser granular representation* relation (the white broad arrows). The granulation is of the scale dependent grain-size-according-to-resolution granularity type (*sgrG*, Keet, 2008a). The different levels of the two RBCR granular perspectives, on the other hand, are granulated according to the *has coarser non-countable granular representation* relation and the *has finer countable granular representation* relation (dotted gray arrows). Their granulation is of the scale dependent grain-size-according-to-resolution granularity type (*sgrG*, Keet, 2008a). All three perspectives use the combination of the granulation relation together with the scale provided through the set of different spatio-structural frames of reference that are sequentially ordered through the associated CBB granular perspective (= the building block levels hierarchy). As a consequence, the RBR granular perspective comprises six granularity levels, whereas the two RBCR granular perspectives each comprise only two granularity levels, because the granulation relation is *not* transitive (its domain and range differ).

*'spatio-structural entity'* $^{X}$ hasCoarserGranRep *'spatio-structural entity'* $^{X+1}$;
*'spatio-structural entity'* $^{X+1}$ hasFinerGranRep *'spatio-structural entity'* $^{X}$;

X=a specific spatio-structural frame of reference; X+1=the next coarser spatio-structural frame of reference adjacent to X.

This perspective has a granulation of the scale dependent grain-size-according-to-resolution **granularity type** (*sgrG*, Keet, 2008a). It is based on the granular representation relation as its **granulation relation**. Because this RBR granular perspective directly depends on the CBB granular perspective, the number of its granularity levels corresponds with the number of CBB granularity levels.

### *Resolution-Based Countability Representation (RBCR) Granular Perspectives*

The RBR granular perspective does not differentiate whether a representation is of the countable building block level entity kind or the non-countable *'portion of matter entity'* kind, as it allows all kinds of spatio-structural entities to be granulated. In order to identify changes from countable to non-countable representations of a given real entity across different spatio-structural frames of reference, two complementary resolution-based countability representation (RBCR) granular perspectives are suggested. For this reason the following two **granular countability representation relations** are introduced: (i) *has coarser non-countable granular representation* (co_n-c_GranRep), with building block level entities (e.g. *'eukaryotic cell level entity'*) as its domain and *'portion of matter entity'* as its range, together with its inverse relation *has finer countable granular representation* (fi_c_GranRep), and (ii) *has coarser countable granular representation* (co_c_GranRep), with *'portion of matter entity'* as its domain and some building block level entity as its range, together with its inverse relation *has finer non-countable granular representation* (fi_n-c_GranRep). Based on these two relations two complementary RBCR granular perspectives can be distinguished: (i) countable to non-countable RBCR granular perspective, and (ii) non-countable to countable RBCR granular perspective. The countable to non-countable perspective has the **granulation criterion** (Fig. 9):

*'spatio-structural entity'* $^{X}$ co_n-c_GranRep *'portion of matter entity'* $^{X+1}$;
*'portion of matter entity'* $^{X+1}$ fi_c_GranRep *'spatio-structural entity'* $^{X}$;

and the non-countable to countable perspective has the **granulation criterion**:

*'portion of matter entity'* $^{X}$ co_c_GranRep *'spatio-structural entity'* $^{X+1}$;
*'spatio-structural entity'* $^{X+1}$ fi_n-c_GranRep *'portion of matter entity'* $^{X}$.

X=a specific spatio-structural frame of reference; X+1=the next coarser spatio-structural frame of reference adjacent to X.

These two complementary perspectives have both a granulation of the scale dependent grain-size-according-to-resolution **granularity type** (*sgrG*, Keet, 2008a). Each is based on its respective granular countability representation relation as its **granulation relation**. Because the domain and range of their respective granulation relation differ, the granulation relation is *not* transitive and thus both RBCR granular perspectives comprise only two distinct granularity levels.

### *Function-Based Representation (F-BR) and Historical/Evolution-Based Representation (H/E-BR) Granular Perspectives*

The functional frame of reference requires its own granular representation due to cross-granular multiple instantiation (analogue to cross-granular multiple instantiation due to different spatio-structural frames of reference). This function-related granular representation is required because some instances of *'spatio-structural entity'* are at the same time also instances of *'functional unit'*. The filter apparatus of a terminal cell of a protonephridium, for instance, instantiates *'fiat eukaryotic cell part'*, because the filter apparatus consists of the cell's cilium, a filter and a set of microvilli, but not the other parts of the terminal cell. The filter apparatus, however, also instantiates *'functional unit'*, because it functions as a filter during excretion.

The historical/evolutionary frame of reference also requires its own granular representation due to cross-granular multiple instantiation. Every anatomical entity that is a homolog and thus instantiates *'historical/evolutionary unit'* also instantiates *'spatio-structural entity'*.

For this reason the following two **granular representation relations** are introduced: (i) *has functional granular representation* (FuncGranRep), with *'spatio-structural entity'* as its domain and *'functional entity'* as its range and its inverse relation *functional has spatio-structural representation* (FuncSp-StrGranRep), and (ii) *has historical/evolutionary granular representation* (Hist/EvGranRep), with *'spatio-structural entity'* as its domain and *'historical/evolutionary entity'* as its range and its inverse relation *historical/evolutionary has spatio-structural representation* (Hist/EvSp-StrGranRep). Based on these two relations two granular perspectives can be distinguished: (i) a function-based representation (F-BR) granular perspective and (ii) a historical/evolution-based representation (H/E-BR) granular perspective. The F-BR granular perspective has the **granulation criterion**:

*'spatio-structural entity'* FuncGranRep *'functional entity'*;
*'functional entity'* FuncSp-StrGranRep *'spatio-structural entity'*.

The H/E-BR granular perspective has the **granulation criterion**:

*'spatio-structural entity'* Hist/EvGranRep *'historical/evolutionary entity'*;
*'historical/evolutionary entity'* Hist/EvSp-StrGranRep *'spatio-structural entity'*.

These two perspectives have both a granulation of the scale dependent grain-size-according-to-resolution[50] **granularity type** (*sgrG*, Keet, 2008a). Each is based on its respective granular representation relation as its **granulation relation**. Because in both perspectives the domain and range of the respective granulation relations differ, the granulation relations are *not* transitive. Therefore, both granular perspectives comprise only two distinct granularity levels.

## CONCLUSION

The here proposed framework for the development of a domain granularity framework for the life sciences comprises a core set of granular perspectives that can be utilized for efficiently managing large semantic graphs that contain data about material entities that range from atoms to multi-cellular organisms and beyond. The framework provides a meta-layer that (i) defines the relations between entities that belong to different granularity levels of the same granular perspective and between entities across different granular perspectives; (ii) integrates various frames of reference within a single framework, all of which are essential for the life sciences, ranging from purely spatio-structural frames of reference, to functional, developmental, ecological, and evolutionary frames of reference; (iii) improves searching and navigating through large complex

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[50] Resolution here in the sense of depending on a specific frame of reference that functions like a lens that filters out all aspects irrelevant to the given frame of reference.

graphs by using one or a combination of several of its granular perspectives as filters; and (iv) facilitates reasoning and inferencing by providing additional hierarchical structures that can be used for measuring semantic similarities *between* different semantic graphs and between resources *within* a graph.

This domain granularity framework complies with Craver's (2015) claim of descriptive pluralism about the levels idea. It comprises various hierarchies of different levels. The compositional building block (CBB) granular perspective (Fig. 4) takes in a key position in the domain granularity framework, because it provides the backbone hierarchy that facilitates the integration of all the other granular perspectives within the framework. It resembles a purely compositional account of the levels idea, without making the mistake to mix entities relevant in different frames of reference (see problems discussed further above regarding Eldredge's somatic hierarchy, Eldredge, 1985). Furthermore, with its focus on physical covering and evolving building blocks, the CBB granular perspective is also influenced by the evolutionary systems-theoretical accounts of the levels idea, in particular the operator-based approach, thereby integrating purely spatio-structural considerations with functional and evolutionary aspects. The set of region-based granular perspectives, on the other hand, do not have a pre-defined structure in terms of a fix number of granularity levels, but must be determined on a local case-by-case approach, thereby reflecting one of the criticism regarding the single compositional hierarchy of the compositional account of the levels idea.

The set of functional parthood-based granular perspectives resemble the mechanism-based account of the levels idea. The lack of a globally applicable general granular perspective comparable to the CBB granular perspective for functional parthood thereby reflects that functional parthood-based granularity levels depend on a given mechanism (i.e., function, and therefore also causal process) and thus are local, case-specific, and cannot result in a universal scheme that is globally applicable (Bechtel, 2008). And finally, the different spatio-structural frames of reference, with their diverse sets of parthood-based granular perspectives, together with the granular perspectives mediating between these and other frames of reference, reflect many aspects that Wimsatt (1976, 1986, 1994, 2007) discussed in his prototypical account of levels of organization.

Although this domain granularity framework for the life sciences comprises all these different accounts of the levels idea, it nevertheless is characterized and defined in a formally coherent framework that integrates all these diverse granular perspectives. There might be conceptually and computationally simpler and more elegant solutions to the theoretical, conceptual, and computational challenge of modeling the granularity of cumulative-constitutively organized biological material entities, but these solutions are less realistic. If we want to do justice to the complex nature of reality, our models must be complex as well.

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