ELSEVIER
Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Biomedical Informatics 39 (2006) 350–361
Journal of Biomedical Informatics
www.elsevier.com/locate/yjbin

Biomedical ontologies: What *part-of* is and isn't

Stefan Schulz [a,*], Anand Kumar [b], Thomas Bittner [c]

[a] *Department of Medical Informatics, University Hospital, Freiburg, Germany*
[b] *Institute for Formal Ontology and Medical Information Science (IFOMIS), University of Saarbrücken, Germany*
[c] *Department of Philosophy, Department of Geography, New York State Center of Excellence in Bioinformatics and Life Sciences, University at Buffalo, USA*

Received 20 June 2005
Available online 19 December 2005

Abstract

Mereological relations such as **part-of** and its inverse **has-part** are fundamental to the description of the structure of living organisms. Whereas classical mereology focuses on individual entities, mereological relations in biomedical ontologies are generally asserted between classes of individuals. In general, this practice leaves some basic issues unanswered: type constraints of mereological relations, e.g., concerning artifacts and biological entities, the relation between parthood and time, inferred parts and wholes as well as a delimitation of parthood against spatial inclusion. Furthermore, mereological relations can be asserted not only between physical objects but also between biological processes and medical procedures. We analyze these ambiguities and make suggestions for a standardization of mereological relations in biomedical ontologies.

Keywords: (Bio)medical ontologies; Mereology; Knowledge representation; Partonomies; Terminological standards

1. Introduction

It is widely recognized that the construction of biomedical ontologies should obey formal ontological criteria, a necessary condition for interoperability between human and electronic agents. Beside *is-a*, the class subsumption relation, the mereological relations *part-of* and its inverse *has-part* play a pivotal role in all ontologies which describe the structure of biological organisms and their constituents. A wide variety of partonomies are present in the Foundational Model of Anatomy (FMA) [1,2], the NCI thesaurus [3], the anatomy schemata of the GALEN CORE model [4], the SNOMED CT [5] anatomy branch, the Gene Ontology [6], and in the diverse ontologies of the Open Biomedical Ontologies (OBO) platform [7]. Several authors [8–10] grant the relation *part-of* the status of a *foundational* relation. This is supported by top-level ontologies such as DOLCE [11], BFO [12], and GOL [13].

It is critical to any effort of ontology engineering in a given domain that relations characterized as foundational are formally grounded and robust with regard to individual interpretations in order to prevent human-dependent semantic bias. This requirement is roughly fulfilled for the well-studied *is-a* relation [14]. However, it has been shown that matters become more complicated when not arbitrary classes but properties or universals and their changes over time are considered [15–18].

In this paper, we concentrate on the mereological relations **part-of** and **has-part**. The work on these relations, as far as their assertion between individual entities is concerned, is extensive [19]. In biomedical ontologies, attempts to provide formal foundations for mereological relations are more recent [20,9,21,22]. Here, in contrast to standard mereology, *Part-Of* and *Has-Part* denote relations between *classes* (such as in *Part-Of* (*Cell Nucleus, Cell*)) and not relations between *individuals*, and they consequently have different properties. Moreover, parthood relations between classes are complex and go beyond what has been formalized in standard mereology. Related ontological questions that need to be answered prior to the construction of for-

* Corresponding author. Fax: +49 761 203 6711.
E-mail address: stschulz@uni-freiburg.de (S. Schulz).

1532-0464/$ - see front matter
doi:10.1016/j.jbi.2005.11.003

mal bio-medical ontologies generally fall into the following categories:

- *Parthood between material and non-material entities:* Are left ventricles parts of hearts, and is the boundary of this liver part of this liver?
- *Parthood over time:* Is a lost hair or a surgically removed appendix still part of the body? Is a tissue sample in a laboratory still part of the organism from which it was taken?
- *Parthood and spatial location:* Are transplanted organs part of the donor organism, the receptor organism, or both? Is a given molecule part of the cell in which it is located at a given moment? Is a tooth filling part of a tooth?
- *Parthood between occurrents:* Is the suturing process part of an appendectomy, or is the interphase part of mitosis?

Obviously, such mereological puzzles are concerned with basic classes of biological entities and are, hence, relevant to medicine (e.g., transplanted organs, tissue samples, and heart ventricles) as well as to cell and molecular biology.

The formal treatment of mereological relations in bio-medical ontologies is still insufficient. We claim that the specific aspects of partonomic bio-medical structures pointed out above need to be made more explicit. Otherwise, implicit assumptions in the different uses of *Part-Of* and *Has-Part* will vary among ontology engineers, users and applications; unintended interpretations may occur, and, as a consequence, system interoperability may be at risk.

In the following, we will first clarify basic ontological categories and then discuss mereological relations between individuals and between classes of individuals. We will, furthermore, address dimensions in which *part-of* related ambiguities still exist: time-dependent parthood, parthood vs. location, and parts of occurrents. Our proposals focus on the practice of ontology engineering in the biomedical domain. None of these proposals are entirely new. We, therefore, refrain from formal definitions and restrict ourselves to natural language. More detailed formalisms can be found in the literature cited.

2. Basic assumptions and definitions

2.1. Four basic categories

The basis of our analysis is a four-category scheme depicted in Table 1. Distinctions between biomedical entities can be drawn on the basis of their classification either as a universal or a particular and either as a continuant or an occurrent. Most upper-level ontologies are concordant in this respect. *Particulars* are the concrete and countable entities in the world: this cell, my hand, my childhood, Susan's left femur, Susan's femur operation, etc. *Universal* properties or universals are entities which are instantiated by particulars, e.g., the universal Human Being is instantiated by particulars like Susan, the universal Cell is instantiated by this particular cell, the universal Femur is instantiated by Susan's left femur, the universal Hip Osteotomy is instantiated by Susan's mother's hip osteotomy, etc.[1] We make the distinction between universals and particulars explicit by strict naming conventions: names of universals use *Upper Case* initials while names of particulars are written in *lower case* letters.

Table 1
Four mutually disjoint categories for material objects and processes

	Occurrents (Endurants)	Continuants (Perdurants)
Particulars (Instances, Individuals)	Susan's life	Susan's body
	Mitosis of that cell at t_1	That epithelium cell
	Susan's appendicitis (process)	Susan's appendix
	Susan's hip arthroplasty	Susan's left femur
Universals (Classes)	Human Life	Human Body
	Appendicitis (process)	Appendix
	Hip Arthroplasty	Hip
	Mitosis	Cell

Particulars fall into two major categories: *continuants* (also called endurants) and *occurrents* (also called perdurants) [19]. This distinction is based on different modes of persistence through time and is also deeply rooted in common sense. *Continuants* persist through time by present in their entirety at every point in time at which they exist. For example, I am a continuant and I am wholly present at every moment I exist. All the parts I have at a given moment in time are present at this moment in time. Notice, however, that I do not have the same parts at every moment in time. For example, many cells of my gastrointestinal tract are exchanged within days. Organisms, populations, organs, cells, and molecules are also examples for continuants, as well as material artifacts or geographic entities.

Occurrents, on the other hand, are never present in their entirety at a given instant. They have phases and temporal parts which correspond to intervals through which they perdure. For example, the process of you reading this paper is not fully present at this moment. It might take you another hour to complete this process. Other examples for occurrents include my life, my childhood, and the process of insulin synthesis that currently occurs in my body, etc.

The distinction between continuants and occurrents at the level of particulars is reflected at the level of universals

[1] In the context of this paper, the term *universal* can be considered synonymous with the terms *class*, *sort*, and *type*; similarly, *particular* can be considered synonymous with the terms *instance, individual*, and *token*, thus bridging philosophical and computer science terminologies. The exact meaning of these terms is still subject to controversy. We refrain from the use of the term *concept* due to its multiple, partly contradictory senses.

in the sense that there are no universals which have both, continuants and occurrents, as instances. Consequently, there are universals whose instances are continuants like *Heart*, *Human being*, etc. and there are universals which instances are occurrents like *Human Life*, *Osteoarthrosis*, *Hip Arthroplasty*, *Insulin Synthesis*, *Mitosis*, etc. Most upper level ontologies agree on these basic principles: DOLCE [11], BFO [12], and GOL [13].

This distinction between continuants and occurrents is also replicated at the mereological level. Parthood relations hold among continuants (my heart is part of my body, this cell nucleus is part of this cell) and among occurrents (my childhood is part of my life) but not between continuants and occurrents [19]. More specifically, among continuants, parthood is *time-dependent*, i.e., a ternary relation: The tooth was part of Susan's body at time t_1, i.e., **part-of** (Susan's tooth, Susan's body, t_1). After the tooth was extracted at time t_2 it ceased to be part of Susan's body, i.e., NOT **part-of** (Susan's tooth, Susan, t_3).

Among occurrents, parthood is time independent, i.e., a binary relation: My childhood is part of my life. This relation is fixed and does not change. Therefore, it can truly be asserted timeless.

2.2. Instances vs. classes

We reiterate that parthood relations represented in biomedical ontologies relate pairs of universals and not pairs of particulars. This can easily be confirmed by introspection into any biomedical vocabulary. Here, *Part-Of* (*Thumb*, *Hand*) does not mean that an individual thumb is part of an individual hand, but rather that the class of thumbs and the class of hands stand in some special relationship which uniquely exists between universals. Such class-level relations must be carefully kept apart (and distinguished by a different notation) from instance-level relations such as **part-of** (*my thumb*, *my hand*), **part-of** (*italy*, *europe*). We shall adopt the convention of referring to relations in which one or more instances are involved by means of **bold face expressions and lower case initials.** Relations involving only classes are picked out by *Upper Case Initials and Italic Fonts.*

The distinction between class-level *Part-Of* and instance-level **part-of** has been largely neglected in biomedical vocabularies. One reason for this is the priority given to a conceptual, thesaurus-like abstraction of word senses over the representation of concrete entities in the world. As much as this is sufficient and adequate for the purpose of indexing and annotation of texts and has, up to now, proved to be sufficient for many clinical coding purposes, it definitely falls short when automated reasoning is required.

As concept oriented vocabularies were increasingly moving towards more precise semantics, conflicting interpretations of mereological relations began to evolve: The Gene Ontology [6], for instance, used to interpret *Part-Of* as "can be a part of, not is always a part of [23]. More recently, this definition was changed to "The part-of relationship (...) is usually *necessarily is-part* [24].

In the Foundational Model of Anatomy (FMA) [25], on the other hand, the class-level relation *Part-Of* (A, B) was originally understood as a relation which was defined as follows [9]: the universal A is part of universal B if and only if every instance of B has some instance of A as part and every instance of A is part of some instance of B. Due to the fact that there are various other class-based parthood relations (to be explained below) the vocabulary of the FMA will be extended to do justice to those relations [22]. For the OBO ontologies, a consensus has recently been reached which also takes the various class-based relations into account [10]. The different readings of class-level *Part-Of* can be summarized as follows:

1. All instances of A are **part-of** some instance of B. For example, every instance *of Human Female Reproductive System* is a part of some instance *of Human Body.*
2. All instances of B have some instance of A as a part. For example, every instance of *Heart* has some instance(s) of *Cell* as part(s).
3. All instances of A are **part-of** some instance of B and all instances of B have some in stance of A as part. For example, every instance of *Human Nervous System* is a part of some instance of *Human Body* and every instance of *Human Body* has some instance of *Human Nervous System* as a part.
4. There is at least one instance of A which is **part-of** some instance of B. For example, there are instances *of Organ* which have *Cardiac Muscle* as part. But neither are all instances of *Cardiac Muscle* part of an instance of *Organ*, nor do all instances of *Organ* have instances of *Cardiac Muscle* as part.

These regularities were formally captured in similar ways by defining several kinds of class-level *Part-Of* relations on the basis of instance-level parthood with different notations, for example in [26,9,8,22]. We summarize this in Table 2. To this end, we introduce the ternary instantiation relation **Inst** which relates an individual to a universal at time t. The formal definitions based on time-dependent instantiation and parthood are summarized in Table 2. In addition, we subscribe to the following linguistic convention: "all *Cells*" means "all instances of the universal *Cell.*" The expression "a *Cell*" refers to some instance of the class *Cell.*

- (1) is expressed by means of the class-level relation *Part-Of* (A, B), e.g., *Part-Of* (*Human Female Reproductive System*, *Human Being*);
- (2) is expressed by the class-level relation *Has-Part* (B, A), e.g. *Has-Part* (*Heart*, *Cell*). Notice, however, that *Has-Part* (*Human Being*, *Human Female Reproductive System*) is not equivalent to *Part-Of* (*Human Female Reproductive System*, *Human Being*) because not all human beings have female reproductive systems. Also

Table 2
Class level mereological relations

Suggested notation	Formal definition	(Schulz 02) [30]	(Smith 04) [9]	(Donnelly 05) [22]	(Smith 05) [10]
Part-Of (A, B)	$\forall x,t$: $\mathbf{Inst}(x,A,t) \rightarrow \exists y$: $\mathbf{Inst}(y,B,t) \wedge \mathbf{p}(x,y,t)$	*A hmw B*	*A part_for B*	$PP_1(A,B)$	*A part_of B*
Has-Part (B,A)	$\forall y,t$: $\mathbf{Inst}(y,B,t) \rightarrow \exists x$: $\mathbf{Inst}(x,A,t) \wedge \mathbf{p}(x,y,t)$	*A hmp*$^{-1}$*B*	*B has_part A*	$PP_2(A,B)$	*B has_ part A*
Part-Of $(A,B) \wedge$ *Has-Part* (B,A)	$\forall x,t$: $(\mathbf{Inst}(x,A,t) \rightarrow \exists y$: $\mathbf{Inst}(y,B,t) \wedge \mathbf{p}(x,y,t))$ $\wedge \forall y,\ t$: $(\mathbf{Inst}(y,B,t) \rightarrow \exists x$: $\mathbf{Inst}(x,A,t) \wedge \mathbf{p}(x,y,t))$	*A hmw B* $\wedge$ *A hmp*$^{-1}$*B*	*A part_of B*	$PP_{12}(A,B)$	*A integral_ part_of B*
Possible-Part-Of (A,B)	$\exists x,y,t$: $\mathbf{Inst}(x,A,t) \wedge \mathbf{Inst}(y,B,t) \wedge \mathbf{p}(x,y,\ t)$	*A how B*			

Notations from different sources, **p** is an abbreviation for instance-level **part-of**.

notice that *Part-Of* (*Heart*, *Cell*) does not hold, since not all cells are part of a heart. Class-level *Has-Part* is, therefore, *not* the inverse relation of class-level *Part-Of* as can be shown formally [26,22];

- (3) is expressed by the conjunction of (1) and (2), for the sake of simplicity, instead of by means of the introduction of a new class-level relation, as suggested in [9,22,10];
- (4) is expressed by the relation *Possible-Part* (*A*, *B*) [27,28]. This is the weakest class-level relation and signifies nothing more than the following: There is at least one instance of *A* which is part of an instance of *B*. It holds between the classes *Cardiac Muscle* and *Organ*, because there is some instance of cardiac muscle which is part of an organ (e.g., in my heart). This explicit use *of Possible-Part* (*A*, *B*) can be avoided by addressing only the most specific classes so that the strict *Part-Of* or *Has-Part* is fulfilled, e.g., *Has-Part* (*Heart*, *Cardiac Muscle*), with *Heart* being a subclass of *Organ.*

All these relations have been introduced previously using different, even conflicting notations. A synopsis is presented in Table 2.

The degree to which we can represent these relations in a specific biomedical ontology may vary according to the representation language and its underlying semantics. The distinction between *Part-Of* (1) and *Has-Part* (2) is of utmost importance and needs to be representable in any formalism suitable for the representation of bio-medical ontologies. (3) can, subsequently, always be expressed in terms of (1) and (2). The relation *Possible-Part-Of* is dispensable when we resort to a representation in description logics. In contrast to database and frame systems, description logics are based on the open world assumption [29]. As a consequence, we need to explicitly rule out classes for which there are no instances related by **part-of**, such as the class pair *Right Extremity*/*Left Extremity* [21]. Otherwise, any assertion of the type **part-of** (*a*, *b*) is valid.

From the definitions in Table 2 it is obvious that in order to understand class-level relations it is critical to understand individual-level relations and the relation of instantiation. In the next section, we will focus on semantic aspects of the instance-level **part-of** relation and give suggestions for its use in biomedical ontologies.

2.3. Basic properties of the instance level **part-of** *relation*

There is an impressive corpus of work published regarding ontological, logical, cognitive, and linguistic properties of mereological relations, cf. overviews in [19,31–35]. Throughout this paper, we restrict ourselves to a discussion of **part-of** as related to biomedical reality and deliberately ignore contributions which deal with the analysis of mereological notions in the context of human language or cognition [36–38]. The following points deserve our interest, however, because they address ambiguities and therefore require clarification, as justified above.

2.3.1. Proper vs. improper parts

2.3.1.1. Problem. Classical mereology generally builds upon the instance-level relation **part-of** which is axiomatized as transitive, antisymmetric, and reflexive. As an alternative convention, Simons [19] proposed to take the irreflexive relation **proper-part-of** as primitive and to define general parthood in terms of proper parthood and identity. The latter approach is more suitable when taking into account the commonly accepted meaning of *part* in our domain, which is generally assumed not to include identity, e.g., a body is not seen as a kind of body part [39].

Transitivity and antisymmetry, however, are generally accepted as properties in ontological (non-cognitive) formalizations of **part-of** and **has-part.** This does not necessarily hold true for more specific parthood relations like the relation ‘immediate proper part of,’ which is not transitive. Examples of these relations can be found in GALEN [40] as well as in the FMA [25]. A discussion of these relations is, however, beyond the scope of this paper (cf. [41,42] for the discussion of non-transitive parthood relations).

For the sake of completeness, we do mention an unorthodox interpretation such as to include the notion of proper overlap into parthood, e.g., **part-of** (*myVagusNerve*, *myThorax*) or **part-of** (*myEsophagus*, *myMediastinum*) as proposed by [43]. This interpretation—which is even supported by evidence gathered from medical textbooks—may arise out of a confusion regarding the referent of *Vagus Nerve or Esophagus*: instead of the entire anatomical structure, something like “the whole structure or some of its parts” may be referred to.

2.3.1.2. Suggestion. We propose to interpret **part-of** and **has-part** in the sense of proper parthood, i.e., excluding identity. The reason for this is our observation that there is no evidence that these relations have ever been used in the "improper" meaning in our domain. On this interpretation **part-of** (x, x) is false.

From the irreflexivity of individual **part-of** does NOT follow that class-level *Part-Of* is irreflexive [22]. Therefore, one can generally admit the improper case, e.g., *Has-Part* (*Amount Of Matter*, *Amount Of Matter*), even when defining *Has-Part* in terms of the proper **part-of** relation as introduced above. This means that any amount of matter has a (smaller) amount of matter as part. With the weak relation *Possible-Part-Of* there are plausible (and numerous) cases for reflexivity, e.g., *Possible-Part-Of* (*Biological Structure*, *Biological Structure*).

Furthermore, we clearly distinguish **part-of** from **proper-overlap**. The latter relation holds whenever two objects share a proper part.

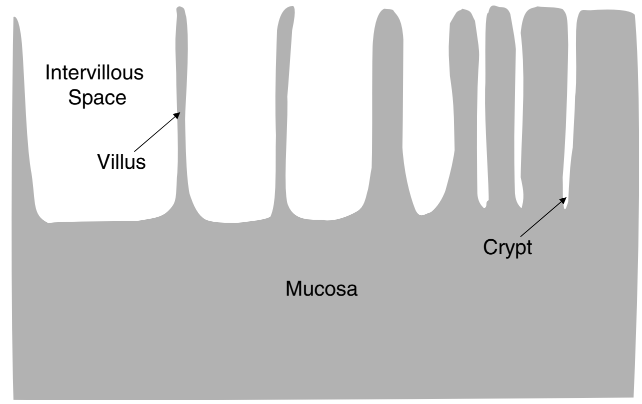

Fig. 1. External immaterial parts.

2.3.2. Sortal restrictions

2.3.2.1. Problem. Some controversy exists about domain and range restrictions for the **part-of** relation, especially with regard to immaterial parts such as holes (cavities, passageways, intrusions, etc., cf. [44]) as well as boundaries such as surfaces, lines, and points [45]. There is vast literature on boundaries discussing various kinds of boundaries: bona fide boundaries, which correspond to discontinuities in reality (e.g., the boundary between my skin and the surrounding air), and fiat boundaries which are boundaries that are created by human demarcation and other cognitive acts, e.g., the boundary between the left and the right part of my body. See [46] for details. Unfortunately, in the literature there are different opinions on whether a boundary is a part of the object it delimits [47]. Is, for example, the surface of my arm a part of my arm? In the FMA, for instance, boundaries are *not* parts of the entities they bound.

Another controversial question is whether cavities are parts of their hosts [48–50]. Is, for example, the cavity of my stomach part of my stomach? Moreover, the distinction whether hollow spaces at the surface of solid objects are parts is essentially vague and depends on the demarcation of these objects. A good example is the intestinal mucosa (Fig. 1). We may argue that crypts are part of the mucosa, but not the empty space between villi (intervillous space). There is a smooth transition between both surface patterns, so that any attempt of exact demarcation is arbitrary [51].

Finally, there are different approaches regarding the status of collectivities, i.e. pluralities of uniform objects. Examples are presented by the red cells in my blood or the collection of goblet cells in my stomach. The question is whether the relation between one red blood cell and the totality of red blood cells or between a bigger and a smaller amount of red blood cells should be covered by the general **part-of** relation [52,42].

2.3.2.2. Suggestion. We propose that (both fiat and bona fide) boundaries as well as empty spaces, subcollectivities, and their individual elements can be within the domain and the range of **part-of** and **has-part.** The inner surface of my stomach is, therefore, **part-of** my stomach as well as its cavity. One distinct goblet cell in my stomach is **part-of** the collection or plurality of goblet cells in my stomach which is **part-of** my stomach.

Concerning sortal constraints, the following cases have to be accounted for: an immaterial entity cannot have a material entity as part and the dimensionality of a part cannot be higher than that of the object it is **part-of**. Inversely, the dimensionality of a boundary part must be lower than the one of the object it bounds. This rules out, for instance, the common sense abstraction that the skin is a boundary of a body: Though having only a small extent in the third dimension, the skin is, nevertheless, a three-dimensional object.

The dimensionality constraint also rules out vague boundaries which are commonly regarded as body regions, e.g., the boundary between the upper arm and the forearm, since body regions are not lower-dimensional entities. We suppose that vagueness is a feature of human concepts which affects fiat boundaries, i.e., boundaries that do not correspond to discontinuities in reality. According to this view, human concepts are often underdetermined in the sense that they do not allow for the delineation of a single fiat boundary. (Notice that this is a feature rather than a shortcoming of concepts, since it allows for simplicity. Imagine, for example, how complicated our concept of forearm would have to be in order to exactly fix the boundary between upper arm and forearm). This indeterminacy results in multiple, equally good boundary candidates, which are located in body regions which are regarded as (single) vague boundary. Consider, again, the boundary between the upper arm and the forearm. It is clear that this boundary is neither near the shoulder joint not near the wrist. However, there are many equally passable boundary candidates close to the elbow. Notice that every single one of these boundary candidates is a perfectly crisp lower-dimensional boundary. They are all located in the pertinent body region that is, by mistake, regarded as a vague boundary. The same applies to cases such as the mucosa example discussed above. In this paper, we do not elaborate on the difficult issue of vagueness. Cf. [53] for details. Notice also that the distinction between *bona fide* and *fiat* boundaries is far from being simple and unproblematic [51].

2.3.3. Mereological principles

2.3.3.1. Problem. Beyond the algebraic properties of **part-of** and its inverse, formal mereology deals with additional principles related to these relations. Here, we mention only the weak supplementation principle (WSP), the proper part principle (PPP), as well as the existence of atoms (entities which do not have parts). Among others, WSP rules out that there is an entity which has only one proper part. PPP states that no two distinct objects have exactly the same set of proper parts [19]. Questions have been raised concerning the latter principle, a cornerstone of what is called *extensional* mereology [35]. For example, it is not difficult to imagine that the same set of proper parts can be *arranged* in quite different ways which results in distinct objects.

2.3.3.2. Suggestion. We are aware of the limited relevance of these issues to the construction of biomedical ontologies. The acceptance or rejection of WSP or PPP would be an issue much better suited for reasoning about instances. There are no straightforward correlates to these principles when we consider parthood relations between classes. The fact that a class in an ontology has only one direct *has-part* descendant is not per se a contradiction of the WSP. Examples for this can be found whenever describing a class of objects which are constituted by uniform compounds, e.g., *Has-Part* (*Leukocyte Collection*, *Leukocyte*), which, by no means, can be interpreted to signify an instance *of Leukocyte Collection* has only one instance *of Leukocyte* as part. We, therefore, do not argue for the introduction of these principles on a class level.

Focusing on the instance-level relations, we suggest to claim WSP and to subscribe to PPP for an atemporal view on parthood: if two entities have exactly the same parts at a given instant they are identical at this instant.

3. Parts and time in continuants

Biological continuants endure through time but may undergo changes. In extreme cases, such as observed in intestinal or endometrial mucosas, tissue structures are completely exchanged within days. Growth phenomena give rise to new entities, e.g., tumors, tumor vessels, embryos, and their parts. Biomedical ontologies should, therefore, pay tribute to these phenomena, as they make universal assertions regarding classes of entities which are mereologically variable [19], i.e., they are characterized by continuously losing and gaining parts.

3.1. Problem

There are many concurrent theories about parts and time [54]. The main reason of divergence is the discrepancy on whether continuant entities exist which are present with all their (actual) parts at every time, e.g., an organism which exists now as well as in other time instants (even having lost some parts and gained others). The alternative view is that there is only one such thing as the organism's life and each stage in its life corresponds to a time-dependent (temporal) part. For practical ontology engineering purposes (which should be equally communicable and not too far from common sense [19]) this latter perspective, which expresses the whole physical reality in terms of four-dimensional spatiotemporal objects, is problematic. Hence, we do not challenge the categorial distinction between continuants and occurrents introduced above.

More relevant for biomedical ontology engineering is rather the inquiry regarding the objects which are not parts of a biological continuant during their whole simultaneous existence [55]. We call them *temporary* parts [19]. Is an amputated toe, a blood sample, or a biopsy in a laboratory still part of the organism they belonged to? As we included collectivities of disconnected elements in our concept of part, we could argue that these objects are still parts, albeit disconnected ones. A hardly acceptable consequence of this would be that the spatial extension of an organism would then include every lost hair or skin particle scattered around the organism's habitat.

3.2. Suggestion

According to [56], we introduce the ternary relation **part-of** (a, b, t) which is interpreted as follows: a is **part-of** b at instant t. An amount of blood, for example, is part of an organism at t_1 (when it is still in the organism), but it is no longer part at the instant t_2 when it is in the lab. This means that we reject the position that it continues as a disconnected part of the organism even in the lab. In [57], the instance-level relation **temporary-part-of** (a, b) is introduced in order to describe that a at some instant in its life is part of b, whereas **permanent-part-of** (a, b) means that a is part of b at all instants of a's lifecycle. The relation **temporary-part-of** is, therefore, the most general relation.

Finally, we introduce **historic-part-of** which holds whenever **temporary-part-of** is true and **permanent-part-of** is false. We do not consider future hypotheses, a may be **permanent-part-of** b now and **historic-part-of** b in the future.

Notice that the class-based relations *Part-Of* (A, B) and *Has-Part* (A, B), as defined above, are neutral with regard to time.

Part-Of (A, B) expresses that at every time t every instance of A at t is, at instant t, **part-of** some instance of B. *Has-Part* (A, B) means that at every t every instance of A at t has, at t, some instance of B as a part, cf. Table 2. For example, *Has-Part* (*Liver*, *Hepatocyte*) is a true statement because at any time t any liver, which exists at t has, at t certain hepatocytes as parts.

However, *Part-Of* (*Hepatocyte*, *Liver*) is not true (at least in a domain of clinical reality), because a tissue sample taken during a liver puncture also contains hepatocytes, which are not part of the liver any longer. Thus, we express the notion of time independent parthood by introducing the class-level relation *Temp-Part-Of*. Two classes A and B are related by Temporary Parthood if and only if every instance of A is **part-of** some B at at least one instant of time. *Has-Temp-Part* is defined analogously. To recapture the liver example, *Has-Temp-Part* (*Liver*, *Hepatocyte*) would hold true as well because *Has-Part* is the stronger relation. *Temp-Part-Of* (*Hepatocyte*, *Liver*) would then mean that every hepatocyte was once part of a liver (an assertion challenged by recent advances in tissue engineering). Note that the class-level relations do not make any statement about the permanence of a given part or whole at an instance level. They only make a universal statement about the class of wholes and parts, as the following example shows: *Has-Part* (*Piece of Metal*, *Amount of Electrons*). This solely means that every piece of metal contains some amount of electrons but not that the same piece contains exactly the same electrons over time.

4. Parts and location

Every continuant particular occupies a unique spatial region at every moment in time at which it exists. According to [58], we introduce the partial function **r** which relates a continuant a to the spatial region s that a occupies at time-instant t: $s = \mathbf{r}(a, t)$. In other words, at time t the continuant a takes up the whole region s but does not extend beyond it. **r** is a partial function since most continuants do not exist at every time t.

We can subsequently define the relation **located-in** between two continuant entities as follows [59,58]: Entity a is **located-in** entity b at time t if and only if the region occupied by a at t is **part-of** the region occupied by b at t. According to this definition, all parts of biological structures are also located in their corresponding wholes. For example: My mitral valve is **part-of** my heart. Therefore, it is also **located-in** my heart. Notice, however, that not every entity which is **located-in** a biological structure is also **part-of** that structure. For example, a bolus of food is **located-in** my stomach, i.e., at a given time the region of the bolus of food is a part of the region of my stomach, but the bolus of food is NOT **part-of** my stomach. We consequently introduce the relation **contained-in** which holds if one entity is **located-in** another one without being **part-of** it. For example, the bolus of food is **contained-in** my stomach.

Corresponding to **located-in** and **contained-in** we also introduce the inverse relations **location-of** and **contains.** Additionally, we may introduce, analogously to the relations **temporary-part-of** and **permanent-part-of** the relations **temporarily-located-in** and **permanently-located-in** as well as **temporarily-contained-in** and **permanently-contained-in**.

4.1. Problem

Now, for some biological objects the following problem arises: biological objects are involved in a constant exchange of matter with their environment, so that many location relationships, e.g., the location of a given protein molecule in a cell, are short-lived.

Moreover, the continuous nature of the processes of matter exchange [60] suggests that it might be very difficult if not impossible to exactly specify the moment in time at which parts of a given bolus of food (e.g., fat or carbohydrate molecules) cease to be merely contained in a given anatomical structure but really become a part of it. More specifically, when food decomposes into its components, the portions of the substances in the lumen of the intestine are contained therein but they are, nonetheless, not parts thereof. Thus, we can ask at what stage of the process of matter exchange they do become **part-of** the relevant circumcluding whole. For example, are the oligosaccharides and lipids which are absorbed by the intestinal mucosa part of it, even when they remain herein less than a millisecond?

4.2. Suggestion

We could propose that the notion of parthood, at least when applied to biological continuants, intrinsically bears some element of indeterminacy. If we make this claim it would require to accept vagueness with regard to relations, which is definitely not a well-grounded assumption.

Instead, we argue that in cases such as discussed above, given the current knowledge about digestion processes and the means available to observe them directly, it is relatively easy to determine how entities are located relative to each other but much more difficult to gain knowledge about whether or not some entity is part of another. Following [61], we now discuss circumstances under which the fact that the individual a is **located-in** the individual b is sufficient to derive that a is a **part-of** b.

4.3. Artifacts and biological objects

For an object a to be **part-of** an object b, it must be assured that a and b instantiate suitable classes. In addition to the general sortality criteria outlined in Section 2.3.2, we introduce two other sorts which are relevant to our domain: artifacts (material objects of human creation) and biological objects (genetically determined material objects). Thus, if **part-of** (a, b) holds and b is a *Biological Object*, we rule out that a is an *Artifact* (e.g., a heart pacemaker, a bullet, a dental filling). An artifact located in a biological object is, therefore, not part of it.

Furthermore, we state that any biological object a **located-in** b is only **contained-in** b (i.e., not **part-of** b) if their genetic origins are different. Thus, applying this principle, an embryo is not a part of the body of its mother. Similarly, a bacterium which is **located-in** some tissue is **contained-in but** not **part-of** that tissue. Notice, however, that from the facts that a **located-in** b that a and b are biological entities with the same genetic origin it does NOT follow that a **part-of** b. For example, a lymphocyte which is **located-in** a piece of tissue may or may not be **part-of** this tissue.

This principle cannot be applied to many biological micromolecules such as sugars, lipids, or amino acids which have no genetic origin. It also encounters problems if we take into account that important cell organelles such as chloroplasts or mitochondria (so-called endosymbionts) have their own DNA which means that they are of different genetic origin as their host cells.

Finally, this principle can only be used to assert containment (by ruling out parthood) but it is not yet sufficient to assert parthood.

4.4. Life cycle

As further parthood principle, we suggest: *a* is **part-of** *b* in the case that *a* is **located-in** *b* and there is no point in time at which *a* is not **located-in** *b*. In other words, **permanently-located-in** would then imply **permanent-part-of** while temporary location would not be sufficient for asserting parthood. Note that this also covers those cases in which *a* comes into existence later than *b*.

For example, my brain is, for the given reason, part of my head and, for the same reason, a given cell membrane is part of the cell it surrounds. This concept can also be applied to pathological structures which originate within an organ, such as a glioblastoma in a brain or a cyst in a kidney.

The life cycle principle has the following limitations, however: at any given instant, we can only assess the hitherto existing "biography" of an object but we cannot make any future truth assignment for individuals, since ontological claims must be independent of the fact that we do not know how the world turns out to be in the future.

If we take a snapshot of a protein molecule in a secretory cell immediately after biosynthesis, we still record the relation between the two objects as **permanently-located-in** according to our definition. It may even be the case that at a given instant three indistinguishable molecules are located in a cell. Let us consider the example of thyroid hormone molecules in a cell of the thyroid gland. One molecule was synthesized in this cell moments before, a second one originated from an adjacent cell, and a third one was manufactured and ingested in form of a drug. According to the past history of these three molecules, only the first one would be a part when we apply our principle in a strict way.

4.5. Functionality

The last principle which helps us to specify under which circumstances **located-in** (a, b) implies **part-of** (a, b) takes into account what we call biological function and which constitutes the principle manifestation of living structure.

Again, we take two objects *a* and *b*, with *a* being **located-in** *b*. Let *a* have a biological function *f* which is *essential* to the proper functioning of *b*. This means that *b* becomes dysfunctional when *f* cannot be executed.

For example, the pumping function of the heart is essential to the proper functioning of the cardiovascular system, just as the function of the collection of hepatocytes is essential to the proper functioning of the liver. In contrast, the functioning of one individual macrophage which happens to be **located-in** some organ at some moment *t* is not essential to the functioning of the organ, nor is the function of one given glucose molecule essential to the functioning of a cell.

The functionality principle faces problems when applied to parts of anatomical structures which are spatially included into other ones but are assumed not to be essential to the proper functioning of the latter; or whose functional relevance has disappeared during evolution. Examples are terminal hairs of the skin, nasal sinuses, or the appendix. Since these entities are not essential to the proper functioning of the body, we cannot use the functionality principle to specialize location to parthood in this case. Furthermore, this principle is not applicable to *granular parts*, as introduced by [42]. Let us consider a single hepatocyte which is **located-in** the liver. Its functionality (protein synthesis, carbohydrate and lipid metabolism, and detoxification) is essential to the liver. However, if one such single cell becomes dysfunctional or dies within the normal turnover of liver tissue components, this the functionality of the organ is not affected because there are innumerous other cells with the same function.

When we advocate the application of the functionality principle in order to infer parthood from location, conflicts with the above sortality principle arise: transplants and implants often fulfill the same essential biological function as genetically identical structures. We could argue that the functioning of a heart valve or kidney is essential to the functioning of the body, therefore, it is **part-of** the body, and this holds true even in cases where it was transplanted from another body earlier.

4.6. Consequences for class-level relations

All these considerations have been made for instance-level relations. For the purpose of practical ontology engineering, we have to analyze the consequences of the above discussion for the class-level relations *Part-Of*, *Located-In*, and *Contained-In*, on the one hand, and for the related (not inverse) relations *Has-Part*, *Location-Of*, and *Contains*, on the other hand.

As far as sortality is referred to, we can transfer the same principle to the class level relations because sortality intrinsically deals with classes (sorts) of individuals. Yet, this does not solve the trade-off between the genetic and the functionality arguments. This puzzle cannot be solved merely by introspection into nature. Two proposals have to be discussed: On the one hand, we could completely refrain, in these cases, from any specialization of the location relation. One the other hand, in these cases, we could draw a boundary by fiat, which, however, depends on consensus as a result of a prescriptive or normative process.

As for the life cycle principle, our argument above allows us to infer *Part-Of* (A, B) from *Located-In* (A, B)

for all those cases which are not ruled out by the sortality principle and for which the assumption holds that every instance of A is always located in the *same* instance of B. Analogously, we can argue for *Has-Part* and *Location-Of.*

In contrast to this very strict ontological dependence between instances, the normal class level dependence such as expressed by the class-level relations introduced in Section 2.2 is not sufficient: all (living) hearts contain some blood cells, though not of the same ones, because they are constantly exchanged. Therefore, we cannot assert parthood between a heart and an individual blood cell. The statement *Has-Part* (*Heart*, *Blood Cell*) can therefore not be derived by the application of our refinement.

A different scenario arises when we ascribe an identity criterion to certain circumscribed amounts of matter such as "atrial blood" or "the cerebrospinal fluid." Such entities remain the same despite constantly gaining and losing parts. With regard to these cases, a statement such as *Has-Part* (*Heart*, *Atrial Blood*) would be correct.

Admitting or not admitting such entities is a matter of convention. It may be made plausible when certain properties, such as volume, protein concentration, temperature, etc., are assigned to these kinds of entities and used for clinical or scientific reasoning.

The functionality principle finally shows how information about the "standard" behavior (i.e., the behavior of fully functional entities) is influenced by whether we opt for parthood or containment. Here, again, the life cycle argument comes into play. If we analyze two classes and discover that permanent parthood between their instances is not the "standard" situation, we have good reasons to use the relation pair *Contained-In*/*Contains.* This could serve to answer the thyroid hormone/thyroid cell puzzle: the fact that thyroid hormone molecules are located in a thyroid cell for a very limited period of their existence only could support the argument for asserting *Contains* (*Thyroid Cell*, *Thyroid Hormone*) and not using the relation *Has-Part* in describing this situation.

5. Parts and occurrents

At first sight, one may be tempted to limit the relevance of the part-of relation to biological continuants. To the best of our knowledge, there is no medical terminology system which relates classes of occurrents by relations named *part-of* or *has-part.* Only in biology is the *part-of* relation between occurrents present in the *Reactome* curated knowledge base of biological processes.[2] Furthermore parts of occurrents are indirectly addressed by formalisms for the representation of clinical guidelines. Guidelines represent plans which sanction classes of clinical occurrents. Such clinical occurrent classes can be ordered by taxonomic as well as mereological relations. For example, *Gastrotomy* is a subclass of the class *Operation*, and for every instance *of Gastrotomy* there is an instance of the class *Incision.* We express this by the statements *Is-A* (*Gastrotomy*, *Operation*) and, just as with continuants, we use the mereological class-level relation *Has-Part* for the assertion *Has-Part* (*Gastrotomy*, *Incision*) [62]. A thorough analysis of parts of occurrents reaches well beyond the scope of this paper. We only select one problem which is relevant to the construction of ontologies of biomedical occurrents and which we have analyzed in more detail in [63].

5.1. Problem

Let us take a class of a complex procedure, e.g., the class $E =$ *Extraction of Foreign Body from the Stomach by Gastrotomy.* Any instance of E is a complex occurrent which is (roughly) characterized by the sequence of the surgical opening of a stomach (i), the extraction of a foreign body from this stomach (ii), and the surgical closure of the stomach (iii). We could then argue that, at the beginning of such a (token) procedure p (e.g., during the opening phase), an instance of the whole procedure is created but this instance is not complete until the whole procedure ends. It is only at the end that the instance becomes completed. This notion of completeness is not present for continuants, unlike for processes, as their instances exist in totality only at one particular instant.

In line with this argument, during a time interval i_1, p is an instance of both the class E and the class *Gastrotomy.* In the subsequent phase i_2, p instantiates E, again, together with the class *Extraction of Foreign Body.* A rationale for this is that a surgeon, during i_1 is already performing an instance of E.

The counterargument would be the following: one cannot exclude that, during the first phase of an operation, the patient dies and the operation is aborted, p would, therefore, never instantiate *Extraction of Foreign Body* and it would be highly problematic to consider p an instance of E. We would, therefore, require that E can only be instantiated when all its subprocedures (which are implied by E according to E's definition) have been instantiated.

Either position has strong implications on ontologies of biomedical occurrents, especially for the taxonomic arrangement of classes. The first approach would be concordant with a taxonomy in which the subprocedures feature as taxonomic parents: *Is-A* (E, *Gastrotomy*) AND *Is-A* (E, *Extraction of Foreign Body*). The second approach would, instead, introduce the subprocedure classes as nodes in a partonomy. All instances of E have an instance of *Gastrotomy*, as well as an instance *of Extraction of Foreign Body* as parts.

Both approaches have their correlates in existing biomedical terminologies. Whereas the first one corresponds to simpler fashioned procedure classification systems, the latter one is at least partly paralleled by SNOMED CT [5].

[2] http://www.reactome.org.

5.2. Suggestion

We strongly support the second approach. The main reason is that it can be consistently applied without explicit reference to time. The first one, however, leads to inconsistencies when time is not considered. Let us define *Gastrotomy* as an *Incision* which *acts-on* some *Stomach* and *Extraction of Foreign Body* as *Extraction* which *acts-on* some *Foreign Body*. Introducing *E* as a subclass of both, we have no way to express that the stomach and not the foreign body undergoes incision, unless we reintroduce time (This is one reason why SNOMED CT, in these cases, uses the idiosyncratic "role group" operator, cf. [63]).

In our second approach, we express the relation between complex and component processes by a mereological structure which is not different from the one that would be employed for continuants. The SNOMED role group operator would then simply be mapped to the class-level *Has-Part* relation: accordingly, we would express the above situation as *Has-Part* (*E*, *Incision*) AND *Has-Part* (*E*, *Gastrotomy*) AND *Has-Part* (*E*, *Extraction of Foreign Body*) [63].

6. Conclusion

In this paper, we have shown that the way mereological relations are specified in biomedical ontologies is insufficient. In the common practice of carrying over instance-level relations to a class-level, ambiguities inherently arise, which, however, can be resolved by introducing clear definitions. Another aspect is taking time into account, both with regard to continuants and occurrents. Here, again, clear definitions are helpful in order to determine what the standard reading of part-of is and is not.

Both on the level of instances and on the level of classes there is a fundamental difference between parthood and (spatial) location. Whereas it is, for various reasons, relatively easy to specify what is meant by '*a* is located in *b*,' it is much more intricate to differentiate it from '*a* is a part of *b*' or '*a* is contained in *b*.' This is particularly the case when relations between changing objects and objects at different levels of granularity are considered. Difficulties also arise when both, biological and non-biological entities, are taken into account.

We presented a methodology that addresses at least some issues raised. This methodology is to consider under which circumstances the fact that *a* is located in *b* implies that a is a part of *b*. We showed that taking into account facts about relative location over time, as well as facts about participation in biological functionalities often provides necessary and sufficient conditions that support valid inferences of facts about parthood from facts about location. Due to this reason we consider *located-in* as a foundational relation in its own right.

This has practical implications for using ontologies as the backbone of formal reasoning systems. There are typical reasoning patterns which exploit mereotopological characteristics of biological entities, e.g. the propagation of properties, as extensively discussed in [40,64,65,52,21]. For these purposes, a clear distinction between parthood and containment is fundamental.

The limitations of our approach are mostly due to vague boundaries between kinds, controversial conceptualizations of the lives of biological objects of different types, conflicts between functionality and genetic origin, and an imprecise understanding of biological functionality, for which a well-founded ontological account is still required.

Acknowledgments

This work was supported by the *EU Network of Excellence Semantic Interoperability and Data Mining in Biomedicine* (NoE 507505), cf. http://www.semanticmining.org. We acknowledge Maureen Donnelly (Buffalo), Barry Smith and Boris Hennig (Saarbrücken), and Philipp Daumke (Freiburg) for useful discussions and valuable suggestions. We also thank Udo Hahn (Jena) for the suggestion of the title.

References

[1] Rosse C, Mejino JLV. A reference ontology for bioinformatics: the Foundational Model of Anatomy. J Biomed Informat 2003;36:478–500.

[2] Rosse C, Shapiro LG, Brinkley JF. The DIGITAL ANATOMIST foundational model: Principles for defining and structuring its concept domain. In: Chute CG, editor, AMIA '98—Proceedings of the 1998 AMIA Annual Fall Symposium. A Paradigm Shift in Health Care Information Systems: Clinical Infrastructures for the 21st Century, Orlando, FL, November 7–11, 1998. Philadelphia, PA: Hanley & Belfus; 1998, pp 820–4.

[3] Hartel FW, de Coronado S, Dionne R, Fragoso G, Golbeck J. Modeling a description logic vocabulary for cancer research. J Biomed Informat 2005;38(2):114–29.

[4] Rector AL, Gangemi A, Galeazzi E, Glowinski AJ, Rossi-Mori A. The GALEN model schemata for anatomy: Towards a re-usable application-independent model of medical concepts. In Barahona P, Veloso M, Bryant J, editors. MIE '94—Medical Informatics Europe 94. Proceedings of the 12th Conference of the European Federation for Medical Informatics, Lisbon, Portugal, 22–26 May 1994. Amsterdam: IOS Press; 1994, pp 229–33.

[5] SNOMED Clinical Terms. Northfield, IL: College of American Pathologists; 2004.

[6] Gene Ontology Consortium. Creating the gene ontology resource: design and implementation. Genome Res 2001;11(8):1425–33.

[7] OBO. Open Biological Ontologies (OBO). [http://obo.sourceforge.net], 2005. Last accessed June 26th; 2005.

[8] Bittner T, Donnelly M, Smith B. Individuals, universals, collections: On the foundational relations of Ontology. In Varzi AC, Vieu L, editors. Formal Ontology in Information Systems. Proceedings of the 3rd International Conference—FOIS 2004, number 114 in Frontiers in Artificial Intelligence and Applications, Turin, Italy, November 4–6, 2004. Amsterdam etc.: IOS Press; 2004, pp 37–48.

[9] Smith B, Rosse C. The role of foundational relations in the alignment of biomedical ontologies. In Fieschi M, Coiera E, Yu-Chan Jack Li, editors. MEDINFO 2004—Proceedings of the 11th World Congress on Medical Informatics, vol. 1, number 107 in Studies in Health Technology and Informatics, San Francisco, CA, USA, September 7–11, 2004. Amsterdam: IOS Press; 2004, pp 444–8.

[10] Smith B, Ceusters W, Klagges B, Kohler J, Kumar A, Lomax J, Mungall C, Neuhaus F, Rector A, Rosse C. Relations in biomedical ontologies. Genome Biol 2005;6(5).

[11] Gangemi A, Guarino N, Msolo C, Oltramari A. Sweetening ontologies with DOLCE. In Asuncion Gomez-Perez, V. Richard Benjamins, editors. Knowledge Engineering and Knowledge Management: Ontologies and the Semantic Web. Proceedings of the 13th International Conference—EKAW 2002, Lecture Notes in Artificial Intelligence, vol. 2473. Sigüenza, Spain, October 1–4, 2002. Berlin: Springer; 2002, pp 166–81.

[12] Smith B, Grenon P. The cornucopia of formal-ontological relations. Dialectica 2004;58(3):279–96.

[13] Heller B, Herre H. Ontological categories in GOL. Axiomathes 2004;14(1):57–76.

[14] Brachman RJ. What is-a is and isn't: an analysis of taxonomic links in semantic networks. IEEE Comput 1983;16(10):30–6.

[15] Welty C, Guarino N. Supporting ontological analysis of taxonomic relationships. Data Knowledge Eng 2001;39(1):51–74.

[16] Guarino N, Welty CA. An overview of ONTOCLEAN. In: Staab S, Studer R, editors. Handbook on Ontologies, International Handbooks on Information Systems. Berlin: Springer; 2004. p. 151–71.

[17] Smith B. Beyond concepts: Ontology as reality representation. In Varzi AC, Vieu L, editors. Formal Ontology in Information Systems. Proceedings of the 3rd International Conference—FOIS 2004, number 114 in Frontiers in Artificial Intelligence and Applications, Turin, Italy, November 4–6, 2004. Amsterdam etc.: IOS Press; 2004, pp 73–84.

[18] Bittner T, Smith B. A theory of granular partitions. In: Duckham M, Goodchild MF, Worboys MF, editors. Foundations of geographic information science. London: Taylor & Francis Books; 2003. p. 117–51.

[19] Simon P. Parts: a study in ontology. Oxford: Clarendon Press; 1987.

[20] Schulz S. Bidirectional mereological reasoning in anatomical knowledge bases. In: Bakken S, editor. AMIA 2001—Proceedings of the Annual Symposium of the American Medical Informatics Association. A Medical Informatics Odyssey: Visions of the Future and Lessons from the Past, Washington, DC, November 3–7, 2001. Philadelphia, PA: Hanley & Belfus; 2001, pp 607–11.

[21] Schulz S, Hahn U. Part-whole representation and reasoning in biomedical ontologies. Artif Intell Med 2005;34(3).

[22] Donnelly M. A formal theory for spatial representation and reasoning in biomedical ontologies. Artif Intell Med, 2005, doi:org/10.10106/j.artmed.2005.07.004.

[23] Smith B, Williams J, Schulze-Kremer S. The ontology of the Gene Ontology. In Musen MA, editor. AMIA'03—Proceedings of the 2003 Annual Symposium of the American Medical Informatics Association. Biomedical and Health Informatics: From Foundations to Applications, Washington, DC, November 8–12, 2003. Philadelphia, PA: Hanley & Belfus; 2003, pp 609–13.

[24] Gene Ontology Consortium. GO editorial style guide; 2004. [http://www.geneontology.org/GO.usage.html. Last accessed: October 23th, 2004].

[25] Rosse C, Mejino JLV, Modayur BR, Jakobovitis R, Hinshaw KP, Brinkley JF. Motivation and organizational principles for anatomical knowledge representation: the DIGITAL ANATOMIST symbolic knowledge base. J Am Med Informat Associat 1998;5(1):17–40.

[26] Schulz S, Hahn U. Representing natural kinds by spatial inclusion and containment. In de Mantaras RL, Saitta L, editors. ECAI 2004—Proceedings of the 16th European Conference on Artificial Intelligence, Valencia, Spain, August 22–27, 2004. Amsterdam: IOS Press; 2004, pp 403–7.

[27] Uschold M. The use of the typed lambda calculus for guiding naive users in the representation and acquisition of part-whole knowledge. Data Knowledge Eng 1996;20(3):385–404.

[28] Donnelly M, Bittner T. Spatial relations between classes of individuals. In COSIT 2005: Spatial Information Theory. Foundations of Geographic Information Science, International Conference, Lecture Notes in Computer Science, Springer; 2005, pp 182–99.

[29] Baader F, Calvanese D, McGuiness DL, Nardi D, Patel-Schneider PF, editors. The Description Logic Handbook. Theory, Implementation, and Applications. Cambridge, UK: Cambridge University Press; 2003.

[30] Schulz S, Hahn U. A knowledge representation view on biomedical structure and function. In Kohane IS, editor. AMIA 2002—Proceedings of the Annual Symposium of the American Medical Informatics Association. Biomedical Informatics: One Discipline. San Antonio, TX, November 9–13, 2002. Philadelphia, PA: Hanley & Belfus; 2002, pp 687–91.

[31] Burkhardt H, DuFour C. Part/whole I: history. In: Burkhardt H, Smith B, editors. Handbook of metaphysics and ontology. München: Philosophia Verlag; 1991. p. 663–73.

[32] Simons P. Part/whole II: mereology since 1900. In: Burkhardt H, Smith B, editors. Handbook of metaphysics and ontology. München: Philosophia Verlag; 1991. p. 673–5.

[33] Lambrix P. Part-Whole Reasoning in an Object-Centered Framework. Number 1771 in Lecture Notes in Artificial Intelligence. Berlin: Springer; 2000.

[34] Casati R, Varzi AC. Parts and places. The structures of spatial representation. Cambridge, MA: MIT Press/Bradford; 1999.

[35] Varzi AC, Mereology. In Zalta EN, editor. Stanford Encyclopedia of Philosophy. Stanford: The Metaphysics Research Lab, plato.stanford.edu; 2003.

[36] Winston ME, Chaffin R, Herrmann DJ. A taxonomy of part-whole relations. Cognit Sci 1987;11(4):417–44.

[37] Alan Cruse D. On the transitivity of the part-whole relation. J Linguist 1979;15(1):29–38.

[38] Iris MA, Litowitz BE, Evens MW. Problems of the part-whole relation. In: Evens MW, editor. Relational models of the lexicon. Representing knowledge in semantic networks. Cambridge, UK: Cambridge University Press; 1988. p. 261–88.

[39] Bittner T, Donnelly M. Computational ontologies of parthood, componenthood, and containment. In Proceedings of the Nineteenth International Joint Conference on Artificial Intelligence; 2005.

[40] Rogers J, Rector AL. GALEN's model of parts and wholes: experience and comparisons. In J. Marc Overhage, editor. AMIA 2000—Proceedings of the annual symposium of the American Medical Informatics Association. Converging information, technology, and health care, Los Angeles, CA, November 4–8, 2000. Philadelphia, PA: Hanley & Belfus; 2000, pp 714–18.

[41] Johansson I. On the transitivity of parthood relations. In: Hochberg H, Mulligan K, editors. Relations and predicates. Frankfurt: Ontos Verlag; 2004. p. 161–81.

[42] Rector A, Rogers J, Bittner T. Granularity scale and collectivity: when size does and doesn't matter. J Biomed Informat 2005;38.

[43] Schubert R. Symbolisch-räumliche Computermodelle der Anatomie. Technical report, Fachbereich Medizin, Universität Hamburg, 1999. (Habilitationsschrift).

[44] Casati R, Varzi AC. Holes and other superficialities. Cambridge, MA: MIT Press/Bradford; 1994.

[45] Varzi AC. Boundaries, continuity and contact. Nous 1997;31:26–58.

[46] Smith B. Boundaries: an essay in mereotopology. In: Hahn L, editor. The philosophy of Roderick Chisholm. LaSalle: Open Court; 1977. p. 534–61.

[47] Varzi AC. Boundary, In: Zalta EN. editor. Stanford encyclopedia of philosophy. Stanford: The Metaphysics Research Lab, plato.stanford.edu; 2004.

[48] Schulz S, Hahn U. Mereotopological reasoning about parts and (w)holes in bio-ontologies. In Welty C, and Smith B, editors. Formal Ontology in Information Systems. Collected papers from the 2nd international FOIS conference, Ogunquit, Maine, USA, October 17–19, 2001. New York, NY: ACM Press; 2001, pp 210–21.

[49] Donnelly M, Smith B. Layers: a new approach to locating objects in space. In Werner Kuhn, Michael F. Worboys, Sabine Timpf, editors. COSIT 2003: Spatial Information Theory. Foundations of Geographic Information Science, Proceedings of the International Conference, Proceedings, vol. 2825, Lecture Notes in Computer Science,

Ittingen, Switzerland, September 24–28, 2003. Berlin: Springer; 2003, pp 46–60.

[50] Donnelly M. On parts and holes: The spatial structure of the human body. In Marius Fieschi, Enrico Coiera, Yu-Chan Jack Li, editors. MEDINFO 2004—Proceedings of the 11th World Congress on Medical Informatics, vol. 1, number 107 in Studies in Health Technology and Informatics, San Francisco, CA, USA, September 7–11, 2004. Amsterdam: IOS Press; 2004, pp 351–4.

[51] Smith B, Mejino JLV, Jr, Schulz S, Rosse C. Anatomical information science. In COSIT 2005: spatial information theory. Foundations of geographic information science, international conference, lecture notes in computer science, Springer; 2005, pp 149–64.

[52] Schulz S, Hahn U. Parthood as spatial inclusion: evidence from biomedical conceptualizations. In Didier Dubois, Christopher Welty, Mary-Anne Williams, editors, Principles of knowledge representation and reasoning. Proceedings of the 9th international conference—KR 2004, Whistler, BC, Canada, June 2–5, 2004. Menlo Park, CA: AAAI Press; 2004, pp 55–63.

[53] Bittner T, Smith B. Vague reference and approximating judgments. Spatial Cognit Comput 2003;3(2):137–56.

[54] Hawley K. Temporal parts. In Zalta EN. editor. Stanford encyclopedia of philosophy. Stanford: The Metaphysics Research Lab, plato.stanford.edu; 2003.

[55] Grenon P, Smith B. SNAP and SPAN, towards dynamic spatial ontology. Spatial Cognit Comput 2003;4:69–103.

[56] Thomson JJ. Parthood and identity across time. J Philos 1983;80:201–20.

[57] Bittner T, Maureen D. The mereology of stages and persistent entities. In Ramon Lopez de Mantaras, Lorenza Saitta, editors. ECAI2004—Proceedings of the 16th European conference on artificial intelligence, Valencia, Spain, August 22–27; 2004. Amsterdam: IOS Press, 2004, pp 283–7.

[58] Donnelly M. Relative places. In Varzi AC, and Vieu L. editors. Formal Ontology in Information Systems. Proceedings of the 3rd International Conference—FOIS 2004, number 114 in Frontiers in Artificial Intelligence and Applications, Turin, Italy, November 4–6, 2004. Amsterdam etc.: IOS Press; 2004, pp 249–60.

[59] Donnelly M. A formal theory of reasoning about parthood, connection, and location. Artif Intell 2004;160:145–72.

[60] Cohn AG. Formalising bio-spatial knowledge. In Welty C. and Smith B. editors. Formal ontology in information systems. Collected papers from the 2nd international FOIS conference. Ogunquit, Maine, USA, October 17–19, 2001. New York, NY: ACM Press; 2001, pp 198–209.

[61] Schulz S, Daumke P, Smith B, Hahn U. How to distinguish parthood from location in bio-ontologies. In AMIA 2005—Proceedings of the annual symposium of the american medical informatics association. Biomedical informatics: from foundations to applications to policy; 2005.

[62] Schulz S, Hahn U. A description logics approach to CGPs. In K. Kaiser, S. Miksch, and S.W. Tu, editors. Computer-based support for clinical guidelines and protocols. Proceedings of the symposium on computerized guidelines and protocols—CGP 2004, number 101 in studies in health technology and informatics, Prague, Czech Republic, 12–14 April 2004. Amsterdam: IOS Press; 2004, pp 137–41.

[63] Schulz S, Rogers J, and Hahn U. Semantic clarification of the representation of procedures and diseases in SNOMED CT. In MIE 2005—Proceedings of the 19th international congress of the European federation of medical informatics, Geneva, Switzerland, August 28–September 1, 2005. Amsterdam: IOS Press; 2005, pp 773–8.

[64] Rector AL. Analysis of propagation along transitive roles: formalisation of the GALEN experience with medical ontologies. In Horrocks I, Tessaris S, editors. DL 2002—Proceedings of the 2002 international workshop on description logics. Toulouse, France, April 19–21; 2002. Published via [http://CEUR-WS.org/Vol-53/] .

[65] Horrocks I, Patel-Schneider PF, Harmelen Fv. From SHIQ and RDF to OWL: the making of a web ontology language. J Web Semant 2003;1(1):7–26.