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Granularity scale and collectivity: When size does and does not matter

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Abstract

Bridging levels of "granularity" and "scale" are frequently cited as key problems for biomedical informatics. However, detailed accounts of what is meant by these terms are sparse in the literature. We argue for distinguishing two notions: "size range," which deals with physical size, and "collectivity," which deals with aggregations of individuals into collections, which have emergent properties and effects. We further distinguish these notions from "specialisation," "degree of detail," "density" and "connectivity." We argue that the notion of "collectivity"—molecules in water, cells in tissues, people in crowds, stars in galaxies—has been neglected but is a key to representing biological notions, that it is a pervasive notion across size ranges—micro, macro, cosmological, etc.—and that it provides an account of a number of troublesome issues including the most important cases of when the biomedical notion of parthood is, or is not, best represented by a transitive relation. Although examples are taken from biomedicine, we believe these notions to have wider application.

Keywords: Ontologies; Knowledge Representation; Terminology; Part–whole relations

1. Introduction

It is a truism that a major challenge for bioinformatics is to bridge levels of granularity and scale, from molecular, to cellular, to organ, to organism, to ecology. However, it is rarely made clear exactly what is meant by "granularity" or "scale" or what the consequences are of differences in granularity and scale for which any explanation must account.

This paper argues that it would be clearer to distinguish unambiguously two dimensions. We term these two dimensions "collectivity" and "size range" despite the risk of adding yet further neologisms to the field.[1] The basic notion that we put forward is that entities considered individually at one level are considered as collectives with emergent properties at the next level—e.g., collectives grains of sand form a beach, collectives of stars form galaxies, collectives of cells form tissues. In general, for convenience, we shall refer to the "grains" of a "collective" and correspondingly to "granular parts."[2] The notion of "collective" used here is similar to that of "groups" used by Artale [1,2] and by Winston and Odell [3,4]. Winston and Odell also put forward an analogous line of argument to what are here called granular parts in discussing why the "feet of geese" are not parts of a "flock of geese." However, neither they nor Padgham and Lambrix [5] investigate this notion extensively. No analogous notion is discussed by authors such as Gerstl and Pribennow who discuss parts and wholes

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[1] Although we would prefer to reserve the term "granularity" for the notion here termed "collectivity", the term "granularity" has become so overloaded with different meanings in different fields that we reluctantly opt for a neologism rather than risk further confusion and controversy. "Scale" conforms more closely to "size." However, to avoid confusion we have likewise been explicit in this paper and used the term "size range."

[2] Alternatively we might refer to collectives as "emergent wholes," but we have avoided this usage as collectives are usually themselves parts of greater wholes leading to awkward expressions such as "the emergent whole that is part of the whole."

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from a more linguistic perspective [6], nor do notions analogous to "collectives" and "granular parts" figure in the foundational relations discussed by Smith et al. [7]. In biomedical ontologies, the notion of "granular parts" is hinted at by the distinction between "constituent parts" and other forms of part–whole relation in the Foundational Model of Anatomy [8], but it is not extensively developed or explored. Overall, we suggest that this is a seriously under investigated aspect of representation and can be used to account for several important phenomena.

Our fundamental contention is that there are properties and effects of collectives that are emergent and do not depend on differentiation amongst the properties of the grains. By "emergent" we mean that (a) these properties and effects cannot be predicted from the properties of the individual grains and therefore must be attributed to the collective as a whole, and that (b) all grains play the same role with respect to these properties and effects in the collective. Some properties only make sense of a collective—e.g., the pattern of a tiling or the arrangement of cells in a tissue. It makes no sense to speak of the pattern of a single tile or the alignment of a single cell. In other cases the emergent properties are distinct from that of the grains even if related, e.g., the mood of a crowd is distinct from the mood of its constituent individuals, a beach has area and galaxies have mass independent of the size of the grains of sand or the mass of the stars in the galaxy; tissues have strength, grow, etc., in ways distinct from the strength, growth, etc., of the individual cells that comprise them. The fundamental point is that properties of the whole and the information about it pertain to and are determined by the collective rather than its grains. Here we take as our prototype a classic hourglass. In some idealised world it might be possible to determine how long it took the sand to pass through an hourglass by examining the glass and the individual grains of sand and their initial configuration. In practice, no one would attempt such a feat. The time required for the sand to flow through the hourglass is a collective property of the sand in relation to the specific hourglass that contains it and would be measured as such. Even were someone, say a physicist specialised in fluid mechanics to attempt such a feat, the 'gold standard' would remain the observed time—i.e., the emergent property of the collective.

Although the phenomenon of emergence is widely applicable, our fundamental motivations are biological. We seek:

1. To distinguish the way in which, for example, a cell is part of the body from the way a finger is part of the body—specifically that the loss of a cell does not necessarily diminish the body whereas the loss of a finger does;
2. To use this to motivate an important criterion for when parthood as used in biomedicine should, or should not, be represented by a transitive relation;
3. To represent loosely repetitive patterns in tissues—that the "cells in the mucosa are aligned"—and more generally patterns and other emergent properties of collectives;
4. To deal with the collective effects of cells, organelles, etc.—e.g., the process of secretion and regulation of hormones by the cells of endocrine organs or the collective strength of muscles made up of indeterminate numbers of muscle fibres.

More often than not, collectives are themselves portions of larger entities.[3] Galaxies are more than mere collectives of stars; tissues are more than collectives of cells; even a beach is more than a collective of sand. If we have independently measurable commensurable features for both the collective and the larger entity, we can speak of the proportion of the greater entity formed by the collective, e.g., the proportion of water or salt in an amount of sea water, collagen in tissue, or the proportion of the mass of galaxy comprised of the visible stars.

Our goal is a set of broadly applicable principles. The paper follows broadly the intent and lessons, although not always the execution, of the *Open*GALEN Common Reference Model[9,10]. As an illustration we present this paper and an implementation in the framework of OWL-DL[4]. However, the issues are general and independent of any particular implementation.

1.1. Outline of approach

We distinguish two notions often confused under the heading of "granularity":

Collectivity	*Grains vs. Collectives*—the degree of collectivisation, e.g., with respect to water filling a lake, the relation 'filling' is to the water as, amongst other things, a collective of water molecules, not to the individual molecules themselves.
Size range	*Large vs. Small*—the size of an object with respect to the phenomena that affect it, e.g., quantum scales of distance or relativistic scales of speed. However, less extreme differences in scale can have major effects. Surface tension is critical at the scale of a water flea's interaction with water but not at that for a human.

Furthermore we distinguish two types of parthood as subrelations of the basic mereological part–whole relation related to collectivity.

[3] Hence our reluctance to use the phrase "emergent whole" (See Footnote 2).
[4] An OWL-DL ontology illustrating the principles can be found at http://www.cs.man.ac.uk/~rector/ontologies/collectivity.

Granular parthood	e.g., the relation of the cells in the finger of the skin to the finger, in which an indeterminate number of grains are parts of the whole by virtue of being grains in a collective that is part of the whole, and in which removing one granular part does not *necessarily* damage or diminish the whole.
Determinate parthood	e.g., the relation of the finger to the hand, in which a determinate number of parts (at any given time) are directly part of the whole, and in which removing one determinate part *necessarily* damages or diminishes the whole.

Note that the difference is in what follows *necessarily*—removing grains may diminish the whole but removing one grain does not *necessarily* diminish the whole, whereas removing one finger *necessarily* diminishes a hand.

Our major contentions are that:

1. Collectives
   - (1a) "Collectives" are made up of "grains" all of which play the same role in the collective.
   - (1b) "Collectives" are not mathematical sets—their identity is not determined by their membership. (The issue of the identity of collectives is discussed in Section 4.4.1).
   - (1c) Being a "collective" ("collectivity") is independent of the number of grains in the collective.
   - (1d) There are emergent effects and characteristics of collectives as a whole not determinable from the individual characteristics of their grains.

2. Granular and determinate parts
   - (2a) "Determinate parthood" is transitive; granular parthood is not.
   - (2b) Loss of or damage to "determinate parts" necessarily diminishes or damages the whole; loss of or damage to granular parts does not. More generally, many effects on determinate parts have corresponding or related effect on the whole; this is rarely true for granular parts.
   - (2c) A collective that is a "determinate part" of a whole remains a part of that whole regardless of the loss or gain of grains. (The issue of "empty collectives" is dealt with in Section 4.3.2.)

There are two criteria of distinguishing granular and determinate parthood. The first is ontological; the second is cognitive or "informational":

Ontological	Whether there is a fixed, or nearly fixed number of parts—e.g., fingers of the hand, chambers of the heart, or wheels of a car—such that there can be a notion of a single one being missing, or whether, by contrast, the number of parts is indeterminate—e.g., cells in the skin of the hand, red cells in blood, or rubber molecules in the tread of the tyre of the wheel of the car.
Informational	Whether the information to be conveyed pertains to the individual parts—e.g., the laceration to the fourth finger—or to the collective of parts—e.g., the arrangement of the cells in the skin of the finger.

hese two criteria do not always correspond. In particular, we sometimes wish to refer to the collective properties of a fixed number of entities—i.e., to treat what are ontologically determinate parts informationally as being granular parts. We will return to this issue towards the end of this paper after the basic notions are established (see Section 4.3.)

1.2. Other notions sometimes labelled "granularity"

We further distinguish "collectivity" and "size range" from four other notions with which they may be confused, and which other researchers have referred to as 'granularity' in addressing mereological issues.

Specialisation	*Category vs. kind*—the usual notion of "is-kind-of," e.g., that "mammal" is a generalisation including, amongst other things, dogs and elephants. Sometimes also labelled 'abstraction.'
Degree of detail	The amount of information represented about each entity, regardless of its level of specialisation. Crudely in an ontology represented in OWL, the number of axioms and restrictions concerning each entity.
Density	The number of semantically 'similar' concepts in a particular conceptual region. How "bushy" the subsumption graph is. High local density in an ontology usually co-occurs with high levels of specialisation and degree of detail, but in two different ontologies of the same overall depth, in a particular section one may find the same two categories separated by different numbers of intervening categories or possessing very different numbers of sibling categories.
Connectivity	The number of entities connected directly and indirectly to a given entity either through generalisation/specialisation or by other properties.

The notion of "granular partitions" described by one of the authors [11,12] deals with specialisation and degree of detail. Avoiding confusion with this usage is one of the motivations for adopting the phrase "collectivity" rather than "granularity." The notion of "granular partitions," along with the above four notions, are beyond the scope of this paper.

1.3. Criteria for success of the proposed approach

Our purpose in developing "ontologies" is to support information systems. The test of their adequacy is whether they can effectively represent the entities about which information must be communicated so that communication is "faithful." This focuses our interest as much on the relations[5] as on the entities related.

Our specific application is biomedicine, so that we will test our solution primarily with respect to well-known biomedical knowledge resources including the Digital Anatomist Foundational Model of Anatomy [8,13], the Open Biology Ontology (OBO) and more particularly the Gene Ontology [14–16] and *Open*GALEN [10,17,18]. In addition, Johansson [19] provides a detailed analysis of the issue of transitivity discussed in item 1 below against which we will compare our results in Section 3.2.

More specifically, we seek a set of patterns,[6] schemas and properties in OWL that are adequate to capture five notions and exclude as many as possible of their counterexamples:

1. Transitive vs. non-transitive parthood—the difference between the way skin cells of the finger are parts of the body and the way fingers themselves are part of the body. More precisely speaking, we seek to elucidate when the notions spoken of in biomedicine as "parts" are best represented by the part–whole relation as formulated in mereology and when they are better represented by some subrelation or alternative relation. In cases where a notion is better represented by an alternative relation, we seek to elucidate for each such relation whether it is best formulated as transitive or non-transitive.
2. The relation of faults and procedures to parts and wholes—e.g., that the disease of the part is necessarily a disease of the whole and that certain procedure—e.g., repair—on a part are necessarily procedures on the whole.
3. Patterns and characteristics of collectives e.g., that the cells of the intestine are typically aligned (with each other) or that the cells in bone are sparsely distributed.
4. Collective or emergent effects of collectives, e.g., the total secretion of enzymes by the liver cells or the total force exerted by the cells in a muscle.
5. Persistent vs. non-persistent parthood—e.g., that "Jack's finger" will still be referred to as "Jack's finger" even when it is severed from his hand. However, insulin secreted by a cell is not considered to be a part of that cell.

1.4. Independence of collectivity and size

1.4.1. "Collectivity" does not depend on physical size

Necessarily, grains are not physically larger than the collective of which they are members (except perhaps for some odd quantum cases). There is a tendency to talk of things as being at, for example, the "cellular level" or the "organ level" or the "subatomic" level, etc. However, such talk indicates a general tendency and conflates size and collectivity. Hairs are macroscopic entities of the same general size as small organs, yet most of the information we have to convey about hairs concerns the collective "hair" rather than individual "hairs." Sperm and eggs are both cells, but much of what we have to say about eggs pertains to individual eggs, whereas much more that we have to convey about sperm concern the collective, although we need a mechanism to cross levels of collectivity to speak of a single sperm fertilizing a single egg. Indeed, one of the issues in fertility research is to determine which factors depend on the collective of sperm and the fluids in which they are swimming, and which depend on the individual sperm cells themselves. Hence, we explicitly reject any notion of a fixed set of levels of granularity as would seem to be suggested by, for example, Kumar et al. [20].

To extend the biological examples, within cells there are both individual entities, such as the nucleus, and collectives such as mitochondria and chloroplasts. Within the nucleus there are a determinate number of chromosomes that are usually treated individually, but an indeterminate number of macromolecules that form collectives. Furthermore, on occasion, the same entities may be sometimes treated collectively and sometimes individually. The rigidity and shape of a chromosome are a collective property of the DNA molecules (and other supporting structures) that make it up; the "genes"[7] inheritance of characteristics is usually a feature of discrete sequences of base pairs (with complex dependence on context and regulation).

1.4.2. "Size range" does not depend on collectivity

There are many effects that are specific to physical size, distance, speed, density, etc. Most obviously, quantum and relativistic effects are generally relevant only for the very small, very large or the very rapidly moving.[8] Closer to

[5] Known as "properties" in OWL; "roles" in most DLs; and "attributes" in GRAIL.

[6] See Semantic Web Best Practice and Deployment Working Group, http://www.w3.org/2001/sw/BestPractices/.

[7] The definition of what constitutes a gene is problematic, at least in eukaryotic cells, but that need not concern us here.

[8] Relative to the observer of course.

Table 1
Concise infix notation used in this paper with equivalents in OWL and standard DL notation

Abbreviated Informal	OWL Abstract Syntax	DL German Syntax
A AND B	interseotionOf(A B)	A•B
A OR B	unionOf(A B)	A•B
NOT A	complementOf(A)	¬A
has_property SOME C	restriction(has_property someValuesFrom(C))	∃ has_property . C
has_property ONLY C	restriction(has_property allValuesFrom(C))	∀ has_property . C
has_property EXACTLY-n C	restriction(has_property cardinality(1, C)[a]	∃! 1 has_property . C
B → A	subclassOf(B A)	B•A
A	subclassOf(B A)	B•A
— B	subclassOf(CB)	C•B
— — C		
A•B	equivalentClass(A B)	A•B
P_1 propagates_via P_2	not applicable	$P_1 \circ P_2 \rightarrow P_2$

[a] Not supported in the current OWL standard although proposed for extensions.

everyday life, the surface tension and vortex effects that govern insects ability to fly, walk on walls, skim over water, etc. are highly relevant at their size range but almost irrelevant at the size of most mammals. Within biology, chemical bonding, van der Waals forces, other electrostatic forces, and many other effects are important at one physical size range but not at another. When they are relevant, they are relevant both for individuals and for collectives that conform to that size range.

2. Semi-formal presentation

2.1. Notation

Neither of the XML concrete syntaxes for OWL is compact or readable enough for easy use in a paper, and even the official abstract syntax becomes bulky and difficult to read when there is any significant embedding. This paper therefore adopts the following conventions for a simplified syntax. In addition, this allows us to introduce syntax for two constructs not currently standard in OWL although likely in subsequent versions and supported by known description logics, qualified cardinality restrictions (e.g., "exactly-1") and general inclusion axioms ("propagates via").[9]

1. Subset and subproperties are indicated by indentation made explicit by '–'s. Where only two are involved a simple arrow is used, e.g., "Heart → Organ" for "Heart is a kind of Organ."
2. Properties are presented with their inverse separated by a slash; whether the property is transitive, symmetric, functional, etc., are listed to the right, as in Table 1 above.
3. The OWL key words are adapted to a concise infix notation as shown in Table 1.
4. In complex expressions, indentation will be used rather than bracketing wherever the meaning is clear.
5. Schema variables will be given in italics sans serif in place of parts of names, e.g., *X*, *Y*, *Z* as in part_of_*X*. Schema variables range over OWL class names.

In OWL as in all description logic based formalisms, properties hold between individuals. Expressions involving classes are always implicitly about all individuals of the class—that all members of one class are related by the given property to some, only, at least, at most *n*, or exactly *n* members of some other class.

2.2. Basic properties and entities

We shall assume an upper ontology similar to DOLCE [21,22] that includes a notion of "*Physical entity*" that includes both material entities, i.e., "*Physical objects*" and non-material entities such as holes and lines. We shall assume a distinction between "*Physical objects*" such as fingers and statues and "*Amounts of matter*" such as skin and clay as in DOLCE. We leave open until later the discussion of the controversy between cognitivist and realist over the nature of the link between physical objects and amounts of matter. However, we will take it that it is useful to distinguish two subproperties of the parthood relation, one between instances of "*Physical objects*" which we shall term "*determinate parthood*" and the other between instances of "*Amounts of matter*" which we shall call "*ingredienthood*." The common parent of "*determinate parthood*" and "*ingredienthood*" we shall term "*gross parthood*" which we shall treat as a direct subproperty of the most general part–whole relation and a sibling of "*granular parthood*." (This is slightly more elaborate than the simple scheme presaged in 1.1 but necessary to the formalisation.) Normally, collectives are treated as amounts of matter. Roughly speaking, collectives of objects that are discrete at one level of collectivity form amounts of matter at the next. (The exception is for "determinate collectives" dis-

[9] "exactly *n*" and "propagates via" are special cases of the more general constructs known as "qualified cardinality restrictions" and "role inclusion axioms," respectively. Qualified cardinality constraints are supported by many description logics, and some OWL tools support an extension to them. Tractable algorithms for description logics with role inclusion axioms are known but robust implementations are not currently available.

cussed in 4.3.) As in DOLCE we shall also assume that the representation is atemporal,[10] i.e., that it represents entities as viewed from a single point in time, or in the language of the BFO, in a single "snap" (see [23].)

The basic notions to be captured are that:

1. The parent part–whole relation, "*is part of*"/"*has part*" corresponds to the basic mereological relation and both it and the two subrelations "*is determinate part of*"/"*has determinate part*" and "*is ingredient of*"/"*has ingredient*" and their common parent "*is gross part of*"/"*has gross part*" satisfy the usual mereological axioms, i.e., that they are reflexive, transitive, and antisymmetric, and satisfy the weak supplementation principle [24]. This means that: (i) everything is a part of itself[11]; (ii) parts of parts are parts of wholes; (iii) nothing is a part of a part of itself, and (iv) if a part not equal to the whole is removed, a residual is left behind.
2. The "*is grain of/has grain*" relation is irreflexive, antisymmetric, and non-transitive, i.e., that (i) nothing can be a grain of itself; (ii) a collective cannot be a grain of one of its own grains; and (iii) that grains of grains of a collective are not grains of that collective.
3. The "*is grain of*" relation propagates via the "*is part of*" relation, i.e., if an entity is a grain of collective that is part of a whole then that entity is also part of the whole. More formally: "*is grain of* → *is part of* → *is part of*."

2.3. Approximation in OWL

Owl supports transitive properties (relations) and the notion of subproperties. It lacks the notion of propagates_via (sometimes known as inheritance across transitive roles—see 2.2 point 3 above), but this can be approximated by use of the role hierarchy by making is_grain_of a subproperty of is_part_of, which is a slightly stronger condition. This has the undesirable consequence that grains, which are analogous to members of a set, count as parts of the collective, which runs counter to the usual usage in for example Winston and Odell [3,4]. However, in practice this causes little difficulty because most classifications and queries involve the relations is_gross_part_of or is_determinate_part_of, both of which exclude is_grain_of. (In fact, in this case, the approximation may be an advantage as it avoids users having to make a distinction that many subject matter experts find unintuitive.) OWL also lacks representations for the notions of reflexive, irreflexive and antisymmetric properties. The consequences of these limitations are discussed in Section 4.5. Despite these limitations, a sufficient representation of part–whole relations to cover the important positive inferences from the more general axioms is possible. A demonstration following the development in this paper is available.[12]

The basic property hierarchy for the OWL approximation is presented in Table 2A using the conventions described in 2.1 above. The additional properties of is_gross_part_of and is_ingredient_of are explained in 2.4.3 below. The corresponding entity hierarchy is presented in Table 2B.

2.4. Basic schemas

2.4.1. Defining collectives

Collectives are defined using universal restrictions following the schema below, where the upper case italics indicates schema variables that range over class names.

Collective_of_X ≜ Collective AND has_grain ONLY X

There are two consequences of this schema:

1. Empty collectives are allowed. This is convenient when we want to talk about concentrations of zero or things that are empty or missing. We can define Non_empty_collective in the obvious way as: Collective AND has_grain SOME Anything[13]
2. All the grains in a collective must be of the same type. This does not rule out collectives of a type that is a disjunction of other types. However, any collective defined in terms of a disjunction should be viewed with suspicion, as it is more likely to be more appropriately represented as a mixture (see 2.4.3)

2.4.2. Reflexive parts

Because reflexive properties cannot be expressed directly in OWL, it is necessary to represent the axioms to allow the required inferences by means of class definitions rather than property definitions. To this end, we use a series of schemas for "reflexive parts" which behave as mereological parts—i.e., they include the whole and all of its parts. One such schema is defined for is_part_of and each of its major subproperties:

Reflexive_part_of_*X* ≜ *X* OR is_part_of SOME *X*
Reflexive_gross_part_of_*X* ≜ *X* OR is_gross_part_of SOME *X*
Reflexive_determinate_part_of_*X* ≜ *X* OR is_determinate_part_of SOME *X*

[10] A detailed discussion of time in ontologies and their use in biomedical informatics would take us far beyond the scope of this article.

[11] The usual formulation of the axiom the part–whole axioms in mereology is in terms of what is here called "reflexive parthood." "Proper parthood" is then defined as a part of the whole that is not equal to the whole.

[12] http://www.cs.man.ac.uk/~rector/ontologies/collectivity/Collectivity-demo.owl.http://www.cs.man.ac.uk/~rector/ontologies/collectivity/Collectivity-demo-classified.owl.

[13] owl:Thing

Table 2A
The property hierarchy for the OWL implementation

Property	Transitive	Domain/Range	Comments
is_part_of / has_part	Y	Physical_entity / Physical_entity	The generic part-whole relation Reflexive & antisymmetric properties not captured directly in OWL.
— is_gross_part_of/ has_gross_part	Y	Physical_entity / Physical_entity	The common parent (in effect the disjunction) of measurable portions and determinate parts and other properties indicated by the ellips is (“...”)
— — is_determinate_part_of / has_determinate_part	Y	Physical_entity / Physical_entity	The relation between determinate parts and wholes, e.g., fingers and hands.
— — is_portion_of/ has_Dortion	Y	Amount_of_matter/ Amount_of_matter	The relation between the water in the bay and the water in the lake. See 2.4.3
— — is_ingredient_of / has_ingredient	Y	Amount_of_matter/ Amount_of_matter	The relation between plasma and blood See Section 2.4.4 and Table 3
— — ...			
— is_grain_of / has_grain	N	Physical_object / Collective	The relation between a grain and the collective. Represented as a subproperty of is_part_of in OWL as an approximation of propagates via see 2.2 item 3 and 2.3.

Table 2B
The high level entity hierarchy for the OWL implementation

Class	Use in this paper	Comments
Physical_entity	Domain/range of is_part_of and is_determinate_part_of	Common ancestor of all physical entities
— Physical_object	Domain for is_grain_of	Material physical entities
— Non_material_object	Excluded from domain for is_grain_of	Non-material physical entities, *e.g.* holes, lines, etc.
— Amount_of_matter	Range for is_ingredient_of	Amounts of “stuff’, roughly corresponding to mass nouns. (NB the Relation between Physical_object and Amount_of_matter depends on the debate between the cognitivist & realist stance and is not directly relevant to this paper. See 4.3)
— — Mixture	Domain for is_ingredient_of	Abstract including solutions, suspensions etc.
Collective	Range of is_grain_of	Whether or not Collectives are considered physical and whether or not they are to be disjoint from Physical_object, is deferred. See 4.3 and 4.4.3.

Which schema is appropriate depends on the requirement. In simple “part explosions” only determinate parts are required, for example an explosion of the parts of a car would normally only be expected to include the determinate parts—e.g., body, motor, wheels, etc. If both constituents—e.g., steel and rubber[14]—as well as determinate parts are needed (see “Mixtures” below), then Reflexive_gross_part_of_*X* is required. If all parts are needed, including granular parts as in the Digital Anatomist Foundational Model of Anatomy [8] where cells and even macromolecules are counted as parts, then the most general notion of Reflexive_part_of_*X* is required.

These schemas also make it easy to express constructs related to Schulz and Hahn’s SEP Triples [25–27]. Schulz and Hahn transform partonomies in order to make inference over part–whole reasoning require only less expressive description logics. In their transformation, each original entity becomes a triple of three nodes termed the “Structure” (“S”), “Entity” (“E”), and “Part” (“P”) nodes. In terms of the above schemas, for each entity *X*, the “reflexive part” corresponds to the “Structure” (“S”) node and *X* itself to the “Entity” (“E”) node. The “Part” (“P”) node can be represented by the schema: is_part_of SOME *X*, i.e., all the proper parts of the entity *X*.

2.4.3. Mixtures

Collectives and reflexive parts provide the basic mechanisms required, but almost all interesting cases involving collectives involve not just one collective but mixtures of collectives with other collectives and/or amounts of matter.

We treat most collectives as mass entities or “amounts of matter” in DOLCE’s terminology—i.e., e.g., a “Collective of cells” is treated as an “Amount of cells” by analogy to the “Amount of clay” that makes up the statue or the “Amount of plasma” in blood. (The exceptions are discussed in 4.3.) There are two further subrelations the parthood relation with respect to “amounts of matter”—“portions” and “ingredients.” Roughly, portions are separable and analogous to determinate parts—e.g., the portion of the water in the lake that is in the bay, the portion of

[14] Strictly speaking we should say “Steel that is part of car” and “rubber that is part of car” since not all steel nor all rubber is part of a car.

milk poured into the pitcher, etc. For purposes of this paper, every portion of a mixture will be considered to have the same ingredients in the same proportions, i.e., we will consider only homogeneous mixtures. (An account of non-homogeneous mixtures is beyond the scope of this paper.) We place is_ingredient_of and is_portion_of as siblings of is_determinate_part_of and under is_gross_part_of because some classes and queries to be formulated include all three, e.g., the gross parts of a car include both wheels and rubber; the gross parts of the arm include both the biceps and fascia.[15]

The basic schema for mixtures is:

Amount_of_Mixture_of_X_1_and_X_2_and_. . ._and_X_n
≜ Amount_of_Mixture AND has_ingredient SOME X_1 AND has_ingredient SOME X_2 AND. . .AND has_ingredient SOME X_n

Formally, the domain constraint on is_ingredient_of guarantees in this simple version that anything that has portions is a mixture. However, for clarity it is better to include Mixture as a conjunct explicitly. A Mixture can be defined by being an amount of matter that has ingredients.[16]

Amount_of_Mixture ≜ Amount_of_matter AND has_ingredient SOME Amount_of_matter

For example, one might represent that blood is a mixture of—amongst other things—plasma, red cells and white cells:

Amount_of_blood →
Amount_of_Mixture AND
has_ingredient SOME Amount_of_plasma AND
has_ingredient SOME (Collective AND has_grain ONLY White_blood_cell) AND has_ingredient SOME (Collective AND has_grain ONLY Red_blood_cell)

Note that, in common with most biomedical definitions, we have not closed the list of ingredients in the mixture. There is nothing in the above axiom to imply that blood does not contain other things, only that it does contain the ingredients mentioned. Nor have we made this a definition, merely an implication, as indicated by the use of the symbol "→" rather than "≜"; it does not imply that *any* mixture of plasma, red cells, and white cells is blood, only that all blood is a mixture of plasma, red cells, and white cells.

The above implication likewise leaves open the question as to whether blood with a no white cells or no red cells is still blood. If we wish to represent an implication that requires the collectives to be non-empty, then we can expand the above to:

Amount_of_blood →
Amount_of_Mixture AND
has_ingredient SOME Amount_of_plasma AND
has_ingredient SOME (Collective AND has_grain ONLY White_blood_cell AND has_grain SOME White_blood_cell) AND has_ingredient SOME (Collective AND has_grain ONLY Red_blood_cell AND has_grain SOME Red_blood_cell)

However, even this formulation requires only that there be at least one of each kind of cell. For a further discussion of sized of collectives see 4.3.2.

In most situations we want the mixture to consist of just one portion of each kind of ingredient. This can be done if qualified cardinality restrictions are supported.[17] We need simply say that there is exactly one amount or collective of each kind as follows:

Amount_of_blood →
Amount_of_Mixture AND
has_ingredient exactly-1 Amount_of_plasma AND
has_ingredient exactly-1 (Collective AND has_grain ONLY White_blood_cell) AND
has_ingredient exactly-1 (Collective AND has_grain ONLY Red_blood_cell)

There are a number of other axioms linking portions and ingredients that are discussed briefly in 4.5 but which are largely outside the scope of this paper.

2.4.4. Proportions

The relative amounts in a mixture are so often important, and the means of determining relative amounts vary—e.g., by weight, volume, activity, etc. Therefore, in a binary relational formalisms such as RDF or OWL, it is often appropriate to reify the relation has_ingredient, i.e., to re-represent it as a class—which we shall term Proportion—plus three new subproperties—which we shall term has_proportion, is_of_ingredient, and has_percentage. The schema then becomes that a mixture consists of a set of ingredients related to the mixture by proportions. (NB: Do not confuse "proportions" with "portions." Despite the similarity of the words, the notions are completely different. A Portion is an Amount_of_matter; A Proportion is a reified relation between two amounts of matter, one the ingredient of the other, in some specific ratio[18]—see 2.4.5.) If we include a property of the Proportion to represent the ratio in the relationship, e.g., the percentage as weight per unit volume rep-

[15] Again, strictly speaking we should say "rubber that is part of the car" and "fascia of the biceps."

[16] A given ontology might, for consistency, wish to insist that all amounts of matter were mixtures. That issue is deferred here.

[17] "Qualified cardinality restrictions"—the ablity to say exactly 1 of a class, at least one of a class, at most one of a class, etc.—were omitted in the final editing of the OWL standard. They are supported by essentially all reasoners used for OWL-DL, many tools, and are likely to be reinstated at the first revision of the standard.

[18] A complete account would require dealing with the measure of the ratio, e.g., by mass, by volume, by number, etc. However, this would add undue complexity here.

Table 3
Property hierarchy reconciling ingredients and proportions

Property	Transitive	Domain/ Range	Comments
is_ingredient_of/ **has_ingredient**	Y	Amount_of_matter/Amount_of_matter OR Proportion_of_matter	Ingredients of ingredients are ingredients of the whole
— of_mixture/ **has_proportion**	N	Proportion/Amount_of_matter	Proportions of proportions are not proportions of the whole.
— is_proportion/ **is_of_ingredient**	N	Amount_of_matter/Proportion	

Note that the relevant properties are the inverses (given in bold) to remain consistent with Table 2A.

resented for brevity by has_percentage,[19] the basic schema becomes:

Amount_of_Mixture_of_X_1_and_X_2_and_. . ._and_X_n ≜
Amount_of_Mixture AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient SOME X_1 AND has_percentage VALUE p_1) AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient SOME X_2 AND has_percentage VALUE p_2) AND
. . .AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient SOME X_n AND has_percentage VALUE p_n)

The example of blood extended to this schema therefore becomes:

Amount_of_blood →:
Amount_of_Mixture AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient *SOME Plasma AND has_percentage VALUE p_1) AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient (Collective AND has_grain ONLY White_blood_cell) AND has_percentage VALUE p_2)) AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient (Collective AND has_grain ONLY Red_blood_cell) AND has_percentage VALUE p_3))

where the p_i are, in this example, appropriate weight per unit volume concentration quantities. Other such properties of the proportion can be represented by analogy. Note that, as always when reifying properties, care must be taken with cardinalities so that a given Proportion can pertain to exactly one Amount_of_Mixture and exactly one ingredient.[20]

2.4.5. Allowing proportions and simple ingredients to coexist

It is possible to allow the two patterns—for simple ingredients and for proportions of ingredients—to coexist if we arrange the property hierarchy as shown in Table 3. Given this arrangement, to say that an mixture has a proportion of some ingredient is to imply that it has that ingredient i.e., that the OWL schema below always holds:

Amount_of_matter AND has_proportion SOME (Proportion AND is_of_ingredient SOME X) →
Amount_of_matter has_ingredient SOME X.

The fact that proportions of proportions are not themselves the same proportions of the whole is reflected in the facts that has_proportion and is_of_ingredient are not transitive. Since the percentages attached to each proportion will have to be recalculated at each step down the chain, the relationship is not simply transitive but follows a more complex rule. That rule must be handled by reasoning mechanisms outside the scope of OWL or most other ontology languages. What can be captured in OWL is that ingredients of ingredients, by either mechanism, are ingredients of the whole, which is represented by the fact that the parent property, has_ingredient, is transitive.

2.4.6. Characteristics of collectives and patterns of collectives in mixtures

2.4.6.1. Characteristics of the collective itself. Members of a collective often have collective characteristics, e.g., that the cells of a tissue are aligned or that the atoms of a crystal form a particular lattice structure, that neurons fire synchronously or asynchronously, etc. Such characteristics pertain to the collective; they make no sense if applied to its individual grains. Nor do these characteristics depend on the collective's relation to any other entity of which it may be a part. Furthermore, just as collective's identity is not extensional, their characteristics are not universal over their extensions, i.e., they can be considered true even if they do not apply to every member of the collective, e.g., a crystal will still be said to have a particular alignment even if it has flaws.[21] Hence it is appropriate to represent such characteristics as properties of the collective,[22],e.g.

[19] A complete exposition of the quantitative aspects of proportions would involve a lengthy diversion into issues around quantities and units and is omitted here.

[20] In OWL, this is represented by declaring has_proportion to be inverse functional—i.e., that its inverse is single-valued—and declaring is_ingredient_of to be functional—i.e., single valued. See Defining N-ary Relations on the Semantic Web: Use With Individuals, Natasha Noy and Alan Rector, Editors' Draft, Semantic Web Best Practice Working Group, http://www.w3.org/TR/swbp-n-aryRelations/.

[21] How completely such characteristics are true belongs with a discussion of fuzziness or precision and is beyond the scope of this paper.

[22] For a discussion of the use of classes in value partitions, see Semantic Web Best Practice Committee's note http://www.w3.org/TR/swbp-specified-values/.

Collective AND
has_grain ONLY Cell AND
has_pattern SOME Alignment

2.4.6.2. Characteristics of the collective in relation to other entities. On the other hand, there are characteristics that pertain to the relation between a collective and other items in a mixture—e.g., that cells are suspended in plasma or that the water and alcohol molecules are intermingled in a miscible liquid. In this case the properties are best represented as additional characteristics of the Proportion, e.g.

Amount_of_blood →:
Mixture AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient SOME Plasma
AND has_percentage VALUE p_1
AND has_role SOME Suspensor_role)
AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient (Collective AND has_grain ONLY White_blood_cell)
AND has_percentage VALUE p_2
AND has_role SOME Suspensee_role))
AND
has_proportion EXACTLY-1 (Proportion AND is_of_ingredient (Collective AND has_grain ONLY Red_blood_cell)
AND has_percentage VALUE p_3
AND has_role SOME Suspensee_role))

The form above is chosen over a representation in the spirit of "Blood is plasma in which are suspended red and white cells" since this variant has the undesired implication that "Blood is a kind of Plasma"—a statement that is clearly false.

2.4.7. Emergent effects of collectives

Each cell in most glands secretes a portion of the hormone or other substance secreted; each granule in a synapse releases a portion of the neurotransmitter that fires the synapse; each muscle fibre exerts a measurable force when it contracts; each strand of a cable has its own tensile strength. However, in each of these cases, the information of interest is almost always about the collective effect. The collective effect is a function of the individual effects, but may be so highly non-linear that it would be difficult to predict, even if all the individual effects were known. The function is also highly variable for different collectives. Consider for example the different relationships between the collective strength of chains with respect to their links and of cables with respect to their strands. Furthermore, in many cases such as cables, minor changes in the effects of individual grains (i.e., strands) are irrelevant provided the collective effect remains unchanged.

Emergent effects are dealt with straightforwardly by schemas such as:

(*Collective_X* AND has_grain ONLY *Entity_Y*)→
has_effect *Effect_Z*

A simple example would be:

(Collective AND has_grain ONLY Pancreatic_islet_cell) →
has_effect SOME (Secretion AND has_target SOME Insulin
AND has_rate VALUE *r*)

where *r* is a quantity with a numeric magnitude and units of type volume per unit time or weight per unit time.

The concern is not with the rate of secretion of individual islet cells, or indeed of individual islets, but with the rate of secretion of the entire collective of islet cells.

3. Use and consequences

3.1. Propagation of faults

In general, faults propagate only across gross parthood, e.g., disorder to the liver is usually considered as a disorder of the digestive system, body, etc., whereas we would not normally consider a disorder of a single liver cell in this way. The liver cell is a grain of a collective that forms part of the liver (whether or not via a constitutes relation). Likewise, while we would consider a disorder of the metabolism of all, or a significant portion of, red cells—e.g., sickle cell anaemia—as a disorder of blood, we would not consider a disorder of the metabolism of a single red cell as a disorder of blood. Indeed, since both liver and red blood cells constantly die and are replenished, were we to consider the state of individual cells, all organisms would suffer from liver and blood disorders, which is clearly nonsense.

Hence the schema for disorders is normally

Disorder_of_*X* ≜ Disorder has_locus SOME Reflexive_gross_part_of_*X*.

where has_locus is the property linking disorders to their anatomical or functional "site." This captures the above two examples and analogous cases while excluding the case of damage to individual cells, etc. It is a slight adaptation of the method of SEP triples introduced by Schulz and Hahn [25,28].

Note that the issue of propagation across boundaries of collectivity is orthogonal to the issue of whether the disorder applies to the entity as a whole or to its reflexive parts. There are disorders—gastritis, inflammatory bowel disease, septicaemia (infection of the blood), etc. that refer to the whole taken as a whole rather than its parts. For these cases, the appropriate schema excludes all parts, whether gross or granular:

Disorder_of_*X*_as_a_whole ≜ Disorder has_locus SOME *X*.

Furthermore, the issue is not dependent on size. Analogies can be found at all physical size ranges.

3.2. Transitivity of part–whole relations

The issue of propagation of faults is closely related to the issue of when best to represent the biomedical notions of parthood by transitive or non-transitive subrelations of is_part_of. Effectively, the argument in this paper is that most cases where the best representation is a non-transitive relation involve transitions across levels of collectivity, i.e., they involve chains of reasoning that include the is_grain_of relation, which is not transitive. Confusion arises because our usual language does not distinguish the broader is_part_of relation from its more specialised subrelations, here termed is_gross_part_of and is_grain_of. The is_grain_of relation marks boundaries between levels of collectivity, or what are often called levels of granularity. However, we argue that the critical issue of whether a transitive or non-transitive subrelation should be used to represent parthood in a particular case is not one of physical size, per se, but of whether or not the subrelation deals with collectives or individuals.

As a partial validation of this view, consider the list of cases provided by Johansson of anomalies where the appropriate relation to reprsent parthood is not considered to be transitive [19]. Table 4 lists these issues and whether or not they are accounted for by the distinction between gross parthood and granular parthood.

We would argue that cases 4–8 and 11–12) are clearly accounted for by the distinction between gross and granular parthood.

Of the remainder, for cases 1 and 2, Johansson puts forward the argument that there is a narrow, non-transitive subproperty of parthood, which we usually term "direct parthood," that is not transitive and that the problem arises out of a confusion of the direct subproperty and the parent transitive property. He draws support for this distinction from Simons [29]and Casati and Varzi [30]. This seems to us entirely correct. However, Johansson also includes case 3 in this category. We would argue that it was better accounted for by the distinction between gross and granular parthood. We might even stretch the issue to case 2, and claim that it demonstrates that platoons are better treated as granular than determinate parts.

Case 9 Johannson explains by noting that two notions of parthood being used are fundamentally different. Again we would agree, a point we would signify by the incompatibility of parthood for occurrents and continuants, i.e., "eating" and "spoon."

Case 10 is dealt with cursorily but seems clearly to raise a host of questions, not least whether the shard per se existed prior to the shattering of the plate. Such cases cannot be dealt with in the context of an atemporal representation such as that used in this paper.

Johansson's thesis is that intransitive parthood predicates are not binary predicates. Our argument is that for the cases where it applies, the distinction between gross and granular parthood—i.e., between parthood within levels of collectivity and parthood across levels of collectivity—is simpler, easier to apply, and arguably more fundamental.

3.3. Persistent and non-persistent part-hood

It is a general pattern that things continue to be spoken of as 'parts' even after they have been separated from the whole. Thus, we speak of "John's finger" even after it has been amputated. Even if it has failed to develop we may speak of it as being absent. By contrast, we do not speak of the secretions from an individual cell as remaining part of that cell, although we might speak of them as being from an organ or tissue. Hence we might legitimately seek to distinguish, for example, testosterone produced by the adrenal gland from testosterone produced by the testes, or oestrogen from the ovary from oestrogen from adipose tissue. However, we would be unlikely to distinguish testosterone originating from individual cells. Likewise, although we might talk of the "piece of John's liver" or "cells from John's liver" following a biopsy, we would be unlikely to consider the cells as parts of John or his liver, present or missing, in the same sense as we would his amputated finger or even the "piece of John's liver."

As in the above cases, we would argue that "persistent parthood" is something that pertains to things arising from gross parts but not from granular parts. This point, we accept, remains somewhat speculative and requires further investigation. (Note, we find "persistent parthood" as used here closer to common clinical usage than "permanent parthood" as advocated in Smith et al. [7]).

4. Discussion

4.1. Biomedical cases

4.1.1. Tissues and substances

A major motivation for the current work is to deal with specific problems in the adequate representation of the biological notions of tissue and substance. In this formulation both are "mixtures" some of whose "ingredients" are "collectives."[23] The schemas offered here provide both for properties that are intrinsic to the collective—e.g. arrangements and patterns—and for properties of the relation of the collective to the rest of the mixture, e.g., the proportion, distribution, etc. The claim is not that tissues *are* collectives, but that they are best viewed as amounts of matter some of whose ingredients are collectives.

[23] The label "ingredient" is perhaps not ideal here. No better has yet been suggested, but the authors are open to suggestions.

Table 4
Johansson's list of cases for non-transitivity of part-whole relations

1. A handle, x, can be part of a doer, y, and a door can be part of a house, z, but yet the handle need not be (is not) a part of the house. That is, '$x < y$' and '$y < z$' but '$\neg(x < z)$'. (Of course, 'part' cannot here and elsewhere in the list be synonymous with 'spatial part'.)	*Not accounted for*: confusion of direct and indirect partonomy.
2. A platoon is part of a company, and a company is part of a battalion, but yet a platoon is not part of a battalion.	*Possibly accounted for*: Is a platoon a grain or a part of a company?
3. A cell's nucleus is part of a cell, and a cell is part of an organ, but yet the nucleus is not part of an organ.	*Accounted for*. Cells are granular parts of the organ, not gross parts.
4. Heart cells are parts of the heart, and the heart is part of the circulatory system, but yet the cells are not parts of the circulatory system.	*Accounted for*. Cells are granular parts of the Heart, not gross parts.
5. Person P is part (member) of the football club FC, and FC is part (member) of the National Association of Football Clubs, NAFC, but yet P is not a part (member) of NAFC.	*Accounted for*. The person is a grain (member) of the football club, not a part of it and, similarly, the football club is a grain (member) of the association.
6. Simpson's finger is part of Simpson, and Simpson is part of the Philosophy Department, but yet Simpson's finger is not part of the Philosophy Department.	*Accounted for*. Simpson is a member (grain) of the philosophy department (or possibly in some other relation to it), but not "part" of it in the sense used here.
7. Hydrogen is part of water, and water is part of our cooling system, but yet hydrogen is not part of our cooling system.	*Accounted for* and a false example. Hydrogen is not part of water. Hydrogen atoms are part of water molecules, collectives of which constitute water used in the cooling system
8. Cellulose is part of trees, and trees are parts of forests, but yet cellulose is not part of forests.	*Accounted for*. Trees are grains for forests.
9. A handle is part of a spoon, and a spoon is part of eating soup, but yet a handle is not part of eating soup.	*Not accounted for*; A different issue. Continuants and occurrents cannot be parts of each other for reasons not discussed in this paper.
10. This shard was part of a plate, and the plate was part of a dinner service, but yet the shard was not part of the dinner service.	*Odd case not accounted for*. An adequate discussion requires consideration of time. It is unclear whether or not the shards existed prior to the shattering of the plate.
11. This tree is part of the Black forest, and the Black forest is part of Germany, but yet this tree is not part of Germany.	*Accounted for*. Trees are grains of forests. (Also the notion of geographical parthood might be treated differently by some authors)
12. These grains of sand are part of the beach, and the beach is part of the island, but yet these grains of sand are not part of the island.	*Accounted for*. The grains of sand are grains of the beach.

However, the schema for proportions and mixtures given here is limited in complex cases, e.g., where one might want to say that the water plays the role of solute for sodium but suspensor for cells. In this case there would need to be two different roles for the same substance.

Note that for this purpose it would be necessary to reify Proportions even in a formalism supporting n-ary relations. Since there are an arbitrary number of ways by which a given proportion might be characterised, any fixed arity relation capturing only a fixed number of such characteristics would almost certainly become inadequate as the ontology evolved.

Much work remains to be done to describe patterns within tissues, but the schemas given provide a starting point. The "Mixture" and the "proportion" are suitable reified entities to be described—although one might want to change the labelling of the entities we here call "proportions" to indicate the wider range of information potentially expressed about them.

4.1.2. Why do current bio ontologies not make the distinction between granular and determinate parts?

An obvious question is: "If the distinction between determinate and granular parthood is so important, why is it not already standard?" The simplest answer is that few of the large bio-ontologies built to date have been required or used to support inferences that require this distinction.

In the Foundational Model of Anatomy [8,31], the distinction is prefigured by the notion of "constituent parts." However, the FMA is based exclusively on structure rather than function, so that the issue of emergent effects does not arise. Even when dealing with structure, the FMA does not represent attributes that apply to collectives such as the alignment of cells in the mucosa of the intestine (although the example is due to Cornelius Rosse.[24]) Likewise, the FMA does not support detailed cardinality with respect to parts, so the distinction between fixed numbers of parts—e.g., fingers—and indeterminate numbers of parts—e.g., cells—does not arise. However, these limitations do present difficulties. The issue of the status of tissues and their structure is a significant problem and has, for example, plagued discussions in the SAEL consortium[25] in its efforts to reconcile various anatomic representations in mouse and man. The notions in this paper provide a framework for representing a number of the important notions raised in those discussions and a route towards reconciliation of some of the controversies.

In principle, the *Open*GALEN ontology supports the distinction between collectives (termed "multiples") and determinate parts (termed "components"). However, in

[24] Private communication, 2004.
[25] http://www.sofg.org/sael/.

practice it has usually been elided. The prime use for *Open*GALEN has been for defining surgical procedures and the drug actions and usages. In the first case attention is confined to determinate parts; in the second, almost exclusively to granular parts (e.g., receptors). In very few cases is there room for confusion; hence the lack of distinction has not proved troublesome. Were the *Open*GALEN model to be extended to include stronger modelling of physiology and function, then it is almost certain that the distinctions presented in this paper would become critical.

In SNOMED-CT, the primary use for anatomy is for the site, or locus, of diseases and the target of surgical and other interventions. Both uses are predominantly on the level of gross anatomy where collective effects are uncommon. Although this mean that in SNOMED, notions such as "hair loss" must be defined as being literally "loss of at least one hair" rather than "a collective of hairs" (above some fuzzy threshold in size), in practice no inferences or issues of classification within SNOMED itself turn on such detailed representations.

Does this neglect of the distinction between determinate and granular parts mean that the distinction is purely "academic"? We believe not. It merely reflects the current state of the art whereby representations are typically restricted to a single level of "collectivity," or if you prefer, "granularity."

As the demand for stronger functional representation across "levels of granularity" grows, including through the interoperation of extant 'single level' ontologies, so too will the need for a precise language to describe individual and collective effects and to distinguish them from effects of physical size.

4.2. Collectives and normalisation of ontologies

To support modularisation and maintenance, a major goal of the *Open*GALEN ontologies is to maintain a "normalised" structure in their implementation in which all primitives form disjoint trees and all multiple classification is the result of inference rather than assertion [32]. The schemas put forward here all lend themselves to normalisation in this sense. At least in its cognitivist/multiplicative versions, the different aspects of each entity are clearly factored so that they can be described independently.

4.3. Cognitivist vs. Realist/Multiplicative vs. unitary representation

4.3.1. "Amounts of matter" and "Physical objects": the "constitutes" relationship

The discussion so far has made no link between entities of type Amount_of_matter and entities of type Physical_object. This relation is a matter of controversy between the cognitivist/multiplicative view represented by Guarino and Welty in OntoClean and DOLCE [22,33,34] and Smith and his colleagues' realist / unitary view in the Basic Formal Ontology (BFO) [35,36]. The authors are split between these two traditions. Fundamentally, given a "Statue made of clay," Guarino and Welty's cognitivist/multiplicative view is that there are two entities—a "Statue" and an "Amount of clay"—and that the "'Amount of clay' *constitutes* the 'Statue'." Smith's realist/unitary view is that there is a single entity and that the "'Amount of clay' *is* the 'Statue,'" or more precisely that the "'Amount of clay' *is* (during some time span) the 'Statue'." In the formulation presented here, "collectives" are treated as "amounts of matter" with the exception of "determinate collectives" (see 4.3.2 below).

4.3.2. Number of entities in collectives: empty, small, and determinate collectives

From a cognitivist, or perhaps better termed "informationalist," viewpoint, there is no problem with empty collectives. There is information to be conveyed about them—that they are empty—therefore it is appropriate to represent them. Likewise, the number of grains in a non-empty collective is irrelevant to whether or not it can be considered a collective. If there is information to be conveyed about the collective properties of some entities, it is irrelevant that, in a particular case, there happen to be only a few, one, or even no grains in the collective.

This view also means that there is no problem with the notion of "determinate collective." "Collectives" have been discussed so far in this paper as having an indeterminate number of grains. There are, however, collective effects of determinate collections of entities—the collective grip of the fingers, acuity of the eyes, the total capacity of the plates in a dinner service, etc. Note that in each of these cases, the collective effect is not determined by the precise number of grains in the collective even though there may be a 'normative' number. For example, a grip has strength whether one or more fingers is missing (or indeed a supernumerary finger were present), a person's visual acuity is typically recorded whether a person has one or two functioning eyes, as being the best visual acuity with all the available eyes.

From the point of view of the formal theory, there need be nothing to prevent the same entity being a determinate and granular part of the same whole, indeed to impose such a constraint would significantly increase the complexity of the axiomatization. From the cognitivist or "informationalist" perspective there is no problem—there is distinct information to be conveyed both about the collective and the individual entities that comprise it, hence it is appropriate to represent them separately. However, for the realist, having both the collective and the grains poses as separate entities would seem to pose the same problem as having the clay and the statue as separate entities. A realist must reconcile collective and deterministic parthood without introducing multiple entities apparently occupying the same space and time.

From either point of view, determinate collectives are the exception to the rule that collectives are treated analogously with "amounts of matter." For example, it seems odd to say that "the fingers constitute (part of) the hand" in the same way that "skin cells constitute (a portion of) the skin of the hand." A fully adequate handling of determinate collectives remains an unresolved issue.

Most other issues discussed in this paper are largely independent of this controversy. For purposes of this paper and presentation in OWL, the factorisation provided by the cognitivist/multiplicative view is clearer and briefer, so we shall adopt it here and in the illustrative ontologies on the Web. To do so requires adding the relation constitutes/is_constituted_by to Table 2A at the point marked by the ellipsis ("...") as one of the additional kinds of "gross parthood" and a sibling of is_portion_of/has_portion. The domain of constitutes is Physical_object, and the range is Amount_of_matter. Since the domain and range are different, and in most formulations disjoint, constitutes/is_constituted_by is non-transitive.

4.4. Other unresolved issues

4.4.1. Identity of collectives

If the identity or equivalence of collectives is not determined extensionally as for mathematical sets, how is it to be determined? We present no complete answer to this problem. From a cognitivist or informationalist point of view the problem is manageable: Two collectives are the same if there is the same, or a continuation of the same, information to be conveyed about them; they are different if there is different information to be conveyed about them. Under what circumstances can the collective of red cells in my blood be considered to be the same entity to have preserved their identity (i.e., to be the same entity) even though the individual grains (i.e., cells) may have been completely replaced? This issue is particularly important with respect to Guarino and Welty's DOLCE ontology and OntoClean methodology [33] because they distinguishes between categories according to whether or not they "carry identity." Hence, in DOLCE what sort of thing the category "Collective" is considered to be depends on whether and under what circumstances individual collectives can be said to preserve their identity. Likewise the issue of identity is important in the Smith's Basic Formal Ontology [35,36] because it seeks to track the lifetime of entities over time. However, as stated in the introduction, in practical use, e.g., to support terminologies and medical records, most biomedical ontologies are largely atemporal. They seek only to represent the view from a particular point in time. Issues of identity and continuity over time are normally be dealt with by separate reasoning mechanisms outside the ontology, e.g., by "temporal abstraction" [37]. Hence, for ontologies intended for such use, the issue of a precise definition of identity is less critical and perhaps moot.

4.4.2. Operations on collectives

The most common requirement for operations on collectives is for variants of union and flattening. The collective of members of several collectives—e.g., the cells in the skin of the thumb and forefinger—can be easily expressed. Likewise, where collectives are nested, the flattened version can be easily captured—e.g., the collective of all cells in the collective of pancreatic islets. Although logically possible, the authors have encountered no practical applications requiring intersections of collectives.

4.4.3. Are collectives of physical entities physical? material?

Whether non-empty collectives of physical entities should or should not count as physical has been deliberately left open in this paper. Likewise, it is left open whether empty collectives should be material or non-material—i.e., physical objects (material) as opposed to holes, corners, etc. (non-material). Because the schema for collectives uses "only" (allValuesFrom) rather than "some" (someValuesFrom), it is perfectly reasonable to assert axioms of the form, for example, that "all collectives of only physical entities are physical" and that "all non-empty collectives of only physical entities are material." These axioms seem both natural and helpful in biological applications. Similarly, it seems natural to treat empty collectives of only physical entities as non-material, analogous to holes. To what degree such axioms would generalise to other domains remains to be seen.

4.4.4. Temporal relations

The entire presentation in this paper is atemporal. This corresponds to the common situation in health informatics in which temporal relationships are expressed in information or decision support models rather than the 'ontology.' Temporal considerations have been introduced only external to the formal representation for notions such as "persistent parthood." A thorough integration of temporal considerations is a major undertaking.

4.5. Representation in OWL: loss over a full first order theory

The primary goal of this paper is to provide a basis for a representation in description logics and OWL in particular. These languages are deliberately limited with respect to first order logic in order to make them computationally tractable. What is lost in the reduction?

1. The inability to represent irreflexive and antisymmetric properties means that certain incorrect representations cannot be excluded (inferred to be unsatisfiable). If one is willing to accept that no collective can be a grain of another collective without being an ingredient of something else—a desirable restriction in our formulation, then the effect of the irreflexivity of is_grain_of can be obtained by making its domain NOT Collective and its range Collective. No such solution is possible for antisymmetry, so ontologies represented in OWL cannot exclude cycles in the part–whole relationship, although cycles can be checked for by separate tools.

2. The inability to represent reflexive properties requires making "proper parthood" primitive defining the usual "reflexive parthood" via schemas as described in 2.4.2.
3. The lack of "qualified cardinality constraints" including "EXACTLY-n" means that it is usually most expedient to approximate the relation between ingredients and wholes by simple existential restrictions. In theory this means that the formal model cannot exclude having two identical ingredients. This issue should eventually disappear as qualified cardinality constraints are expected to be included in future versions of OWL and are already supported by some tools.
4. The lack of a construct for propagates_via construct allowing 'inheritance' across transitive properties, means that is_grain_of/has_grain must be represented as a subproperty of is_part_of/has_part (see 2.2, item 3).
5. The fact that OWL is strictly binary relational and lacks any construct to say that two values must be the same[26] has at least three consequences:
   - (4a) Many constructs must be represented by schemas rather than axioms, the schema variables taking the role of the required extra variable, Reflexive_part_of_*X*. Unless well supported by tools, the resulting ontologies are cluttered with many instances of the schema that obscure its underlying structure.
   - (4b) If the notion of the role played by substances in a mixture is extended so that, for example, "amount of plasma" can play the role of solute for salt but suspensor for blood cells, then there is no way to ensure that the two "amounts of plasma" are the same.However, note that the need to reify proportions is more fundamental and does not arise merely because OWL is binary relational. Any complex representation might have a number of varied ways of characterising proportions that would be likely to require treating proportions as entities in their own right even in a formalism supporting relations of more than two arguments ("n-ary relations").
   - (4c) The relation between ingredients and portions cannot be captured. For example, that the salt in the water of the bay of the ocean is a portion of the salt in the ocean as a whole. This problem is discussed elsewhere [38]. It is a serious limitation but peripheral to the issues in this paper.

The effect of the above is that although most of the positive inferences from part–whole relations are supported in the OWL representation because they follow from the transitive property of the part–whole relations and the property hierarchy, important constraints cannot be, e.g., that nothing can be a part of itself, directly or indirectly. Hence the representation is reliable for inferring what *is* part of something but not for inferring what *could not be* part of something.

5. Conclusion: a basis for describing tissues and biological phenomena at multiple "granularities"

The word "granularity" has been used in so many different ways by so many different authors in so many different contexts that to try to enforce a single meaning on the term seems unlikely to succeed. We have therefore used the words "collectivity" and "size range" to distinguish two notions that are often lumped together under the general heading of "granularity." We have labelled the relation between grain and collective is_grain_of rather than the more familiar is_member_of to avoid confusion with mathematical sets defined extensionally. Correspondingly we propose a series of subrelations of which the two most important are:

1. "*Determinate parthood*"—the relation between fingers and hands;
2. "*Granular parthood*"—the relation between cells of the skin of the hand and the hand.

For convenience we also define an intermediate relation *Gross parthood* between *Determinate parthood* and the most general mereological parthood in order to accommodate the notions of *Portions* and *Ingredients*.

We argue that the distinction between determinate and granular parthood and the inclusion of collectives provides a means of representing emergent phenomena—at whatever size. We also argue that the distinction provides useful approaches to two further troublesome problems:

1. When to treat parthood as transitive.
2. When to treat parthood as persistent.

We argue that determinate parthood can be treated as transitive and persistent, whereas granular parthood cannot, although both imply the parent mereological parthood relation which is, of course, transitive. An implementation using the OWL property hierarchy is presented within a cognitivist framework analogous to DOLCE [33,39]. The elaboration of the techniques within a realist framework remains to be demonstrated. Correspondingly significant work remains to be done to formalise the relations between constituents, portions, and ingredients, but that lies outside the main topic of this paper.

We argue that the two notions of collectivity and size are effectively independent and that boundaries between levels of collectivity occur at all size ranges. In general, notions such as "cellular scale," "atomic scale," and "cosmic scale" are nominally focused on size but often conflate the two notions. For example, on the cellular scale one may want to refer to the collectives of organelles such as mitochondria or macromolecules. Furthermore, at least in biomedi-

[26] Known as "role value maps" in description logics.

cal applications, it is frequently necessary to refer both to individual grains and to the collectives that they form—e.g., both to ‘‘the sperm in the seminal fluid’’ and to ‘‘the individual sperm that fertilises the egg.’’

In an area where the language is fraught, we invite alternative suggestions for the labelling of any of the notions in this paper. However, whatever the labelling, we suggest that the central notion of collectives and grains is ubiquitous and accounts for important phenomena both in biomedical and broader ontologies and accounts for the criteria set out in the introduction in Section 1.3.

Our primary motivation has been to provide a basis for representation of the structure of biological materials and substances—e.g., the pattern of arrangement of cells in a tissue or the concentration of red cells in blood. To represent information in standard formalisms, there must be entities in the representation to which the information applies. In the representation presented this role is played by the classes Mixture, Proportion, and Collective—respectively, for the material as a whole, the relation of each ingredient to the mixture, and the ingredients themselves, respectively. These notions have been used in representations on a limited scale. The next stage is to use them to try to provide a comprehensive account of some small set of tissues for a practical application. Likewise, the applicability of these representations to broader areas outside biomedicine remains to be demonstrated.

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