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Anatomy Ontologies for Bioinformatics

Principles and Practice

Albert Burger
Duncan Davidson
Richard Baldock

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The Foundational Model of Anatomy Ontology

Cornelius Rosse and José L. V. Mejino Jr.

Summary. Anatomy is the structure of biological organisms. The term also denotes the scientific discipline devoted to the study of anatomical entities and the structural and developmental relations that obtain among these entities during the lifespan of an organism. Anatomical entities are the independent continuants of biomedical reality on which physiological and disease processes depend, and which, in response to etiological agents, can transform themselves into pathological entities. For these reasons, hard copy and in silico information resources in virtually all fields of biology and medicine, as a rule, make extensive reference to anatomical entities. Because of the lack of a generalizable, computable representation of anatomy, developers of computable terminologies and ontologies in clinical medicine and biomedical research represented anatomy from their own more or less divergent viewpoints. The resulting heterogeneity presents a formidable impediment to correlating human anatomy not only across computational resources but also with the anatomy of model organisms used in biomedical experimentation. The Foundational Model of Anatomy (FMA) ontology is being developed to fill the need for a generalizable anatomy ontology, which can be used and adapted by any computer-based application that requires anatomical information. Moreover it is evolving into a standard reference for divergent views of anatomy and a template for representing the anatomy of animals. A distinction is made between the FMA ontology as a theory of anatomy and the implementation of this theory as the FMA artifact. In either sense of the term, the FMA is a spatial-structural ontology of the entities and relations which together form the phenotypic structure of the human organism at all biologically salient levels of granularity. Making use of explicit ontological principles and sound methods, it is designed to be understandable by human beings and navigable by computers. The FMA's ontological structure provides for machine-based inference, enabling powerful computational tools of the future to reason with biomedical data.

4.1 Introduction

The Foundational Model of Anatomy (FMA) ontology is both a theory of anatomy and an ontology artifact. The theory defines anatomy and its content domain and thus provides a unifying framework for grasping the nature of the diverse entities that make up the bodily structure of biological organisms together with the relations that exist among these entities. In other words, FMA theory is a theory of structural phenotype. The FMA ontology artifact, on the other hand, is the computable implementation of the FMA theory. In this chapter we give an account of the FMA theory; the FMA ontology artifact, however, although readily comprehensible when accessed by computer, cannot be reproduced in its entirety on the printed page. We use portions of the artifact to illustrate both the theory and its implementation.

The ontology is designated as foundational for two reasons. First, the high-level nodes of the FMA's taxonomy generalize to vertebrates and, in several respects, to metazoa; second, the entities encompassed by FMA theory are the salient participants of all biological processes which ultimately become manifest as health or disease. Thus, ontologies designed to project to non-anatomical domains of biomedical reality must make explicit or implicit reference to anatomical entities.

The FMA conforms to the definition of an ontology advanced by Grenon et al.:

"An ontology grasps the entities which exist within a given portion of the world at a given level of generality. It includes a taxonomy of the types of entities and relations that exist in that portion of the world seen from a given perspective." [36]

A terminology or vocabulary, on the other hand, is a system of terms relying largely on linguistics and is established for coding or annotating particular kinds of data [78].

Unlike biomedical terminologies and vocabularies, and most extant ontologies, the FMA is not intended to meet the needs of any particular user group or support any particular task, such as the learning of anatomy or the annotation of biomedical data of different sorts. Rather, the FMA ontology is being developed as a *reference ontology*, intended to be reused in *application ontologies* designed to support any computational tool - with or without advanced inference capabilities - which calls for anatomical information. In this sense, the FMA is, in fact, the first of biomedical *reference* ontologies. Consistent with its foundational nature, it is providing the basis not only for several evolving application ontologies, but also for reference ontologies in other basic biomedical sciences, such as physiology, pathology, developmental biology and neuroscience.

The developers of the FMA have greatly benefited from extensive and substantial collaboration with leading investigators in knowledge representation and ontological methodology. The need for depicting the complexity of anatomy in the FMA has served as a motivation for refining such methods and enhancing knowledge representation systems and reasoners. Largely as a consequence of these interactions, the FMA has come to be regarded by the biomedical informatics community as an example of a principled ontology constructed with sound ontological methods [80, 99].

We first introduce a case study to illustrate the kinds of distinctions an anatomy ontology has to make. We shall see that these distinctions are diverse and complex, making the sorting of anatomical entities into types quite challenging. We derive from this case study the need for a theory of anatomy, and then we illustrate the implementation of this theory in the FMA ontology artifact. Before concluding, we illustrate the realization of the FMA's potential as a reference ontology in the basic and applied biomedical sciences.

4.2 Case Study: The Esophagus

We present the esophagus of the human species as a case study to illustrate the challenges for developing an ontology and to provide a consistent cohort of examples in subsequent sections of this chapter. The following account would fit well in a textbook of anatomy intended for biomedical education.

The esophagus connects the pharynx, located in the neck, to the stomach in the abdomen. Its cervical part begins at the level of the 6th cervical vertebra and its abdominal part ends at the level of 10th thoracic vertebra. Its cervical and abdominal parts are connected by a thoracic part, which is located in the posterior mediastinum. Much of the esophagus runs more or less vertically in front and to the left side of the vertebral column. The esophagus is part of the upper gastrointestinal tract and is derived embryologically from the foregut.

The esophagus has the shape of a tube, the lumen of which is surrounded by a multi-laminar wall: innermost is the mucosa, succeeded concentrically by a layer of submucosa, a muscle layer (tunica muscularis) and, on the outside, the adventitia. Each of the inner three layers has its own layers: the mucosa, for example, has epithelium, muscularis mucosae and lamina propria; the tunica muscularis has circular and longitudinal layers. All of these layers consist of portions of different types of tissue. The character of these tissues varies along the length of the esophagus because of differences in cellular composition: the muscle tissue, for example, is striated muscle in the upper part and smooth muscle in the lower part. To support assertions in the last sentence, this account would need to be extended to the types of muscle cells and their respective parts, including some macromolecular complexes, by virtue of which the cell types are distinguished from one another.

The lumen of the esophagus contains portions of swallowed air, saliva and mucus secreted by the mucosa, which cover the luminal surface of the esophageal epithelium; from time to time, it also contains a bolus of food. On its external surface, the esophagus is loosely attached to several of its neighboring structures by extensions of its adventitia, and to the diaphragm by the phreno-esophageal ligament. The structures adjacent to – in other words, touching – the circumference of the esophagus vary from vertebral level to vertebral level and include the trachea and aorta.

A comprehensive account of the anatomy of the esophagus would also include the nerves, arteries, veins and lymphatic vessels which supply or drain (are distributed to) the esophagus. Much anatomical information about the esophagus, however, remains unspecified in available sources, because it is taken for granted; for example, no mention is made in textbooks of the plexuses of blood and lymphatic capillaries which pervade all layers of the esophageal wall, except its epithelium. On the other hand these texts routinely make reference to function.

4.3 Challenges for an Anatomy Ontology

The account of the esophagus is replete with anatomical terms but omits to specify whose esophagus the talk is about. Ontology developers seem to assume that anatomical terms point to plural entities, usually understood to be classes instantiated by individual objects or entities in the real world, such as my or your esophagus and their lumina. Although anatomists – and our case study – may implicitly share this assumption, no explicit reference is made to classes or types in anatomy texts or *Terminologia Anatomica*, the international standard of anatomical nomenclature [29]. Only case reports of anatomical variants or abnormalities make it clear that their accounts pertain to one or a few particular individuals. If the intent of our case study is to describe the “normal” type of esophagus, then the bounds of normality and the meaning of the term type call for specification.

If one is to respect the definition of ontology cited earlier [36], then we must sort the entities which exist in the anatomy domain of biomedical reality into a taxonomy of types, choosing a perspective in which we selectively see these entities. This particular perspective or context will constrain the kinds of entities and relations that come under the ontology’s purview. How can the boundaries of anatomical reality be decided and which of the contexts prevalent in anatomical sources and discourse should we choose? Clearly, we must resort to different methods, approaches and even ways of thinking than those employed in text-based artifacts of communication.

In devising an ontological account of the esophagus we must consider the great variety of material entities such as the neck, the esophagus and its various parts; also cells, mucus and a bolus of food; as well as immaterial entities such as a lumen, surfaces, levels or coordinates, the shape of the esophagus and of its cells. Moreover, the particular arrangement of these entities entails diverse relations, such as location, containment, continuity, adjacency, attachment and implied boundaries. Such plurality of properties is not unique to anatomical entities of the size of the esophagus. For example, the anatomy of a pyramidal cell in the cerebral cortex or one of its mitochondria is manifest through similar kinds of properties and relations as those of the esophagus. It seems therefore that anatomical entities of different sorts, size, appearance and complexity share a number of fundamental properties or qualities, whereas other properties distinguish them from one another. We must first focus on those properties which, according to Aristotle, determine their *essence* [10, 58].

We can then begin the sorting with the intent to assure inheritance of general properties by entities of more and more specialized type distinguishable from one another by some properties they do not share. The result should be an inheritance class subsumption hierarchy or taxonomy. The nodes of the taxonomy should be marked by appropriately descriptive anatomical terms, many of which exist in the anatomy literature. We shall see, however, that terms for denoting many types have to be newly introduced. Thus established, such a taxonomy forms the essential part of an ontology which distinguishes it from a term list. The ontology itself should, however, take account also of nonessential or non-definitional properties of the entities under its purview. The association of the latter with nodes of a taxonomy will assure that the ontology can provide anatomical information which will inevitably be called for by different sorts of reasoners and applications.

The essence of the entities on the basis of which a taxonomy is to be established depends largely on the context or view in which its developers regard the domain of their interest. In the scientific literature anatomical entities are, more often than not, viewed in several parallel contexts. Textbooks of human anatomy fall into two main categories: those that subdivide the body into so-called functional systems such as the respiratory or reproductive system, and those that treat it according to so-called regions or body parts, such as the upper limb and abdomen; in each category, however, reference is usually made to structure and function, and even dysfunction, as well as embryonic development. The purpose of these artifacts, however, is not the sorting of the entities under their purview, but rather to serve the needs of particular groups of students and professionals.

Which of these contexts to choose as the predominant one may not be self-evident. The functional orientation is proclaimed by many time-honored sources of human anatomy and some anatomy terminologies. A taxonomy of functional anatomy has in fact been proposed [43]; however, it has not been exploited by developers of anatomy terminologies/ontologies. As the case study may suggest, it is problematic to sort many anatomical entities by virtue of their function. In fact, function tends to be used only for classifying and naming the major systems of the body; whereas the components of these systems are often viewed in structural contexts (see for example *Terminologia Anatomica* [29] and a number of other anatomy terminologies).

Single inheritance, a desirable feature of a sound taxonomy, is more often than not disregarded in anatomy terminologies/ontologies; it presents formidable problems in a functional context. For example, functions of the kidney include the disposition for excreting urine and secreting erythropoietin and renin. Should the kidney be classified both as an excretory and an endocrine organ? Likewise, should a bone such as a vertebra or humerus be classified in three ways: a support organ, a hematopoietic organ and an electrolyte-regulating organ, since in addition to supporting a part of the body, a vertebra and humerus also accommodate bone marrow, and store and release calcium into the circulation to be used in a variety of cellular processes? How could such a classification account for the anatomical differences between a humerus and a vertebra? This is not to deny the fact that functional anatomy is well-nigh indispensable in applications of anatomy such as those for education, biomedical research and clinical practice.

Sorting of anatomical entities into types in a predominantly structural context, however, is not without its challenges either. For example, if the taxonomy is to have one node as its root, the following kinds of questions call for an answer: At one end of the size scale, what are the structural properties shared by the thorax and the lumen of the esophagus? At the other end of the scale, what are the structural properties that distinguish a myofilament in a striated muscle fiber from that in a smooth muscle cell found in different regional parts of the esophageal wall? What properties are shared by the portion of mucus that coats the internal surface of the esophageal wall and the wall itself, and what properties distinguish them? The same questions should be asked about a bolus of food and the esophagus, or any other pair of entities mentioned in the case study. Similar questions arise pertaining to distinctions between relations. Are containment, parthood, adjacency and coordinates, such as 'level of,' different kinds of locations? If not, how are they distinct from one another? Likewise, is attachment a kind of continuity, and if not, how are the two different?

Choosing a predominant context for sorting anatomical entities should be influenced by the essential properties of anatomy itself. These properties should distinguish anatomy from its sister domains, such as physiology and pathology. It follows therefore that before addressing the foregoing problems and questions, we have to answer the question 'what is anatomy'. The answer should assist us in distinguishing essential properties of anatomical entities from incidental or nonessential properties. Coherence of a taxonomy for a domain as large and complex as anatomy can only be assured if decisions about essential (definitional) and nonessential (non-definitional) properties are guided by a unifying theory of the domain.

4.4 Theory of Anatomy

By the term theory we mean a tentative explanation of a portion of reality, derived from principles independent of the phenomena to be explained. The principles for guiding the establishment of an anatomy ontology artifact must be rooted in such a theory. The quality of this artifact will depend to a great extent on the distinctions its underlying theory makes about the portion of reality to which the artifact projects. These distinctions are of two sorts: those made by top-level ontologies, which generalize to any domain of reality, and those specific to a particular domain, such as anatomy. The theory of anatomy propounded by the FMA is rooted in high-level ontology; in particular, the FMA adopts and extends into the anatomy domain *Basic Formal Ontology (BFO)* [36], a domain-independent, spatio-temporal theory which provides a rigorous ontological framework. Some of the challenges of establishing an anatomy taxonomy will be met from the distinctions made by BFO; others by the FMA's unifying theory.

4.4.1 Basic Formal Ontology

BFO deals with the philosophy of reality; the distinctions it makes between the following pairs of entities are fundamental to the FMA:

1. **Reality and knowledge.** Instead of transcribing the content of textbooks, the FMA regards anatomy as a domain of biological reality and comprehends this reality at a more general or higher level than textbooks.

2. **Instances and universals.** Instances exist as discrete, specific individuals, also called tokens or particulars (e.g., my and your esophagi and their lumina); they instantiate universals, such as 'esophagus' referenced in the case study, which implies any esophagus that is presumably "normal". BFO distinguishes between instances and universals by virtue of their location in space and time. Instances exist in particular places at particular times; universals, on the other hand, are multipley located in space and time (all entities conforming to the notion of the term esophagus, which exist in any place at any time: past, present and future).

   Synonyms of the term universal are kind, category, class and type. The FMA selects type as the preferred name for universal; the more widely used term 'class' in some contexts implies the extension of the class (the sum of individuals which instantiate the corresponding universal at a particular time). In the FMA instances of a type are marked out by the fact that, in Aristotelian terms, they share a common essence [10, 58].

3. **Continuant and processual entities**. A continuant is an entity which endures *in toto* while it undergoes changes during the period of its existence; it is bound with respect to space and has spatial parts. A process – designated in BFO as an occurrent – is an entity which does not endure in time; rather it unfolds from its beginning in successive temporal phases to its ending; it is bound with respect to time and it has temporal parts. The instances of the type 'esophagus' as well as the universal they instantiate qualify as continuants, as do the respective surfaces, lumina and their contents.

4. **Dependent and independent entities.** In addition to the orthogonal continuant and process categories, BFO draws distinctions between dependent and independent entities. Processes depend for their existence on their participants. The act of swallowing cannot exist without some esophagus; nor can the process of peristaltic contraction proceed without the muscle layers of the esophageal wall. Such processes are all dependent on some continuant entity, which in an organism is an anatomical structure or a portion of some body substance. BFO also

draws distinctions between dependent and independent continuants. The lumen of the esophagus or its surfaces cannot exist without some esophagus also existing. Function is likewise a dependent continuant, rather than a process. The function of a sperm endures while the sperm exists even if it is never realized through engaging in the process of fertilizing an ovum.

The adoption of such fundamental distinctions by any domain ontology is a requirement for the soundness of the ontology. As far as we are aware, the FMA is the only extensively populated ontology which takes advantage of the theoretical foundations of a top-level ontology and extends the latter into the biomedical domain.

4.4.2 The FMA Theory

Theories are conspicuous by their absence in the biomedical domain. The cell theory advanced in 1838 and 1837 by Schleiden [73] and Schwann [75], respectively, seems to be the only one that has been proposed in the field of anatomy. None of the time-honored textbooks or sources declares a theory for sorting into types cellular and acellular entities, which together make up the anatomy of the human body or that of a metazoan organism. The FMA ontology was the first attempt to fill this gap [71, 72]: it is a theory of anatomy which provides the rationale for implementing the FMA as an ontology artifact. Since its first inception more than ten years ago, the theory has been refined substantially by virtue of the insight its authors have gained during the implementation of the corresponding artifact, and – not the least – as a result of guidance by, and interactions with, leaders in the fields of knowledge representation and ontological theory.

Adoption of the foregoing distinctions made by BFO means that FMA theory should apprehend the anatomy domain of reality by sorting independent and dependent continuants into types. The theory should then account for relations prevailing between these entities such that the relations capture the anatomical characteristics of these entities. The tasks are to 1) draw the boundaries of this domain and demarcate it from other domains; 2) specify distinctions between independent continuants of anatomy and other domains; 3) select a predominant context for viewing anatomical reality; 4) comprehend essential properties of anatomical entities on the basis of which they may be grouped together and distinguished from one another as types; 5) establish a taxonomy of anatomical types supported by Aristotelian definitions that assert the essential properties of instances subsumed by increasingly specific types; 6) define anatomical relations and link a given node of the anatomy taxonomy with other nodes.

4.4.3 What is Anatomy?

The term anatomy commands a plurality of meanings. A recent addition is the one which refers to anatomy ontologies simply as anatomies. Regarding an ontology artifact as an anatomy is a new permutation of an established use of the term for a textbook of anatomy such as Gray's anatomy [93]. Before the 20th century, the term anatomy was also used for the public demonstration of dissections of executed criminals, and as a *mise en scène* for group portraits of surgical societies, exemplified by the so-called 'Anatomy Lesson' of Rembrandt, the correct title of which is 'The Anatomy of Dr. Nicolaas Tulp'.

Dictionaries, on the whole, view anatomy as a branch of biological science. The FMA distinguishes this meaning from the one implying the structure of a biological entity. Anatomy of the hand and anatomy of the mouse are expressions that imply the structure of these biological entities, whereas the human activity primarily concerned with investigating, recording and comprehending the structure of biological organisms and their parts is the science of anatomy, distinct for example from the science of physiology. In other words, anatomy as structure exists as a portion of biological reality and is independent of the way human beings analyze it or create artifacts depicting it.

Despite the fact that *morphe* is shape in Greek and anatomy is a contraction of *ana* and *temnein* – meaning in Greek apart and to cut, respectively – the FMA regards the term morphology as synonymous with anatomy, pointing to both anatomy-science and anatomy-structure. The justification for the synonymy is that 1) *form* is dependent on the *structure* of biological organisms and their parts; 2) the study of form is not the principal component of contemporary anatomical knowledge, whereas structure is; 3) investigators who profess to be morphologists primarily study structure not just form; and so on.

The noun 'structure' is a homonym for a material object composed of parts and for the spatial arrangement and interrelation of the parts of a material or immaterial entity within a whole. In the FMA these two meanings of structure are conjoined, which means that the FMA takes account of anatomical entities and their mereotopological relations. In other words, the essence of anatomy is structure; whereas the essence of physiology is processes in which at least one salient participant is an anatomical structure. Although the terms process and function are often used interchangeably in biomedical discourse, their ontological distinction is fundamental. The demarcation of anatomy and pathology is contingent on the definition of anatomical structure. The association of the dependent continuants functions and pathological entities, as well as processes, with appropriate anatomical entities must be accomplished by inter-ontology relations once an ontology of each of these non-anatomical entities has been established.

4.4.4 Independent Anatomical Continuants

Extrapolating from the adopted meanings of the terms 'anatomy' and 'structure', FMA theory regards each instance of the type anatomical structure as an independent anatomical continuant. We introduce anatomical structure here independent of its taxonomic position, because it stands as the cornerstone of FMA theory. The definition of an instance of anatomical structure is key to comprehending all other types of anatomical entities by virtue of the relations they bear to anatomical structures.

Anatomical structure:

material anatomical entity which is generated by coordinated expression of the organism's own genes that guide its morphogenesis; has inherent 3D shape; its parts are connected and spatially related to one another in patterns determined by coordinated gene expression.

The first and foremost essential property that distinguishes anatomical structures from other material objects is the involvement of genes in their generation or morphogenesis. By morphogenesis we mean the development of an organism's structure or that of any of its parts. A bullet or a swallowed coin is excluded. A prosthesis of a cardiac valve, or one transplanted from another individual, be that a member of the same or different species, does not qualify as a particular individual's own anatomical structure; nor do parasites and bacteria that invade the organism. Similarly, tumors, granulomas and other so-called space occupying lesions are excluded from the type *anatomical structure*.

On the basis of this first essential property, a boundary may be drawn for excluding biological continuants from anatomy and – more importantly – including continuants in this domain. A pathological formation such as a carcinoma of the esophagus is excluded, because gene expression patterns implicated in its generation are distinct from those involved in the morphogenesis of the esophagus or any of its parts. The largest and smallest structures to be included in anatomy may also be specified by virtue of possessing this property. At one end of the spectrum is the body or carcass of the organism itself, and at the other end are the macromolecules synthesized as a consequence of DNA-RNA transcription. Subatomic particles, oxygen and carbon atoms, and carbon dioxide and water molecules are also parts of an organism and participate in biological processes; they are ignored by the theory, however, since they are not gene products. Embryos, fetuses, their parts, and other gestational structures such as the placenta and yolk sac are embraced by FMA theory, because they satisfy the definition of anatomical structure.

The second essential property, inherent 3D shape, distinguishes anatomical structures from other anatomical entities illustrated by the example of the esophagus: the esophagus, its wall, layers of the wall and muscle fibers qualify as anatomical structures because of the shape they possess; whereas the esophageal lumen, portions of mucus and swallowed air, which assume the shape of their container, do not.

The third essential property, the gene-dependence of the arrangement of an anatomical structure's parts, distinguishes *bona fide* anatomical structures from *ad hoc* collections of cells or molecules that may come about within an organism. For example a rouleau, consisting of erythrocytes adherent to one another like a stack of coins, has its inherent 3D shape, but its members are not connected and their ordered arrangement is not influenced by genes, whereas both requirements are fulfilled by the esophagus and the layers and cells of its wall. Likewise the arrangement of cells within a carcinoma does not conform to those established during morphogenesis.

The second and third properties together stipulate that each anatomical structure is a maximally connected entity and that – except for the organism itself – some complement entity must exist for any one of its parts in order to account for the whole.

The FMA theory assigns a dominant role to anatomical structure for three reasons: first, the definition of anatomical structure distinguishes material objects that are alive at some phase of their existence from inanimate objects and thus sets the boundaries of the theory; second, the types of anatomical structures determine the salient levels of organization – also known as levels of granularity – within biological organisms on which distinct levels of biological processes depend; and third, dependent continuants that come under the purview of the theory can be best systematized by virtue of their relation to anatomical structures at various levels of granularity. The elements of the theory discussed thus far should be of assistance in establishing an anatomy taxonomy.

4.4.5 The Anatomy Taxonomy (AT) of FMA

A taxonomy is a tree in the mathematical sense and has the following properties: 1) it has a unique root which serves as maximal universal or type, and 2) the *is_a* relation connects all other types and instances to this root in conformity with the principle of single inheritance. We use the *is_a* relation in accord with its formal definition which includes both the *subtype_of* and *instance_of* relations [83].

The challenges for establishing a taxonomy of anatomy are recounted in Section 4.3. The elements of FMA theory discussed thus far solve several of these challenges: 1) the AT traces over instances, and its nodes point to types of anatomical structures and other entities that depend for their existence on anatomical structures; 2) structure is the predominant context, since structure is the essence of anatomy; 3) types are established on the basis of shared structural properties of instances; processes and functions are excluded.

Several decisions, however, remain to be made: 1) the sense in which the terms entity and type are used; 2) the criteria of normality and deviations from it; 3) the principles for formulating definitions; and 4) selecting the root of the taxonomy.

Entity and Type

Dictionary definitions of the term entity assign it the most general meaning, including things that have real existence and those that do not, such as beliefs and thoughts; some distinguish entities from relations, as seems to be the case also in BFO. The definition of ontology cited earlier [36], however, includes relations along with entities. FMA theory adopts the meaning consistent with the latter definition and includes anatomical relations in the AT.

The term type is generally meant to imply a plural entity which encompasses the majority of the members of a species (see, for example [40]). As we have seen, BFO regards type – synonym of universal – as the entity instantiated by instances or individuals. FMA theory restricts the meaning of the term anatomical type by introducing the factor of *idealization*. The morphogenetic process is subject to a variety of (micro-) environmental influences and consequently its fidelity varies to a greater or lesser extent from individual to individual. Qualitative observations of members of the human and other species, which have been refined and sanctioned by generations of scientists and recorded in textbooks and atlases, however, have resulted in an implicit consensus about the ideal or prototypical anatomy to which each individual and its parts should conform. The nodes of FMA's AT point to such idealized types.

The introduction of idealization has several consequences, in that the theory 1) can sidestep the need for defining the normal; 2) establishes a benchmark with reference to which anatomical variants can be specified and represented as types of anatomical variants (distinct from pathological structures and formations); and 3) makes a distinction between canonical and instantiated anatomy [72].

Canonical anatomy ranges over those types which are idealizations of an organism's body and its component parts. The case study deals with canonical anatomy and the esophagus it describes is an idealized type. *Instantiated anatomy* comprises anatomical data obtained by invasive and non-invasive methods of clinical practice or experimentation about individual organisms which can be documented in clinical and other records and stored in databases. Instantiated anatomy does not come under the purview of the FMA; however, the FMA may provide the framework or schema for storing anatomical data in computable form.

Definitions

The FMA formulates its definitions consistent with Aristotle [58], exemplified by the definition of anatomical structure in section 4.4.4.

The first assertion in the definition specifies the *genus* as *is_a* 'material anatomical entity', which is the immediate taxonomic ancestor or super-type of 'anatomical structure'; the subsequent assertions are the *differentiae*, which, as discussed earlier (section 4.4.4), assert the essential properties shared by instances of the type and by which they may be distinguished from those of other types. It will be observed that only the last differentia conforms to the predominant context of the FMA; the first refers to a process and the second to a physical property indirectly related to structure (e.g., the shape of a cell is determined primarily by the arrangement of its cytoskeleton). These exceptions to the ontology's predominant context, however, are justified for defining high-level types by reference to properties that are independent of the domain of the theory.

The definition does not account for all properties inherent in anatomical structures. Through a lineage of broader ancestor types, anatomical structure inherits additional distinguishing properties asserted by the differentiae of its successive ancestors (Taxonomy 1 [Figure 4.1] and Appendix Table 4.1). This means that the definition of a type is incomplete without those of its taxonomic ancestors. The line of this inheritance becomes evident when anatomical structure is inserted as a node of a taxonomic tree along with its ancestors.

- anatomical entity
  - physical anatomical entity
    - material anatomical entity
      - **anatomical structure**
      - portion of body substance
    - immaterial physical anatomical entity
  - non-physical anatomical entity

Fig. 4.1. Taxonomy 1. High-level nodes of the anatomy taxonomy; here, as in subsequent taxonomies, displayed through the Foundational Model Explorer – FME [32]. Each indentation signifies the *is_a*, or more specifically, the *subtype_of* relation.

The properties inherited from successive taxonomic ancestors may be illustrated by the esophagus, which – we will agree – is an anatomical structure. Material anatomical entities have mass (e.g., muscle fiber, portions of mucus and swallowed air), whereas immaterial anatomical entities (e.g., lumen and surfaces of the esophagus) do not. Both material and immaterial anatomical entities, however, qualify as physical anatomical entities because they have spatial dimensions including the imaginary plane at the level of the 6th cervical vertebra; whereas non-physical anatomical entities such as the longitudinal and circular patterns in the layers of the tunica muscularis and the relations *has_part* and *surrounds* lack this property. All these entities, however, are anatomical entities by virtue of the definition of the root of the taxonomy: anatomical entity (Appendix Table 4.1).

The genus of the type 'anatomical entity' links the AT to the higher-level domain ontology OBR – Ontology of Biomedical Reality [70]; bona fide boundary as a differentia is defined in section 4.4.8 and Appendix Table 4.4.

Thus, all anatomical structures are anatomical entities, possess three-dimensions, their own inherent shape, and are the products of those genes of an individual organism which encode its structure. Although the lumen and surfaces of the esophagus and a portion of mucus do not qualify as anatomical structures, they are anatomical entities. Anatomical entity, therefore, fulfills the requirement for the root of the AT.

Although definitions must be consistent with the understanding of a domain by its experts, in an ontology their primary purpose is to marshal arguments in support of the ontology's taxonomy. The order of succession of the nodes of the taxonomy is established by the genus of successive definitions; instead of relying on mere opinions, the differentiae explicate the justification for including an instance in a given type or excluding it from the type.

4.4.6 Types of Anatomical Structure

The Challenge

As far as we are aware, the entities represented in Taxonomy 1 (Figure 4.1) have not been recognized in the published legacy of anatomy science. With the exception of anatomical structure, the terms pointing to these entities are not to be found in these publications or in the versions of terminologies which predate the FMA. Anatomy science has been primarily concerned with anatomical structures; however, the treatment of these structures by established sources is problematic and presents a number of challenges for the developers of ontologies.

As noted in section 4.4.3, the international standard of anatomical nomenclature [29] and many textbooks organize their content according to so-called functional systems, but do not make the meaning of this term clear. What kinds of anatomical structures constitute such systems? For example, why does the conducting system of the heart not qualify as one of them? Some sources include joints in the skeletal system; in others they are regarded as a separate system, and in yet others, bones and joints are grouped together with muscles as the musculoskeletal system. What type of anatomical structures are bones, joints and muscles? The same question may be asked about the components of body parts or regions such as the upper limb or the back.

Likewise, although the term organ is omnipresent in biology and medicine, *Terminologia Anatomica* provides no indication as to which of its terms point to organs. In fact, the general term organ is omitted from TA altogether. While there is implicit consensus that the liver and uterus are organs, opinions would vary widely about whether or not a nerve such as the vagus, a bone such as the femur, or the knee joint, should be regarded as organs. Although most anatomical terms are defined in dictionaries, the term organ serves as an example to illustrate that such definitions often compound rather than resolve ambiguities.

Organ:

> *a fully differentiated structural and functional unit in an animal that is specialized for some particular function [94].*

a somewhat independent part of the body that is arranged according to a characteristic structural plan and performs a special function or functions; it is composed of various tissues, one of which is primary in function [26].

These definitions mirror the perceptions of anatomists and probably also zoologists; the definitions, however, are satisfied by a number of anatomical structures cited in our case study. The esophagus conforms perhaps best to the most widely held intended meaning of the term. But the definition also holds just as well for the esophageal mucosa, the muscularis and any one of the other laminae of the esophageal wall, as well as the wall itself. The mucosa and the circular and longitudinal muscle layers are arranged in distinctive patterns characteristic for each, have specific functions and are composed of one primary tissue (epithelium and muscle tissue respectively), along with subsidiary connective tissue. The WordNet definition is satisfied by the esophageal wall just as well as by the thorax, the knee joint and the big toe.

A similar difficulty is presented by the current use of the term tissue and its implied meanings. The terms muscle and bone illustrate the difficulty. Depending on their context, these terms may project to macroscopic entities such as the biceps or the humerus, respectively, or to specialized cohorts of cells which are the respective parts of the biceps and humerus. Unfortunately, developers of some ontologies have enhanced rather than improved on these ambiguities. For example, the Adult Mouse Anatomy Dictionary, an ontology of the OBO library [66], classifies connective tissue as an organ system, along with the cardiovascular and nervous systems [1, 38]. The same kind of confusion between tissues and organs pervades another ontology of anatomy [41]. In a treatise on the computational representation of anatomy, a joint, a participating phalanx, its hyaline cartilage, and also the atrial septum and the right and left ventricles of a developing mouse, are all regarded as candidates for the class tissue, because "a distinct name such as right ventricle ... is cumbersome ... and not really required in a computational context" [7].

Such examples highlight the need for sound ontological methods as an approach to eliminating ambiguity prevalent in scientific discourse; an ambiguity which presented no serious problems while human experts were its primary participants. We should not only introduce specificity about the context in which a given ontology views anatomy, but also guard against the injudicious use of anatomical terms by assigning them meanings which make sense only in the context of a particular application domain, such as the annotation of gene expression maps or computational models of physiological function. Such practices will hamper interoperability between computational resources which target anatomical entities at different levels of granularity, discussed in the next section.

Units of Structural Organization

FMA theory approaches the task of sorting anatomical structures into types by considering salient structural units of an organism's corporeal framework. We look for precedence to the cell theory, which established the cell as the fundamental organizational unit of plants and animals [73, 75].

All multicellular organisms begin their existence as a single cell. This cell is destined not only to multiply, but also – governed by the regulation of groups of genes – its descendants become more and more specialized and aggregate into more or less distinct anatomical structures of increasing levels of complexity. Levels of the resulting structural organization have long been recognized by biologists. Since its earliest iterations, the FMA adopted these levels and specified the organizational unit of each [72]. A formal theory has been propounded about granular partitions which correspond to levels of structural organization in biological organisms [13].

Modern biology has focused attention on the products of DNA-RNA transcription. Such *biological macromolecules* are viewed by the FMA as the elementary units of structural organization for three reasons: they satisfy the definition of anatomical structure; they are essential components of all cells; and, suspended in body substances, they exist as discrete anatomical structures. The unit of the level of complexity beyond cell, if properly defined, is *tissue*. We saw in examples cited earlier that supra-cellular units and levels are much more open to opinion and interpretation than molecule and cell, which calls for applying sound ontological methods for the definition and classification of such complex structures. The FMA was the first to propose *organ* as the unit of organization at the macroscopic level in human anatomy, because the units at higher levels can be best defined in terms of the organs which constitute them. These units are *cardinal body part* and *organ system*, which, unlike units at lower levels, overlap each other. The meronymic sum of either cardinal organ parts or organ systems, respectively, is the maximal structural unit, namely the *body* or carcass of an entire vertebrate organism. Some organisms, of course, exist at the cellular or tissue levels and lack organs and cardinal body parts.

Two cautions must be raised. The first is proclaimed by the third differentia in the definition of anatomical structure: as implied by the name 'units of structural organization,' the assembly of units of a lower level into units at higher levels must be governed by genes implicated in morphogenesis. Secondly, in more highly evolved organisms, it seems necessary to define subdivisions of their tissues, organs, body parts and organ systems and treat them as types of anatomical structure for two reasons: the great variety and specialization of anatomical structures at each of these levels; and the prevailing elaborate detail and specificity in which anatomical structures are analyzed and treated in biomedical research and clinical practice. Such subdivisions and so-called cardinal parts of the salient units of organization are *bona fide* types in their own right and serve a transition to the next higher level.

The salient units of granularity levels are highlighted in Taxonomy 2 (Figure 4.2). In the first part of the taxonomy, nodes are aligned in decreasing order of structural complexity, starting with the whole vertebrate body and ending with biological macromolecule, followed by types which span more than one granularity level. The definitions of most types – in reverse order from simple to complex – are shown in Appendix Table 4.2; others may be retrieved from the FME [32].

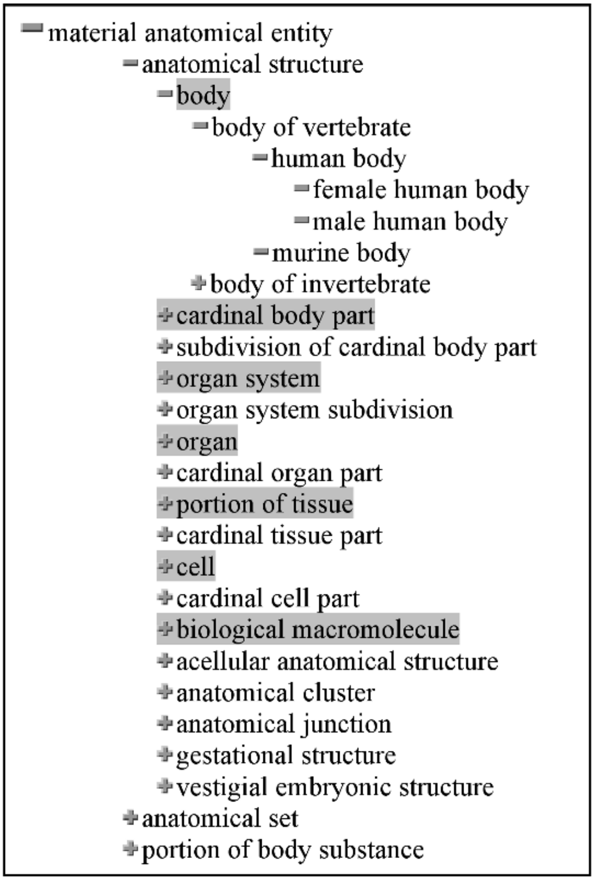


Fig. 4.2. Taxonomy 2. Types of anatomical structure. Salient units of structural organization are highlighted.

It is in the definitions of types of anatomical structure that the structural context is most strictly applied. Some qualifying comments about some of these types, however, are in order.

Cell

All biologists profess to know what a cell is. Quite surprisingly, however, it is not a simple matter to find a satisfactory definition; most sources leave it undefined. A key reference textbook for cell biology asserts: “All living creatures are made of cells – small membrane bound compartments with a concentrated aqueous solution of chemicals.” [3]. The assertion is problematic, not only because as the authors demonstrate such compartments can be created by agitating a vessel containing some lipid admixed with an aqueous solution, but also because the assertion is true for several cell parts, such as a cistern of the Golgi apparatus or a mitochondrion, as well as macroscopic entities such as a cyst. WordNet’s definition captures the meaning from several hard copy dictionaries: “the basic structural and functional unit of all organisms” [94]. The Cell Type ontology (CL) adopts the definition from MeSH: “Minute protoplasmic masses that make up organized tissue, usually consisting of a nucleus which is surrounded by protoplasm which contains the various organelles and is enclosed in the cell or plasma membrane. Cells are the fundamental, structural, and functional units of living organisms” [18].

The latter definition excludes so-called solocytes which exist independent of any organized tissue; as a consequence of its neglect to distinguish protoplasm from cytoplasm, it also excludes non-nucleated eukaryotic cells, such as erythrocytes, reticulocytes and lens fibers, which lack any nuclear material. In order to include bacterial and plant cells, the Gene Ontology (GO) extends the definition: “The basic structural and functional unit of all organisms. Includes the plasma membrane and any external encapsulating structures such as the cell wall and cell envelope” [34]. If the cell wall and cell envelope are an integral part of the cell, what is the complement of wall or envelope; namely the one bound by the outer surface of the plasma membrane within the wall or envelope; or a cell which lacks such external casings?

All types of cells – including prokaryotic and eukaryotic cells – share two essential properties: a maximally connected cytoplasm surrounded by a maximally connected plasma membrane. The FMA’s definition of cell is dependent on the definitions of cytoplasm and plasma membrane, shown in Appendix Table 4.3, along with those of some other cell parts and the whole cell. The latter definition regards the outer surface of a maximally continuous plasma membrane as the boundary of the cell; hence it distinguishes from a cell as a whole cell appendages such as a dendrite or pseudopodium (which consist of less than maximal parts of the plasma membrane and cytoplasm). The distinction of protoplasm and cytoplasm assures that cells lacking nuclear material are classified as *bona fide* cells. This definition holds for cells in interphase and any phase of mitosis and meiosis, as well as their enucleated progeny; it may also be elaborated to include prokaryotic cells.

While some organisms consist of only one cell, in the human body several hundreds of cell types have been distinguished. CL – employing multiple inheritance – classifies cells along the parallel axes of function, histology and lineage [6]; whereas the cell section of the FMA, which antedates CL, sorts cells into a rich hierarchy of 665 types adhering to single inheritance in a predominantly structural context. The high level nodes of the resulting ontology are shown in Taxonomy 3 (Figure 4.3):

- anatomical structure
  - cell
    - nucleated cell
      - haploid nucleated cell
        - oocyte
        - sperm cell
      - diploid nucleated cell
        - somatic cell
          - epithelial cell
          - muscle cell
          - connective tissue cell
          - neural cell
          - hemal cell
          - stem cell
        - diploid germ cell
          - primordial germ cell
          - primary oocyte
        - zygote
    - non-nucleated cell
      - non-nucleated solocyte
        - erythrocyte
        - platelet
      - non-nucleated colligocyte
        - corneocyte
        - non-nucleated lens fiber
  - cardinal cell part

Fig. 4.3. Taxonomy 3. The major categories of FMA's cell types. Except for five leaf nodes, a hierarchy of subtypes in most categories remains unopened.

Tissue

Tissues are usually referred to in the biomedical literature in the context of types (e.g., columnar epithelium, mesenchyme), whereas in reality, tissues exist as concrete portions within an organism, rather than as mass objects – a requirement for them to qualify as anatomical structures; hence the corresponding organizational unit is *portion of tissue*; the types in FMA's AT point to such portions. In Taxonomy 4 (Figure 4.4) and the FMA artifact, however, the phrase 'portion of' is omitted in the name of subtypes of the four major tissues types, taking it for granted that all these subtypes exist also in portions. The FMA's definition of portion of tissue honors the definition of tissue in established textbooks of histology (Appendix Table 4.2); however, as noted earlier, it is at variance with the use of this term in some fields of biomedical discourse and some terminologies or ontologies.

- anatomical structure
    - portion of tissue
        - portion of epithelium
            - unilaminar epithelium
                - simple squamous epithelium
                - simple cuboidal epithelium
                - simple columnar epithelium
            - multilaminar epithelium
                - stratified squamous epithelium
                - stratified cuboidal epithelium
                - stratified columnar epithelium
                - mixed stratified cuboidal and columnar epithelium
                - transitional epithelium
            - atypical epithelium
        - portion of connective tissue
            - regular connective tissue
            - irregular connective tissue
        - portion of muscle tissue
            - smooth muscle tissue
            - striated muscle tissue
                - skeletal muscle tissue
                - cardiac muscle tissue
        - portion of neural tissue
        - portion of heterogeneous tissue
            - lymphoid tissue
            - myeloid tissue
    - portion of cardinal tissue part

Fig. 4.4. Taxonomy 4. Types of portion of tissue.

The classification extends to several tiers of subtypes beyond most of the nodes shown, mirroring the specialization of tissues by virtue of the cells of which they are predominantly composed. Depending on the tissue type, there is a varying degree of anatomical – or morphological – similarity among its predominant cells. Unilaminar epithelia are more homogeneous; the stratification of several multilaminar varieties reflects the structural differences in the cohort of cells as they move in unison from a basal to a superficial stratum through a maturational gradient. The heterogeneity is most startling in the epidermis, a keratinized subtype of stratified squamous epithelium. Although there is a direct developmental lineage between cells of the basal and keratinized strata, arguments could be advanced for regarding each stratum as a distinct tissue type. To respect traditions, however, the FMA classifies such subdivisions of a tissue as *cardinal tissue part* (see below), a sibling node of portion of tissue.

The definition accommodates incidental cells in a portion of tissue of a particular type (Appendix Table 4.2). Although, in most cases, they are too few to be visible, there is experimental evidence that stem cells are present in the majority of, if not all, tissues. Also, various types of macrophages and other immunologically competent cells normally pervade loose connective and other tissues. Portions of connective tissue provide the bulk of such anatomical structures as ligaments and bones; however, with the exception of epithelia, some type of connective tissue is also present in portions of various types of muscle, neural and heterogeneous tissue. During development, this incidental connective tissue is largely responsible for establishing the patterns in which the principal cells are arranged. It will be recalled from the definition of anatomical structure (Appendix Table 4.1), that such a characteristic pattern is a requirement for a cohort of cells to qualify as portion of tissue. Moreover, the incidental connective tissue component of portions of tissue of all other types contains nerve fibers, blood and lymphatic capillaries, and larger pre- and post-capillary vessels, essential for the survival and functioning of the principal cells of a tissue other than epithelia. Thus it is erroneous to think of tissues as mere aggregates of similar cells.

Organ

In fully developed vertebrates, portions of types of tissue are not found outside the confines of organs, except for a subtype of connective tissue – areolar connective tissue – which loosely connects organs around their circumference, allowing them to move and modify their shape independent of one another. Such connections are illustrated by the extensions of the esophageal adventitia to neighboring organs. The breaking of such tenuous connections permits ready separation and demarcation of one organ from another (e.g., esophagus from trachea or vertebrae) without the use of sharp tools in either the living or dead body of most vertebrates, which is one factor that justifies regarding organ as the unit of macroscopic anatomy.

Although continuity may prevail between portions of two types of tissue (e.g., non-keratinized stratified squamous epithelium of esophagus and microvillous columnar epithelium of the stomach), as a rule, it is also connective tissue that secures portions of two or more types of tissue to one another as they contribute to structures of a higher order, such as the wall of the esophagus.

As the definition of organ suggests (Appendix Table 4.2), multi-tissue complexes may qualify as *simple organ* by virtue of their relative independence from other similar structures - particularly the case in organisms of lower orders. In vertebrates, however, as a rule, multi-tissue complexes are united to form anatomical structures which by themselves do not qualify as organs; they need to be ‘welded’ to other similar multi-tissue complexes to form *compound organs*. The FMA classifies structures intermediate in complexity between portion of tissue and organ as *cardinal organ part*. At one end of the size and complexity scale is, for example, the circular muscle lamina of the cervical esophageal wall – consisting of striated muscle and connective tissue; at the other end of the scale is the wall of the entire esophagus or the cervical part of esophagus; all these cardinal parts connected together qualify as the compound organ esophagus. It follows, therefore, that unless the requirements asserted by the differentiae in the definition of organ are fulfilled, a structure should not be classified as an organ, even though this term may be part of its conventional name (e.g., organ of Corti, which in the FMA is an organ component).

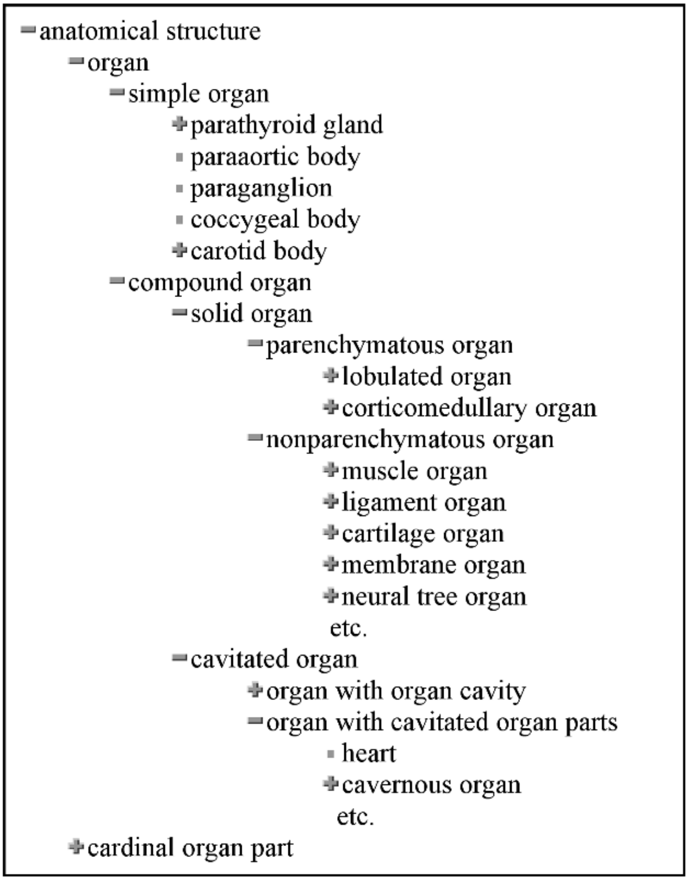


Fig. 4.5. Taxonomy 5. The high-level types of organ.

Definitions of organ types may be retrieved via the FME. These definitions employ as differentiae salient structural properties of instances of each type: whether or not organs have a cavity; if they are solid, whether their cardinal parts are arranged in lobules and lobes or as an inner core, the medulla, capped by a cortex; or whether they conform to neither of these typical arrangements; and if a cavity is present, whether it occupies the entire organ (e.g., lumen of the esophagus, cavity of urinary bladder), or major parts of the organ (e.g., a cardiac chamber, an air cell of the ethmoid bone). At a lower nodal level, the differentiae for cavitated organs, for instance, are specified by the organs with which each connects. For example instead of the conventional definition of the human heart by its functioning as a pump, in the FMA the heart *is_a*

> *organ with cavitated organ parts which has as its parts chambers continuous with the systemic and pulmonary arterial and venous trees;*

and the liver *is_a*

> *lobular organ which has as its parts lobules connected to the biliary tree.*

No anatomical structure other than the heart and liver satisfy these definitions, respectively, whereas major arteries also pump blood, though perhaps less forcefully than the heart.

Even parenchymatous organs, such as liver, lung or kidney, are not truly solid; they resemble a sponge in that some of their parts contain spaces of a lesser dimensional magnitude than the organs themselves. These spaces include the bile canaliculi, air filled cavities of alveolar sacs and the lumina of renal tubules, as well as the lumina of blood and lymphatic capillaries. Hence, for an organ to qualify as a cavitated organ, it must have as its parts one or more anatomical spaces of the same dimensional order of magnitude as the organ itself.

Cardinal Parts and Subdivisions

Rather than implying any part transitively removed from the whole (e.g., as an epithelial cell as part of the esophagus), the intent with the use of the terms cardinal part and subdivision in Taxonomy 2 is to point to anatomical structures of distinctive types. The corresponding definitions specify the criteria for assigning instances to these types (Appendix Table 4.2).

Cardinal Organ Part

Although *cardinal organ parts* are also composed of more than one portion and type of tissue, they are distinguished from simple organs by virtue of their continuity with their complement in constituting a compound organ. As a rule, they cannot be demarcated from one another by blunt dissection as most organs can.

Each of the circular and longitudinal layers of the tunica muscularis, for example, qualifies as a cardinal organ part, because its direct parts include not only portions of muscle tissue, but also portions of connective tissue. The latter is essential for packaging portions of muscle tissue into bundles and sheets, and arranging these bundles within a sheet in circular or longitudinal patterns. During development the establishment of these distinctive patterns of muscle fiber arrangement seems to be mediated by gene products in embryonic connective tissue (mesenchyme). Such arrangements of portions of striated or smooth muscle account for the emergent structural and functional properties of these cardinal organ parts and distinguish them from portions of tissue. For example, contraction of any portion of muscle tissue results in its shortening; whereas the summation of the contraction of muscle laminae in esophageal wall is manifest as a peristaltic action; a similar summation of contraction of portions of muscle tissues in the muscle belly and long and short heads of the biceps results in flexion of the elbow and supination of the hand. The explanation for these rather startling differences in muscle action in these two organs is to be found in the distinct patterns in which quite similar muscle fibers are arranged in their cardinal organ parts.

In addition to the wall of cavitated organs and their laminae, characteristic cardinal organ parts are the cortex and medulla of the human kidney, the head and shaft of the humerus, a cardiac chamber and a lobule or lobe of the liver.

Lobes of lung and liver may seem to be exceptions to the requirement for continuity among cardinal organ parts. In some species lobes of these organs have free surfaces whereas in others they do not. Lobes of the human lung and murine liver can be freely separated from one another; those of the human liver and mouse lung cannot. Continuity between these distinct lobes is always present at their root or the hilar region of the organ they constitute. The fundamental architecture of lobulated organs is established by the branching pattern of the hollow tree responsible for their morphogenesis; fissures which carve the lobular or acinar parenchyma into the larger chunks of lobes are inconsequential and variable among and within species.

Cardinal Body Part and Organ System Subdivision

Terminologia Anatomica lists a number of body parts and body regions which overlap to a great extent in both name and meaning [68]. The FMA's definition distinguishes *cardinal body part* and admits only four types of anatomical structures in this category: head, neck, trunk and limb. Likewise, only those body systems qualify as instances of *organ system* which have as their direct parts organs connected to one another. Thus, the gastrointestinal and respiratory systems qualify, whereas the conducting system of the heart, cited earlier, does not, since its parts are portions of specialized tissue; neither do functional systems made up of unconnected organs (e.g., endocrine and immune systems), the sum of which does not constitute one anatomical structure.

Both cardinal body parts and organ systems are subdivided into structures larger than organs which are designated in the FMA as their respective *subdivisions* (Taxonomy 2 [Figure 4.2]). For example, thorax and abdomen are classified as subdivisions of trunk; forearm and hand subdivisions of the upper (pectoral) limb; the upper and lower gastrointestinal and respiratory tracts as subdivisions of the alimentary and respiratory systems, respectively. Both types of subdivisions have entire organs as their direct parts (e.g., lungs and stomach or discrete bones and muscles); whereas other organs cross the boundary between subdivisions as does the tracheobronchial tree between upper and lower respiratory tracts and the tendons of several muscles between forearm and hand.

Miscellaneous Anatomical Structures

A theory of anatomy must also account for anatomical structures that do not fit naturally into the units of structural organization. The last five nodes of Taxonomy 2 (Figure 4.2) project to such structures.

Acellular anatomical structure is the type that subsumes, for example, basement membrane (on which an epithelium is supported), collagen fiber, zona pellucida of ovum, an otolith in organs of balance or an intracellular crystal.

The root of the lung and the renal pedicle consist of cardinal parts of several organs (principal bronchus, a pulmonary artery, pulmonary veins, lymphatic vessels and nerves in the lung root) grouped together in a predetermined manner; the collection, however, dos not qualify as either the cardinal part of an organ or the body, nor as a subdivision of an organ system. To account for such structures, we introduce the type *anatomical cluster*. A joint, such as the interphalangeal joint, is an anatomical cluster made up of the joint capsule, synovial sac (each an organ) and the proximal and distal ends of phalanges (cardinal organ parts) covered by articular cartilage (a portion of tissue, part of the articulating bones). Anatomical clusters exist at various levels of granularity exemplified by the juxtaglomerular complex (made up of the macula densa and juxtaglomerular and mesangial cells) or a nerve fasciculus, the parts of which are zones of a number of axons surrounded by a perineurial sheath.

Anatomical junctions, such as the pharyngo-esophageal and esophagogastric junctions mentioned in the case study, and others at the cellular level such as synapses, neuromuscular junctions and desmosomes, establish continuity between two or more anatomical structures. Each type of junction has its own characteristic components and structure.

The embryo, fetus and their parts, qualify along with the placenta, amnion and umbilical cord as anatomical structures. They are grouped together under the type *gestational structure*. Some embryonic structures persist postnatally in a vestigial state and assume a different character. In human beings, examples of such *vestigial anatomical structures* include a lateral umbilical ligament (distinct from ligaments of the musculoskeletal system) which, before birth, was an umbilical artery, and the appendix of the testis, which persists as the fibrous transformation of some mesonephric ductules.

All the above miscellaneous structures qualify as anatomical structure because they possess an inherent 3D shape and come about, directly or indirectly, as the result of morphogenetic processes regulated by particular groups of genes.

Summary of Anatomical Structure

In conclusion, anatomical structures at each level of granularity share some structural properties inherited from their taxonomic ancestors, and also exhibit additional properties specific to their own level. These inherited and level-specific attributes account for the emergent properties of anatomical structures at levels of increasing structural complexity. One of these emergent properties is the potential they manifest for participating in higher level biological processes than those at a lower level, illustrated earlier by different actions exerted by portions of muscle tissue and those of the esophagus and biceps.

Thus, as a result of designating not only cell but also biological macromolecule, portion of tissue, organ, cardinal body part and organ system as units of granular partitions, the human body, or the body of any vertebrate, can be stratified into seven salient levels of structural organization. Five transitional levels provide the connection between the salient levels (Taxonomy 2 [Figure 4.2]).

Such a structural stratification of the vertebrate organism advanced by theories of the FMA and granular partitions is by no means original. Notions similar to the levels here propounded are implicit in many time-honored accounts of anatomy. However, the notable distinction is that the types of anatomical structures, body substances and boundary entities encompassed by each organizational level are explicitly defined in the context of FMA's taxonomy, whereas in other sources such entities, notably tissue and organ, remain more or less ambiguous.

4.4.7 Other Material Anatomical Entities

Anatomical Set

Singular material objects forming part or the whole of an individual organism are classified as the type anatomical structure. Such singular structures need to be distinguished from plural material objects which exist as collections, distinct from types. Such collections are the referents of terms such as ribs and spinal nerves. These terms as used in anatomical discourse do not point to any number of ribs or spinal nerves, but rather to their maximal number in a canonical member of a given species; for example 12 pairs of ribs and 32 pairs of spinal nerves in a human being. We designate such maximal collections as the type *anatomical set*, which is a sibling, rather than a subtype of anatomical structure in the ontology (Taxonomy 1 [Figure 4.1]; Appendix Table 4.1). Set of ribs and set of cranial nerves are two subtypes of anatomical set.

These particular sets consist of organs; anatomical sets, however, exist at all levels of granular partitions. For example, all skeletal muscle fibers innervated by a single alpha motor neuron are members of the anatomical set myone; these members intermingle with members of other myones, an arrangement which offers significant functional advantages.

The foregoing examples illustrate that, unlike anatomical clusters, anatomical sets have members rather than proper parts in that sets lack one maximal boundary; no direct continuity or spatial adjacency prevails between the members; and members are of the same type which is not the case for parts of anatomical clusters.

Members of an anatomical set are distinct from elements of a mathematical set in at least two respects: 1) indirect connections exist between them since, with a few notable exceptions, all anatomical structures of an organism are interconnected directly or indirectly; and 2) as a rule, the members are ordered in accord with genetically determined patterns. For example, the oculomotor nerve is the third pair in the row as cranial nerves emerge from the brainstem; the second rib on the right is not interchangeable with the left second rib or with the right third rib. To our knowledge, the pattern of intermingling between members of particular myones within a muscle has not been analyzed; it is, however, unlikely to be random.

Portion of Body Substance

Anatomical structures, including clusters and members of anatomical sets, have their own inherent 3D shape. Material anatomical entities which lack this property adopt the shape of cavities and spaces within or among anatomical structures (e.g., swallowed air, saliva and mucus in the esophagus) or, like enamel, are molded to the surfaces of anatomical structures. To designate this type of entity at the highest level, we borrow the term body substance from current clinical usage, which is distinct from substance in Aristotle's categories [4]. Portion of body substance is defined in Appendix Table 4.1 and its subtypes are shown in Taxonomy 6 (Figure 4.6).

Like tissues, body substances exist in biological organisms as distinct portions rather than as mass entities. The differentiae for distinguishing subtypes include composition and containers. For example,

portion of blood:
portion of body substance which has as its direct parts blood cells suspended in a portion of plasma.

Blood cell and portion of plasma are defined independently of blood.

Leaf nodes in this taxonomy point to specific anatomical spaces which contain the corresponding instances of portion of body substance. As for tissues, the phrase 'portion of' is taken for granted in most cases. For example, portions of blood can be

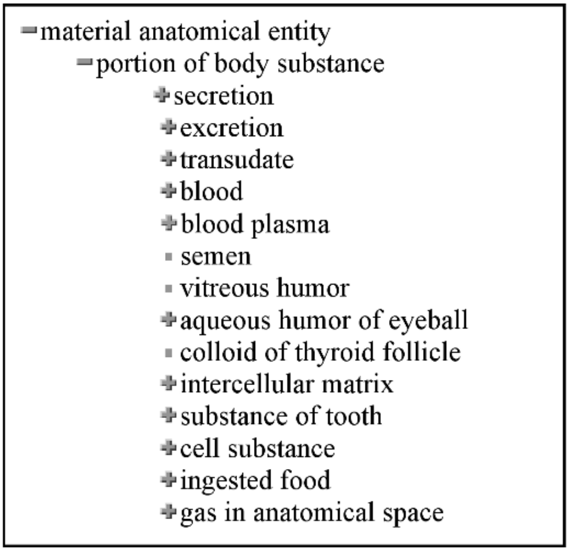


Fig. 4.6. Taxonomy 6. Types of portion of body substance.

distinguished by the vascular trees or the blood vessels that contain them. For example, the portion of blood in a pulmonary arterial tree is distinct not only from that in a pulmonary venous tree, but also from the portion of blood in a coronary arterial tree. Such distinctions and their refinements have practical importance in physiology and clinical medicine. For example, during coronary angiography, oxygen saturation is assessed separately for zones and branches of a coronary artery distal and proximal to a partial blockage in order to inform therapeutic decisions. The annotation of such detailed clinical data calls for corresponding resolution in the parts of the coronary arterial tree and their contents, levels of specificity not to be found in any current anatomy textbook. Similar levels of specificity are called for also by computational mathematical models of physiological processes (e.g., [45]).

The taxonomy of portion of body substance in the FMA is as yet tentative: many subtypes have not been defined and some of the definitions rely for differentiae on the structures that synthesize or filter the particular substances (e.g., secretions, exudates, transudates), which, though sensible and useful, is not strictly consonant with a structural context.

One of the salient distinctions made by FMA theory is that between portion of body substance and portion of tissue. Time-honored textbooks of anatomy and histology have for long been regarding such body substances as blood and lymph as subtypes of connective tissue. Because of the fundamental properties they share, portions of blood and lymph are classified in the FMA together with the substances that fill the cavities of anatomical structures at all levels of granularity. They all lack a defining property of portion of tissue: a predetermined pattern of their architecture.

4.4.8 Immaterial Anatomical Entities

Unlike portions of swallowed air, saliva and mucus, the lumen of the esophagus which contains portions of these substances has no mass, although it has spatial dimension. By virtue of these properties lumen is classified as immaterial anatomical entity, a subtype of physical anatomical entity. The external and internal surfaces of the esophagus fall also into the same category, as do the virtual planes which demarcate the esophagus from the pharynx (plane of pharyngo-esophageal junction) and the stomach (plane of esophagogastric junction). Immaterial entities are categorized on the basis of whether they have three or fewer spatial dimensions (Taxonomy 7 [Figure 4.7]); the former are anatomical spaces and the latter operate as boundaries. These and further distinctions are captured by the definitions (Appendix Table 4.4).

Anatomical Space

The first criterion for sorting anatomical spaces into cavities and compartment spaces is whether or not their boundary is provided by the surface of one or more anatomical structures (Appendix Table 4.4). The second criterion is the content of the spaces: anatomical cavities contain portions of body substances, whereas compartment spaces contain anatomical structures.

The lumen of the esophagus and the lumina of blood vessels qualify as cavities, as do the spaces enclosed by the pleura, peritoneum, stomach and right ventricle. Compartment spaces contain cells or organs such as members of thoracic viscera (e.g., space of mediastinum). Despite its name, the abdominal cavity is classified as a compartment space because it is bound by the surfaces of a number of muscle organs and it is filled by organs such as the kidneys and the peritoneal sac, rather than by body substances; whereas the space within the peritoneal sac is a cavity, because it is surrounded by the wall of the sac and contains a portion of peritoneal fluid. Likewise, the space bound by the internal surface of the plasma membrane contains a maximal portion of cytosol; therefore, the FMA classifies it as an anatomical cavity, although this space is spoken of by biologists as a compartment [3].

The FMA also distinguishes anatomical conduits, which connect two or more spaces with one another and may contain either portions of body substances (e.g., ostium of coronary artery, median aperture of fourth ventricle known also as the foramen of Magendie, atrioventricular orifice), or anatomical structures (e.g., foramen magnum, space of inguinal canal, pulmonary hilum).

Spaces in a developing organism can be categorized according to these three types. Such spaces are, however, left in gestational space, a category of their own for the time being, mainly for the purpose of drawing attention to them by ontology

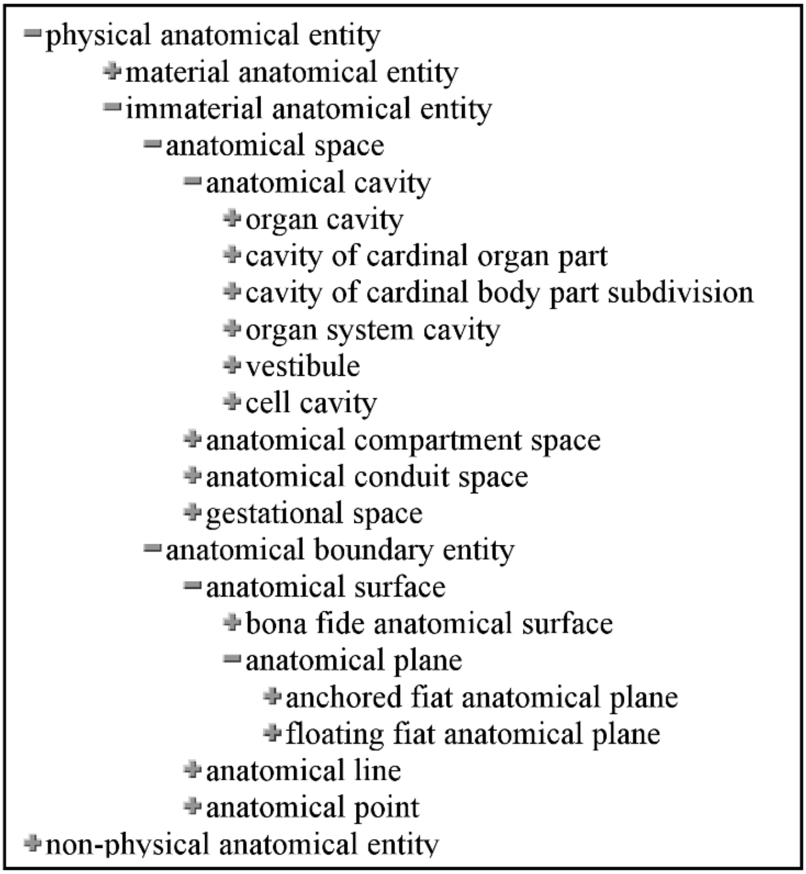


Fig. 4.7. Taxonomy 7. A selection of high-level types of immaterial anatomical entity.

developers concerned primarily with embryonic development (e.g., [27, 37]).

The distinction between anatomical cavities and compartment spaces is not a matter of gilding the lily. It is called for by the need to forestall erroneous conclusions by reasoners. For example, the presence of portions of body substance in compartment spaces, such as blood in the space of posterior mediastinum, would signal a medical emergency.

Anatomical Boundary Entity

Boundaries exist in reality in that they mark a natural discontinuity between objects. They are also employed extensively to subdivide an organism and its components into parts where natural discontinuities may not exist. In human anatomy, only spaces are said to have a boundary, which is equated with the wall or walls of the space. The FMA makes a distinction between boundary entities and walls. A physical anatomical entity must have fewer than three spatial dimensions to qualify as a boundary. For example, because it has two dimensions, the internal surface of the esophagus is a boundary entity, and as we shall see, it may be associated with either the wall of the esophagus or its lumen as the second relatum linked by the *has_boundary* relation (section 4.4.9). Although biomedical discourse makes routine reference to anatomical surfaces (e.g., cell surface, body surface, diaphragmatic surface of lung, abluminal surface of epithelium), they are not usually regarded as boundaries. Since they are taken for granted by traditional sources, boundaries are in general ignored by ontologies in the biomedical domain, although they have been thoroughly treated in ontology theory [77]. Boundaries are implicit in systems of categorization or sorting; they operate in the decomposition of an entity into its parts, notwithstanding the fact that some theories of mereology do not account for boundaries explicitly. FMA theory adopts Smith's treatment of boundary [77] and with his guidance extends it.

There is a distinction between the surfaces of the esophagus and the planes that demarcate the esophagus from the pharynx and stomach. The surfaces mark a discontinuity between the wall and the lumen, and also the neighborhood, of the esophagus; whereas the pharyngo-esophageal and esophagogastric planes, which demarcate the esophagus superiorly and inferiorly, respectively, are imposed by consensus across continuities which exist between the walls and spaces of the pharynx, esophagus and stomach. The surfaces are natural or *bona fide* boundaries, such as the one which demarcates an organism from its external environment, or a red blood cell within the portion of blood in which it is suspended. The planes are *fiat* or *virtual* boundaries, across which natural continuity prevails. The FMA extends these distinctions by designating some fiat boundaries as anchored and others as floating fiat boundaries. The position of the plane of the thoracic inlet which demarcates the cervical from the thoracic part of the esophagus is anchored by the level of the first pair of ribs. No comparable fixed reference exists, however, for the plane that demarcates the upper part of the esophagus from the lower part (in which the muscularis has distinct properties), the apical and basal parts of the lung or the apical and basal parts of a columnar epithelial cell. All the latter planes fall into the category of floating fiat boundary. Anatomical planes, both anchored and floating, are widely used for subdividing the body and other anatomical structures in anatomical and clinical descriptions of the human body.

Both bona fide and fiat boundaries operate also in demarcating 2D surfaces and planes by 1D anatomical lines. The sharp anterior border of the somewhat semi-cone-shaped human right lung is a bona fide boundary because it is an anatomical line formed by the intersection of the lung's costal and mediastinal surfaces; whereas the so-called posterior border is rounded and the demarcation between the two surfaces posteriorly is a floating fiat boundary. The intersection of the line of the horizontal fissure with the anterior border of the right lung marks an anatomical point, which is a bona fide boundary between the anterior borders of the upper and middle lobes.

A number of anatomical points and anchored fiat lines, such as McBurney's point and Nelaton's line, serve as useful landmarks and guides for clinical diagnosis and surgical procedures.

4.4.9 Anatomical Relations

The term relation has many meanings. In ontology theory, relation is a primitive which asserts some kind of association between two or more entities, such as A *is_a* B or A *contains* B. Relations in anatomy assert associations between anatomical entities. Relations between anatomical entities and those of other domains (physiology, pathology) do not come under the purview of a theory of anatomy or of anatomy science as defined here. Since they have no spatial dimension and cannot be quantified, the FMA classifies anatomical entities as one of the three subtypes of non-physical anatomical entity (Taxonomy 8 [Figure 4.8]).

The case study (section 4.2) illustrates the indispensable role relations play in taking account of the structure – i.e., anatomy – of anatomical entities. Such relations figure extensively in anatomical and clinical descriptions, but except for the part relation they have for long been largely ignored or inadequately treated by anatomy terminologies. For example, the Adult Mouse Anatomical Dictionary limits structural relations to parthood and seems to use the *is_a* relation for specifying location and containment, as in heart *is_a* thoracic cavity organ [1, 38]. The hierarchies of the international standard of anatomical nomenclature fail to specify the nature of links between their terms and only those familiar with human anatomy can imply that in a given hierarchy a link may be intended to mean *is_a*, *part_of* or *branch_of* [68]. A notable exception to these unsatisfactory practices is GALEN [33], the anatomy module of which predates the FMA, and employs several anatomical relations.

The challenge for a theory of anatomy is illustrated by the following kinds of questions related to the case study: Are the surfaces, wall, lumen and portions of mucus and swallowed air all part of the esophagus? Is the nature of the connection between the stomach and the esophagus the same sort as the one that anchors the esophagus to the diaphragm? Are the arborizations and networks of nerves and blood vessels embedded in the esophagus part of its wall, or part of the respective neural and vascular trees, or both? How can the location and position of the esophagus be specified with respect to the posterior mediastinum and the anatomical structures that surround it? And so on.

Adopting some of the precedents in GALEN and UMLS (Unified Medical Language System; [90]) – which also includes and defines several anatomical relations – evolving versions of the FMA have incorporated an increasing number and kinds of relations. Not only the number but also the expressivity and specificity of relations pertaining to anatomy has been extended and refined. As a result, the FMA has motivated much of the recent interest in relations by biomedical ontologists

[25, 64, 65, 79, 82, 83]. Taxonomy 8 (Figure 4.8) shows the salient relations employed by the FMA, which are defined in Appendix Table 4.5.

FMA theory distinguishes between two major categories of relations: taxonomic and structural. The former generalize to any domain; while none of the latter is unique to anatomy, they are particularly apt for specifying the arrangement of the physical parts of an organism.

- non-physical anatomical entity
  - anatomical relation
    - taxonomic anatomical relation
      - is_a
        - has_instance < > instance_of
        - has_type < > type_of
    - structural anatomical relation
      - has_spatial_dimension < > spatial dimension of
      - has_shape < > shape_of
      - has_boundary < > boundary_of
      - has_part < > part_of
        - has_generic_part < > generic_part_of
        - has_constitutional_part < > constitutional_part_of
        - has_regional_part < > regional_part_of
          - has_branch < > branch_of
          - has_tributary < > tributary_of
        - has_member < > member_of
      - has_orientation
      - connected_to < > connected_to
        - continuous_with < > continuous_with
        - attached_to <> receives_attachment_of
      - has_location < > location_of
        - contained_in < > contains
        - adjacent_to < > adjacent_to
          - surrounds < > surrounded_by
        - has_anatomical_coordinate < > anatomical_coordinate_of
          - has_qualitative_anatomical_coordinate
          - has_geometric_coordinate
      - has_organizational_pattern < > organizational_pattern_of
      - has_segmental_innervation < > segmental_innervation_of
  - organizational pattern
  - segmental innervation

Fig. 4.8. Taxonomy 8. Anatomical relations. The symbol <> designates inverse relations.

Taxonomic Relations

As noted earlier, the FMA employs the *is_a* relation strictly in accord with its formal definition [83] and implements its specifications along with their inverses (Taxonomy 8 [Figure 4.8]). Although instances are excluded from the anatomy taxonomy implemented in the FMA artifact, the theory conforms to high-level ontology in that it adopts the distinction between instances and types (Section 4.4.1). Consistent with the distinction between canonical and instantiated anatomy, the FMA takes account of the *instance_of* relation between individuals and types, as well as the *subtype_of* relation between types.

Structural Anatomical Relations

Structural relations can be defined primarily with reference to instances. The type esophagus has no parts - only your and my esophagi do. Instance to instance relations, however, are extrapolated to obtain between types under the constraints propounded elsewhere [12, 25, 82]. Taxonomy 8 (Figure 4.8) presents such type to type relations, which are defined in Appendix Table 4.5.

Several published accounts about the FMA deal with these structural relations and justify the need for introducing them [53, 56, 57, 62, 82]. They also explicate some of the rules and principles for distinguishing between relations of different sorts. Here it should suffice, as an illustration, to provide answers to some of the foregoing questions about the esophagus.

By virtue of the definitions of the relations, the wall and lumen qualify as parts of the esophagus because, although each entity is of a different type, they all have three dimensions; moreover wall and lumen are complements of one another in that together they account for the whole of the esophagus. The case study, however, also refers to the cervical, thoracic and abdominal parts of the esophagus; together they also account for the whole organ. None of the latter can substitute either for the wall or the lumen and each has its own wall and lumen. Such overlapping partitions of an anatomical structure highlight the need for specifying different kinds of part relations: an entity in one partition cannot qualify as part or complement in another partition of the whole. The distinction between constitutional and regional part relations – which obtain for anatomical structures at all levels of granularity – resolves such conflicts and ambiguities (Figure 4.9).

Yet another distinction is called for when considering the surfaces of the esophagus. Because they have two, rather than three dimensions, the surfaces must be associated with the wall, lumen and the whole of the esophagus through the *boundary_of*, rather than the *part_of*, relation [62]. The internal surface of the esophagus is the boundary of both the wall and the lumen. Such a specific view invalidates the one prevalent in anatomical discourse, in which the wall of the esophagus is generally regarded as the boundary of its lumen.

To clarify the relation of portions of air and mucus to the esophagus and its parts, location – and in particular – containment relations need to be considered, the need

A

has_constitutional part

Esophagus	wall of esophagus	lumen of esophagus
cervical part of esophagus	wall of cervical part of esophagus	lumen of cervical part of esophagus
thoracic part of esophagus	wall of thoracic part of esophagus	lumen of thoracic part of esophagus
abdominal part of esophagus	wall of abdominal part of esophagus	lumen of abdominal part of esophagus

B

has_constitutional part

Neuron	plasma membrane of neuron	cytoplasm of neuron
soma of neuron	plasma membrane of soma of neuron	cytoplasm of soma of neuron
axon	plasma membrane of axon	cytoplasm of axon
dendrite	plasma membrane of dendrite	cytoplasm of dendrite

Fig. 4.9. Regional and constitutional part relations shown for the esophagus (A) and a neuron (B).

for distinctions between which will soon become apparent. Location is the most general relation which associates objects, substances and spaces with spatial regions into which the universe is divided by mereotopology [12, 25, 82]; some of these regions are enclosed by an organism's maximal boundary. Thus, not only portions of mucus but also the esophagus, its lumen, bacteria or a swallowed coin, are located within the human body. The FMA distinguishes parthood from location and further specifies the latter as containment, adjacency and having anatomical coordinates [53, 57]. Parthood in biological organisms must meet a number of other criteria [74, 82], the pertinent one in the current context enforced through the rule of dimensional consistency [53, 57].

Whereas part relations can be asserted between instances of two types of physical anatomical entity of the same dimension, the *contains* relation associates anatomical cavities with portions of body substances, and compartment spaces with anatomical structures. By virtue of these constraints, the valid assertions are: lumen of esophagus *contains* portion of mucus; lumen of esophagus *part_of* esophagus; space of posterior mediastinum *contains* thoracic part of esophagus. Imposing such restricted meaning on the *contains* and *contained_in* relations may seem pedantic. The purpose of such specificity, however, is to assure that the role of container is constrained to anatomical structures which have anatomical space as their part.

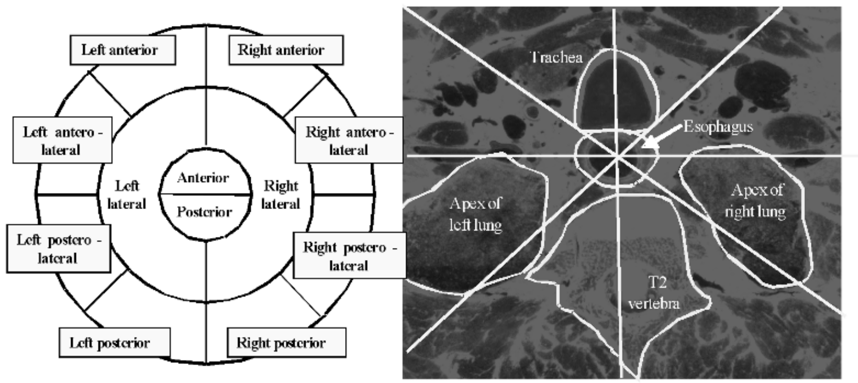
The formal properties of these relations in the FMA have been analysed [11, 25, 64, 79]. It deserves emphasis, however, that whereas part relations are transitive within their regional and constitutional categories, containment relations are not. To assert that a portion of esophageal mucus is contained in the lumen of the esophagus must not imply that such mucus is also contained in the space of the posterior mediastinum, in which the esophagus itself is contained.

In addition to containment relations, the location of the esophagus can also be specified by its adjacencies and anatomical coordinates. For example, the adjacencies of the thoracic vertebral column and trachea give an approximate location for the esophagus, which can be specified by attributing the adjacency with anatomical coordinates illustrated in Figure 4.10. For a particular regional part of the esophagus we may assert

'trachea' *adjacent_to* 'esophagus' *left_anterior*, *right_anterior*
'apex of left lung' *adjacent_to* 'esophagus' *left posterolateral*.

These qualitative coordinates refer to the standard 'anatomical position' of bipedal erect posture and therefore hold regardless of the position an individual assumes. They translate into a quadrupedic orientation of non-human species if – for example – anterior and posterior are equated with ventral and dorsal, respectively; and superior and inferior correspond with rostral and caudal. When anterior is used to mean rostral, however, as often is the case, it becomes problematic to identify interspecies homologies such as those between lobes of the human prostate and members of the murine prostate anatomical set [88].

In clinical medicine, not only qualitative but geometric coordinates are also employed (e.g., anteroposterior diameter of thoracic inlet, conjugate diameter of pelvis). In an individual human being, such as the Visible Human [92], location of an anatomical structure can be stated by a set of numerical coordinates, which, however, need to be translated into qualitative anatomical coordinates to be meaningful to human beings. Orientation provides additional information relevant to location, and like adjacency, is also attributed. For example, esophagus *has_orientation* pharyngo-esophageal junction *superior*, esophagogastric junction *inferior*.



Adjacency **Esophagus**

Value	coordinate	laterality
Trachea	Anterior	Right, Left
Second thoracic vertebra	Posterior	Right, Left
Apex of right lung	Postero -lateral	Right

Fig. 4.10. A system of qualitative anatomical coordinates superimposed on the esophagus in a transverse section of the male Visible Human cadaver specimen [92]. The lower part of the figure shows the attributed adjacency relations of the esophagus implemented in the FMA artifact.

4.5 The FMA Ontology Artifact

Selected parts of FMA theory have been implemented as ontology artifacts in a variety of terminology and ontology authoring and editing environments. The master copy, populated and maintained by the FMA's curators, is in Protégé and is stored in a relational database [65, 71]. It is the largest anatomy ontology or terminology and one of the largest ontologies in the biomedical domain: its more than 135,000 terms point to 75,500 types, which are interrelated by over 2.5 million iterations of 198 kinds of specific relations. (We shall see that a number of these relations, such as *has_FMA_ID*, *has_synonym*, are not anatomical or even ontological relations.) A main reason for such extensive data entry was to test and validate the theory, which, as a consequence, has been revised and enhanced through several cycles, an activity which continues to this day. Whereas the objective with the FMA theory is to treat the anatomy domain comprehensively, for several of its subdomains the artifact is populated merely with examples to illustrate a particular aspect of the theory. For example, although we have proposed a high-level ontological scheme (theory) for developmental continuants and relations [71], they have not been introduced in the FMA artifact in any detail. The main focus has been the macroscopic and microscopic anatomy of the entire body, including neuroanatomy [50]. Cell and its parts are extensively covered (a feature not widely appreciated); with surprisingly little overlap with the GO [5] and CL, and substantial differences in their ontological perspectives.

Such extensive population of an ontological framework required the selection of a particular species as model organism. For a variety of reasons, the FMA artifact is concerned with the canonical anatomy of *Homo sapiens*. Its nodes and relations become the more specific to this species the further removed they are in the taxonomic tree from the root node. This circumstance accounts for the prevailing view that the FMA is an ontology of human anatomy. Except for ‘human body’, the ontology’s terms do not specify that they point to parts of the human body; it is taken for granted that the types esophagus and stomach, for example, are instantiated by organs of human canonical anatomy.

We use the frame of esophagus, the subject of our case study, to illustrate the expressive machinery of the Protégé system for representing aspects of the theory.

A frame is a data structure which displays all the information in the ontology about a named anatomical type, including the properties which its instances share and the relations they have with instances of other types. The left panel (Figure 4.11) shows the node esophagus along with its taxonomic ancestors and siblings. Related information is displayed in the right panel in slots that bear the name of a particular property or relation. The contents of the slots are its values, and are admitted into a slot only if they point to a node of the anatomy taxonomy or one of the ancillary taxonomies of the FMA. Exceptions are the slots for numerical identifiers, preferred name, synonyms and foreign language equivalents associated with the taxonomic node of the frame, the definition of the corresponding type and comments about it (the latter not shown in Figure 4.11). Other slots cannot be filled unless the terms are imported from one of the taxonomies of the FMA. For example, the Dimensional Ontology provides the values for the slot *has_shape* (e.g., cylinder, polyhedron, which

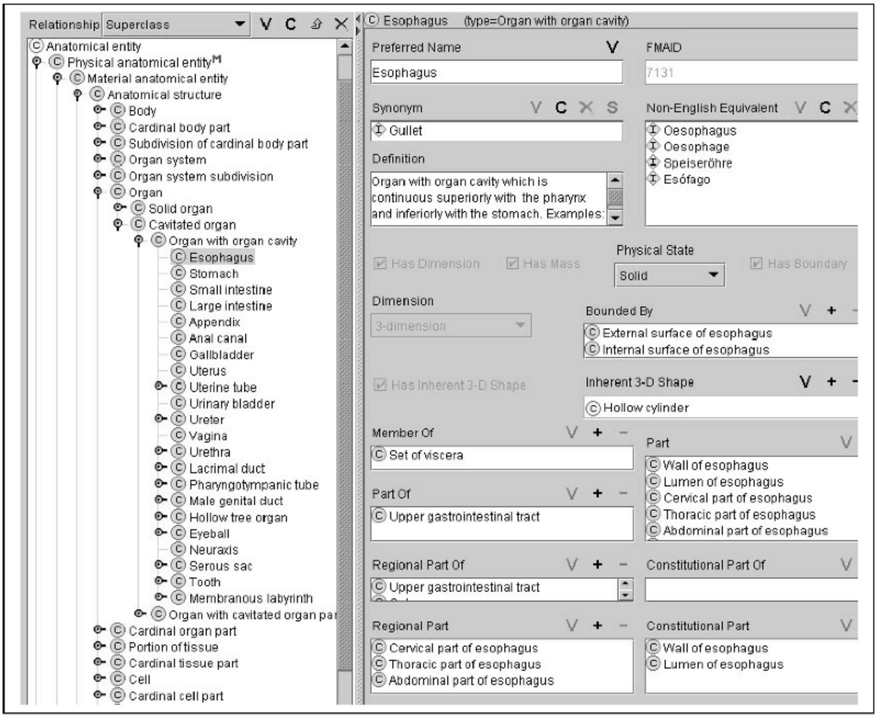


Fig. 4.11. The Protégé frame of esophagus in the FMA artifact.

are subclasses of 3-D volume), whereas the values for the part and adjacency slots in a frame are derived from the AT.

4.5.1 Identifiers and Terms

In addition to identifiers built into Protégé, each node has its unique numerical FMA identifier. When the corresponding type has an accepted name, it is adopted as the preferred name from *Terminologia Anatomica* [29] or established textbooks of subdomains of anatomy [3, 17, 28, 39, 49, 69, 93]. The FMA is the only anatomy ontology or terminology which comprehensively incorporates the approximately 10,000 terms comprising the international standard of anatomical nomenclature, accommodating also plural terms through the type anatomical set (section 4.4.7) [47].

In addition to those for most of the high-level types in the AT, new descriptive terms are also associated with a large number of leaf nodes; these point either to the unnamed complement of previously named parts, or are more specific than the terms in extant sources. The construction of new compound terms follows the rule of progression from the most specific to the most general component of the phrase (e.g., 'apex of heart' – not 'heart apex'; 'upper lobe of right lung' – not 'right upper lobe of lung'; 'left third rib' – not 'third left rib'; 'meningeal branch of left eighth thoracic spinal nerve' – not 'eighth thoracic spinal nerve meningeal branch'). Where not all parts of the entity have been named, a descriptive name is assigned to the complement (e.g., 'upper segment of uterus' where only the lower segment had been named previously).

We use the term 'proper' to designate the major unspecified part of an anatomical structure to distinguish it from lesser parts; for example, we distinguish 'epithelium proper of esophagus' from 'epithelium of esophageal gland' – both *part_of* 'epithelium of esophagus'; 'cytoplasm proper of neuron' from 'axon hillock' – both *part_of* 'cytoplasm of neuron'.

An audit is maintained of the terms adopted from other sources. For example the English language synonym of the preferred name 'esophagus' is 'gullet'; its non-English language equivalent in German is 'Speiseröhre', and in Latin 'oesophagus.' The audit for the latter records the term's derivation from *Terminologia Anatomica* (Figure 4.12). The audit can also indicate when a term is erroneous or outdated, as is the case for example for 'Botallo's ligament', the preferred name of which is 'ligamentum arteriosum'.

These examples are intended to illustrate that although the FMA is primarily ontologically rather than terminologically oriented, it is more inclusive, specific and comprehensive for terms of human anatomy than are other sources that we are aware of. The inclusion of such a spectrum of terms pointing to a node of the taxonomy enables searches of the FMA by a variety of users.

4.5.2 Properties and Relations

The machinery Protégé provides for distinguishing between inherited slot values and "own" slot values is explained elsewhere [65]. In the frame 'esophagus', the values for the slots of dimension, mass, physical state and 3-D shape are inherited from the frames of a hierarchy of taxonomic ancestors (Figure 4.11); so are the kinds of slots the esophagus frame can have (e.g., preferred name, definition, part of, adjacency, nerve supply, but, among others, not *has_branch*). A particular feature of the FMA, for which Protégé makes special accommodation, is attributed relations, illustrated for the kinds of adjacencies the esophagus has (Figure 4.10).

Protégé imposes constraints on the values of a slot. For example, the *part_of* slot in the frame of organ specifies that there can be multiple values for the slot and that the values can be derived only from AT types organ system, organ system subdivision, cardinal body part and cardinal body part subdivision. Since esophagus is a subtype of organ, the allowed values for its *part_of* slot include upper gastrointestinal tract, which is a subdivision of the GI tract, in turn a subdivision of the alimentary system. Another example is the restriction for the *nerve_supply* slot; values for this

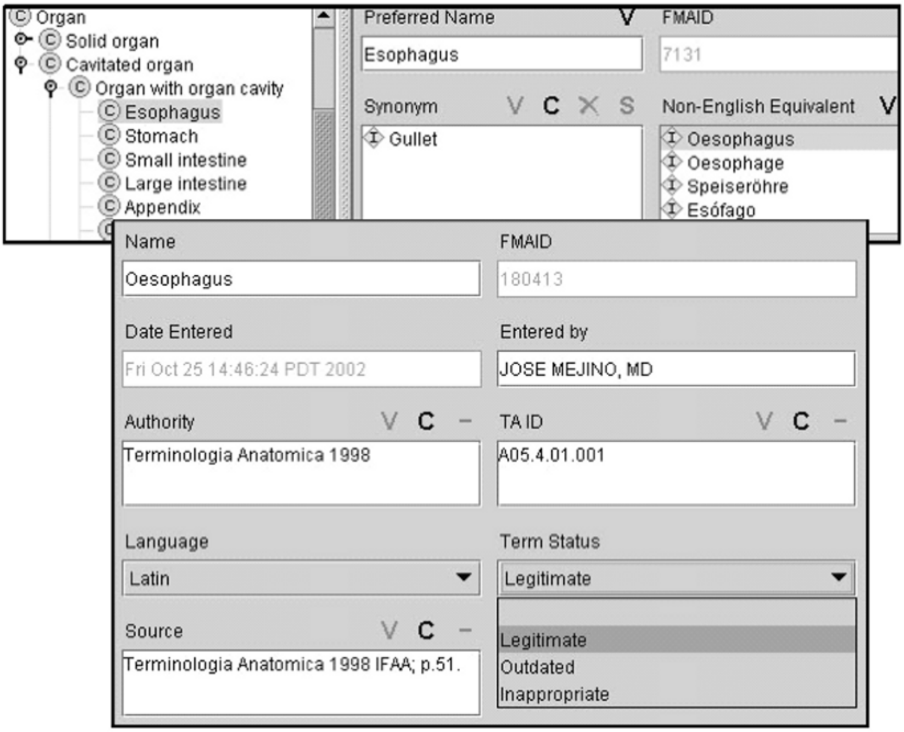


Fig. 4.12. A record of a term entry for a non-English equivalent of the preferred name esophagus in the FMA artifact.

slot may only be derived from AT types cranial nerve, spinal nerve and peripheral nerve. Also, the value 'lumen of esophagus' is allowed for the part slot, because lumen is a kind of organ cavity, and having a cavity as a part is inherited from the frame of 'cavitated organ'. Selecting a particular value in a slot, automatically opens the frame of the corresponding node of the taxonomy, both in Protégé and the FME [32].

We cite these examples to illustrate the discipline the Protégé ontology authoring environment has imposed on the FMA artifact and thereby significantly enhanced its ontological soundness.

4.5.3 Automatic Derivation of Hierarchies

The implementation of the FMA in Protégé enables the automatic generation of hierarchies linked by a uniform transitive relation, such as *has_part*. A number of the current anatomy terminologies employ this relation as a primary link within their hierarchies, as noted earlier, and may enter both *has_part* and *is_a* relations in the same directed acyclic graph, an approach promoted by some tools for terminology authoring.

The partonomy of the esophagus, based on the *has_generic_part* relation and illustrated in Figure 4.13, was automatically derived from the frame-based representation. Selected nodes of the hierarchy have been opened up at all levels of granularity, starting with the whole human body, moving onto organ system, its subdivision, an organ, cardinal organ parts, portions of tissue, cell, organelle, organelle part and biological macromolecule, as well as an acellular anatomical structure, the basement membrane and its molecular components; all seamlessly included in the same tree. Similar trees can be automatically generated on the fly for other transitive relations [60].

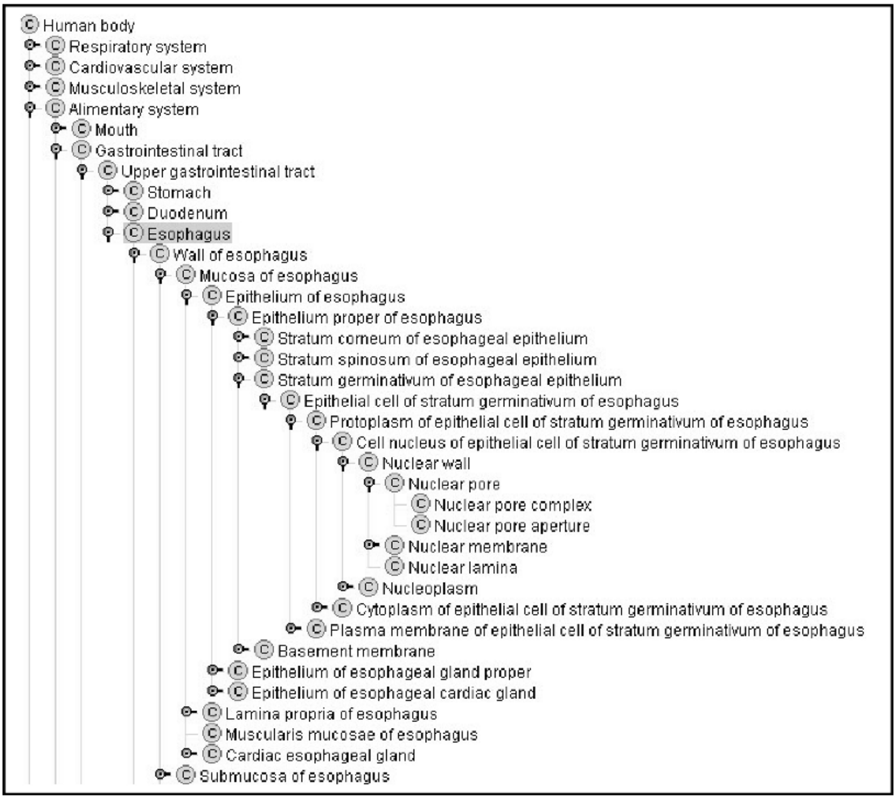


Fig. 4.13. A part hierarchy automatically generated from FMA's Protégé's frame-based representation. The partonomy spans all levels of granularity from the whole body to biological macromolecules.

4.5.4 Artifact Alternatives

The initial iteration of the Digital Anatomist vocabulary, the first incarnation of the FMA, was implemented in a simple terminology editing tool designed in-house at the University of Washington. This tool delivered the data for incorporation in the Unified Medical Language System to the National Library of Medicine; the vocabulary was then merged into the concept-based system of UMLS. At a later stage, the vocabulary was migrated to earlier versions of Protégé and its evolution into an increasingly complex ontology was a significant motivating factor for the realization of the current Protégé system.

As noted in Section 4.1, more recently the FMA also motivated a number of avenues of research in ontology and biomedical informatics, a notable one being to serve as a substrate and case-study for solving the problem of migrating complex frame-based systems to Web Ontology Language (OWL). Most comprehensive is the approach led by Golbreich at the University of Rennes, France and the National Library of Medicine [35], but other investigators at Stanford University [20], and at the University of Mannheim, Germany [30] have also undertaken similar tasks. Work is also in progress on migrating the FMA to the OBO edit modeling environment [61] and a new format of UMLS [63].

A simplified web browser, the Foundational Model Explorer or FME, has also been developed for providing ready access to a streamlined version of the Protégé-based artifact [22, 32].

Thus the FMA grew and was transformed from a simple terminology into one of the most complex and disciplined ontologies without having to discard any of the data entered over more than a 10 year period.

4.6 The FMA as Reference Ontology and Bioinformatics Resource

Since anatomy pervades essentially all subdomains of biology and medicine, the FMA was designed and developed as a general-purpose resource to fill a need for a unifying ontological framework of biological structure. It was the lack of such a reference, or standard, which had led to the creation of overlapping and often inconsistent representations of human anatomy in clinical terminologies. For example, in addition to SNOMED [85], GALEN [33], the Medical Entities Dictionary [52] and others, there are at least six terminologies in UMLS with a substantial anatomical content. Each of these terminologies was designed to support some task, application or activity in clinical medicine.

Unlike these terminological resources, the FMA was not tailored to the needs of any particular user group; rather, it was designed to serve as a resource for the developers of application ontologies in any specialized biomedical field. Indeed, the FMA is the first example of a *reference ontology* in the so-called basic biomedical sciences, and as such it has contributed to an awareness of a necessary distinction between application and reference ontologies in given domains of biomedicine. Knowledge pursued and represented by the basic biomedical sciences – anatomy, physiology, pathology, biochemistry, pharmacology, and the more recent additions to the list such as molecular and developmental biology and genome science – is not only indispensable and reused in such application domains as clinical medicine and experimental biology, but also often remains unarticulated, sinks to subconscious levels or is taken for granted. These basic sciences are the very fields of biomedicine that call for the establishment of their own reference ontologies as a solid backing to application ontologies.

Currently some tensions prevail between the promoters of sound ontological methods and many practitioners of clinical medicine and biomedical research. The demand for ontologies grows as knowledge-based applications gain increasing deployment. Practitioners in biomedical domains, however, look for knowledge organization schemes in these applications which mirror the ones they absorbed during their training. Our case study and many cited examples illustrate that such schemes are often not compatible with ontological principles and may not be suited for supporting nontrivial inference. These tensions can be resolved if developers of application ontologies 'mine' relevant reference ontologies, reuse segments appropriate for targeted tasks and design interfaces which accommodate the expectations of particular users. Such an agenda is reflected in a number of uses for which the FMA has already been exploited.

With the collaboration of investigators in computer science, members of the FMA's team have experimented with the development of knowledge-based applications and interfaces to facilitate access to the FMA. Although an application ontology for anatomy education has not yet been derived from it, the FMA has been used for the annotation of radiographs [54] and the 3D anatomical atlases of Digital Anatomist [23], which experience many thousands of hits per day from 95 countries. The FMA is the ontology back-end to a client-server anatomy information system which supports the semi-automatic generation of such atlases and also enables the interactive disassembly and assembly (virtual dissection and its reverse) of 3D computer graphics models of the human body [16]; it was also a key component in an open source toolkit for building biomedical web applications [42]. The FMA served as a test bed for developing the query agent OQAFMA for large semantic networks, which classifies and processes different types of queries [60]. In addition to its own interface for database queries, OQAFMA is also the agent behind a prototype interface to the FMA, which served for experimenting with the formulation of natural language queries [24]. The problem of constraining queries to entities and relations present in the FMA was solved by 'Emily', another "intelligent" interface [21]. The evaluation of 'Emily' revealed that correct answers, matching the key, could be generated to multiple-choice questions used in anatomy exams, which were culled from published compendia [76]. Since many of the answers were not hard-coded and had to be generated on the fly by traversing several paths, the results provide assurance that the FMA's ontological structure and content can support nontrivial inference comparable to the reasoning expected of medical students.

A number of ontological questions of general nature have been addressed in the course of the development of the FMA by its authors and independent investigators. Traditional representations of anatomical entities in terminologies have been influenced [2] and proposals have been advanced for assuring consistency in such representations [55]. Using the FMA as a reference, similar objectives were pursued for enriching the UMLS semantic network [95] and for designing metaschemas for it [96].

A particular topical problem is the development of methods for correlating or mapping ontologies with overlapping content to one another. The FMA has been used as one of the test ontologies in several such projects. Different investigators and approaches have compared the FMA to the anatomy module of GALEN [59, 97]. The rather surprising result with each method was that only around 5% match could be demonstrated between approximately 60,000 and 23,500 nodes in the FMA and GALEN ontologies, respectively. This match could not be improved substantially by combining the two independent methods [100]. The explanation of the divergence has not been analyzed systematically; however, it is likely related to the fact that the anatomy module of GALEN is primarily intended as an application ontology for diagnostic and therapeutic procedures; a substantial number of anatomical entities are classified in terms of their accessibility to such procedures, exemplified by some non-canonical structures designated by conjunctions pertaining to the esophagus: 'GITractFromEsophagusToDuodenum', 'EpibronchialPartOfEsophagus' and 'UnamedTractOfEsophagus'. The level of correspondence between the FMA and SNOMED's current version was found to be only somewhat better [14], despite the fact that – in contrast with SNOMED's earlier versions – the schemes of representation had much similarity in the two ontologies.

A comparison of a narrower scope was made, using yet a different approach, between cell parts in the FMA and the cell component section of GO [5]. After taking synonymy into account, 972 of 1,172 cell part terms remained unique to the FMA and 1,479 of 1,807 GO's cell component terms could not be aligned with the FMA. The two ontologies were comparable in their scope of breadth and depth and were found to be largely complementary rather than overlapping.

A finding suggestive of the advantage reference ontologies offer for improving alignment between application ontologies comes from the mapping of the human anatomy subset of the NCI Thesaurus and the Adult Mouse Anatomical Dictionary of Jackson Labs [98]. The correlation was improved when each terminology was first aligned with the FMA compared to when they were directly aligned with each other.

In addition to proving to be a substrate in biomedical informatics research, the FMA has also been exploited for some clinical informatics applications. A number of investigators at the National Library of Medicine have made use of segments of the FMA in systems designed for analyzing arterial branching patterns in cardiac catheterization reports [67], evaluating anatomical terminology in medical texts [84], facilitating integration of endoscopy terminology into the UMLS [90] and automating the interpretation of anatomical spatial relations in medical reports [8]. The FMA has provided the anatomical information for a system of radiation treatment planning in cancer therapy [44] and the development of a related application ontology for fields of lymphatic drainage and regions of predicted cancer spread [9, 86]. The anatomy component of another evolving clinical application ontology, *RadiO*, designed for radiology task reporting, is derived from the FMA [51].

In addition to its substantial section which takes account of neuroanatomical entities and relations [50] – a domain often treated as distinct from other anatomical entities – the FMA has also influenced bioinformatics ontology research in other fields of the basic sciences. An information system has been developed for the comparative anatomy of vertebrate species with the FMA serving as its reference ontology [87]. A high-level Ontology of Biomedical Realty – OBR – has been proposed as a framework for linking to one another the basic biomedical sciences [70]. The guiding principle of OBR is the designation of anatomical structures as independent continuants on which other continuants such as pathological lesions, functions, malfunctions and also processes depend. Actually, OBR is an explicit iteration of our long-held opinion that a sound conceptual framework of anatomical entities is at the root of sorting and ontologically organizing entities in other biomedical domains [15]. Reference has been made already to CARO, a common anatomy reference ontology which extends the FMA's orientation to vertebrate anatomy to all animals and developmental entities in particular [37]. The current version of CARO adopts from the FMA nearly half of its nodes and definitions, with or without modifications appropriate for its expanded scope.

OBR will realize its potential once basic science reference ontologies beyond anatomy become available. Examples of such ontologies include an evolving physiology reference ontology which integrates the FMA as the participants in physiological processes [19], and a reference ontology for pathology which adopts anatomical structures from the FMA as the continuants on which pathological entities are dependent [48, 81]. Although not reported in the literature, or noted in the artifacts, we hear from developers and curators that without adopting the FMA as such, they develop new terminologies/ontologies or update existing ones with reference to the FMA as a template. It is indeed rewarding to see the FMA reflected in these evolving resources. Access to the FMA as open source [31] should facilitate and enhance the role of the FMA as a reference ontology.

4.7 Concluding Remarks

The dual purpose of this chapter is to assist ontology developers only superficially familiar with biology in gaining some appreciation of the complexities of anatomy; and introduce anatomists unfamiliar with, but interested in, ontology – or "anatomical informatics" as it is currently designated [89] – to a new paradigm for viewing their discipline. Biologists, anatomists, health care professionals and students should not be more than peripherally concerned with high level types in the FMA, such as physical, non-physical, material and immaterial anatomical entities: they are necessary for an all-encompassing domain theory and for linking ontologies in different domains through anatomy to one another. There is a great need for application ontologies in anatomy tailored to diverse curricula in the basic science and clinical disciplines in order to raise web-based education and training to new levels [46]. The FMA should prove to be a useful resource for filling this need.

Soon after its initiation as a terminology, the FMA became a research project in biomedical informatics concerned with the development of methods for ontologically representing a fundamental and complex domain of biomedicine. As a consequence, its objectives are quite distinct from those of GO, GALEN or the Adult Mouse Anatomical Dictionary, for example, which were developed to support targeted tasks. We regard the FMA as an ongoing experiment in the evolving science of ontology and anticipate that it will continue to change and improve as it has during its ten year history. In addition to the examples cited, several chapters in this book attest to the influence the FMA has exerted on the thinking of ontologists about anatomy; some illustrate as well the challenges the FMA continues to pose for its own curators and others in ontological research. Although the FMA as yet has no substantial penetration in anatomy science and education, several professional societies and international organizations are in the process of considering its adoption as the standard for human anatomy.

In summary, the FMA has broken new ground in the science of anatomy, as well as in biomedical ontology and informatics, in that it has 1) defined anatomical structure and proposed it as the independent continuant of biomedical reality; 2) made the notion of canonical anatomy explicit and distinguished it from instantiated anatomy; 3) distinguished anatomy as structure from anatomy science; 4) drawn the boundaries for the scope of anatomy and demarcated it from the other biomedical basic sciences; 5) introduced Aristotelian definitions for the types of anatomical entities based predominantly on their structural properties; 6) proposed a unifying theory of anatomy; 7) distinguished this theory from its representation in a computable artifact; and 8) populated this artifact with types of anatomical entities such that its content is both more generalizable and detailed or specific than contemporary hard-copy or computable resources of human anatomy.

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Appendices

Table 4.1. Definitions of types of high-level anatomical entities

Anatomical entity	Organismal continuant entity which is enclosed by the bona fide boundary of an organism or is an attribute of its structural organization.
Physical anatomical entity	Anatomical entity which has three or fewer spatial dimensions.
Non-physical anatomical entity	Anatomical entity which has no spatial dimension.
Material anatomical entity	Physical anatomical entity which has mass.
Immaterial anatomical entity	Physical anatomical entity which is a three-dimensional space, surface, line or point associated with a material anatomical entity.
Anatomical structure	Material anatomical entity which is generated by coordinated expression of the organism's own genes that guide its morphogenesis; has inherent 3D shape; its parts are connected and spatially related to one another in patterns determined by coordinated gene expression.
Portion of body substance	Material anatomical entity in a gaseous, liquid, semisolid or solid state, with or without the admixture of cells and biological macromolecules; produced by anatomical structures or derived from inhaled and ingested substances that have been modified by anatomical structures.
Anatomical set	Material anatomical entity which consists of the maximum number of members of the same class which are not directly continuous with one another. Examples: set of cranial nerves, ventral branches of aorta, set of mammary arteries, thoracic viscera, dental arcade.

Table 4.2. Definitions of salient types of anatomical structures

Biological macromolecule	Anatomical structure which has as its parts one or more ordered aggregates of nucleotide, amino acid, fatty acid or sugar molecules bonded to one another. Examples: collagen, DNA, neurotransmitter, troponin.
Cell	Anatomical structure which has as its boundary the external surface of a maximally connected plasma membrane.
Cardinal cell part	Anatomical structure which is demarcated by bona fide or fiat boundaries within a cell. Examples: plasma membrane, mitochondrion, cell nucleus, axon, apical part of columnar epithelial cell.
Portion of tissue	Anatomical structure which has as its parts cells of predominantly one type and intercellular matrix.
Organ	Anatomical structure which has as its direct parts portions of two or more types of tissue or two or more types of cardinal organ part which constitute a maximally connected anatomical structure demarcated predominantly by a bona fide anatomical surface.
Cardinal organ part	Anatomical structure which has as its direct parts portions of two or more types of tissue and is continuous with one or more anatomical structures likewise constituted by portions of two or more tissues distinct from those of their complement. Examples: neck of femur, bronchopulmonary segment, left lobe of liver, right atrium, head of pancreas, long head of biceps.
Organ system	Anatomical structure which has as its direct parts instances of predominantly one organ type interconnected with one another by zones of continuity. Examples: skeletal system, cardiovascular system, alimentary system.
Cardinal body part	Anatomical structure which has as its direct parts instances of anatomical sets of organs and cardinal organ parts spatially associated with either the skull, vertebral column, or the skeleton of a limb; in their aggregate are surrounded by a part of the skin. Examples: head, neck, trunk, limb.
Body	Anatomical structure which is the aggregate material substance of an individual member of a species.
Anatomical cluster	Anatomical structure which has as its parts anatomical structures which are adjacent or attached to one another and are together demarcated by a maximal boundary. Examples: joint, root of lung, renal pedicle, nerve fasciculus.

Table 4.3. Definitions of cell, cardinal cell parts and cell substance

Cell & Cardinal cell part	See Table 2
Nucleated cell	Cell which has as its direct part a maximally connected part of protoplasm. Examples: hepatocyte, erythroblast, skeletal muscle fiber, megakaryocyte.
Non-nucleated cell	Cell which has as its direct part a maximally connected part of cytoplasm. Examples: erythrocyte, reticulocyte, corneocyte, lens fiber, thrombocyte.
Cell component	Cardinal cell part which is demarcated from other cell parts predominantly by one or more bona fide anatomical surfaces. Examples: golgi complex, endosome, myofilament.
Cell region	Cardinal cell part which is demarcated from other cell parts by one or more anatomical planes. Examples: apical part of cell, endoplasm, head of spermatozoon.
Plasma membrane	Cell component which has as its parts a maximal phospholipid bilayer and two or more types of protein embedded in the bilayer. Examples: plasma membrane of hepatocyte, sarcolemma, plasma membrane of erythrocyte.
Cytoplasm	Cell component which has as its direct parts a portion of cytosol and one or more organelles. Examples: cytoplasm of hepatocyte, cytoplasm of erythrocyte, cytoplasm of thrombocyte, cytoplasm of neuron.
Protoplasm	Cell component which has as its direct parts a maximally connected part of cytoplasm and one or more cell nuclei. Examples: protoplasm of hepatocyte, sarcoplasm, protoplasm of megakaryocyte.
Organelle	Cell component which is surrounded by a portion of cytosol. Examples: endoplasmic reticulum, ribosome, cytoskeleton, nuclear envelope, nucleus, mitochondrion.
Cell nucleus	Organelle which has as its direct parts a nuclear membrane and nuclear matrix.
Portion of cell substance	Portion of body substance in liquid state contained in a cell cavity proper, cavity of cell nucleus or cavity of cytoplasmic organelle. Examples: mitochondrial matrix, vacuoplasm.
Portion of cytosol	Portion of cell substance in which organelles and intracellular biological macromolecules are suspended.

Table 4.4. Definitions of some high-level types of immaterial anatomical entities

Immaterial anatomical entity	See Table 1
Anatomical space	Immaterial anatomical entity which has three spatial dimensions.
Anatomical cavity	Anatomical space which is bounded by the internal surface of one maximally connected anatomical structure and contains portions of one or more body substances. Examples: lumen of esophagus, cavity of urinary bladder, cavity of lysosome, lumen of microtubule.
Anatomical compartment space	Anatomical space which is bound by the bona fide anatomical surface of two or more anatomical structures and contains two or more anatomical structures. Examples: space of anterior compartment of forearm, thoracic cavity, synaptic cleft.
Anatomical conduit space	Anatomical space which connects two or more compartment spaces or two or more anatomical cavities. Examples: pupil, nuclear pore aperture, urogenital hiatus.
Anatomical boundary entity	Immaterial anatomical entity of one less dimension than the anatomical entity it bounds or demarcates from another anatomical entity.
Anatomical surface	Anatomical boundary entity which has two spatial dimensions.
Bona fide anatomical surface	Anatomical surface which marks a physical discontinuity between two or more anatomical structures or is an interface between an anatomical space and one or more anatomical structures.
Anatomical plane	Anatomical surface which, as an imaginary plane, bisects an anatomical structure or an anatomical space.
Anchored anatomical plane	Anatomical plane which bisects an anatomical structure or anatomical space across two or more anatomical landmarks.
Floating anatomical plane	Anatomical plane which bisects an anatomical structure independent of anatomical landmarks.*
Anatomical line	Anatomical boundary entity which has one spatial dimension.
Bona fide anatomical line	Anatomical line which corresponds to the intersection of two bona fide anatomical surfaces.
Fiat anatomical line	Anatomical line which corresponds to the intersection of two anatomical planes.
Anchored fiat anatomical line	Fiat anatomical line which subdivides an anatomical surface across one or more anatomical landmarks.
Floating fiat anatomical line	Fiat anatomical line which subdivides an anatomical structure independent of anatomical landmarks.
Anatomical point	Anatomical boundary entity which has zero spatial dimension.

* *Anatomical landmark: part of an anatomical structure in an individual organism which is palpable or visible and can serve for anchoring a fiat anatomical line or a fiat anatomical plane.*

Table 4.5. Definitions of anatomical relations

Anatomical relation	Non-physical anatomical entity which asserts an association between two or more physical and/or non-physical anatomical entities
Taxonomic anatomical relation	Anatomical relation which asserts the instantiation of types.
Is_a	Taxonomic anatomical relation which asserts the instantiation of a type by two or more subtypes or instances (individuals).
Sub_type of	Taxonomic anatomical relation which asserts the instantiation of a broader type by two or more narrower (more specific) types (subtypes).
Instance_of	Taxonomic anatomical relation which asserts the instantiation of a type by two or more instances (individuals).
Structural anatomical relation	Anatomical relation which asserts associations of a physical nature between two or more anatomical entities.
Has_dimension	Anatomical relation which associates an anatomical entity with the number of its spatial dimensions.
Has_shape	Structural anatomical relation which associates an anatomical entity with some geometric shape.
Has_boundary	Structural anatomical relation which holds between each anatomical entity of one to three dimensions and some immaterial anatomical entity of one lower dimension such that the latter demarcates (delimits) the former from its neighborhood.
Has_part	Structural anatomical relation which holds between each entity of type A and some anatomical entity of the same dimension of type B such that if A *has_part* B, there is a complement C which together with B accounts for the whole (100%) of A.
Has_generic_part	*Has_part* relation which generalizes to all specifications of the part relation.
Has_constitutional_part	*Has_part* relation which holds between each maximally connected anatomical structure and its compositionally distinct anatomical element demarcated from the complement by a predominantly bona fide boundary.
Has_regional_part	*Has_part* relation which holds between each maximally connected anatomical structure and its part demarcated from the complement by a predominantly fiat boundary.
Has_member	*Has_part* relation which holds between each anatomical set and any of its elements.
Connected_to	Structural anatomical relation which holds between each anatomical structure of type A and some anatomical structure of type B such that each structure shares some part of its bona fide anatomical surface with that of the other.
Continuous_with	*Connected_to* relation which holds between each anatomical entity of type A and some anatomical entity of type B such that there is no bona fide boundary between their contiguous constitutional parts.

Attached_to	*Connected_to* relation which holds between each anatomical structure of type A and some structure of type B such that some of the constitutional parts of the structure in type A are intermingled with some of the constitutional parts of the structure in type B across a fiat part of their maximal boundary which the related structures share.
Has_location	Anatomical structural relation which holds between an entity of any type or domain and some spatial region occupied by some physical anatomical entity.
Contained_in	Location relation which holds between a material anatomical entity and some anatomical space if the related entities are part of the same organism.
Adjacent_to	Location relation which holds between each physical anatomical entity in type A and some anatomical entity of the same dimension in type B such that their bona fide boundaries are spatially proximate, share no parts, and are separated by no physical anatomical entity of the same dimension.
Surrounds	Adjacency relation which holds between each physical anatomical entity of type A and some anatomical entity of the same dimension in type B such that the proximate bona fide boundaries of the related entities are adjacent for most of their extent.
Has_anatomical_coordinate	Location relation which holds between each physical anatomical entity in type A and some anatomical plane, line or point.
Has_organizational_pattern	Structural relation which holds between an anatomical structure and some organizational pattern.
Has_segmental_innervation	Structural relation which holds between an anatomical structure and some segment of the spinal cord.