Running Title: Building Blocks and Domain Granularity Framework

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

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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 and 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 metaphor**[1] is simple and elegant and can be flexibly used in many different contexts (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 and 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

[1] By using the term 'metaphor' I am not intending to say that all notions of levels in science are *mere* metaphors, but rather that a vague and general idea about levels seems to be widely spread and intuitively accepted.

explanation, complexity, reduction, and emergence (e.g., Alexander, 1920/2013; Morgan, 1927; Simon, 1962; Schaffer, 2003; Craver & Bechtel, 2007; Eronen, 2013). Various particular applications of the levels metaphor have been proposed in science and philosophy (e.g., *levels of sciences, theories, and explanation*, Oppenheim and Putnam, 1958; *levels of complexity*, Simon, 1962; *levels of processing*, Craik and Lockhart, 1972; *levels of sizes/composition*, Wimsatt, 1976; *levels of implementation*, Marr, 1982; *levels of organization*, Churchland and Sejnowski, 1992; *levels of analysis*, Churchland and 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 metaphor 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) [2].

Various attempts have been made for establishing criteria for the levels metaphor, 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 notion of levels, Craver therefore (2015, p.2) suggests **descriptive pluralism** about the levels metaphor, claiming that *"the world contains many distinct, legitimate applications of the levels metaphor that are either unrelated or that have only indirect relations with one another."* Anyhow, the different notions of the levels metaphor 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 metaphor presupposes that entities exist for which it makes sense to understand them as being at the same level.

[2] 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.

In the following, on the basis of four specific examples I briefly discuss the diversity of different notions of the levels metaphor relevant in the life sciences. Before I turn to ontology research and Keet's (2008a) formal theory of granularity, I introduce a specific notion of general building blocks, which gives rise to a hierarchy of levels of building blocks that is intended to function as an organizational backbone for integrating various granular perspectives that are relevant in the life sciences. Each such granular perspective employs its own specific application of the levels metaphor, which is integrated with the other perspectives within a general domain granularity framework for the life sciences, therewith following Craver's claim of descriptive pluralism regarding the levels metaphor. The resulting granularity framework is meant to provide the initial basis on which a desperately required overarching and more comprehensive information framework (Larson and Martone, 2009) for the life sciences can be developed.

The domain granularity framework for the life sciences has a strong focus on morphology, because morphology is *"[...] one of the* covering *disciplines that spans every single entity in any biological organism"* (Gupta *et al.* 2007, p. 65), providing essential diagnostic structural knowledge and data for almost all disciplines within the life sciences (Masci et al., 2009; Vogt et al., 2010). Morphological terminology provides the **basic reference system and the 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). Here, 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.

Compositional Notion of the Levels Metaphor in Biology and Ontology Research

Several authors have interpreted the levels metaphor taking a **mereological perspective** in which part-whole relations are fundamental for distinguishing levels, resulting in a **compositional notion of levels**. According to this notion, 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 rather sparse (e.g., Nagel, 1961; Kauffman, 1971; Wimsatt, 1972, 1994), but the topic gained considerable attention in biology (e.g., Raff, 1996; Wagner and Altenberg, 1996; Wagner, 1996, 2001; Bolker, 2000; McShea, 2000; McShea and Venit, 2001; Rieppel, 2005; Winther, 2001, 2006, 2011), and even more so in ontology research (e.g., Smith, 1996; Bard and 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 and Artale, 2007; Varzi, 2007; Jansen and Schulz, 2014). Winther (2006) argues that there is an entire style of biological theorizing that he calls *compositional biology*[3] that is based on the notion of parts and wholes and their functions and capacities.

When comparing an exemplary compilation of 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 insofar problematic as 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, as for instance *'atom'*, *'molecule'*, and *'cell'*, alongside with primarily functionally individuated entities, as for instance *'organ'* and *'individual organism'*. A hierarchical system 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: A mono-cellular organism, as for instance a protozoan like *Paramecium* or *Euglena*, belongs to the *'cell'* level as well as to the *'individual organism'* level, but does

[3] *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.

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.?

Whereas the compositional approach to the levels metaphor 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 notion 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 parthood-based notion of the levels metaphor, has been suggested by Wimsatt (1976, 2007). Wimsatt contrasts his notion of levels of organization 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 idea 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, and higher-level entities are 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 mostly 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 approach 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 to, 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 and Eronon, 2011).

Wimsatt embraces descriptive pluralism regarding the levels metaphor, 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, and in an evolutionary time scale, through natural selection, the direction of influence can even be reversed from phenotype to genotype (e.g., Wagner, 2014). We 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 and Hamilton, 2007; Craver, 2015). However, Wimsatt's list of characteristics nevertheless gives a good account on how complex the levels metaphor actually is.

MECHANISM-BASED NOTION OF THE LEVELS METAPHOR

An alternative approach to the levels metaphor, that does not aim at developing a globally and universally applicable scheme of compositional levels, understands levels as locally applicable schemes, and claims that the compositional levels approach must go beyond a levels approach that is 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 approach to the levels metaphor, 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 and Hamilton, 2007). In other words, at the higher level is a mechanism that performs a specific function, and at the lower level are its working parts that contribute to the operation of the 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 notion of the levels metaphor depends on the compositional notion. In fact, one could characterize it as an account of **mechanistic composition** (Eronen, 2013): 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 notion of the levels metaphor, in which the properties of the parts of simple aggregates of entities are summed, in the mechanisms-based approach, 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 mechanisms-based approach is influenced by Wimsatt's prototypical idea of levels of organization, but focuses on component-mechanism relations.

The mechanism-based notion of the levels metaphor 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[4]. This, and other inconsistencies (see, e.g., Eronen, 2013), make the mechanism-based notion of the levels metaphor not suitable as a basis for developing a general information framework for the life sciences.

An Evolutionary Systems-Theoretical Perspective on the Levels Metaphor

Simon's Parable of the Watchmaker

Are hierarchies artifactual and thus mind-dependent constructs? If we use the levels metaphor merely because it takes a central role in our representations of reality,

[4] 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)

why should we bother to ask nature which hierarchy is most realistic? Whereas these questions are legitimate, evidence exists that suggests that evolution*[5] 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. 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.

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[6]. 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*

[5] From here on throughout the remainder of this paper, evolution* refers to evolution in a broad sense, including the evolution of the universe (e.g., Hawking, 1988).
[6] *"survival of the fittest—i.e., of the stable"* (Simon, 1962, p. 471).

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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 and Kirschner, 1997), and how they strongly affect development of morphological structures, their evolutionary stability, and their evolvability (e.g., Müller and Wagner, 1996; Wagner and Altenberg, 1996; Schlosser and 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).

Anyhow, 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 approach to the levels metaphor has been suggested. According to this interpretation, 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 and Van Straalen, 1998; Jagers op Akkerhuis, 2001).

Operator-Based Notion of the Levels Metaphor: an Evolutionary Systems-Theoretical Perspective

Based on a focus on **hypercyclic dynamics** and **containment**, 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'**, is a building block system that has a hypercycle set of elements that is contained by a layer they call **'interface'**, which mediates the interactions between the elements of the hypercycle[7] and the environment of the building block system. Jagers op Akkerhuis and Van Straalen (1998) argued that one can derive an unambiguous hierarchy of building block systems from studying mechanisms of hypercycle formation and subsequent compartmentation through an interface.

With this operator approach, consideration about the evolution* of building block systems is no longer limited to biological material entities and biological evolution. Atoms, for instance, can link to form molecules via atomic linkage. Based on atomic linkage, however, all that can evolve are different kinds of molecules. In order to escape that limitation and transform into a building block system of a higher level, another interaction in addition to atomic linkage must emerge, for instance by catalytic interactions, in which enzymes transform substrate molecules. If the product of such a catalytic process is the catalyst of a next catalytic process, a hypercycle evolves. This catalytic hypercycle performs a newly emerged property, an autocatalysis. If now a boundary (i.e., interface) evolves that contains this catalytic hypercycle, a new operator emerges. Cell membranes represent 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 and Van Straalen, 1998).

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

[7] A hypercycle is a cyclic process that creates a secondary reaction cycle (Eigen and Schuster, 1979; Kauffman, 1993).

different operators (Jagers op Akkerhuis and 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, like for instance the sequence *'sand'* < *'stone'* < *'planet'* allows bypassing the *'stone'* level by constructing a planet from sand alone (Jagers op Akkerhuis and Van Straalen, 1998, p.331)[8]. 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

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

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 and Van Straalen, 1998).

This evolutionary systems-theoretical account of the levels metaphor picks up some aspects from the mechanism-based approach discussed further 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.

HIERARCHY OF BUILDING BLOCKS

Evolving Building Blocks

Whereas the evolutionary systems-theoretical perspective that Jagers op Akkerhuis and Van Straalen (1998) and others have followed seems to provide a promising framework for developing a globally and universally applicable hierarchy of levels of material composition, their focus on hyperlinc dynamics and thus their notion of an 'operator' unnecessarily restricts its applicability. Therefore, I want to suggest a notion of a **general building block** that follows this evolutionary systems-theoretical perspective, but only to a certain degree, leaving out the notion of an 'operator'. 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[9]. Contrary to a mathematical notion of boundary (cf. Smith, 1994, 1995, 2001; Smith and Varzi, 1997; Smith et al., 2015), however, the physical covering 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**[10] (Wimsatt, 1994; see also Levins, 1966). The physical covering is not only a boundary region, but also a functional unit that provides the surface and 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**[11] 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 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*'). Building blocks of a higher level are composed of building blocks of lower level(s). As a consequence, a building block of a higher level is necessarily **existentially dependent** on some building block of a lower level, resulting in a **hierarchy of irreducible levels**. Building blocks of higher levels can only evolve after lower 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

[9] 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.
[10] *"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).
[11] Bona fideness is used here in the general sense of being a natural functional unit that exists independent of any human partitioning activities.

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* 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*.

The physical covering of a building block can be related to Smith et al.'s (2015) notion of causal unity via physical covering. According to Smith et al., a material entity is unified through causal unity via physical covering if *"the parts in the interior of the unified entity are combined together causally through a common membrane or other physical covering. The latter points outwards toward and may serve a protective function in relation to what lies on the exterior of the entity"* (Smith et al., 2015, p.32). However, the here discussed building block's notion of physical covering is more general, because it also treats electron shells as a physical covering.

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 by 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 higher level. This also applies to lumps of metal, in which several atomic nuclei share a common electron shell[12]. As a consequence, causal unity via physical covering in the

[12] 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).

here proposed notion of general building blocks would include atoms, lumps of metal and molecules[13] 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 **aggregates of molecule building blocks**.

Biological Building Blocks

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 successful in combining and recombining lower level building blocks to built building blocks of the next higher level. Because biological building blocks continue to evolve, a variety of different forms exist, all of which, however, share some common characteristics so that they can be referred to as instances of the same prototypical building block categories. As a consequence, 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.

Bio-Membrane-Enclosed Building Blocks

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

[13] 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 that are based on intramolecular (strong) force in molecules.

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[14]. 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 membrane-enclosed material entities within eukaryotic cells, the Golgi apparatus itself is not an organelle, but an aggregate of organelles, because its cisternae are physically disconnected. Cells and organelles are therefore biological building blocks. 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.

[14] 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.

Several eukaryotic cells can fuse to form a syncytium[15], 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 **aggregates of molecule and cell building blocks**.

Epithelially-Delimited Building Blocks

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 sheet of cells. Every epithelium has an apical surface and a lower basal surface that is attached to a basal lamina, which 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[16]. The epithelium thus functions as a

[15] E.g., skeletal muscles and cardiac muscle in humans and the syncytiotrophoblast in vertebrates, which is the epithelial covering of a placenta.
[16] Therefore, following Smith et al.'s (2015) definition of bona fide objects, each epithelium as such is a cell aggregate that is a bona fide object that is causally unified via internal physical forces, i.e. the tight junctions or septate junctions respectively.

diffusion barrier, like for instance the hemato-encephalic barrier in humans. Epithelia can have various 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 molecule, cell and epithelially-delimited compartment building blocks**.

A Hierarchy of Levels of Building Blocks

Based on the abovementioned characterization of general building blocks one thus can identify the following prototypical building blocks: *'atom'* < *'molecule'*[17] < *'single-membrane-enclosed entity'* (= organelle and prokaryotic cell) < *'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

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

levels that reach across all material domains of reality and that are globally and universally applicable. Because it 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.

Ontologies and Granularity

In times of **high-throughput technologies**, **eScience**, and **Big Data**, data comparability, data standards, data integration, and the computer-parsability of data are becoming increasingly important. They bring about an increasing necessity for researchers to communicate data via the World Wide Web and to use databases and online repositories (Gray, 2009). In biology, for instance, the development and increased application of high-throughput sequencing techniques, such as 454 pyrosequencing or Illumina sequencing, resulted in a continuous decrease of the cost of sequencing (e.g., Giribet, 2015a,b), with the consequence that ever increasing amounts of sequence data are being generated. But also the development and increased use of non-invasive or non-destructive imaging techniques, such as magnetic resonance imaging (MRI) or micro-computed tomography (μCT), allow for high-throughput morphological analyses of multiple specimens, thereby producing increasingly large amounts of image data (e.g., Fernández et al., 2014; Ziegler et al, 2014). Already today, the amounts of data biologists are producing often far exceed their ability to manage them without the aid of modern knowledge management systems. As a consequence, data management, online repositories, and data exploration have become increasingly important in the life sciences, and with it standardization, the necessity of computer-parsability of data and the use of ontologies (e.g., Stevens et al., 2000; Bard, 2003; Bard and Rhee, 2004; Vogt, 2009, 2013; Vogt et al. 2013).

Techniques of the Semantic Web, especially ontologies, play an essential role in reliably communicating and managing data within and between databases and online repositories. 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 hierarchy of levels of building blocks.

BFO and Granularity

The number of biomedical ontologies is continuously increasing (e.g., BioPortal; http://bioportal.bioontology.org/). Unfortunately, they often differ considerably and their taxonomies as well as some of their term definitions are often inconsistent with one another (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 integration. **Formal top-level ontologies**[18], as for instance the Basic Formal Ontology (BFO), 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[19] (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 the top-level categories of *'material entity'* (see 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[20]. 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. 1). 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 1 with additional levels.

[18] 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).
[19] 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).
[20] See next chapter for a discussion of granular partitions and granularity tree. 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 parts, whereas the latter represent granular partitions of entities into their fiat parts.

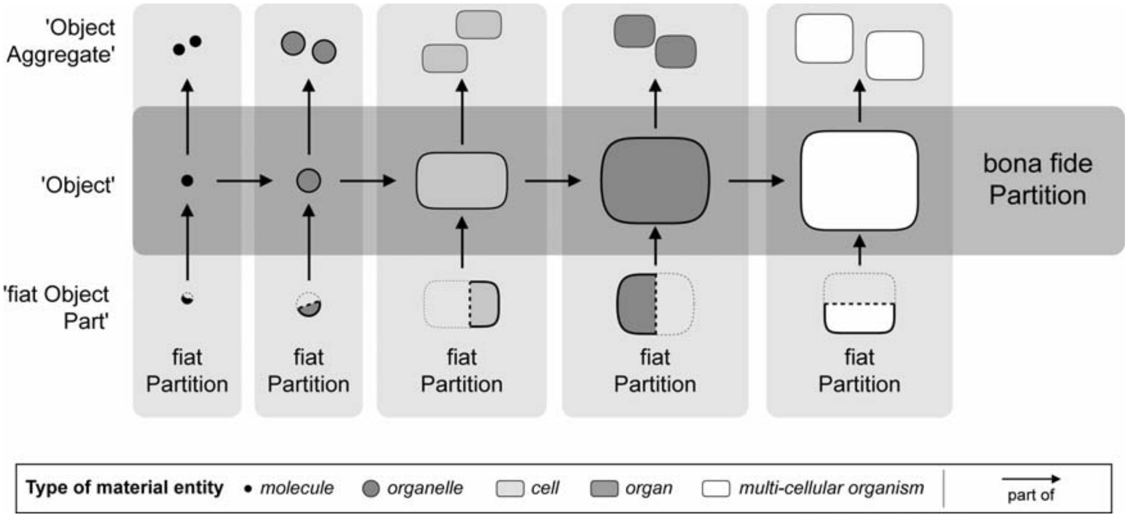

Figure 1. BFO's Basic Granularity Framework. A bona fide partition from *'molecule'* to *'multi-cellular organism'* represents the center of this granularity framework and reflects top-level categories of BFO's *'object'* for the biological domain. According to BFO, each level of the corresponding bona fide granularity tree must be modeled by its own domain reference ontology (i.e., a molecule ontology, a cell ontology, etc.). Within each 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.

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 develop (i) several granularity-specific ontologies, ranging from an ontology for molecules, to an ontology for organelles, for cells, for tissues, for organs to for body parts, and (ii) an additional layer of axioms and relationships to define the granularity relations between entities across these different ontologies.

Formal Theories of Granularity

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 regarding the comparability of biomedical ontologies and consequently substantially limits the comparability of data across databases and online repositories. 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.

Partial Order, Granular Partition, and Granularity Tree

In order to develop a formalized granularity framework it is important to formally characterize the relation between entities that belong to different levels of granularity. 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*: (R*bc*)(R*cd*) → R*bd*), **reflexive** (*b* has relation R to itself: R*bb*), and **antisymmetric** (if *b* has relation R to *c* and *c* has relation R to *b*, than *b* and *c* are identical: (R*bc*)(R*cb*) → *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 and Smith 2001a,b, 2003a; Reitsma and 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[21] that contain subcells. It requires a specific theory of the relation between its cells and subcells that must meet the following conditions (Bittner and Smith 2001a,b, 2003a; Reitsma and 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.

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 and 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 into its

[21] 'Cell' is here used in its general non-biological meaning.

bona fide object parts, from a **fiat granular partition**, which partitions any material entity into its fiat entity parts.

A granular partition can be represented as a **granularity tree** (Reitsma and Bittner, 2003; Kumar et al., 2004; Smith et al., 2004), because every finite partition can be represented as a rooted tree of finite length (Mark, 1978; Bittner and Smith 2001b, 2003a,b), i.e. a rooted directed graph without cycles (Wilson and Watkins, 1990). In a granularity tree a granularity level is a **cut** (*sensu* Rigaux and Scholl, 1995; see Fig.3B) in the tree structure (Bittner and 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 and Bittner, 2003). If the partitioning relation is a mereological relation, as for instance 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 and Bittner, 2003).

The partitioning relation constrains the type of entities that it partitions. The part-whole relation, for instance, exists only between instances (=individual entities, particulars) and not between classes or types[22] (e.g., Smith et al., 2005; Schulz et al, 2006; Craver, 2015; Varzie, 2016; for a translation to a class expression of parthood see Smith and Rosse, 2004; Schulz et al., 2006). As a consequence, parthood-based granular partitions can be represented as **instance granularity trees**. Subsumption relations like the class-subclass relation, on the other hand, are also 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**[23]. The taxonomy of terms of an ontology represents a type granularity tree.

[22] The inverse relation of *'b hasPart c'*, which is *'c partOf b'*, holds only if *b* and *c* are instances and not types (see, e.g., Smith *et al.*, 2005; Schulz *et al.*, 2006).
[23] This also somewhat explains why biomedical ontologies usually only contain a taxonomy as fundamental hierarchy and no partonomy, because biomedical ontologies are about classes/types rather than individuals/particulars.

Keet's Formal Theory of Granularity

Keet (2008a, 2006a,b) has developed a general theory of granularity that circumvents some of the problems of theories of granularity published by then (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**. Lower levels within a perspective contain knowledge or data that is more detailed than the next higher level, and higher levels of granularity simplify or make indistinguishable finer-grained details. This way, several different perspectives of granularity, each with its specific levels of granularity, 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 and Mejino, 2003; Burger et al., 2004; Smith et al., 2004; Jagers Op Akkerhuis, 2008; Winther, 2006), but Keet (2008a) provides the first formal general 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 levels metaphor (Craver, 2015), but nevertheless integrate the resulting set of diverse hierarchies within an integrated strictly formalized framework, her general formal theory of granularity.

A granularity 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. 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 granularity perspective. 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.

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. 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). In other words, Keet's (2008a) formal theory of granularity 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.

According to Keet's (2008a, 2010) granularity framework, the following criteria must be met:

- A criterion of granulation specifies the kind of properties according to which the domain is partitioned, levels identified, and the subject domain (i.e., data, information, or knowledge) granulated.
- This criterion of granulation specifies an aspect that all entities (individuals or types) in a granular level must have in common.
- The contents of a level can be either entity individuals (instances) or types (universals, classes), but not both.
- A particular granularity level must be contained in one and only one granular perspective (Keet, 2008b).
- 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.

- A granularity 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.
- The combination of some criterion of granularity with a type of granularity determines the uniqueness of each granular perspective (i.e. all granularity perspectives contained in a domain are disjoint).
- If a granularity perspective has more than two levels of granularity, the type of relation between adjacent levels in a perspective must be *transitive*. If that relation is intransitive, then the respective perspective has only 2 levels.
- The entities (individuals or types) granulated by a type of granularity are disjoint.
- If there is more than one granularity perspective for a subject domain, then these perspectives must have some relation among each other.

Keet's formal theory of granularity 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[24]. This hierarchy comprises an *'atom'*, *'molecule'*, and *'cell'* level together with an *'organelle'*, *'organ'*, and *'individual organism'* level of granularity. An obvious problem of this granularity perspective 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 higher 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[25]: 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

[24] This criticism applies to many of the published levels schemes, even including Kumar et al.'s (2004) scheme.
[25] "[...] *one should not mix different ways of granulating data within one perspective lest the hierarchy of levels will be inconsistent*" (Keet, 2008a, p.61).

entity can only reside in more than one level if each of these levels belongs to a separate perspective.

Anyhow, 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 a domain by separating types of entities into various different types of hierarchies (=perspectives) that 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 granularity 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).

This meta-layer would not only provide a much needed conceptual framework for representing domains that cover multiple granularity levels, as for instance anatomy/morphology, but also a structure that can be utilized for providing users a more intuitive experience when navigating knowledge bases. 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 layer 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 for this perspective, thereby substantially facilitating browsing and navigating through increasingly complex datasets.

If the hierarchical order of the various granular perspectives contained in this meta-layer 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 (morphological) data (Vogt, *submitted* a,b,c).

BIOLOGICAL REALITY: THE PROBLEM WITH CUMULATIVE CONSTITUTIVE GRANULARITY

Hierarchies are based on **strict partial ordering** relations, which represent **irreflexive** (*b* cannot have relation R to itself: ¬R*bb*) partial ordering relations[26]. Hierarchies thus represent a specific case of granular partitions and granularity trees. The 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 and May 1996; Valentine, 2003; Jagers op Akkerhuis 2008), (i) constitutive hierarchy, (ii) cumulative constitutive hierarchy, (iii) aggregative hierarchy, and (iv) cumulative aggregative hierarchy (Fig. 2), of which only the former two hierarchies are of interest in the here discussed context. Interestingly, constitutive hierarchies are commonly used by ontology researchers to model granularity, whereas biologists use cumulative constitutive hierarchies.

Constitutive Granularity

In a *constitutive granularity* (i.e. *constitutive hierarchy*, Mayr, 1982), material entities of a given level of granularity constitute the entities of the next coarser level, as for instance an aggregate of atoms constituting a molecule and an aggregate of molecules constituting a cell (Valentine and 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

[26] 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.

entities[27] of different levels of granularity are mereologically nested within one another, thus representing a mereological granularity tree (Reitsma and Bittner, 2003). For any 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. 2A).

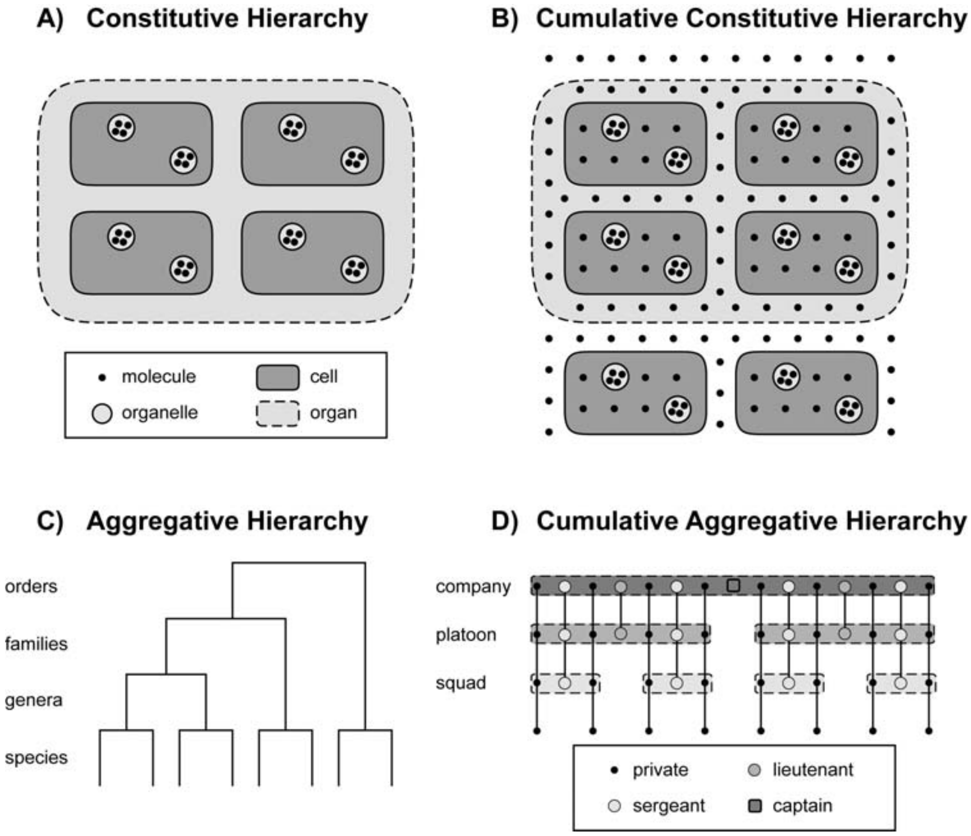

Figure 2. Four different types of Hierarchies. A) A constitutive hierarchy of molecules, organelles, cells, and organs of a multi-cellular organism. It can be represented as an encaptic hierarchy of types, with all molecules being part of some organelle, all organelles part of some cell and all cells part of some organ. Constitutive hierarchies represent mereological granularity trees. **B)** The same set of entities as in A), but not organized in an encaptic hierarchy. The cumulative constitutive hierarchy represents the more realistic model of biological reality, in which 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 and 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

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

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 all entities belonging to one level of granularity are parts of entities 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[28] and blood plasma (both not consisting of cells) demonstrate that not every molecule is part of a cell; 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

[28] 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.

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 according to a *cumulative constitutive hierarchy* (Fig. 2B; 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 over-simplified constitutive granularity. When partitioning an individual multi-cellular organism (=unpartitioned whole, Fig. 3) 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. 3B, 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. 3C, left). Regarding the levels metaphor 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.

Unfortunately, when applying the more realistic cumulative constitutive granularity, 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. 3B, right). For instance the parts that belong to the first cut in the example shown in Figure 3B, 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. 3B, 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 conform with anatomical reality (Vogt, 2010).

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*') belonging 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; Fig. 3C, right). 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. 3C, right). Whereas this is straight forward and 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).

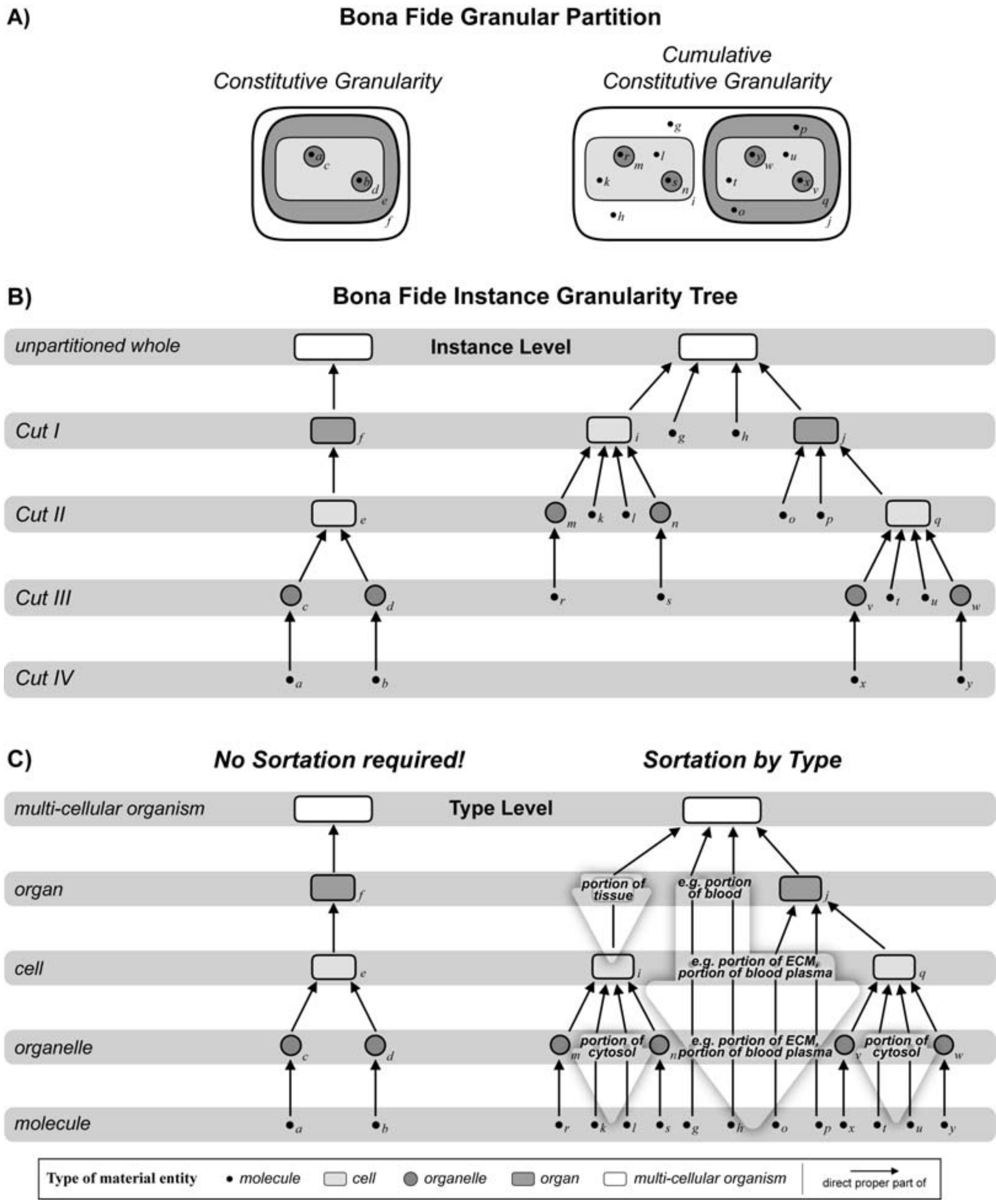

Figure 3. Instance Granularity Tree and Type Granularity Tree for Constitutive and Cumulative Constitutive Granularity . A) Left: Compositional partitions of a constitutively organized idealized multi-cellular organism into its constitutive object parts. Four partitions are shown: (i) into organs (f); (ii) into cells of organs (e); (iii) into organelles of cells of organs (c,d); and (iv) into molecules of organelles of cells of organs (a,b). **Right**: Compositional partitions of a cumulative-constitutively organized idealized multi-cellular organism into its constitutive object parts. The same corresponding four partitions are shown: (i) into organs (j) alongside with cells (i) and extracellular molecules (g,h), both of which are not part of any organ; (ii) into cells of organs (q) and extracellular molecules that are part of some organ (o,p), organelles that are part of cells which are not part of any organ (m,n), and molecules of cells that are neither part of any organ nor any organelle (k,l); (iii) into organelles of organ cells (v,w) and molecules that are part of these organ cells but not part of any organelle (t,u), as well as molecules of organelles of cells which are not part of any organ (r,s); and (iv) into molecules of organelles that are part of cells of organs (x,y). **B) Left**: The four compositional partitions of the constitutively organized multi-cellular organism from above

(A, left side), 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. 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. In other words, the types' extensions do not transcend the boundaries between instance granularity levels. **Right**: The four compositional partitions of the cumulative-constitutively organized multi-cellular organism from above (A, right side), represented as a bona fide instance granularity tree. Instances of the same type of material entity, like for instance of the type '*molecule*', belong to different cuts and thus different levels of the respective instance granularity tree. In other words, the extension of the type '*molecule*' transcends the boundaries between instance granularity levels. **C) Left**: In case of partitioning a constitutively organized multi-cellular organism, 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**: In case of partitioning a cumulative-constitutively organized multi-cellular organism, 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 of sortation-by-type (i.e., a type occupies the same granularity level as its finest grained instance; Vogt, 2010), one can infer the corresponding type granularity tree. Unfortunately, this results in types of entities belonging to type granularity levels for which BFO provides no respective categories as templates for granularity specific ontologies (e.g., *portion of ECM*). For instance when looking at the cellular level, a cellular ontology that is based on BFO provides no category for molecules that are not part of any cell, because such a molecule is neither a cell (= BFO's '*object*'), nor a cell aggregate (= BFO's '*object aggregate*') nor a fiat cell part (= BFO's '*fiat object part*'). By applying the notion of *granular representation* and the additional category of '*portion of matter entity*' (see chapter '*Cross-Granular Instantiation, Granular Representation, and Resolution-Based Representation*'), the transformation of the instance granularity tree into a type granularity tree can be completed. With the additional category and the notion of granular representation one can account for the effects of cross-granular multiple instantiation in cumulative-constitutively organized material entities. (*Figure from Vogt et al., 2012a*)

However, irrespective of these conceptually unpleasant characteristics, the cumulative constitutive granularity scheme is by far more realistic than the cumulative granularity scheme, and therefore all attempts of developing formally stringent granularity frameworks for the life sciences must cope and comply with it (Vogt 2010, Vogt *et al.*, 2012a). The obviously incorrect assumption of an underlying constitutive granularity that many ontologies either implicitly or explicitly make, could be one of the reasons why the granularity schemes of biology and anatomy ontologies show such high degree of variety and why the community cannot agree upon a common biological granularity scheme. It could also explain why most formal theories of granularity proposed so far, which explicitly state formal granularity relations and explicitly rank levels of granularity, as for instance Kumar *et al.*'s (2004) theory of granularity, cause inconsistencies when applied to real entities[29].

[29] Fortunately, Keet's (2008a) formal theory of granularity is agnostic regarding cumulative or cumulative constitutive granularity.

A DOMAIN GRANULARITY FRAMEWORK FOR THE LIFE SCIENCES

Extending and Re-Organizing BFO's Category 'Material Entity'

Top-Level Categories of 'Material Entity'

Smith et al. (2015) characterize BFO's '*object*' category and thus natural units that exist independent of human partitioning activities as **causally relatively isolated** (Ingarden, 1983; Smith and 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:

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)

Causal unity via physical covering[30] unifies an entity through a common physical covering, as for instance a membrane. This covering may have holes, but must be completely connected[31] 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.

Causal unity via engineered assembly of components unifies an entity through screws, glues and other fasteners. Often, the parts are reciprocally engineered to fit

[30] The physical covering of a general building block is based on a similar but more general type of causal unity via physical covering, because it includes electron shells as physical covering. Moreover, it also includes functional aspects of the physical covering.
[31] 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.

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. Functional units and historical/evolutionary units are not covered by them, although they are bona fide entities 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* d). 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* d).

Moreover, because a given material entity can depend on several different types 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 general frame of reference (see Vogt, *submitted* d). Both causal unity via internal physical forces and causal unity via physical covering, at least as conceived by Smith et al. (2015), are associated with a **spatio-structural frame of reference**. This frame of reference is mainly interested 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**. The functional frame of reference is mainly interested in 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. This frame of reference is mainly interested in 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).

Due to the frame-dependence of the relevance of different types of causal unity and the special role of causal unity via physical covering regarding building blocks, I suggest a different set of top-level categories for BFO's *'material entity'* (see Fig. 4). The classes *'functional entity'*, *'historical/evolutionary entity'*, and *'spatio-structural entity'* distinguish 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 internal physical forces[32], respectively. Because of the frame-dependence of the relevance of these different types of causal unity, these three classes are **not disjoint**[33].

Based on the hierarchy of levels of building blocks and the implications of a cumulative constitutive organization of biological material entities discussed further above, I can now suggest top-level categories for *'spatio-structural entity'*. First, I consider each building block level to provide its own **spatio-structural frame of reference**. As a consequence, I interpret BFO's categories *'object'*, *'object aggregate'*, *'fiat object part'* as referring to each building block level separately. As a consequence, *'spatio-structural entity'* should have the top-level sub-categories *'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. 5). Due to the frame-dependence of building block levels, these top-level 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 cell part.

Because each building block level has its own frame of reference and bona

[32] Because causal unity via physical covering supervenes on causal unity via internal physical forces, the former covers the latter.
[33] As a consequence, some given material entity may instantiate *'functional entity'*, *'historical/evolutionary entity'*, and *'spatio-structural entity'* at the same time.

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fideness is level-dependent (see discussion in Vogt et al., 2012b; Vogt, *submitted* d), I treat all bona fide and fiat entities from a given building block level in higher building block levels as **fiat entities**. As a consequence, the top-level category *'portion of matter entity'* is introduced in addition to the set of building block level specific '[building block] *level entity'* categories. It refers to the **representation** of lower-level building block entities at higher building block levels (see Fig. 6).

Top-Level Categories of 'Spatio-Structural Entity'

I consider the distinction between fiat and bona fide material entity[34] as foundational and therefore distinguish between bona fide objects and fiat entities for each building block level, resulting in the basic distinction of '[building block] *level object'* and *'fiat* [building block] *level entity'* (see Fig. 4). In case of the eukaryotic cell building block level, this would translate into the categories *'eukaryotic cell level object'* and *'fiat eukaryotic cell level entity'* respectively (see Fig. 5).

The '[building block] *level object'* category 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 building block objects: On the one hand '[building block]', which are objects that are based on more specific causal unity via physical covering. They comprise the actual building blocks discussed above. Thus, for instance for the building block level of molecules this would be the class *'molecule'*, and for eukaryotic cells (i.e. membrane-within-membrane level entity) it would be the class *'eukaryotic cell'* (see Fig. 5).

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, the category *'bona fide cluster of* [building block]*s'* is required to deal with these types of objects. Thus, for instance the building block level of eukaryotic cells not only has eukaryotic cells as objects (=bona fide entities), but also bona fide clusters 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 higher building block level). Or, in case of the molecular building block level, clusters of molecules can form a bio-membrane or

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

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).

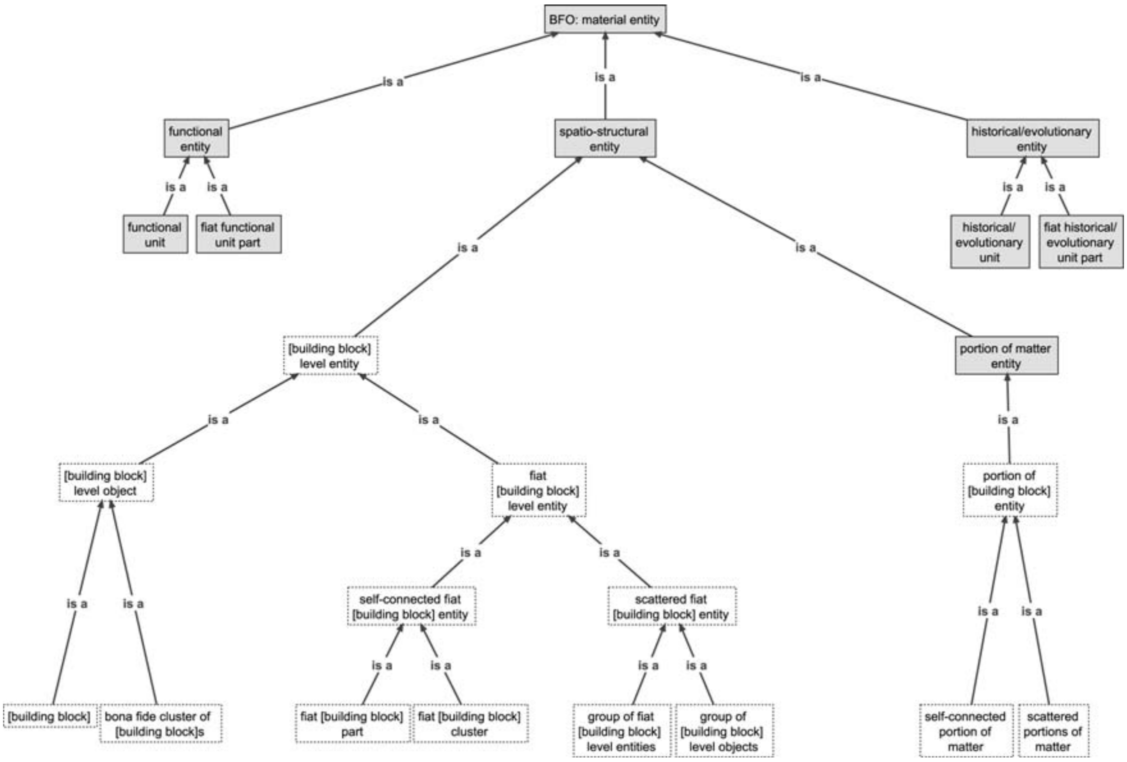

Figure 4. Top-Level Categories of '*material entity*' and the Scheme for Top-Level Categories of each Building Block Level Entity and the Scheme for Top-Level Categories of each Portion of Building Block Entity. The grey boxes represent categories. The category *'spatio-structural entity'* is based on 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 according to the building block level they belong to. The general scheme for the categories for each building block level are shown in white boxes with dotted borders, which can be translated into the actual categories by replacing the term [building block] with the level-specific building block term (see Fig. 5 for an example). Each building block level entity is differentiated into a bona fide '[building block] *level object'* and a *'fiat* [building block] *level entity'* category, which are disjoint. The former is differentiated based on its underlying type of causal unity into '[building block]', which is based on physical covering, and *'bona fide cluster of* [building block]*s*', which is only based on internal physical forces and not on physical covering. The fiat building block entities are differentiated based on their self-connectedness into the disjoint categories of *'self-connected fiat* [building block] *entity'* and *'scattered fiat* [building block] *entity'*. 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, entities from lower building block levels must be represented in higher levels as fiat portions of matter. These representations are covered through the *'portion of matter entity'* category. The white boxes with dotted borders that are connected to the *'portion of matter entity'* category represent the general scheme for the sub-categories of *'portion of matter entity'*, which are specific for each building block level (see Fig. 6). See text for detailed description.

The category *'fiat* [building block] *level entity'* covers BFO's *'fiat object part'* and *'object aggregate'* and comprises all material entities that possess spatio-structurally no causal unity (neither via internal physical forces nor via physical covering)[35]. 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: *'self-connected fiat* [building block] *entity'* and *'scattered fiat* [building block] *entity'*, which translates in case of the eukaryotic cell level into *'self-connected fiat eukaryotic cell entity'* and *'scattered fiat eukaryotic cell entity'*. Self-connected fiat entities can be further differentiated into *'fiat* [building block] *part'* and thus the building block level specific correlate to BFO's *'fiat object part'*, and *'fiat* [building block] *cluster'*. For the cellular 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 of the category '[building block] *level object'*, the scattered entity is a *'group of* [building block] *level objects'* entity. However, if at least one of its component parts is of the category *'fiat* [building block] *level entity'*, the scattered entity is a *'group of fiat* [building block] *level entities'*[36] entity (see Fig. 4; for the translation to the eukaryotic cell level see Fig. 5).

[35] 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.

[36] 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).

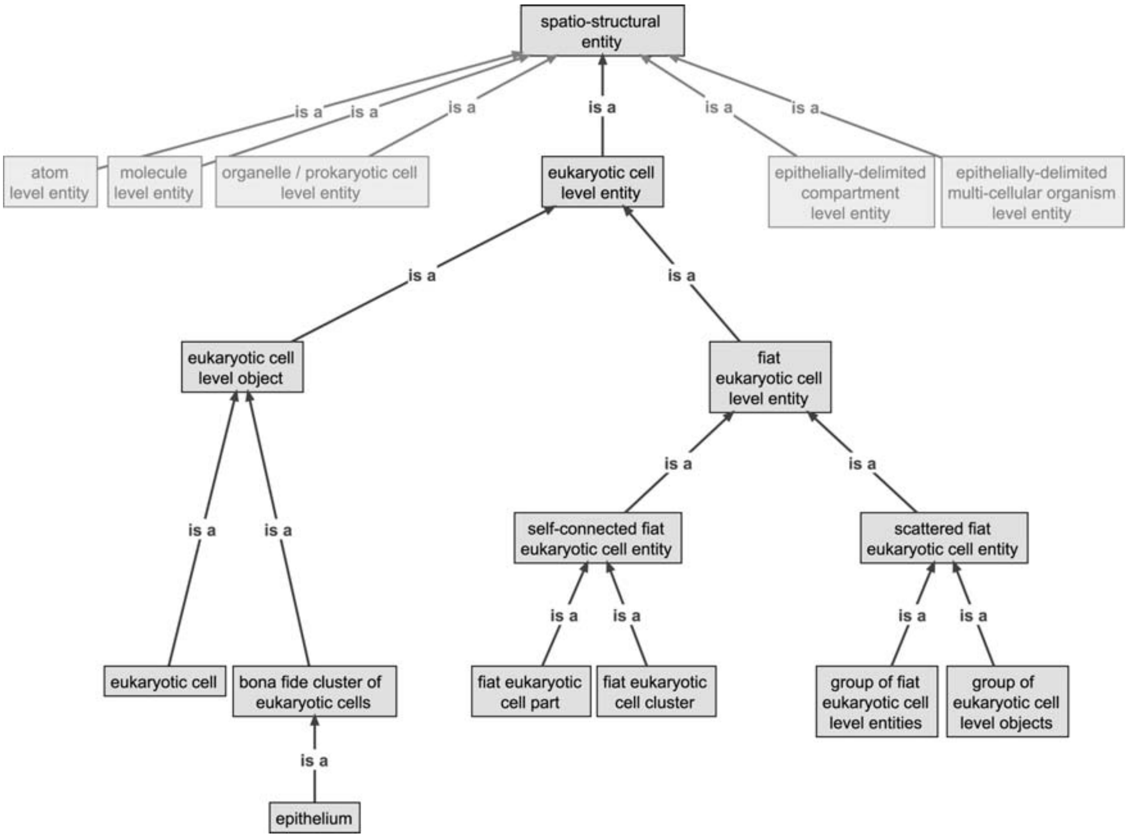

Figure 5. Top-Level Categories of '*eukaryotic cell level entity*'. For a description of the different categories see also figure 4. The transparent boxes indicate the five other building block levels, which have their own set of sub-categories. See text for detailed description.

Consequence from the Cumulative Constitutive Organization of Biological Material Entities'

The abovementioned categories of building block level entities must accommodate all types of material entities found in cumulative-constitutively organized biological material entities. Therefore, these categories always refer to the building block entity of the corresponding building block level, independent of whether lower-level entities are also involved. In other words, *'eukaryotic cell'* comprises all types of eukaryotic cell 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. If the lower-level portions of matter have to be specifically addressed, they can be separately accounted for using the adequate sub-category of *'portion of matter entity'* (see below). 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.[37]

Consequence from the Frame-Dependence of Building Block Level Entities

Because biological material entities are usually cumulative-constitutively organized (see discussion above), entities of lower building block levels can exist outside of building blocks of higher levels. Unfortunately, these lower level entities cannot be covered with the categories of the higher level building blocks, since they are neither a bona fide building block object nor a fiat building block entity of this level. However, they still must be represented in the higher level frame of reference (see *sortation-by-type* and *type granularity trees* problematic discussed in "Cumulative Constitutive Granularity", see Fig. 3). 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. 3). 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'*, which are building block level specific sub-categories of *'portion of matter entity'* (see Fig. 4, 6).

Lower-level entities represent **portions of matter** at higher levels. 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 and Donnelly, 2007; see also *body substance* Rosse et al., 1998; and *portion of body substance* Rosse and Mejino, 2007). In order to count such a lower-level entity in terms of the number of its lower-level building block component parts, one would have to change the spatio-structural frame of reference from the higher-level building block frame to the frame of the building block level of the corresponding 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 building block level, is represented as a self-connected (fiat) portion of molecular matter at all levels above the molecular building block level. The individual molecules that build the cluster

[37] 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.

cannot be differentiated anymore at granularity levels coarser than the molecular level, because their bona fideness disintegrates at these coarser levels[38] (Vogt et al., 2012a). If a portion of matter consists of a mixture of building block entities of different building block levels, as for instance a portion of connective tissue that is a group of cells embedded in a cluster of collagen molecules, the largest building block entity is used for classifying it, which in this case would be a portion of connective tissue[39].

Because lower-level entities are always represented as non-countable fiat portions of matter in higher levels, one can only distinguish between self-connected and scattered portions. A self-connected lower level entity is a *'self-connected portion of matter'* and a scattered lower level entity is a *'scattered portions of matter'* respectively (see Fig. 6).

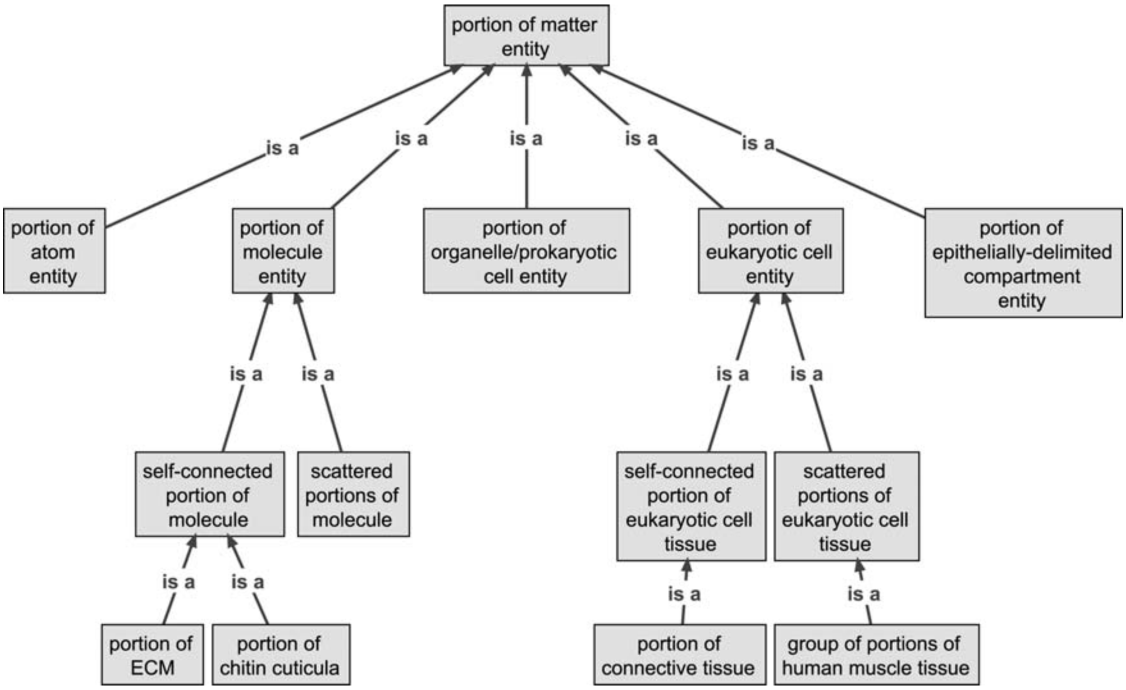

Figure 6. Top-Level Categories of 'portion of matter entity'. The entities of each building block level, except for the highest level of epithelially-delimited multi-cellular organisms, can be represented as a respective portion of matter entity. Therefore, *'portion of matter entity'* is differentiated into building block

[38] This is why all portions of matter are treated as fiat entities.
[39] Portions of tissue always refer to a 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.

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.

Functional and Historical/Evolutionary Entities

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 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).

Compositional Granularity Perspectives

Compositional Building Block (CBB) Granularity Perspective

Based on the organization of top-level categories of *'material entity'* introduced above, the granularity perspective of levels of building blocks can be characterized using Keet's general formal theory of granularity (Keet, 2008a). The **subject domain** in all granularity perspectives discussed in the following is restricted to cumulative-constitutively organized material entities.

The partition of a given biological material entity into its building block components represents a qualitative compositional partition[40]. This compositional building block (CBB) granularity perspective is based on a direct proper parthood

[40] As opposed to a qualitative regional partition or a quantitative resolution-based partition.

relation between instances of different categories of the type '[building block]', and thus has the **granulation criterion** (Fig. 7):

'[building block]'	directProperPartOf	'[building block]';
'[building block]'	hasDirectProperPart	'[building block]'.

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 granularity perspective, instances of at least two different categories of the type '[building block]' 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 granularity perspective are demarcated from one another according to the properties of the subcategories of '[building block]' and they are ordered from lowest to highest granularity level according to the direct proper parthood relation. The number of levels within the CBB granularity perspective directly depends on the number of types of '[building block] *level entity'* are distinguished[41].

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 higher CBB granularity level.
2. Every instance of a building block, except for those belonging to the lowest CBB granularity level, has at least two instances of building blocks of lower levels as its proper parts.
3. The instance of the building block that is granulated is the maximum entity that belongs to the highest 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 highest

[41] Here, I have distinguished six different types (atom, molecule, organelle/prokaryotic cell, eukaryotic cell, epithelially-delimited compartment, epithelially-delimited multi-cellular organism).

CBB granularity level.

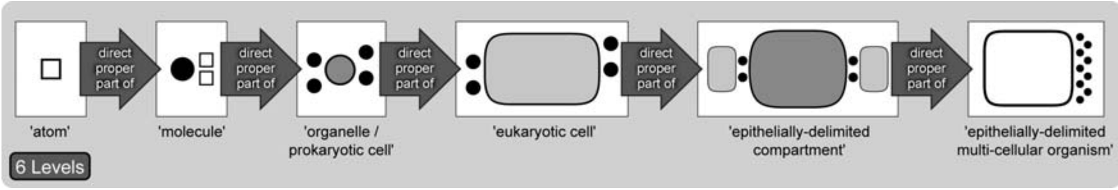

Figure 7. Compositional Building Block (CBB) Granularity Perspective. The different building blocks are granulated according to the direct proper parthood granulation relation (the dark arrows). The granulation is of the non-scale dependent single-relation-type granularity type (*nrG*, Keet, 2008a), and uses the combination of the granulation relation together with the common properties of all categories of the type '[building block]' as its granulation criterion. Due to the cumulative constitutive organization, lower-level building block entities can be considered to be parts associated with higher-level building block entities, as for instance ECM being an associated part of a eukaryotic cell.

The CBB granularity perspective is the formal representation of the building blocks level hierarchy discussed further above (chapter *"A Hierarchy of Levels of Building Blocks"*). Conceptually, the CBB granularity perspective takes in a special position within the domain granularity framework for the life sciences, because it is the only compositional granularity perspective that ranges across all levels of the building block levels hierarchy. All other parthood-based granularity perspectives that are discussed below are always restricted to a given level of the building block levels hierarchy and thus to a single CBB granularity level.

Compositional Building Block Cluster (CBB-C) Granularity Perspectives

Whereas the unity of building blocks in the CBB granularity perspective is based on the more restrictive causal unity via physical covering, the unity and thus the bona fideness of *'bona fide cluster of* [building block]s*'* is only based on the more general causal unity via internal physical forces. Because the latter represents an aggregate of building blocks that can be partitioned into its component building blocks, one can characterize the corresponding qualitative compositional partitions as the compositional building block cluster (CBB-C) granularity perspectives (see Fig. 8). Each CBB granularity level has its own corresponding CBB-C granularity perspective. This CBB-C granularity perspective is based on a direct proper parthood relation between instances of *'building block'* and of *'bona fide cluster of* [building block]s*'* that belong to the same '[building block] *block level entity'*, and thus has the building-block-level-specific **granulation criterion** (Fig. 7):

'[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 building block level.

Like the CBB granularity 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.

The two different types of compositional granularity perspectives introduced so far result in a set of seven different compositional granularity perspectives within the domain granularity framework for the life sciences. This set is sufficient to model all possible compositional partition relations between any given pair of particular building block objects.

Region-Based Granularity Perspectives

Besides the two types of compositional granularity perspectives, each CBB granularity level has its own set of seven different associated region-based granularity perspectives (for an overview, see Fig. 8). 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**.

These seven types of region-based granularity perspectives result in a set of 49 different region-based granularity 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 CBB granularity level.

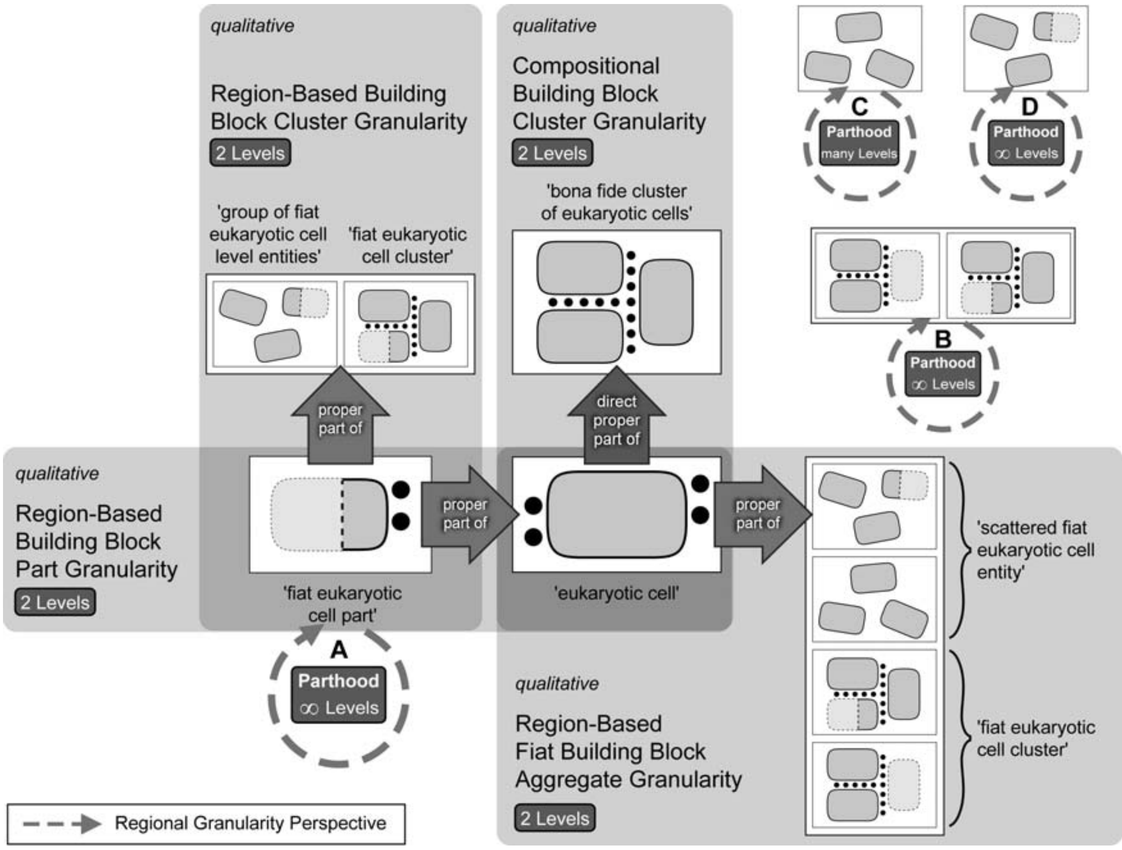

Figure 8. Set of Granularity Perspectives within a given CBB Granularity Level. The figure shows all qualitative granularity perspectives that the domain granularity framework for the life sciences distinguishes for any given CBB granularity level (here, the set of perspectives for the eukaryotic cell 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).

Function-Based and History/Evolution-Based Granularity Perspectives

In analogy to the distinction between the CBB and the region-based granularity perspectives for spatio-structural entities, one can also distinguish between a compositional functional unit (CFU) granularity perspective[42] and various region-based functional entity granularity perspectives, as well as between a compositional historical/evolutionary unit (CH/EU) granularity perspective and various region-based historical/evolutionary entity granularity perspectives respectively.

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

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[43] relation between instances of different sub-categories of *'functional unit'*, which thus represents the **granulation relation** of the CFU granularity 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[44] between instances of different sub-categories of *'historical/evolutionary unit'*, which thus represents the **granulation relation** of the CH/EU granularity 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 granularity 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 granularity perspective, like the CBB granularity perspective does for spatio-structural entities, is missing. Neither the CFU nor the CH/EU granularity 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[45]. 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 granularity perspectives.

Because we do not distinguish between different sub-types of functional and

[43] 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'*.
[44] 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'*.
[45] To stay within the metaphor: we do not know reality's inventory of functional and historical/evolutionary lego-bricks.

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 granularity perspective for functional and historical/evolutionary entities. However, one can differentiate various region-based functional and region-based historical/evolutionary granularity perspectives in analogy to the various region-based granularity perspectives for spatio-structural entities, which I do not discuss here for lack of space.

Cross-Granular Instantiation, Granular Representation, and Resolution-Based Representation (SBR) Granularity Perspectives

Cross-Granular Multiple Instantiation I

Due to its granular nature, any given biological material entity always instantiates several different material entity categories at the same time, one for each building block level (Vogt et al., 2012a). For example, every instance of *'eukaryotic cell'* instantiates at finer levels of granularity 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 levels it instantiates level-specific entity categories. However, which category is instantiated at those coarser levels 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'*. 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 building block levels; 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**[46] (Vogt et al., 2012a) of subcategories of *'material entity'*, all of which do not stand in a subsumption relation to one another[47]. They are a necessary consequence of the fact that every building block level has its own 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.

Granular Representation I

Each particular biological material entity thus necessarily instantiates multiple categories, resulting in various different unrelated individual resources. In order to indicate that these resources reference 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**.[48]

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 building block level (Vogt et al., 2012a).

Resolution-Based Representation (RBR) Granularity Perspectives

Based on the granular representation relation discussed above, and in addition to the various qualitative granularity perspectives discussed so far, one can differentiate

[46] One reason for introducing level-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).
[47] 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.
[48] *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 fine to coarse levels. *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 building block levels (see Fig. 3, C).

several quantitative scale-based granularity 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 building block levels.

All resolution-based representation (RBR) granularity perspectives are based on the combination of the building block levels hierarchy and a strict partial ordering granular representation relation between instances of different subcategories of *'spatio-structural entity'* that belong to different CBB granularity levels. The possibilities for distinguishing different types of RBR granularity 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 granularity perspective that has the **granulation criterion** (Fig. 9):

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

X=a specific building block level; X+1=the adjacent higher building block level 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 granularity perspective directly depends on the building block levels hierarchy, the number of its granularity levels corresponds with the number of CBB granularity levels.

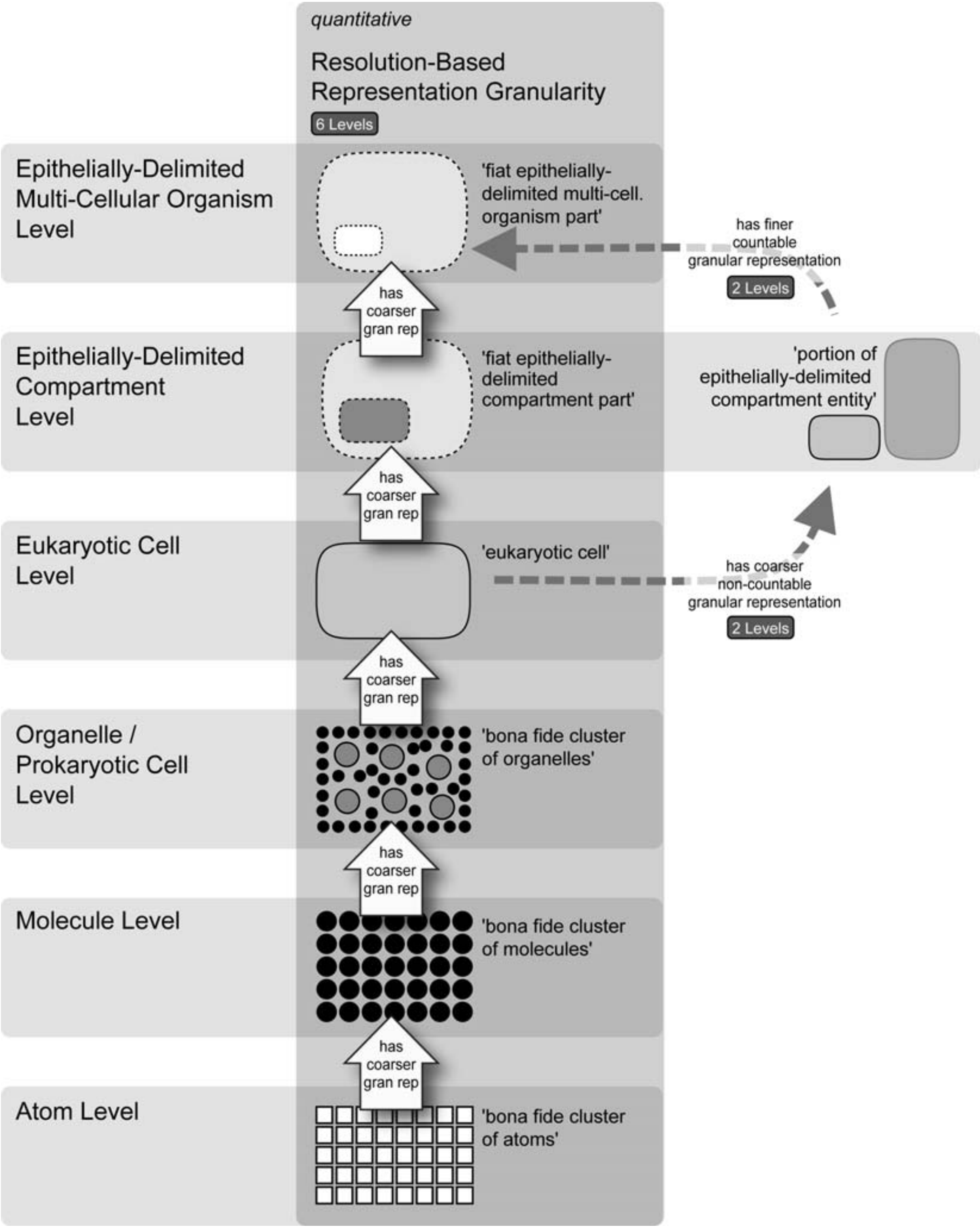

Figure 9. Resolution-Based Representation (RBR) and Resolution-Based Countability Representation (RBCR) Granularity Perspective. The different levels of the RBR granularity perspective are granulated according to the *has coarser granular representation* relation (the white broad arrows). The granulation is of the scale dependent grain-size-according-to-resolution granularity type (*sgrG*, Keet, 2008a). The different levels of the two RBCR granularity perspectives, on the other hand, are granulated according to (i) the *has coarser non-countable granular representation* relation and (ii) *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 by the building block levels hierarchy. As a consequence, the RBR granularity perspective comprises six granularity levels, whereas the

two RBCR granularity perspectives each comprise only two granularity levels, because the granulation relation is *not* transitive (its domain and range differ).

Resolution-Based Countability Representation (RBCR) Granularity Perspectives

The RBR granularity 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 building block levels, two complementary resolution-based countability representation (RBCR) granularity 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 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 '[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 granularity perspectives can be distinguished: (1) countable to non-countable RBCR granularity perspective, and (2) non-countable to countable RBCR granularity 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};

X=a specific building block level; X+1=the adjacent higher building block level to X.

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 building block level; X+1=the adjacent higher building block level 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 granularity perspectives comprise only two distinct granularity levels.

Function-Based Representation (F-BR) and Historical/Evolution-Based Representation (H/E-BR) Granularity Perspectives

Like each building block level has its own spatio-structural frame of reference, resulting in cross-granular multiple instantiation of a given particular material entity across the different spatio-structural frames of reference, the functional frame of reference requires its own granular representation due to cross-granular multiple instantiation. This function-related granular representation is required because some instances of *'material 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 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 granularity perspectives can be distinguished: (1) a function-based representation (F-BR) granularity perspective and (2) a historical/evolution-based representation (H/E-BR) granularity perspective. The F-BR granularity perspective has the **granulation criterion**:

'spatio-structural entity' FuncGranRep *'functional entity'*;

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

The H/E-BR granularity 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[49] **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 granularity 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 granularity perspectives that can be utilized to efficiently manage 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 granularity perspective and between entities across different granularity perspectives; (ii) integrates various frames of reference within a single framework, all of which are essential for the life sciences, ranging from a purely spatio-structural frame of reference, to a functional, a developmental, an ecological, and evolutionary frame of reference; (iii) improves searching and navigating through large complex graphs by using one or a combination of several of its granularity 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 metaphor. It comprises various hierarchies of

[49] 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.

different levels. The compositional building block (CBB) granularity perspective (Fig. 7), for instance, provides the backbone hierarchy that facilitates the integration of all the other granularity perspectives within the framework. It resembles a purely compositional notion of the levels metaphor, 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 granularity perspective is also influenced by the evolutionary systems-theoretical notions of the levels metaphor, in particular the operator-based approach, thereby integrating purely spatio-structural considerations with functional and evolutionary aspects. The set of region-based granularity 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 notion of the levels metaphor.

The set of functional parthood-based granularity perspectives, on the other hand, resemble the mechanism-based notion of the levels metaphor. The lack of a globally applicable general granularity perspective comparable to the CBB granularity 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 granularity perspectives, together with the granularity perspectives mediating between these 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 notions of the levels metaphor, it nevertheless is characterized and defined in a formally coherent framework that integrates all these diverse granularity 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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