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A reference ontology for biomedical informatics: the Foundational Model of Anatomy

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Abstract

The Foundational Model of Anatomy (FMA), initially developed as an enhancement of the anatomical content of UMLS, is a domain ontology of the concepts and relationships that pertain to the structural organization of the human body. It encompasses the material objects from the molecular to the macroscopic levels that constitute the body and associates with them non-material entities (spaces, surfaces, lines, and points) required for describing structural relationships. The disciplined modeling approach employed for the development of the FMA relies on a set of declared principles, high level schemes, Aristotelian definitions and a frame-based authoring environment. We propose the FMA as a reference ontology in biomedical informatics for correlating different views of anatomy, aligning existing and emerging ontologies in bioinformatics ontologies and providing a structure-based template for representing biological functions.
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1. Introduction

Ontology design is becoming increasingly recognized as central to medical informatics [1] and even more so to bioinformatics. New ontologies continue to appear in diverse areas of the biomedical sciences with a particular emphasis on biological macromolecules and the processes in which these molecules participate. The importance of relating such new information resources to medical terminologies (or vocabularies) is illustrated by the recent incorporation of the Gene Ontology [2] in the Unified Medical Language System (UMLS) [3]. UMLS, designed, maintained and distributed by the National Library of Medicine, provides a unified knowledge representation system for correlating a large number of biomedical terminologies. Like most UMLS terminologies, the Gene Ontology and other application ontologies in biomedical informatics are compiled in diverse

contexts with distinct user groups in mind; consequently their correlation and mapping to one another pose a considerable challenge. The challenge is enhanced by the need for aligning these ontologies with evolving, computable information resources in the classical, basic, biomedical sciences (e.g., anatomy, physiology, and pathology), as well as with those in clinical medicine. Such correlations will be critical for the development of knowledge-based applications that will need to rely on inference in order to support clinical research and decision making based on the knowledge of molecular biology.

A *raison d'être* of UMLS is to facilitate the establishment of correspondences in the meaning of terms among its constituent vocabularies. This correlation is largely achieved through assigning the same concept occurring in different terminologies to high level semantic types encompassed within the UMLS Semantic Network [4]. It is more problematic, however, to reconcile divergences in the semantic structure of these sources and other ontologies at levels higher than leaf concepts and discrete terms. For example, while there is

considerable correspondence in the meaning of anatomical terms in UMLS sources that include substantial amounts of anatomy, there is very little similarity in the schemes these sources use for arranging their anatomical terms into a coherent representation of anatomical knowledge. While such correspondences may support the correlation of the meaning of terms, the underlying semantic structure of these abstractions must also be aligned if problem solving calls for inference across the boundaries of related ontologies.

It is particularly important to assure coherence of knowledge domains that generalize to a number of other fields where they will be reused. Such is the case with the classical, basic, biomedical sciences and also with more modern disciplines, such as neuroscience and developmental biology. All these fields are embraced by bio- and biomedical informatics, which deal not only with human biology but also with observations and experimental data derived from non-human species. In order to support the generation of knowledge-based applications that will be increasingly needed in basic science and clinical research, as well as in the delivery of health care, computable knowledge sources must be established not only in the modern but also in the classical disciplines of basic science. Such a widening focus in bioinformatics is inevitable in the post-genomic era, and the process has in fact already begun. Distinct from the large clinical terminologies (e.g., SNOMED RT [5], GALEN [6], Medical Entities Dictionary [7]), a number of ontologies are emerging that represent knowledge in discrete fields of the basic biomedical sciences. One of these ontologies is the Digital Anatomist Foundational Model of Anatomy (Foundational Model or FMA, for short) [8,9]. The FMA symbolically represents the structural organization of the human body from the macromolecular to macroscopic levels.

The initial development of the FMA was supported by UMLS with the intent of enhancing the anatomical content of UMLS source vocabularies and ultimately facilitating the correlation of anatomical concepts represented in these vocabularies. We present a status report on the FMA, major components of which are included in UMLS as the Digital Anatomist vocabulary (known in previous editions of UMLS as UWDA). With this report we wish to promote the evaluation of the FMA with respect to realizing its intended role in UMLS and, in a broader sense, bring the FMA to the attention of the biomedical, and particularly the bioinformatics communities.

The purpose of this paper is to describe the FMA and propose it as a reference ontology for biomedical informatics. Our rationale for this proposal is based on the fact that the FMA's concept domain embraces all material objects, substances and spaces that result from the coordinated expression of structural genes. In their aggregate these anatomical entities constitute the fully formed body and assume the role of "actors" in all physiological and disease processes. Therefore, we contend that a coherent domain ontology of anatomical entities is the best candidate for serving as a foundation and reference for the correlation of other ontologies in biomedical informatics. Our second objective is to illustrate the process of disciplined modeling we pursued in establishing the FMA. We believe that this approach could also serve well the authors of emerging knowledge sources in bioinformatics, in that it synergizes with and enhances broader guidelines and desiderata that have been proposed for the construction of terminologies and knowledge bases [10,11].

1.1. Organization of this paper

We first define the FMA and then illustrate the disciplined modeling approach by focusing on the establishment of the Anatomy Taxonomy (**AT**) and the other two components of the FMA, which relate to structural and developmental attributes of the entities to which concepts in the **AT** refer. The next sections are devoted to accessing, scaling, and evaluating the FMA, before we discuss the FMA's relevance to UMLS and comment on its potential as a reference ontology for biomedical informatics, which leads to our conclusions. Different typographies used in the text have the following associations: Names of concepts represented in the FMA are in `Courier New` font, which distinguishes, for example, `Organ`, a class in the **AT**, from the term 'organ' used in a general context; relationships between concepts are in *italics* enclosed by hyphens, e.g., *-part of-*; italics are also used for emphasis and for Latin terms; abbreviations of the components of the FMA are in bold capitals, e.g., **AT**.

2. The Foundational Model of Anatomy

The Foundational Model of Anatomy is an evolving ontology for biomedical informatics; it is concerned with the representation of entities and relationships necessary for the symbolic modeling of the structure of the human body in a computable form that is also understandable by humans [8,9]. Specifically, the FMA is an abstraction that explicitly represents a coherent body of declarative knowledge about human anatomy as a domain ontology (defined below). The ontology is implemented in a frame-based system and is stored in a relational database. The FMA is intended as a reusable and generalizable resource of deep anatomical knowledge, which can be filtered to meet the needs of any knowledge-based application that requires structural information. It is distinct from application ontologies in that it is not intended as an end-user application and does not target the needs of any particular user group.

We regard this model as *foundational* for two reasons: (1) anatomy is fundamental to all biomedical domains; and (2) the anatomical concepts and relationships encompassed by the FMA generalize to all these domains. By 'anatomical concept' we mean a unit of thought that refers to an anatomical entity (defined in section 3.2.1). The Foundational Model currently contains 70,000 distinct anatomical concepts—representing structures ranging in size from some macromolecular complexes and cell components to major body parts. These concepts are associated with more than 110,000 terms, and are related to one another by more than 1.5 million instantiations of over 170 kinds of relationships. We developed and instantiated this large and complex model through an approach we call *disciplined modeling*.

3. Disciplined modeling

We first describe the elements of disciplined modeling that have guided the establishment of the three major components of the FMA and then deal with each of these components: the Anatomy Taxonomy, Anatomical Structural Abstraction, and the Anatomical Transformation Abstraction.

3.1. Elements of disciplined modeling of anatomy

We borrow the term 'disciplined modeling' from Perl et al. [12,13], who proposed a methodology for restructuring existing vocabularies in order to introduce clarity into their representation scheme. We on the other hand have employed a disciplined approach for the *de novo* creation of a new knowledge base. The elements of our approach consist of a set of declared foundational principles, a high level scheme for representing the referents of concepts and relationships in the anatomy domain, Aristotelian definitions and a knowledge modeling environment that assures implementation of the principles and the inheritance of definitional and non-definitional attributes.

3.1.1. Foundational principles
Principles are assertions that provide the basis for reasoning and action. The nature of the principles we declare is dictated by the definition of the domain we intend to model. This domain is anatomy. We have previously distinguished and defined two concepts for which the term 'anatomy' is a homonym: anatomy (science) and anatomy (structure) [8]. As its definition in a preceding section specifies, the Foundational Model of Anatomy is an abstraction of anatomy (structure), which is the ordered aggregate of material objects and physical spaces filled with substances that together constitute a biological organism. The instantiated symbolic model itself is a concrete manifestation of anatomy (science), which is a biological science concerned with the discovery, analysis and representation of anatomy (structure). We declared the following principles for guiding the formulation and instantiation of the FMA abstraction [8,9]:

1. Unified context principle. The abstraction should conform to a strictly *structural context*. Although anatomical discourse in education and various biomedical fields embraces diverse contexts (e.g., functional, surgical, radiological, and biomechanical), it is the analysis and description of an organism's structure that distinguishes the science of anatomy from other biological sciences. We have found that only in a structural context is it possible to establish a single inheritance hierarchy that subsumes all anatomical concepts. As stated earlier, it is our contention that such a structure-based representation can serve as a reference ontology for correlating other (e.g., functional, clinical) contexts and views of anatomy.

2. Abstraction level principle. The abstraction should model *canonical anatomy* and provide a framework for anatomical variants, but should exclude *instantiated anatomy*.

We have previously distinguished canonical and instantiated anatomy [8]. *Canonical anatomy* is a field of anatomy (science) that comprises the synthesis of generalizations based on anatomical observations that describe idealized anatomy (structure). These generalizations have been implicitly sanctioned by their usage in anatomical discourse. *Instantiated anatomy* is the field of anatomy (science) which comprises anatomical data pertaining to instances (i.e., individuals) of organisms and their parts. Although we exclude instantiated anatomy from the FMA, our intent is for the FMA to serve as a foundation for the representation of the anatomy of individuals and to provide an organizational framework for anatomical data, including images. Thus, the FMA should represent classes, which are multiply located anatomical entities (i.e., universals) that exist in the instances (or particulars) that they subsume.

3. Species specificity principle. The initial iteration of the abstraction should model the anatomy of *Homo sapiens*, but at the same time it should serve as a framework for the anatomy of other mammalian and eventually, other vertebrate species. Although clinical medicine is concerned with the human, animal models of human disease, as well as veterinary medicine in its own right, call for a symbolic representation of anatomy. The highly conserved groups of structural genes that dictate the vertebrate body phenotype provide a rationale for eventually modeling species-specific anatomy as specializations of a generalizable vertebrate body plan [14]. Therefore, the high level abstract classes of the FMA should accommodate the generalized "*Bauplan*" of vertebrates.

4. Definition principle. Defining attributes of a class in the model should be specified in terms of the physical

and other structural (i.e., anatomical) attributes of the anatomical entities that the class subsumes (see Section 3.1.3).

5. Dominant concept principle. An ontology's dominant class is the class in reference to which other classes in the ontology are defined. `Anatomical structure` (defined in Section 3.2) shall be the dominant class in the FMA (see Section 3.2.2.2).

6. Organizational unit principle. The abstraction shall have two units in terms of which subclasses of `Anatomical structure` are defined: `Cell` and `Organ`. Other subclasses of `Anatomical structure` shall constitute cells or organs, or be constituted by cells or organs.

7. Content constraint principle. The largest anatomical structure represented shall be the whole organism (in the current iteration, the human body) and the smallest `Biological macromolecule`. Should the need arise, molecules not synthesized through the expression of the organism's own genes shall be represented in separate ontologies. Within these constraints, the abstraction shall model both concepts and relationships at the most refined level of granularity.

8. Relationship constraint principle. The abstraction shall model three types of relationships that occur between anatomical entities: (1) class subsumption relationships; (2) static physical relationships; and (3) relationships that describe the transformation of anatomical entities during the ontogeny of an organism. Dynamic physical relationships between anatomical entities (e.g., those relating to physiological function and the pathogenesis of abnormalities and disease) shall be modeled in separate ontologies.

9. Coherence principle. The abstraction shall have one root, `Anatomical entity`, which subsumes all entities relating to the structural organization of the body; concepts referring to these entities shall be arranged in a single and comprehensive inheritance class subsumption hierarchy.

10. Representation principle. The abstraction shall be modeled as an ontology of anatomical concepts and should accommodate all naming conventions associated with these concepts.

Because of the diverse and implied meanings associated with the term 'ontology,' (some of which are reviewed by Burgun and Bodenreider [11]), we prefer to refer to the abstraction of the FMA as a symbolic model, rather than an ontology. We define a *symbolic model* as a conceptualization of a domain of discourse represented with non-graphical symbols in a computable form that supports inference. We designate such a symbolic model as a *foundational model*, when it declares the principles for including concepts and relationships that are implicitly assumed when knowledge of the domain is applied in diverse contexts, and explicitly defines the concepts and relationships necessary for consistently

modeling the structure of the coherent knowledge domain. In order to justify its designation as *foundational*, such a model should serve as a reference in terms of which other views (contexts) of the domain can be correlated. Moreover, the concepts represented in a foundational model should be indispensable for the symbolic modeling of, and discourse in, a number if other domains. The *Foundational Model of Anatomy* is a foundational model of the physical organization of the human body—i.e., anatomy (structure)—and its coherent knowledge domain is anatomy (science). Other domains for which anatomy is indispensable include physiology, pathology, clinical medicine, and molecular and developmental biology.

These principles provide the rationale for proposing a high level scheme for the FMA.

3.1.2. High level scheme

A high level scheme encapsulates the concept domain and scope of a symbolic model and defines its main components; in effect it serves as a hypothesis that is tested by the instantiation of the model and may be modified during this process. We have previously proposed such a high level scheme for the Foundational Model of Anatomy [9]:

$$\mathbf{FMA} = (\mathbf{AT}, \mathbf{ASA}, \mathbf{ATA}, \mathbf{Mk}), \qquad (1)$$

where **AT** is the *Anatomy Taxonomy*, which specifies the taxonomic relationships of anatomical entities and assigns them to classes (defined in next section) according to defining attributes which they share with one another and by which they can be distinguished from one another;[1] the **ASA**, or *Anatomical Structural Abstraction* describes the partitive (meronymic) and spatial relationships of the concepts represented in the taxonomy; the **ATA**, or *Anatomical Transformation Abstraction* describes the time-dependent morphological transformations of the concepts represented in the taxonomy during the human life cycle, which includes prenatal development, post-natal growth and aging; and **Mk** refers to *Metaknowledge*, which comprises the principles and sets of rules, according to which the relationships are represented in the model's other three component abstractions.

This abstraction captures the information that is necessary for describing the anatomy of not only the whole body, but also that of any structure (physical object) or space that constitutes the body. Indeed, in practical terms, the foundational model of the whole body must be generated stepwise through aggregating the symbolic models of discrete classes of physical anatomical entities. The foundational model for the anatomy of the entire body

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[1] In previous publications this was called the Ao (Anatomy ontology); we renamed it as AT in order to distinguish it from the entire FMA, which is more appropriately regarded as an ontology.

(FMA$_{BODY}$) may, therefore, be conceived of as the aggregate of the foundational models of physical anatomical entities ({FMA$_{PHYSICAL\_ANATOMICAL\_ENTITY}$}) that constitute the body. Thus,

$$FMA_{BODY} = \{FMA_{PHYSICAL\_ANATOMICAL\_ENTITY}\}. \quad (2)$$

The FMA's high level scheme identifies the anatomy taxonomy as one of the component abstractions of the symbolic model or ontology, a distinction that is rarely made clear in discussions of ontologies. The **AT** forms the backbone of the FMA, and Aristotelian definitions, a third element of principled modeling, play a key role in its establishment.

3.1.3. Aristotelian definitions

In dictionaries the unit of information is a term, and the purpose of the definitions is to define all meanings associated with a given term. For example the term 'organ' may refer, among other things, to a musical instrument, or a part of the human body. In an ontology or foundational model, as we define it above, the unit of information is a concept and the purpose of definitions is to align all concepts in the ontology's domain in a coherent inheritance type hierarchy or taxonomy. This objective imposes a set of requirements that are not satisfied by the majority of dictionary definitions. We have found that, unlike a number of controlled medical terminologies, we could not adopt dictionary definitions for establishing the Anatomy Taxonomy. Therefore, guided by the foundational principles we declared, and relying on precedent set by Aristotle [15], we formulated ten desiderata that definitions must satisfy in order to support the creation of an inheritance type hierarchy, such as the **AT** [16].

In brief, these desiderata specify that definitions should be consistent with the declared context and principles of an ontology. Rather than stating the meaning of terms, definitions should state the *essence* of anatomical entities in terms of their characteristics, consistent with the ontology's context. Paraphrasing Aristotle, the essence of an entity is constituted by two sets of defining attributes; one set, the *genus*, necessary to assign an entity to a class and the other set, the *differentiae*, necessary to distinguish the entity from other entities also assigned to the class. A collection of entities that share the same set of essential characteristics constitutes a class of the ontology. The defining attribute/s shared by all entities within the selected domain should specify the root of the ontology. To assure transitive inheritance of essential characteristics, classes that may not have been explicitly identified in existing sources of domain knowledge should be defined.

Provided these desiderata are satisfied, the hierarchical sequence of classes in the taxonomy will be dictated by the properties shared by collections of entities. The soundness of this hierarchy will then depend on the

explicit specification of the properties (attributes) that define the essence of entities, providing the basis on which they may be grouped together or distinguished from one another. Unlike dictionary definitions, which bear no relationship to their neighbors in the alphabetized list of terms, the definition of a concept in a taxonomy is enriched by the definition of all of its parents within the hierarchy. Thus, a definition of a concept within an ontology is incomplete without that of all of its parents.

Therefore, in creating the Anatomy Taxonomy, two challenges need to be met: a conceptual one, which is to identify the structural attributes in terms of which enetities that constitute the human body may be grouped together and distinguished from one another, and a practical one, which is to identify an authoring program that not only supports but also enforces the implementation of foundational principles and definitional desiderata that are to guide the creation of the FMA. We first describe the knowledge modeling environment we selected, which is the fourth element of disciplined modeling.

3.1.4. Knowledge modeling environment

We have analyzed the challenges posed by the seemingly simple task of formally representing declarative anatomical knowledge and found them to be surprisingly complex [17]. We selected the Protégé-2000 ontology editing and knowledge acquisition environment [18] for encoding the FMA, because its frame-based architecture, which is compatible with the Open Knowledge Base Connectivity (OKBC) protocol [19], provides for an expressive, scalable and tractable representation of anatomical entities and the complex relationships that exist between them. We briefly describe and illustrate with examples how (1) frames are used in Protégé-2000 to represent anatomical concepts; (2) frames allow for distinguishing between classes and instances; (3) Protégé-2000 provides for selective inheritance of attributes; and (4) Protégé enhances the specificity and expressivity of attributes through assigning to them their own attributes.

3.1.4.1. Frames, slots, slot values, and facets.
Anatomical concepts are represented as frames in Protégé-2000. A frame is a data structure that contains all the information in the ontology about a given concept. This information includes the properties of the entity to which that concept refers and also the relationships of that entity to other entities. In the context of the FMA, a frame is a named anatomical entity, such as vertebra. With each frame is associated a defined set of attributes; each of these attributes has a value. Thus each frame consists of a concept and a set of attribute/value pairings. Fig. 1 shows the frame `Vertebra`; the concept highlighted in the left hand pane (the **AT**) and some of
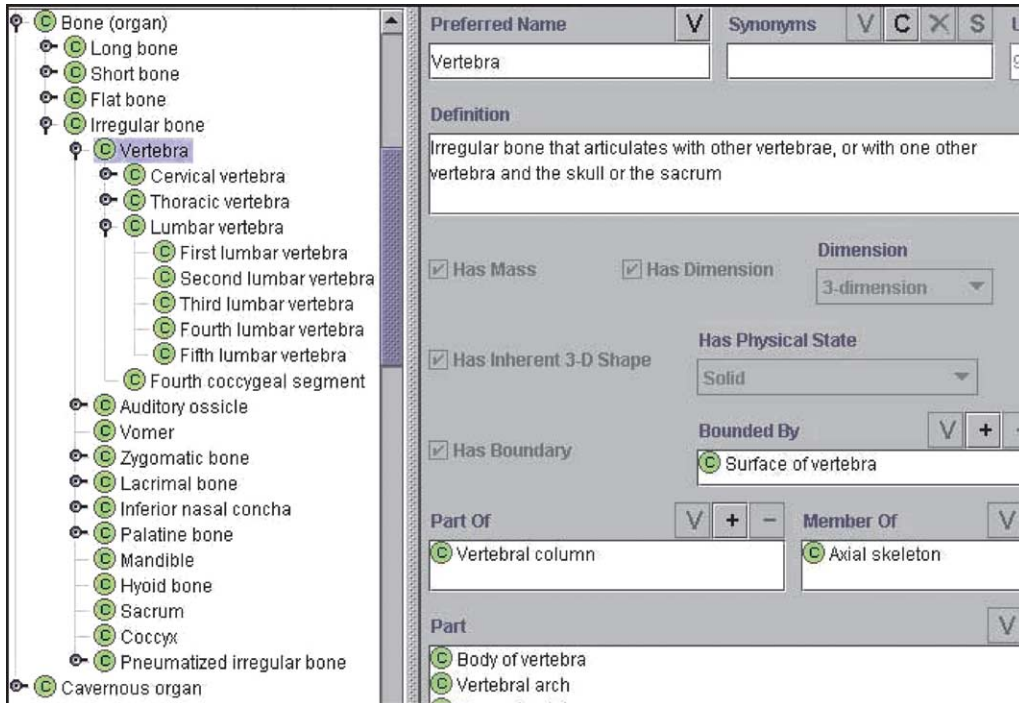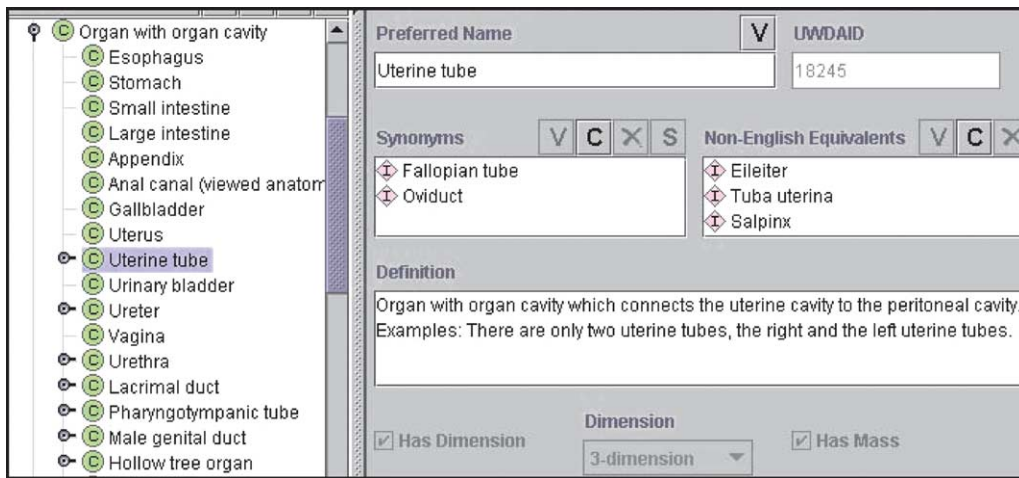
Fig. 1. The frame of the concept Vertebra.

Fig. 2. A variety of terms associated with the concept Uterine tube.

Fig. 3. Attributed adjacency and continuity relationships of the Esophagus.

the attribute/value pairings in the right hand pane of the Protégé graphical user interface (GUI).

Attributes (properties) and relationships of the entity associated with the concept are expressed as slots of the frame. Slots correspond to such non-structural attributes as preferred name, synonyms, and numerical identifiers (UWDA-ID), as well as such structural attributes or relationships as -has part-, -part of-, -has dimension-, -bounded by-, etc. Slots remain empty unless filled with one or more values. In Fig. 1 the synonyms slot is empty because `Vertebra` has no synonyms, whereas the same slot in the frame of `Uterine tube` in Fig. 2 is filled with two values.

Protégé-2000 allows different binary relationships for slots. Some slots, like -has dimension- and -has inherent 3D shape-, have a binary relationship with atomic values like Boolean "true" or "false"; for slots that describe binary relationships between frames, the values are derived from established classes of the **AT** or the FMA's other associated taxonomies. For example, the Dimensional Ontology provides the values for the slot -has shape- (e.g., cylinder, polyhedron, which are subclasses of 3-D volume), whereas the values for the part and adjacency slots in the frame are derived from the **AT**.

In Protégé-2000, facets impose constraints on the values that a slot can have. For example, the facets of the -part of- slot in the frame of `Organ` specify that there can be multiple values for the slot and that the values can be derived only from **AT** classes `Organ System`, `Organ system subdivision`, `Body part` and `Body part subdivision`. Thus the value `Vertebral column` in the -part of- slot of `Vertebra` is allowed, because `Vertebral column` is a subdivision of the skeletal system. Another example is the restriction for the -nerve supply- slot; values for this slot may only be derived from **AT** classes `Cranial nerve`, `Spinal nerve`, and `Peripheral nerve`.

3.1.4.2. Classes and instances. In Protégé-2000 a frame may represent a *class* or an *instance*. As far as most users of the Foundational Model will be concerned, however, (and as explained below) all the nodes of Anatomy Taxonomy hierarchy may be regarded as classes.

A class in the **AT** is a collection of anatomical entities or collections of collections. For example, the class `Vertebra` represents such a collection of collections. It subsumes different collections of vertebrae like cervical, thoracic, and lumbar vertebrae (Fig. 1). Moreover, the members of each of these collections, which in Protégé are represented as *subclasses* of `Vertebra`, are likewise further grouped into more specialized collections. This is true even of the leaves of the `Vertebra` tree, which have no subclasses in the **AT**. The `Fifth lumbar vertebra`, for example, is a class to which the fifth lumbar vertebrae of individuals like a John or a Jane Doe belong. Therefore, unlike the higher classes, `Fifth`

`lumbar vertebra`, as currently implemented, does not subsume collections of collections; rather it subsumes concrete anatomical entities, which, however, are not represented in the **AT**. Should a need arise, this representation allows us to elaborate the **AT** by introducing subclasses of `Fifth lumbar vertebra` specified by gender or race, for example, without having to redefine this class and its ancestors.

Since concrete, real-world objects, such as the vertebrae of a John or a Jane Doe, represent anatomical data, in concurrence with the 'abstraction level principle,' they are excluded from the FMA; they belong in the field of *instantiated anatomy*. By contrast, concepts in the class hierarchy of the Anatomy Taxonomy refer to collections and collections of collections; they belong in the field of *canonical anatomy*.

Although the above explanation suggests that all concepts of anatomical structures in the **AT** are classes, in fact, we had to assign the role of *instance* as well to the frames of these concepts. In the frame-based system of Protégé, this was the technical solution for enabling the selective inheritance of attributes, discussed in the next section. This solution required the establishment of a *metaclass hierarchy* and assigning the frames of **AT** classes as instances of the corresponding metaclasses (see below). Thus, except for its root, all concepts in the **AT** are subclasses of a superclass and also an instance of a metaclass. These dual assignments integrate the **AT** and the metaclass hierarchy. Class-to-class relationships in the integrated **AT** and metaclass hierarchies are encoded in Protégé as -direct superclass- and -direct subclass- links, whereas the inverse relationship between a class and its instances in the metaclass hierarchy is -direct type- and -direct instance-. We distinguish the integrated Anatomy Taxonomy and metaclass hierarchy from other hierarchies (e.g., part-of, branch-of) by calling it the -is a- hierarchy. This technical contrivance is of interest to the authors of the FMA and to other knowledge modelers; it can, however, remain opaque to other users of the ontology.

3.1.4.3. Selective inheritance of attributes. The purpose of the Anatomy Taxonomy is to assure the propagation or inheritance of attributes. It is necessary, however, to distinguish between the attributes that should and should not be propagated. As intimated above, the desired selective inheritance is achieved operationally, in a seemingly contradictory way, by assigning a dual role to each frame: in Protégé each **AT** frame is modeled both as a class and as an instance. Its role as a class allows it to propagate its set of attributes to its subclasses, but in its role as an instance it is prevented from doing so.

The insertion of new slots at appropriate levels of the ontology provides for introducing definitional and other attributes that should be inherited by descendants of a class. Such a class has been designated as a *property*

introduction class [20], whereas in Protégé-2000 new attributes (slots) are introduced in metaclasses. Meta-classes function as templates, and serve to define new classes. Newly created classes in the **AT** are assigned as instances of corresponding metaclasses. Thus an **AT** class is a subclass of its ancestor classes in the **AT** and its frame is an instance of its metaclass. For example, the **AT** class `Vertebra` is a subclass of `Irregular bone` and an instance of `Vertebra metaclass`.

This arrangement allows for discriminating between slots that should and should not be propagated. The definitional attributes are propagated to descendants of the class as *template slots*; they specify which slots each member of the class shall have and what the restrictions (facets) on the values of these slots shall be. Instances of the class, on the other hand, inherit such template slots as *own slots* and assign specific values to them (own slot values). Own slots are not propagated. For example, `Vertebra metaclass` has a template slot *-part of-*, which its instance `Vertebra` inherits as its own slot, and assigns the slot value `Vertebral column`. `Cervical vertebra` is a subclass of `Vertebra` and inherits the template slot *-part of-* but not the slot value `Vertebral column`. Instead it converts the template slot into its own slot, and assigns its own slot value `Cervical vertebral column`. Template slots dictate what attributes or slots a class must impose on its descendants. The example illustrates the principle of modeling at the most refined level of granularity. Although `Cervical vertebra` is part of `Vertebral column`, the most specific relationship holds for `Cervical vertebral column`, which is also a subdivision of the skeletal system and is in turn a part of the `Vertebral column`. It is the role of intelligent query interfaces, described in Section 4, to concatenate such relationships and allow the result `Cervical vertebra` *-part of-* `Vertebral column`.

3.1.4.4. Attributed relationships. The FMA is particularly rich in relationships, which, in addition to defining attributes, describe the part-whole, location, and other spatial associations of anatomical entities. However, for the precise and comprehensive description of the structure of the body, it is not sufficient to state, for example, that the esophagus is continuous with the pharynx and stomach, or that it is adjacent to the vertebral column. It is necessary to specify that the esophagus is continuous with the pharynx superiorly and with the stomach inferiorly; and its adjacency relationship with the vertebral column is posterior, whereas with the fibrous pericardium, it is anterior, on both the right and the left. Thus the continuity and adjacency attributes need to be associated with additional attributes in order to express additional elements of knowledge involved in the relationships. Such attributed relationships are the rule rather than the exception in anatomy. Their representation

in any knowledge-modeling environment is a challenge. The solution we developed in the frame-based environment of Protégé-2000 may seem complex, but it captures the necessary knowledge [17].

The solution is to attach to a slot (e.g., *-continuous with-*, *-adjacency-*) a value that includes not only the simple adjacency relationship between referenced structures but also the additional attributes of that relationship (e.g., superiorly, inferiorly, or anterior, posterior, left and right). Attribution of the slot value is called reification. This can be achieved by assigning the slot value as an instance frame of a class which specifies or describes the additional attributes for the relationship.

For example, in the case of the slot *-adjacency-*, the slot value is an instance of a class `Anatomical adjacency coordinate`. This class carries the template slots that describe the adjacent structure (*-related part-*) and its relative position or coordinate (*-coordinate-* and *-laterality-*) that qualify its adjacency to the reference anatomical structure. As shown in the frame of `Esophagus` (Fig. 3), one value of its *-adjacency-* slot is an instance that shows the related part `Fibrous pericardium` as being anterior and to the right and left (coordinate and laterality, respectively) of the esophagus, which is the reference anatomical structure.

This rather complex reification process allows us to not only comprehensively represent structural relations but also to qualify relations with additional attributes in order to describe the structure of the body with accuracy at the highest level of granularity. The process also illustrates that the challenges of modeling anatomical knowledge push the envelope of available methods [17] and require the collaboration of anatomists and knowledge engineers.

3.2. Anatomy taxonomy

Anatomical discourse in educational, research and clinical contexts proceeds at the level of discrete anatomical structures and spaces, which correspond to leaf concepts of a taxonomy. Although attempts to standardize anatomical terminology are more than a century old, time-honored sources of the domain contain only implied and contradictory schemes for classifying anatomical entities, which are not supported by explicit definitions. The officially sanctioned term list, *Terminologia Anatomica* [21] (and its predecessor *Nomina Anatomica*), compiled by an international group of anatomists, has a number of shortcomings for supporting the establishment of an inheritance hierarchy [22]. Chief among these shortcomings is the lack of abstract classes that could subsume more and more specific collections of anatomical entities on the basis of their shared essential properties. As a consequence, controlled medical terminologies and emerging ontologies in bioinformatics have no choice but to establish their own

scheme for aligning anatomical concepts in a computable representation. Since these sources target the needs of diverse user groups, they represent anatomy in heterogeneous contexts; therefore their anatomy content is hard to generalize to domains beyond their own.

In this section we present the rationale for the class structure of the **AT** in the context of foundational principles, starting with the selection of its root. Next we illustrate the inheritance of definitional and other attributes through the class subsumption hierarchy and comment on the derivation of terms.

3.2.1. Root of the AT

Since our intent is to represent *knowledge* about anatomical structure, the Anatomy Taxonomy must accommodate not only the physical entities (substances, objects, spaces, surfaces, lines, and points) that constitute the body, but also the *descriptors* of these entities that we want to model. Terms, coordinates, relationships, developmental stages and other non-physical concepts that form an indispensable part of anatomical discourse must also be included in the **AT**. A more restricted concept than 'entity' will not subsume these concepts. Therefore, we declared `Anatomical entity` as the root of the **AT** and, in order to satisfy requirements for its Aristotelian definition, we considered the essential properties of this concept. Anatomical entities can be conceptualized only in relation to biological organisms, and they are unique among biological concepts in that they pertain to the structural organization of these organisms. Therefore, the *genus* of 'anatomical entity' is the primitive 'biological entity,' because it manifests the essence of all biological entities (namely that they pertain only to biological organisms), and the *differentia* is the restriction to structure. The definition may therefore be written as:

Anatomical entity
  is a **biological entity**,
      which *constitutes* the structural organization
          of a biological organism, or
      is an attribute of that organization.

We use this first definition of the FMA to illustrate the process of formulating such definitions. The conceptualization and insertion of such a new class in the **AT** is paralleled by establishing the template slots in its metaclass that will be inherited by all of its descendants. Every concept to be entered in the FMA will have a preferred name and a specific, randomly assigned numerical identifier. Therefore slots for these attributes are inserted in the `Anatomical entity metaclass`. This template will also have other slots. For example, all anatomical entities, including anatomical terms, have parts. Therefore the -*has part*- slot, and its inverse, -*part of*-, are introduced at the root of the **AT**.

3.2.2. The inheritance class subsumption hierarchy

3.2.2.1. High level classes. The rationale for selecting the root of the **AT** makes reference to two major types of anatomical entities in terms of whether or not they are physical in nature. Therefore we designated the immediate descendants of `Anatomical entity` as the classes `Physical anatomical entity` and `Non-physical anatomical entity` (Fig. 4). The genus for both is `Anatomical entity`, and in structural terms the differentia that distinguishes these two classes is the structural attribute of *spatial dimension*: All physical entities have spatial dimension, because they are volumes, surfaces, lines or points, whereas non-physical entities have no spatial dimension. Therefore the attribute and its corresponding slot 'spatial dimension' are introduced at this level; the value of the slot in the frame of `Physical anatomical entity` will be 'true.' Not only the slot, but also its value will be inherited by all descendants of this class.

Physical anatomical entities may be further specified on the basis of whether or not they have *mass*, which serves as the differentia of the classes `Material physical anatomical entity` and `Non-material physical anatomical entity`. Subclasses of the latter are `Anatomical space`, `Anatomical surface`, `Anatomical line`, and `Anatomical point`, none of which have mass [23]. These classes are distinguished from one another by the number of spatial dimensions they have.

Even without presenting the definitions of these classes and listing their defining differential attributes, the logic and rationale for establishing these high level abstract classes should become apparent. Although anatomical texts and medical terminologies with an anatomical content deal only superficially, if at all, with anatomical surfaces, lines, and points, it is nevertheless
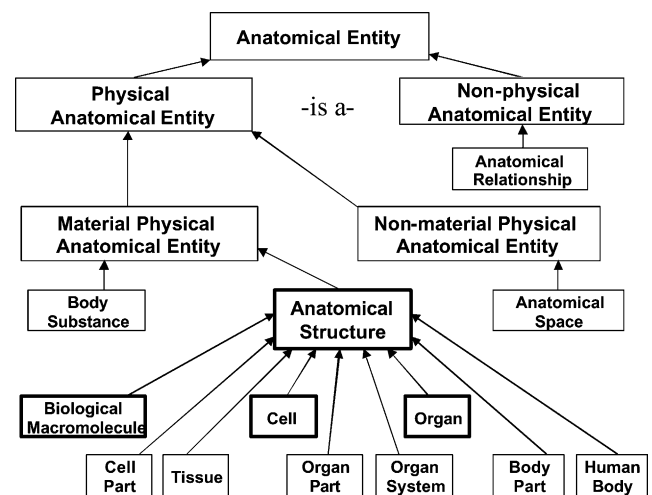

Fig. 4. Schematic representation of the principal classes of the Anatomy Taxonomy.

necessary to represent these entities explicitly and comprehensively in the FMA in order to describe boundary and adjacency relationships of material physical anatomical entities and spaces.

The class of `Material physical anatomical entity` may be subdivided into two major types on the basis of the differentia of *inherent 3D shape*. We designate the collection that lacks this attribute as `Body substance`; its descendants include `Secretion`, `Excretion`, `Blood`, etc.; all of which have mass and accommodate to the shape of their container. The members of the collection that have their own inherent 3D shape constitute the class `Anatomical structure`.

3.2.2.2. Dominant concept. The dominant class principle declares `Anatomical structure` as the dominant class in the FMA; therefore its definition is of particular importance.

> **Anatomical structure**
> *is a* **material physical anatomical entity**
>> which *has* inherent 3D shape;
>> *is generated by* coordinated expression
>>> of the organism's own structural genes;
>> *consists of* parts that
>>> are **anatomical structures**;
>>>> *spatially related to* one another in patterns
>>>> *determined by* coordinated gene expression.

The definition illustrates that inherent 3D shape is a necessary, but not a sufficient, differentia for defining the class `Anatomical structure`. We have to exclude from this class, for example, manufactured objects used as prostheses and biological organisms such as parasites and bacteria that are introduced into an individual, as well as space-occupying lesions such as neoplasms and granulomas. The differentiae in the class definition that exclude such foreign and abnormal structures are specified by constraining the class to biological objects generated by the coordinated expression of groups of the organism's own structural genes and thereby distinguishing these structures from those that result from perturbed or abnormal biological processes. Moreover, by introducing the differentia of the genetically determined arrangement of the parts of an anatomical structure, the definition also excludes from the class such cell aggregates as a rouleau or a sediment of blood cells.

The dominant role of `Anatomical structure` is reflected by the fact that non-material physical anatomical entities (e.g., spaces, surfaces) and body substances (e.g., blood, cytosol) are conceptualized in the FMA, and also in anatomical discourse in general, in terms of their relationship to anatomical structures. For example, `Thoracic cavity` (an `Anatomical space`) can only be conceptualized in terms of the `Anatomical structure` (the `Thorax`) of which it is a part; `Surface of heart` cannot exist without `Heart`, the `Anatomical structure`, which the surface bounds; `Cytoplasm`, a `Cell substance`, can be conceptualized only in reference to `Cell`, an `Anatomical structure`.

The definition of `Anatomical structure` implements the 'content constraint principle' of the FMA, in that it implies that the largest anatomical structure is the organism itself, and the smallest are biological macromolecules assembled from smaller non-biological molecules through the mediation of the organism's genes. In this sense, the definition also distinguishes, in a broader context, animate and inanimate objects.

3.2.2.3. Units of structural organization. The organizational unit principle designates `Cell` and `Organ` as organizational units of the FMA; these are two of the subclasses of `Anatomical structure`. All but two of the other subclasses of `Anatomical structure` are conceptually derived from cell or organ, in that they are either parts of cells and organs or are constituted by cells and organs. We discuss these derivative classes in the next section. The exceptions are `Acellular anatomical structure` (e.g., elastic and collagen fiber and otolith) and `Biological macromolecule`. Such molecules exist in association with cell parts and also independent of cells in body substances. It may be argued that `Biological macromolecule` qualifies as an organizational unit within the FMA. Although we include a substantial number of macromolecules in the FMA, our intent is to link to other ontologies when the need arises for representing the molecular composition and associations of cell parts and body substances.

Cell. With respect to `Cell`, the organizational unit principle is consistent with the cell theory of Schleiden [24] and Schwann [25]. However, notwithstanding some unique exceptions, a cell is a microscopic structure; in practical terms, it is meaningful to consider it as a unit of organization only at the microscopic level. No organizational unit existed at the macroscopic level until we proposed 'organ' to fill this role [8]. It is hard to find satisfactory definitions of cell and organ in dictionaries. Our definitions of these two concepts conform to the definition principle. We first define `Cell` and discuss its subclasses.

> **Cell**
> *is a* **anatomical structure**
>> which *consists of* cytoplasm surrounded by a
>>> plasma membrane
>>> with or without the cell nucleus.

This class subsumes all cell types of the human body and can accommodate those of other metazoan organisms. One may find up to 10 different implied classifications of cells in the literature. However, these classifications are unsupported by explicit definitions. The most consistent scheme was proposed by Lovtrup [26], and is based on such structural properties as the

connectivity of cells to one another and the type of appendages they possess. We have adopted these properties as the differentia for the largest collections of cells [27], and found it necessary to further subdivide these classes based on embryonic derivation (Fig. 5). We recognize that this classification introduces transformational rather than structural attributes as differentiae. However, until the necessary gene expression data become available, the representation of cell lineages cannot be accomplished on the basis of structural attributes alone. Cell classification is a topic that merits further discussion in a separate publication.

Organ. Dictionary and textbook definitions of organ are satisfied by such anatomical structures as the hand or knee, as well as by the liver or the thymus. There are also a large number of macroscopic anatomical structures, which are known by their specific name, but have not been designated as any particular higher level type. For example, by what criteria is the skin generally regarded as an organ, but the underlying layer of superficial fascia is never referred to as such, or as any other type of entity? What are nerves and blood vessels? It has, in fact been suggested that it is not possible to define organ, because the meaning of the term varies so widely. The definition we have proposed for Organ resolves these problems.

> **Organ**
> *is an* **anatomical structure**,
>> which *consists of* the maximal set of **organ part**s
>>> so *connected* to one another that together
>>>> they *constitute* a self-contained unit of
>>>>> macroscopic anatomy
>>>>>> morphologically distinct from other such units.

The definition is contingent on the definition of Organ part.

> **Organ part**
> *is an* **anatomical structure**,
>> which *consists of* two or more types of **tissue**s,
>> *spatially related to* one another
>> in patterns determined by coordinated gene
>>> expression;
>> together with other contiguous organ parts
>> it *constitutes* an **organ**.

Tissue is another concept with a variety of meanings in general discourse. Its dictionary and textbook definitions are violated by regarding such concepts as blood and gingiva as tissues. Before discussing Organ, we also define tissue.

> **Tissue**
> *is an* **anatomical structure**,
>> which *consists of* similarly specialized **cell**s
>> and intercellular matrix,
>>> aggregated according to genetically determined
>>>> spatial relationships.

The differentia of genetically determined spatial relationships among the constituent cells excludes from this class blood, lymph, semen, and cerebrospinal fluid, all of which meet the definition of Body substance. Likewise, gingiva and many other entities conventionally referred to as tissue consist of more than one tissue in terms of the FMA definition. The definition implies, furthermore, that in the fully formed organism tissues do not exist independent of organs. In the embryo, however, tissues are definable before *bona fide* organs are formed.

The definition of Organ part links the microscopic and macroscopic units of structural organization to one another and eliminates any circular element from the definition of Organ. In terms of the definition, the liver qualifies as an organ, because it is constituted by a maximal set of anatomical structures that are composed of tissues, and these structures are connected to one another to form a discrete morphological entity. Although the right lung is composed of the same set of connected organ parts as the left lung, the two sets are not continuous with one another; hence the two lungs are separate organs. The entire skin qualifies as an organ in terms of the definition, and so does the superficial fascia that underlies it. On the other hand, the brain and spinal cord cannot be regarded as two separate organs, since both are made of the same types of organ parts, which are continuous with one another and together constitute a morphological whole. In fact a real boundary between the two cannot be determined. Therefore, the definition mandates that brain and spinal cord be regarded as organ parts and that together they be classified as one organ. We have named and defined it as the Neuraxis [28].

It follows from the definition of Organ that differentiae for distinguishing organ subclasses must be based on the kinds of continuous organ parts of which organs are constituted. Even without presenting definitions, Fig. 6 illustrates the employment of elementary structural attributes, on the basis of which types or organs are grouped together and distinguished from one another. These essential properties (e.g., organ cavity, wall, parenchyma, cortex, medulla, lobe, etc.) are introduced in the corresponding metaclasses and are inherited by the subclasses of the respective organ types. Only at this level of the **AT** do we reach specific organ types, such as lung, esophagus, heart, etc., which are the concepts commonly encountered in anatomical and clinical discourse. Such are also the concepts that are subsumed by derivative subclasses of Anatomical structure.

3.2.2.4. Derivative classes. We regard Organ part and Cell part, referred to in the previous section, as derivative subclasses of Anatomical structure because they are conceived of in relation to Organ and Cell, the organizational units of the FMA. Although each of the remaining derivative subclasses are explicitly defined, we will not present these definitions here; rather

we comment on them and illustrate the kinds of structures each subsumes.

Body part and organ system. Perhaps most important are the classes `Body part`[2] and `Organ system`. Both are constituted by organs. In a body part, such as the `Trunk` or `Upper limb`, organs of different classes are related to one another through genetically predetermined patterns. The same holds true for `Body part subdivisions` (e.g., `Thorax`, `Hand`). Organ systems (and their subdivisions) are constituted of organs predominantly of the same type, which are interconnected by zones of continuity. For example, `Musculoskeletal system` is comprised of the classes `Muscle` (organ), `Bone` (organ), `Joint`, and `Ligament` (organ), which together form an interconnected anatomical structure. Subdivisions of this system, the `Skeletal system` and `Articular system`, for example, consist of sets of bones and joints, respectively; the joints interconnecting the bones and visa versa. So called systems of the body are, as a rule, conceived of in functional rather than structural terms; therefore many of them do not qualify as anatomical structures (e.g., immune system, endocrine system) and are excluded from the `Organ system` class. However, because these concepts are so widely used in anatomical and clinical discourse, we represent them in the FMA as the class `Functional system`, which is a child of `Non-anatomical anatomical entity`.

Anatomical cluster, set, and junction. There are a number of other anatomical concepts in current use that are a composite of organs, organ parts, tissues or cells that are hard to classify, yet we wanted to accommodate them in the FMA. For this purpose we created and defined the classes for `Anatomical cluster`, `Anatomical set`, and `Anatomical junction`.

For example, the root of the lung and the renal pedicle meet the definition of `Anatomical structure`, but do not fit any of its subclasses we described so far. Both consist of a heterogeneous set of organ parts grouped together in a predetermined manner, but do not constitute the whole or a subdivision of either a body part or an organ system. We classify such structures as `Anatomical cluster`. Such clusters can be composed of cells (e.g., splenic cord, consisting of erythrocytes, reticular cells, lymphocytes, monocytes, and plasma cells), organ parts (e.g., tendinous or rotator cuff, consisting of the fused tendons of several muscles), as well as of organs (e.g., lacrimal apparatus consists of the lacrimal gland, lacrimal sac, and nasolacrimal duct, each of which qualify as an organ).

Also problematic are such widely used concepts as viscera, or cranial nerves, which represent a collection of anatomical structures that are members of one class. We assign such collections to the class `Anatomical set`. The FMA does not allow plural concepts and therefore the singular concept `Set of cranial nerves` is entered as a subclass of `Anatomical set`. At the cellular level such a set is `Myone`, for example, which is a set of skeletal muscle cells (muscle fibers) innervated by a single alpha motor neuron. Anatomical sets have members, rather than parts (e.g., `Oculomotor nerve` is a member of `Set of cranial nerves`).

Members of an anatomical set, as defined in the FMA, are distinct from elements of a mathematical set in at least two respects: (1) indirect connections exist between the members, since all anatomical structures of an organism are interconnected directly or indirectly (except for those that are surrounded by body substances; e.g., blood cells afloat in plasma); (2) as a rule, the members are ordered in accord with genetically determined patterns (e.g., the set of cranial nerves associated with the brain and the set of ribs associated with the vertebral column are ordered and their members are not interchangeable; whereas as far as we know, no such ordered pattern exists for the disposition of members of a myone within a muscle fasciculus); and (3) the members do not define an anatomical set (which is a class), whereas a mathematical set is defined by its members.

Finally, we introduced the class `Anatomical junction` to subsume such anatomical structures as a suture, the commissure of the mitral valve, gastroesophageal junction, anastomosis, and nerve plexus, as well as synapse or desmosome. These heterogeneous structures are arranged in appropriate subclasses of `Anatomical junction`. We define this class as an anatomical structure in which two or more anatomical structures establish physical continuity with one another or intermingle their component parts.

Anticipating future enhancements of the FMA, we have also introduced three additional classes. `Vestigial anatomical structure` (e.g., epoophoron, gubernaculum testis) and `Gestational structure`, which includes subclasses for gestational membranes as well as embryonic and fetal structures. The third class, `Variant anatomical structure`, is as yet sparsely populated. Once we focus on anatomical variants, members of this class will be reassigned as variant subclasses of the canonical anatomical structures.

3.2.3. Derivation of terms

Our intent with the FMA is to make anatomical information available in computable form that generalizes to all application domains of anatomy. Therefore, rather than attempting to standardize terminology, we are committed to include in the FMA all terms that currently designate anatomical entities in order to facilitate navigation of the FMA by any user. We relied on time-honored English language scholarly textbooks of

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[2] 'Body part' and 'Body region' are regarded as synonyms by most sources, including *Terminologia Anatomica*; the FMA adopts this convention.

anatomy [29–31] as our primary sources for anatomical terms, enhanced by copious reference to original journal articles from the anatomy and clinical literature. We have developed a tool for semi-automatically integrating existing anatomical term lists into the FMA [32]. Such integration has been accomplished for approximately 10,000 terms of *Terminologia Anatomica* [21], the officially sanctioned anatomical term list, and 6500 neuro-

anatomical terms of *NeuroNames* [33], a structured vocabulary of the brain.

In the FMA each concept has a randomly assigned unique numerical identifier (UWDAID; University of Washington Digital Anatomist Identifier) and is associated with one or more terms. One of these terms is designated as the preferred name of the concept; other terms are synonyms or non-English equivalents (Fig. 2).
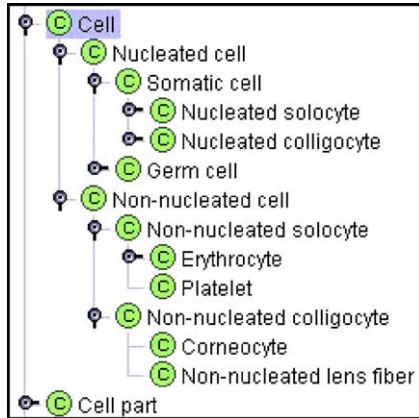
Fig. 5. Major classes of `Cell`.
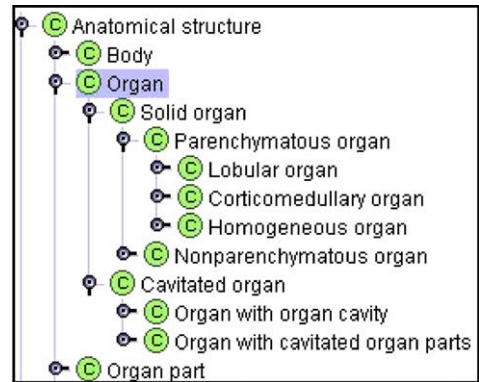
Fig. 6. Subclasses of `Organ`.

Fig. 7. Documentation associated with `Tuba uterine`, a non-English equivalent of the preferred name `Uterine tube`.

Each term is created as an instance of the class `Concept name`. Instances of `Concept name` have associated with them various meta-data that describe the attributes of the term, illustrated in Fig. 7.

A consistent naming convention is used throughout. Unlike in many other terminologies (including *Terminologia Anatomica*), all terms are in the singular form, and conjunctions and homonyms are not allowed. Anatomical entities commonly referred to as groups or collections (e.g., intercostal arteries, spinal nerves) are represented as anatomical sets and designated, for example as `Set of intercostal arteries` and `Set of spinal nerves`, since such concepts conform to the definition of the class `Anatomical set`. Because each term must be unique, commonly used homonyms such as 'muscle' and 'bone' are rendered specific by extensions to discriminate between their different meanings; e.g., `Muscle (tissue)`, a class that subsumes `Smooth muscle` and `Striated muscle` and `Muscle (organ)`, which subsumes such organs as `Biceps brachii` and `Gluteus maximus`.

Although the compendium of available anatomical terms is large, for the comprehensive and logical modeling of anatomical structure we had to include in the FMA concepts that have not been named previously. These concepts include not only the high level classes of the **AT**, but also macroscopic parts of the body that have not previously been named [34]. For example, to satisfy the FMA's requirement that all parts of a whole be explicitly named, we assigned the term `Upper uterine segment` to a previously unnamed part of `Body of the uterus` to complement the other part, which is generally known as the `Lower uterine segment`.

Formulas govern the ordering of descriptors in the complex name of an anatomical entity. For example, the order of adjectives in the term '`Left fifth intercostal space`' is based on the rationale that the noun in the term is 'space'; its primary descriptor is 'intercostal,' further specified by a sequence of numbers, a specificity enhanced by the laterality descriptor. In the term this order is reversed. Based on a similar rationale, the term 'right upper lobe' is not the preferred name of the concept, although the FMA includes it as a synonym of '`Upper lobe of right lung`,' because of its common usage in radiology reports.

3.3. Anatomical Structural Abstraction

Defined in Section 3.1.2, the **ASA** is an aggregate of the structural relationships that exist between the entities represented in the **AT**. A full account of the **ASA** will be the subject of a separate report. Our purpose here is to summarily illustrate the richness and specificity of structural relationships in the FMA. Fig. 8 shows a part of the taxonomy of these relationships as subclasses of
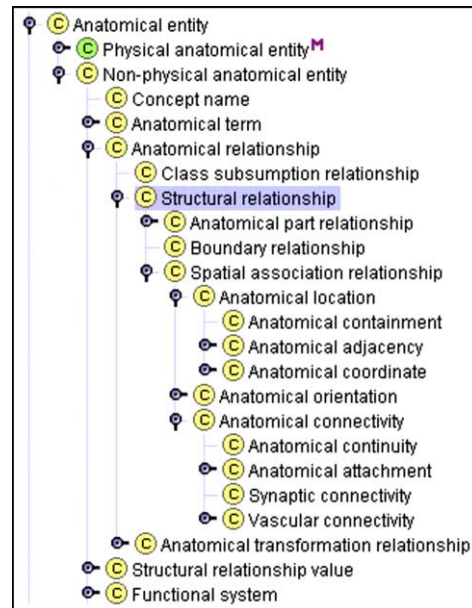

Fig. 8. Part of the taxonomy of structural relationships.

`Non-anatomical anatomical entity`. Fig. 3 illustrates the implementation of some of these relationships in the frame of the esophagus. Reference is made in earlier sections to the fact that the majority of these relationships are attributed, which further enhances the expressivity and specificity of the FMA for describing the structure, not only the constituents, of the human body. Particular attention is paid to attributed partonomic relationships in one of our recent publications [35].

We have conceived of the **ASA** as sets of interacting networks [36], which are schematically represented in Fig. 9. The high level scheme for the **ASA** derives from the FMA's overall conceptual scheme. The example we describe below illustrates the nature and interactions between just two of the **ASA**'s interacting networks. These networks make reference to some of the rules that constrain the concepts that can be linked to one another by these relationships to certain classes of the Dimensional taxonomy (**DT**). The **Do** is a small ontology in the FMA, which represents dimensional entities of zero to three dimensions and shape classes of 3D entities. It also distinguishes between real and virtual surfaces and lines.

The example for illustrating **ASA** networks concerns the heart. The surface of the heart forms the boundary of the heart in the boundary network (Bn), rather than being a part of the heart, because nodes of the partonomy network (Pn) must be of the same dimension in the **DT**, whereas a boundary must have one lower dimension than the entity it bounds. Because they share the same dimension, the diaphragmatic surface of the heart is a part of the surface of the heart (Pn) and forms part of the boundary not only of the heart, but also of the right ventricle (Bn), which is a part of the heart. The Bn
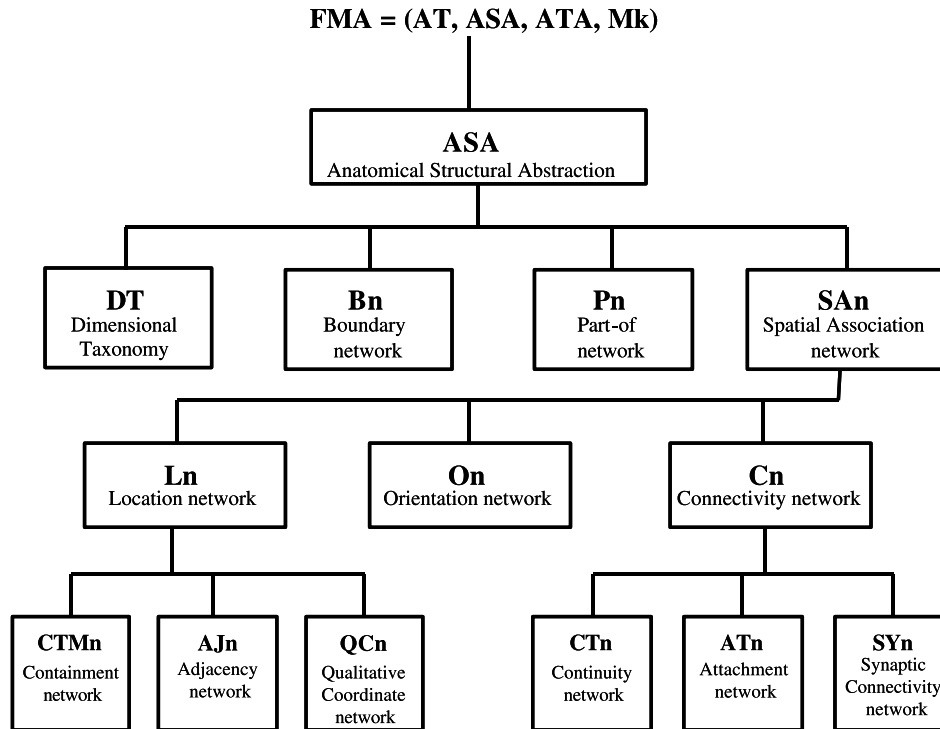
FMA = (AT, ASA, ATA, Mk)

Fig. 9. A scheme for Anatomical Structural Abstraction (ASA).

of the heart comes about by representing not only the surfaces that bound the heart's subvolumes, but also the lines that bound these surfaces (which are the cardiac margins), and the points, which in turn bound the margins. The Pn of the heart comes about by representing transitively the subvolumes of the heart in one network, the subsurfaces of the surface of the heart (e.g., `Surface of heart` -has part- `Diaphragmatic surface of heart`, `Sternocostal surface of heart`, `Base of heart`) and the subdivisions of each subsurface (e.g., `Diaphragmatic surface of the heart` -has part- `Diaphragmatic surface of right ventricle`, `Diaphragmatic surface of left ventricle`) in another network, and those of the margins (lines) of the heart in yet another network. Similar interactions of the Bn and Pn with the other networks, shown in Fig. 9, comprehensively describe the structure and spatial relationships of any anatomical structure or space. A number of authors refer to such a scheme as a mereotopological model or representation, though none have defined it or implemented it to the same level as the FMA. The conception of such a mereotopological model or **ASA** as a set of interacting networks is a particular feature of the FMA.

The **ASA** has been instantiated quite extensively in the FMA for boundary and partonomic relationships, as well for -branch of - and -tributary of- relationships, including their inverses. Other relationships are more sparsely implemented.

More comprehensive implementation will be achieved through semi-automated authoring tools that are under current development, which can reuse the knowledge already embedded in the FMA. Also, we anticipate that investigators who have a need for comprehensive representation of the anatomy of particular parts of the body (e.g., the eye or the knee joint) will collaborate with us in populating the knowledge base for the areas of their interest.

3.4. Anatomical Transformation Abstraction

Defined in Section 3.1.2, we envisage the initial implementation of the **ATA** as a symbolic model of the entities and relationships that link the fertilized egg or zygote to the fully differentiated anatomical structures and spaces that are currently represented in the **AT**. As we initially did for the **ASA**, we propose a high level scheme for the prenatal component of the **ATA** as a hypothesis, which, as in the case of the **ASA**, will be tested and modified as the **ATA** becomes implemented and instantiated. Currently, we are not proposing such schemes for the morphological transformations associated with the processes of growth and aging. Our present purpose with giving a preliminary account of the **ATA** scheme is to illustrate the challenges the symbolic modeling of developmental biology and prenatal development present, and to emphasize that knowledge of embryonic development is as important a component of
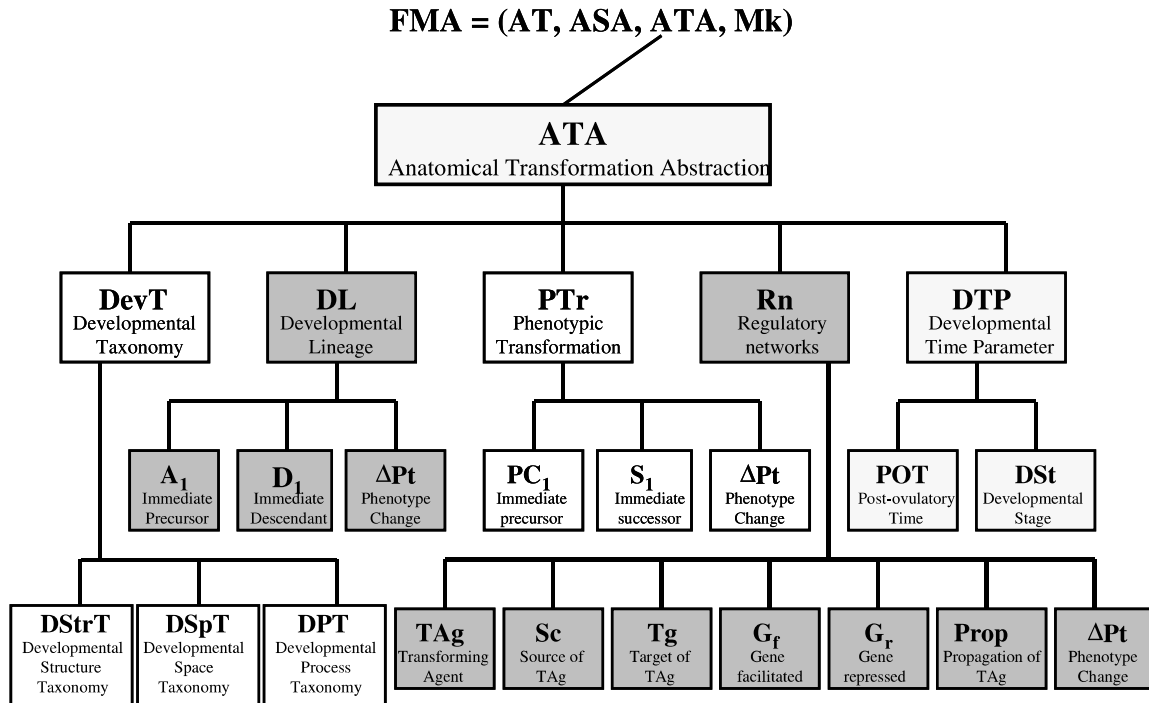
FMA = (AT, ASA, ATA, Mk)

Fig. 10. A scheme for Anatomical Transformation Abstraction (ATA). Shading is used to facilitate the visualization of relationships between cognates of a higher level component of the ATA.

anatomical and medical reasoning as spatial knowledge of the human body. The FMA will not attain its full potential until it is able to support inference based on both structural and developmental relationships.

The significance of the **ATA** scheme as we propose it is that, together with the **ASA**, it formalizes and constrains all the kinds of information that need to be associated with an anatomical entity in order to comprehensively conceptualize and symbolically represent its development starting from the fertilized egg. We propose a scheme for the **ATA** as an extension of the FMA's overall conceptual scheme and illustrate its components in Fig. 10.

We envisage the Developmental Taxonomy (DevT) as the sum of several developmental subtaxonomies linked together through the **AT**. This virtual umbrella taxonomy will consist of taxonomies of developmental structures (DStrO), developmental spaces (DSpO), and developmental processes (DPO).

Developmental lineage (DL) and phenotypic transformation (PTr) relate to the essence of embryonic development. Both are complex concepts. Both can be modeled through the inverse relationships -*gives rise to*- and -*derived from*-, or their synonyms between a 'precursor' and one or more 'successors.' Phenotypic transformation (PTr) is a developmental relationship, which is established between developmental states of one individual, or a class of individuals, on the basis of a change in phenotype (gene expression) between precursor and successor. For example, (using the symbol > to

mean -*gives rise to*-) `Mesodermal primordium of humerus > Cartilaginous primordium of humerus > Ossifying humerus with primary ossification center > Ossifying humerus with secondary ossification center > Fully formed humerus`. Each developmental stage of the same structure is distinguished from the preceding one by a set of newly acquired phenotypes, which, as a rule results from differential gene expression. PTr pertains to all classes of `Developmental structure` and `Developmental space`, even if the phenotypic change is limited to the addition or deletion of one of their components, the structural rearrangement of their parts, or a change in their shape. Therefore, the formalism for phenotypic transformation should specify the immediate precursor (Pc_1), its immediate successor (S_1) and the change in phenotype (ΔPt):

$$PTr = (Pc_1, S_1, \Delta Pt). \qquad (3)$$

Developmental lineage (DL) specifies a line of descent or ancestry in which an ancestor replicates itself and gives rise to two or more descendants, each of which is phenotypically distinct from its immediate ancestor. The formalism for lineage parallels that for PTr by specifying the immediate ancestor (A_1), the immediate descendant (D_1) and the change in phenotype (ΔPT):

$$DL = (A_1, D_1, \Delta Pt). \qquad (4)$$

Note that each ΔPt has to be expressed as an **ASA** attribute of Pc_1, S_1, A_1, and D_1. This is only one of the

ways in which the **ASA** and **ATA** will be closely interrelated, an observation that leads to the conclusion that an ontology of embryonic development should be developed as a logical extension and integral component of the FMA.

Timing of PTr and DL in the context of a developmental clock must be represented through the developmental time parameters of post-ovulatory time (POT) and/or developmental stage (DSt).

A transforming agent (TAg)—which is a gene product—is always required for effecting the expression of a new phenotype. This agent may play a facilitatory or inhibitory role in the expression of the new phenotype by its target (Tg). The expression of this new phenotype (ΔPT) depends on the activity of one or more specific genes (G), which may increase (i.e., is facilitated; G_f) or decrease (i.e., is repressed; G_r).

TAg has not only a target but also a source (Sc). It is, in fact, itself a new phenotype resulting from facilitated or suppressed gene activation within its source. In both target and source, the macromolecule that corresponds to the new phenotype is produced through a change in the activity of a gene or genes, even when this change results from the repression of another gene or genes. Finally, the TAg must be propagated (Prop) from the source to the target, which may occur within cells, through cell junctions or through the intercellular environment.

Thus change in phenotype along a cell lineage or in the phenotypic transformation of multicellular, developing structures is the outcome of a number of interacting networks, which are controlled by the facilitation or repression of selected groups of genes. Therefore, we propose the first iteration of regulatory networks (Rn) that control the expression of new phenotypes as:

$$\text{Rn} = (\text{TAg}, \text{Sc}, \text{Tg}, G_f, G_r, \text{Prop}, \Delta\text{Pt}). \qquad (5)$$

The purpose of the Rn scheme is to establish a framework for the information that emerges from experiments and integrate this new information with existing knowledge. The components of this formalism decompose the complex developmental events into elements that can be entered in the framework of the FMA, even with currently available methods.

We concede that while the establishment of the FMA for static, fully formed anatomy is a Herculean task, this task pales in comparison with the challenges posed by the enhancement of the FMA with the dynamic processes that constitute embryonic development and cell differentiation. These challenges provide the motivation for collaboration, a coordinated, distributed effort, and for the development of knowledge-based authoring tools that facilitate the population of a large knowledge base, such as the FMA, and others that are currently emerging in bioinformatics.
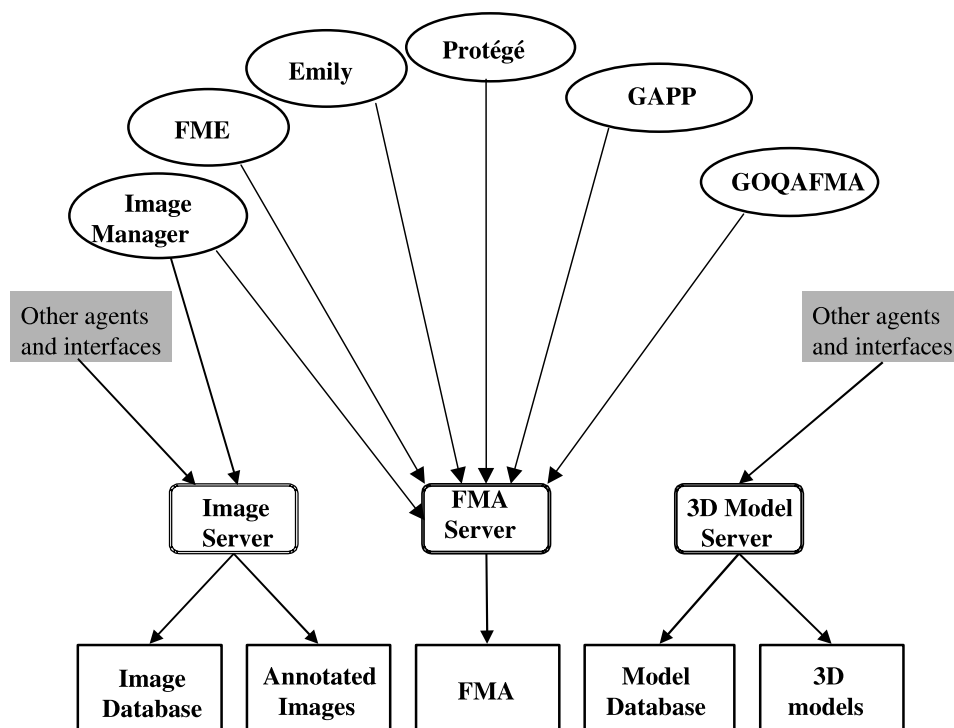

Fig. 11. The distributed, Internet-based architecture of the Anatomy Information System (AIS). Various structural information resources (bottom row) are made available to outside processes by means of specialized servers (center row). Various client applications (top row) are graphical and query user interfaces developed for different users. Other remote agents and interfaces at diverse locations access servers of the AIS via well-defined Internet protocols.

4. Accessing the FMA

The FMA is one of the components of the Anatomy Information System (AIS), shown in Fig. 11, which is a three-tiered software architecture constituted by a set of structural information resources (the chief one of which is the FMA), sets of authoring and end-user programs, and structural information servers, which communicate with the information resources via the web through the mediation of the servers [37].

Currently, the FMA is accessed through six different user interfaces in the AIS, which are shown at the top of Fig. 11: (1) the Protégé-2000 graphical user interface, which supports authoring and also allows browsing through the Protégé class structure; (2) the Foundational Model Explorer (FME), a web-based GUI that provides intuitive browsing capabilities without the complexity of the full Protégé system [38]; (3) the GO-QAFMA Graphical User Interface to the OQAFMA Query Agent for the Foundational Model of Anatomy, which provides a web interface for users to issue low-level database queries to the OQAFMA server [39]; (4) the intelligent EMILY GUI, which constrains the construction of queries to concepts and relationships to those in the FMA and relies on inference to retrieve results not explicitly represented in the knowledge base [40]; (5) GAPP, a natural language interface that allows simple queries about the concepts and relationships represented in the FMA [41]; and (6) the GUI of the Dynamic Scene Generator that provides access to images and 3D models linked to the FMA in order to support knowledge-based generation of interactive scenes [42].

In addition, the part of the FMA's content incorporated in the UMLS as the Digital Anatomist vocabulary is accessible through the UMLS knowledge server. The Digital Anatomist vocabulary contains the Anatomy Taxonomy, except for the concepts and relationships pertaining to the brain and spinal cord, and relationships of partonomy and branch and tributary relationships.

The evolution of the diverse interfaces for accessing the FMA indicates that the FMA has reached a stage at which there is sufficient content to support experiments for interrogating the knowledge base, which is a key requirement for developing knowledge-based applications such as the Dynamic Scene Generator [42], and also for evaluating the FMA. The recent release of the FMA on the Internet [43] should facilitate both these activities.

5. Evaluation and current usage

Evaluation of a large knowledge base, such as the FMA, poses considerable problems and must take place on several levels. At the most fundamental level, the model has to be evaluated for its internal consistency and comprehensiveness. There are no precedents we are aware of for evaluating the overall semantic structure of a computable knowledge source, which is perhaps one of the most critical features of the FMA. At the highest level, a knowledge base that claims to be reusable and "foundational" must be evaluated for its generalizability and usefulness to other projects in knowledge representation and application development. Given the fact that the FMA is still evolving and has not yet been released, its evaluations to date have been largely at the first level.

Internal consistency checks were performed by UMLS staff on segments of the FMA instantiated for different body parts as these segments were delivered for inclusion in the UMLS. Independent projects also assessed the internal consistency of different versions of the FMA as a prerequisite for meeting their own research objectives [44,45, Gu H. personal communication]. Feedback from these investigators revealed an aggregate of a few hundred errors, many of which related to spelling and only a few to cycles in the class subsumption and partonomy hierarchies. Given the size and complexity of the FMA, we found these results very gratifying.

It is problematic to evaluate the FMA for comprehensiveness of its content, since there is no available gold standard for comparison. There is no other source that includes over 100,000 anatomical terms, less than 10% of which correspond to the complete list of officially sanctioned anatomical terms [21]. Nevertheless, a correlation of the incidence of anatomical concepts in a large compendium of clinical reports with the FMA would be informative.

Comprehensiveness seems a relatively trivial problem compared to evaluating the FMA's overall semantic structure and the extensive modeling of relationships. However, the difficulties entailed in such an apparently simple task are illustrated by the mapping of large symbolic models to one another, taking into account their structure as well as their terms [45]. The FMA and GALEN's common reference model (CRM) [46] were selected for developing automated methods for such model matching. Although, after some necessary lexical adjustments, over 3000 matching terms can be demonstrated, there are surprisingly few homologies between the FMA and GALEN-CRM when -is a- and partonomy relationships are also taken into account. The reasons for the differences have not yet been explored, but at least some of them may be the different contexts of modeling. GALEN represents anatomy in the context of surgical procedures, whereas the FMA has a strictly structural orientation.

The ultimate evaluation of the Foundational Model of Anatomy needs to take place through testing the

hypothesis that motivates the establishment of the model: the FMA will provide the anatomical information called for by any knowledge-based application that requires computable anatomical knowledge. We include among such applications those developed for education, biomedical research, and clinical medicine. The prerequisites for such evaluations are currently being generated. The development of query interfaces to the FMA, described in the preceding section, is a requirement for making the FMA accessible for application development.

We have made evolving versions of the FMA available to selected investigators, but its use has been largely limited to associating the terms of the FMA with images and image volumes [47–50], and for integrating these terms in other terminologies [51]. Definitions of the FMA have been used as a basis for characterizing definitions of anatomical concepts in WordNet [52] and in other biomedical ontologies [11], as well as for the automatic semantic interpretation of anatomical spatial relationships [53], enriching the UMLS semantic network [54] and designing its metaschema [55]. As far as we are aware, only one application relies on knowledge embedded in the FMA for interacting with 3D scenes [42]. We hope that the development of knowledge-based applications calling for anatomical knowledge will be stimulated by access to the comprehensive FMA, providing opportunities for its higher level evaluation.

6. Scaling of FMA

The objective of the FMA to represent declarative knowledge about the structure of the body calls for scaling the model to the concept domains of those fields of anatomical science that are not yet included in the FMA. These fields include neuroanatomy, developmental biology and embryology, and also comparative anatomy. Moreover, we contend that since manifestations of health and disease may be conceptualized as attributes of anatomical structures, a logical and comprehensive representation of anatomy should serve as a foundation or template for the computable representation of physiological function, as well as pathology and the clinical manifestations of diseases. Unless the semantic structure of the FMA lends itself for such scaling, the model cannot be regarded as foundational. Moreover, if the FMA is to fulfill its potential as a reference ontology, then it should be feasible to readily align other existing and evolving biomedical ontologies with it.

The first phase of the FMA's development was focused on macroscopic anatomy. Then the scope was extended to include histology and the representation of cells, subcellular entities, and biological macromolecules. There is no other hard copy or computable source

that encompasses a comparable spectrum of anatomical entities at a level above that of elementary textbooks of an introductory nature.

The next scaling up entailed the development of the neuroanatomical component of the FMA [28]. The FMA is unique among neuroscience resources in that it comprehensively represents anatomical concepts of both the central and peripheral nervous systems; moreover it does so in the same information space as other systems of the body. The instantiation of neuroanatomical relationships is in progress.

In Section 3.4 we propose to extend the FMA to knowledge elements that integrate the traditional field of classical embryology with contemporary developmental biology. The FMA's semantic structure accommodates the implemented and projected scale ups quite naturally. We regard this outcome as a validation of the FMA's conceptual framework and disciplined approach to knowledge modeling.

Recently we began to experiment with using the FMA as a template for the representation of the anatomy of non-human species, particularly those that serve as experimental models of human disease [14]. The classes of the **AT** readily accommodate the anatomy of mammals and even other vertebrates. The challenge is to formally represent interspecies similarities and differences at the various levels of structural organization. Solution of this problem will likely generalize to the representation of intraspecies anatomical variation, i.e., differences between individuals. This possibility has important applications not only in clinical medicine but also in anthropology. Plans have been made already for using the FMA to annotate anthropological osteology databases [Drs. Razdan and Clark, personal communication].

We are committed to constrain the FMA's content to biological structure or anatomy. However, we have begun to develop a representation of physiological function using the FMA as a template or reference ontology [56]. Such a Foundational Model of Physiology (FMP) will be distinct from the FMA but it will be intimately linked to it.

7. Discussion

The Digital Anatomist Foundational Model of Anatomy expresses a theory of anatomy that provides a view of the domain consonant with the requirements of formal knowledge representation and also accommodates traditional views of the domain. Coherent theories of anatomy have not been declared as such, although theoretical treatises on mereotopology (e.g., [57]), or on some aspect of it (e.g., [58]), cite, or are even based on, anatomical examples. These proposals, however, as a rule, do not proceed from the examples to implementing

the theory for the entire corpus of the domain, which, of course, is not their purpose. The FMA's theory of anatomy is articulated by its high level scheme, the semantic structure of the **AT**, and the schemes of the model's **ASA** and **ATA** components. Initially proposed as hypotheses, these components of the FMA have now been largely validated by instantiating the symbolic model with tens of thousands of concepts and more than a million relationships.

In this article we focus primarily on the **AT** and defer detailed descriptions of the **ASA** and **ATA** to separate communications. We first summarize the salient features of the **AT**, before commenting on the relevance of the FMA to UMLS in general and to bioinformatics in particular.

7.1. Salient features of the AT

Our intent with the Anatomy Taxonomy is to incorporate in it all concepts that relate to the structure of the body, including those first identified in the contemporary literature and those that are newly discovered. The **AT** introduces a number of classes that are unlikely to be found in the literature or in anatomical discourse. The rationale and justification for creating these classes is to assure that general as well as more and more specific attributes that are shared by increasingly specialized anatomical structures are propagated from the root of the taxonomy to its leaves. The semantic structure of the **AT** also assures that all anatomical entities, ranging in size and complexity from macromolecules to major body parts and the whole organism, are encompassed by one attributed graph. This graph also accommodates classes of substances and non-material entities that are associated with and defined in terms of anatomical structures, which constitute the dominant class of the **AT**. In addition to these non-material physical anatomical entities of zero to three dimensions, the root of the **AT** also subsumes non-physical anatomical entities that have no spatial dimension at all.

To safeguard against ambiguity, explicit Aristotelian definitions specify the classes of the **AT** in terms of predominantly structural attributes, which are formally represented in the frames of the **AT**'s concepts. At the current state of the FMA, however, these definitions are less consistently implemented the further one moves away from the taxonomy's root.

The semantic structure of the **AT**, together with the Protégé-2000 authoring environment, allows the representation of multiple inheritance. However, Aristotelian definitions that specify the essence of the entities to which the concepts refer obviate the need for multiple inheritance, since non-definitional attributes of the concepts can be readily accommodated as slots of their frames. This representation affords searching the knowledge base along the path of any explicitly repre-

sented, transitive relationship, or along a virtual path concatenated from heterogeneous relationships [39].

The structure of the **AT** is a dynamic abstraction that is modified as a result of new insights we gain into the structure of anatomical knowledge. New terms are also added to the FMA as they come to our attention.

7.2. Relevance to UMLS

As noted in the introduction, in the initial phase of the FMA's development, we conceived of the classes of the **AT** as extensions and specifications of UMLS Semantic Types (ST). However, the disciplined approach to modeling we describe in this communication, coupled with the insights we gained into the structure of anatomical knowledge through the instantiation of the model, resulted in the redefinition of many of these classes. The specificity of these definitions has led to a divergence between the definitions of UMLS ST and FMA classes, several of which are designated by the same or similar terms. For example, there are substantial differences in the definitions of the semantic type 'Anatomical Structure' and the FMA class of the same name. Therefore, in submitting to UMLS evolving versions of the Digital Anatomist component of the FMA, we assigned `Anatomical structure` to the UMLS ST 'Body Part, Organ or Organ component' rather than 'Anatomical Structure.' More problematic is the assignment of `Anatomical space` (which subsumes such entities as Peritoneal cavity, Vertebral canal, and Ischio-anal fossa) to ST 'Body Space or Junction,' a descendant of 'Conceptual Entity.' The latter is defined as a broad grouping of abstract entities, whereas the FMA class is a descendant of `Physical anatomical entity`, since the entities to which the class refers have physical dimension.

Similar considerations led other investigators to suggest adding several new semantic types to better describe the anatomy portion of the Enriched Semantic Network they developed for UMLS, allowing multiple parents in the -*is a*- subsumption hierarchy [54]. An abstraction metaschema for this enriched network is given in [55]. Some of these enrichments make use of the FMA's definitions, which suggests perhaps that bidirectional interactions between the UMLS SN and its source vocabularies could benefit not only the vocabularies but also the SN. Thus, in addition to the potential of the FMA for reconciling inconsistencies in anatomical concepts represented in UMLS vocabularies [59] and in traditional, hard-copy sources [34], class definitions of the FMA may prove useful in a review of UMLS semantic types. Such a review is likely to become desirable as a consequence of the expanding scope of the UMLS Metathesaurus, which reflects the growing relevance of bioinformatics to clinical medicine by the inclusion of emerging ontologies in this field of biomedical informatics.

7.3. Relevance to bio- and biomedical informatics

The relevance of the FMA to domains of bioinformatics beyond that of traditional anatomy is illustrated by recent, emerging projects that reuse information from the FMA. Though initially conceived for classical, macroscopic anatomy, the FMA has been successfully scaled to microscopic and neuroanatomy as well as to biological macromolecules. The scheme for modeling embryology and developmental biology, described in this communication, is an integral part of the FMA's conceptual framework. The FMA has also provided a motivation for research related to the modeling of physiological functions [56], comparative anatomy [14], and anthropological osteology, and to querying and matching large ontologies and databases [39–41,45].

We contend that the Foundational Model of Anatomy is the most promising, currently available candidate for serving as a reference ontology in biomedical informatics. The reasons for this contention are inherent in the semantic structure and other distinguishing features of the FMA. By way of summary, we highlight the following features.

1. The FMA is a domain ontology that represents deep knowledge of the structure of the human body by placing an emphasis on the highest level of granularity of its concepts and the large number and specificity of the structural relationships that exist between the referents of these concepts. Modeling at the highest level of detail assures consistency in the representation across different levels of structural organization. A consequence of this approach is that, as far as we are aware, the FMA has developed into the most complex biomedical domain ontology. This conclusion is reached by applying the metric proposed by Gu et al. [13], in terms of which the FMA scores over 10 in comparison with a score of 2–3 for vocabularies included in and similar to those in UMLS. This level of complexity presents its own challenges, which include developing methods to filter the FMA's contents when information is required at coarser levels of granularity. The semantic structure of the FMA will facilitate the development of knowledge-based tools for such a purpose.

2. The concept domain of the FMA integrates in one continuous conceptual and implementation framework subdomains of anatomy that are conventionally handled by independent and largely incompatible sources. The objective is to comprehensively represent in the FMA anatomical entities down to the level of cell parts and provide a framework for linking to the FMA ontologies and other data repositories for biological macromolecules. Comprehensive instantiation of the FMA's **ASA** and **ATA** components can be accomplished through funding that targets the needs of research groups for computable, in-depth anatomical information related to selected parts of the body.

3. By modeling canonical anatomical knowledge and, in particular, by introducing high level, abstract classes of anatomical entities, the FMA also provides a framework for inter- and intraspecies anatomical variation and for the organization of anatomical data that pertain to instances of the human and other species. These data include the clinical record and biological experiments performed on non-human species.

4. The FMA is unusual among traditional and computable knowledge sources in that it strictly adheres in its modeling to one context. Because the majority of the other sources target particular user groups, of necessity, they intermingle different contexts or views of their primary domain of interest. By design, the FMA is intended to meet the needs of diverse user groups and applications that require anatomical information; therefore it is designed as a reusable reference ontology rather than an application ontology. Only the structural context generalizes to and complements all other views of biology and medicine. The structural context proved to be critical for the disciplined modeling of the FMA; we found it to be the only view that allowed the comprehensive and consistent representation of biological structure across all levels of its organization.

Such context-specific modeling results in a number of benefits: (1) it obviates duplication and redundancy in ontology development, since the FMA's contents can be reused; (2) it provides for consistency among independent ontologies that rely on the FMA's contents; and (3) it serves as a template for the development of other ontologies in which the concepts of the FMA assume the role of actors.

8. Conclusions

We attempted to illustrate that the FMA not only encompasses in the Anatomy Taxonomy the diverse entities that make up the human body, but is also capable of modeling through the interacting networks of its **ASA** and **ATA** components a great deal of knowledge about these entities. Anatomical knowledge represented in the FMA parallels in its complexity and depth the knowledge printed in textbooks and journal articles pertaining to the structure of the body. However, unlike the information in these hard copy sources, the FMA's contents are processable by computers and therefore provide for machine-based inference, which is a prerequisite for the development of knowledge-based applications. Most of the current and emerging ontologies in bioinformatics are primarily concerned with representing the entities of their domain and point to publications for the knowledge associated with the referents of the concepts they model. We hope that our report will encourage a trend in the development of bioinformatics ontologies toward incrementally linking the published

information in a computable form to the concepts these ontologies compile in order to make also this information machine-processable. Serving as a reference ontology for bioinformatics, the FMA may facilitate such a process.

Acknowledgments

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