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Lessons Learned in Aligning Multiple Anatomical Ontologies across Different Species

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Objective: To examine the extent to which five anatomical ontologies for different species can be aligned using automatic techniques. The five anatomical ontologies under investigation are the Foundational Model of Anatomy (FMA), Adult Mouse Anatomical Dictionary (MA), Fly Anatomy (FA), Worm Anatomy (WA), and Zebrafish Anatomy (ZFA). **Methods:** Pairwise mappings among the five ontologies were created using a combination of lexical alignment and structural validation techniques. A manual review of a limited number of mappings was performed to identify the limitations of this approach. **Results:** The following numbers of mappings were identified: MA-FMA: 1,568, ZFA-FMA: 522, FA-FMA: 198, WA-FMA: 86, MA-ZFA: 238, MA-FA: 90, MA-WA: 38, ZFA-FA: 112, ZFA-WA: 88, and FA-WA: 88. **Conclusions:** From a quantitative perspective, only a limited number of correspondences could be identified among ontologies with an upper bound of 57% of MA concepts identified in FMA. In contrast, less than 5% of the concepts from a given ontology were identified in another ontology for 15 of the 20 pairs of ontologies investigated. With the exception of MA-FMA, the precision and recall are generally low. The automatic mapping would be best used to bootstrap a mapping curated by domain experts. The structural similarity required for the validation of lexical mappings would benefit from being tightened. Semantic validation based on disjoint top-level categories would have prevented a small number of mismatches. Multiple mappings require disambiguation by a domain expert. Idiosyncrasies in naming and in knowledge representation (including differences in granularity) account for a significant proportion of missed matches. Overall, aligning anatomical ontologies across species remains difficult.

1 Introduction

Biomedical research relies on model organisms [1]. The functional description of experimental data has benefited from the standardization supported by initiatives such as the development of the Gene Ontology (GO) [2], a controlled terminology for the functional annotation of gene products across species embraced by most model organism communities. GO provides terms for molecular functions, biological structures and cellular components (i.e., its coverage of anatomy is purposely restricted to subcellular structures) [3]. Similar efforts have been started specifically for anatomy. The Foundational Model of Anatomy (FMA) has been proposed as an anatomical ontology for vertebrates [4], in addition to humans, but has not been widely adopted by biologists yet. The Common Anatomy Reference Ontology (CARO) is "being developed to facilitate interoperability between existing anatomy ontologies for different species" [5]. The current version (1.3) comprises concepts for 46 high-level anatomical entities. While promising, CARO is currently not usable in practice for the detailed annotation of anatomical structures across model organisms.

Aligning ontologies, especially anatomical ontologies, is a nontrivial task [6-10]. It has been proposed for several years as one task of the Ontology Alignment Evaluation Initiative (OAEI) challenge [11], under the rubric "expressive ontologies". Initially (2005-2006), two ontologies of human anatomy were investigated: the FMA and the anatomy portion of GALEN [12]. Since 2007, the ontologies to be aligned are the Adult Mouse Anatomy (MA) and the anatomy portion of the NCI Thesaurus (NCI). MA-NCI represents a cross-species alignment, between mouse and human anatomy, but still between two mammalian species, where a relatively high level of resemblance is expected. Most alignment systems tested did not perform well, when at all, in the early tears of the competition. One common problem was the use of generic alignment systems for aligning specialized terminologies, yielding poor recall and precision [13]. However, the results have improved over time. Moreover, the existence of a gold standard validated manually by domain experts for the MA-NCI alignment enables the organizers to provide an accurate evaluation of the systems in competition.

Aligning anatomical ontologies not only across mammalian species, but also across species exhibiting fundamental differences from an evolutionary perspective is, of course, more challenging. In addition to genuine anatomical differences among species, different communities might have selected different names to denote similar anatomical entities. Despite these differences, establishing correspondences among anatomical concepts across ontologies for multiple species is important for comparative genomics and, more generally, for translational research, where data integration plays a fundamental role [14].

The objective of this study is to examine the extent to which five anatomical ontologies for species including human, fly, mouse, worm and fish can be aligned using automatic techniques. This paper reports on the lessons learned in performing this alignment and discusses false positives, false negatives, ambiguous mappings and differences among anatomical ontologies.

2 Materials

Anatomical ontologies comprise concepts representing anatomical entities and their interrelations. Two major relationships form the backbone of anatomical ontologies. The *IS-A* relationship is used to represent anatomical taxonomies. In addition, the *PART-OF* relationship defines mereologic (part-whole) relations among anatomical entities. The five anatomical ontologies under investigation in this study are organized around *IS-A* and *PART-OF* relations. Some ontologies define other relationships (e.g., for topology) and may define several types of *PART-OF* relationships, but *IS-A* and *PART-OF* are the only two relationships consistently represented among anatomical ontologies.

The versions of five anatomical ontologies under investigation were downloaded from the Open Biomedical Ontologies web site [15] on October 25, 2007. The OBO format for ontologies specifies for each concept a list of names and relations to other concepts. *IS-A* and *PART-OF* are the two main relationships in these five ontologies in OBO, and are assumed to have a shared semantics across ontologies.

The **Foundational Model of Anatomy** (FMA) [16] is an evolving ontology developed by University of Washington, whose objective is to conceptualize the physical objects and spaces that constitute the human body [4]. The underlying data model for FMA is a frame-based structure implemented with Protégé. 75,147 concepts cover the entire range of macroscopic, microscopic and subcellular canonical anatomy. In addition one preferred term per concept, 45,118 synonyms are provided (e.g., concept *Uterine tube* has synonyms *Oviduct* and *Fallopian tube*). Every concept (except for the root) stands in a unique *IS-A* relation to other concepts. Additionally, concepts are connected by seven kinds of *PART-OF* relationships (e.g., *CONSTITUTIONAL PART OF*, *REGIONAL PART OF*) and their inverses. The OBO version of the FMA replaced with one unique *PART-OF* relationship (with *HAS-PART* as its inverse) the various kinds of partitive relationships present in the frame-based FMA. Moreover, FMA has nearly 60 associative relationships (e.g., *BRANCH OF* and *CONTAINED IN*) which are not present in its OBO version.

Adult Mouse Anatomical Dictionary (MA) is a structured controlled vocabulary describing the anatomical structure of the adult mouse [17], developed at the Jackson Laboratory as part of the Mouse Genome Database [18]. It comprises 2,745 concepts. Each concept has one name (e.g., *head/neck* and *suprarenal artery*). Additionally, 293 concepts have a total of 329 synonyms (e.g., *Limb* has synonym *Extremity*). Every concept is connected to other concepts through *IS-A* or *PART-OF* relationships. 1,057 concepts do not have any *IS-A* relationship to other concepts, while 111 concepts have more than one *IS-A* relationship to other concepts. MA is listed under the name *Mouse adult gross anatomy* in OBO.

Fly Anatomy (FA) is the anatomical and developmental vocabulary developed in conjunction with FlyBase [19], which is a collection "of genetic and genomic data on the model organism *Drosophila melanogaster* and the entire insect family Drosophilidae" [20], developed by the FlyBase Consortium. Each of the 6,024 concepts in FA has one preferred name (e.g., *anterior pharyngeal organ*). In addition, 1,235 unique synonyms (e.g., *postpronotum* has synonyms *humeral callus*, *humerus*, and *prescutal lobe*) are provided. Of note, there are 1,483 additional synonyms that were not used in our study as they are shared by several concepts. For example, eleven concepts share the synonym *b*, including *prothoracic dorsal sensillum trichodeum dh1*, *prothoracic dorsal sensillum trichodeum dh2*, *prothoracic dorsal sensillum campaniformium dc1*, and *mesothoracic dorsal sensillum trichodeum dh1*. Every concept is connected to other concepts through *IS-A* or *PART-OF* relationships. 797 concepts do not have any *IS-A* relationship to other concepts, while 1,139 concepts have more than one *IS-A* relationship to other concepts. There is an associative relationship *DEVELOPS_FROM* in FA (e.g., *dorsal closure embryo DEVELOPS_FROM late extended germ band embryo*). FA is found under the name *Drosophila gross anatomy* in OBO.

Worm Anatomy (WA) is the anatomical and developmental vocabulary developed in conjunction with WormBase [21], which is a "model organism database for *Caenorhabditis elegans* and other related nematodes" [22], developed by the WormBase Consortium. Each of the 6,301 concepts in WA has one preferred name (e.g., *gland cell*). 1,391 unique synonyms are provided (e.g., *pseudocoelom* has synonym *body cavity*). Unlike most ontologies where each name is specific to a given concept, many concepts names in WA are shared by several concepts. For example, 79 concepts share the same name *mu_bod*, the same definition "cell of the body wall muscles", and the same *IS-A* relationship to *body wall muscle cell from MS lineage*. These 79 distinct concepts (i.e., concepts with distinct identifiers) are only distinguishable by their slightly different synonyms, e.g., *lineage name\: MS.pppppp*, *lineage name\: MS.ppppap*, and *lineage name\: MS.pppppa*. Overall, there are 7,046 unique names for the 6,301 concepts in WA.

In WA, most concepts stand in an *IS-A* relation to one parent concept. However, 2,868 concepts do not have any *IS-A* relationship to other concepts, and 728 concepts have more than one *IS-A* relationship. Moreover, 2,616 'dangling' concepts have no *IS-A* or *PART-OF* connections to any other concepts. For example, the only relation of the concept *Ca nucleus*, defined as "nucleus of pedigree Ca", is through an associative relationship (*DESCENDENTOF*) to *C nucleus*. Such concepts were not used in our study where hierarchical relations are crucial as described in the aligning methods as follows. WA is found under the name *C. elegans gross anatomy* in OBO.

Zebrafish anatomical ontology (ZFA), developed by a consortium of researchers, is part of the Zebrafish Model Organism Database [23], which is "a web based community resource and a model organism database that implement the curation of zebrafish genetic, genomic and developmental data" [24]. Each of the 2,132 concepts in ZFA has one preferred name (e.g., *median fin fold*). There are 1,064 unique synonyms (e.g., *bulbus arteriosus* has synonyms *outflow tract* and *truncus*). 28 concepts do not have any *IS-A* relationship to other concepts, while 877 have more than one *IS-A* relationship. Additionally, there are 49 'dangling' concepts in ZFA. Here again, these concepts were not used in our study. ZFA has associative relationships, *DEVELOPS_FROM*, *START* and *END*. ZFA is listed under the name *Zebrafish anatomy and development* in OBO.

3 Methods

In order to align the five anatomical ontologies, we create ten direct, pairwise alignments. Each pairwise alignment is obtained through a combination of lexical and structural techniques. More precisely, we first compare terms across ontologies lexically in order to identify one-to-one concept matches. The second step is the validation of lexical matches using structural information. The interested reader is referred to [25] for details about our method.

3.1 Aligning ontologies pairwise

The **lexical alignment** compares two ontologies at the term level, by exact match and after normalization. Both preferred terms and synonyms in the two ontologies are used in the alignment. For example, the concepts *heart valve* in MA and *Cardiac valve* (synonym: *Heart valve*) in FMA are identified as a match. Moreover, synonymy information from external domain resources is used to identify additional matches. For example, *tooth pulp* in ZFA and *dental pulp* in MA, although lexically different, are considered a match because they name the same anatomical concept in the Unified Medical Language System® (UMLS®) [26].

The **structural validation** first acquires the inter-concept hierarchical relations, *IS-A* and *PART-OF*, and their inverses, *INVERSE-ISA* and *HAS-PART*, respectively. Missing relations are generated through complementation, augmentation and inference techniques [25]. Once all relations are represented consistently, the structural alignment is applied to the matches resulting from the lexical alignment in order to identify similar hierarchical paths to other matches across ontologies. For example, the matching concepts *heart valve* in MA and *Cardiac valve* in FMA exhibit similar hierarchical paths to other matches in these two ontologies, including paths to *Heart* (*PART-OF*) and to *Aortic valve* and *Mitral valve* (*INVERSE-ISA*). Such structural similarity is used as **positive evidence** for the alignment. Instead of similar paths, one match may exhibit paths to other matches in opposite directions in the two ontologies. Such paths suggest a structural conflict across ontologies. For example, in MA *pericardial cavity* stands in a *HAS-PART* relation to *pericardium*, while in the FMA *Pericardial cavity* is defined as *PART-OF Pericardial sac*, which is *PART-OF Pericardium*. These conflicts are used as **negative evidence** for the alignment, indicating the semantic incompatibility between concepts across ontologies in spite of their lexical resemblance.

3.2 Aligning the five anatomical ontologies

We applied the alignment techniques presented above to all pairwise combinations of the five anatomical ontologies, resulting in ten pairwise alignments. Lexical mappings supported by at least one piece of positive structural evidence were considered a match. We excluded mappings not supported by any structural evidence, as well as those exhibiting negative evidence.

4 Results

The number of concepts, concept names (terms) and relations in each ontology is listed in **Table 1**, including relations obtained through augmentation and inference.

Table 1. Terms and relations in the five ontologies.

	FMA	**MA**	**FA**	**WA**	**ZFA**
Concepts	75,147	2,745	6,024	6,301	2,132
Concept names	120,265	3,074	7,259	7,046	3,196
IS-A relations	75,144	1,809	6,372	4,537	1,305
PART-OF relations	22,210	1,639	3,096	882	1,396
Augmented relations	93,539	0	0	0	0
Inferred relations	2,182,991	10,253	50,203	6,769	8,333
Total relations	2,373,884	13,701	59,671	12,188	11,034

The results of the ten pairwise alignments among the five anatomical ontologies are summarized in **Table** 2, along with details about lexical alignment and structural validation. For example, in the mapping between MA and ZFA, 238 matches were identified through lexical alignment, including 37 identified through synonymy in the UMLS. These 238 matches represent 8.67% of the 2,745 concepts in MA and 11.16% of the 2,132 concepts in ZFA. Of these 238 matches, 212 (89.08%) were supported by positive structural evidence and finally reported as matches. The 26 matches not supported by structural evidence were ignored. No conflicts (negative structural evidence) were identified in this alignment. The ten alignments are also illustrated in **Figure 1**.

Table 2. Mappings obtained among five anatomical ontologies (ten pairwise alignments).

Pair of ontologies	**Lexical alignment**				**Structural validation**					
	# of mappings		Mappings / 1st ont.	Mappings / 2nd ont.	Positive evidence		No evidence		Negative evidence	
	Total	through UMLS								
MA-FMA	1,568	75	57.12%	2.09%	**1,459**	93.05%	105	6.69%	4	0.26%
ZFA-FMA	522	21	24.48%	0.69%	**458**	87.74%	62	11.88%	2	0.38%
FA-FMA	198	35	3.29%	2.63%	**116**	58.59%	80	40.40%	2	1.01%
WA-FMA	86	23	1.36%	0.11%	**65**	75.58%	19	22.09%	2	2.33%
MA-ZFA	238	37	8.67%	11.16%	**212**	89.08%	26	10.92%	0	0
MA-FA	90	18	3.28%	1.49%	**66**	73.34%	21	23.33%	3	3.33%
MA-WA	38	10	1.38%	0.60%	**29**	76.32%	9	23.68%	0	0
ZFA-FA	112	15	5.25%	1.86%	**100**	89.29%	12	10.71%	0	0
ZFA-WA	88	8	4.13%	1.40%	**45**	51.14%	43	48.86%	0	0
FA-WA	88	5	1.46%	1.40%	**46**	52.28%	40	45.45%	2	2.27%

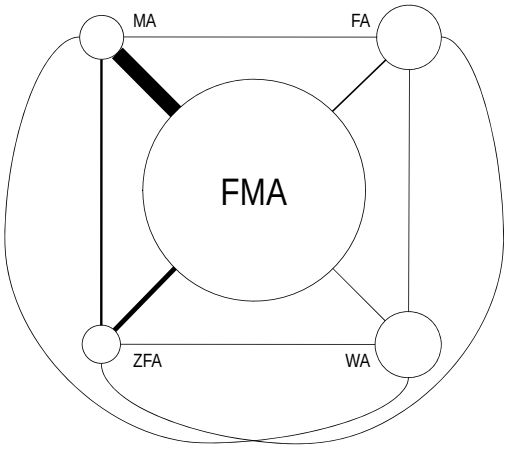

Figure 1. Representation of the number of shared concepts among ontologies (The size of the nodes is roughly proportional to the number of concepts in each ontology. The thickness of the link between two nodes is proportional to the number of shared concepts between the corresponding ontologies).

5 Discussion

The main issues we encountered in mapping among five anatomical ontologies across different species can be grouped into the following categories: false positives, false negatives, multiple ambiguous mappings, and differences among ontologies. This section provides a limited error analysis and outlines solutions for addressing these issues.

5.1 False positives

The presence of false positive mappings can be traced back to limitations in the mapping techniques used, including lack of semantic validation, insufficient structural validation and the influence of acronyms on lexical alignment.

We used **semantic validation** in previous alignment studies, primarily in order to distinguish between anatomical and non-anatomical entities across ontologies. For example, when mapping the FMA, an anatomical ontology, to the anatomical portion of GALEN, a general ontology of biomedicine, we assumed disjointness between top-level anatomical classes and other top-level classes in GALEN. We used such disjointness axioms for semantic validation purposes, preventing FMA concepts from being mapped to GALEN concepts from other hierarchies than anatomy [25]. For example, *Nail* in the FMA and *Nail* in GALEN, although sharing the exact the same name, are semantically distinct, because *Nail* in the FMA is a kind of *Skin appendage* which is an *Anatomical structure*, while *Nail* in GALEN is a *Surgical fixation device* which is an *Inert solid structure.* In the present study, because the five ontologies under investigation are all restricted to the anatomical domain, we thought that the semantic validation would not be necessary. In fact, our limited review of some of the mappings led us to conclude that semantic validation would still be appropriate in this case. For example, in the mapping {FA: *accessory mesothoracic neuromere* (synonym: *ovoid*), FMA: *Ovoid*}, *accessory mesothoracic neuromere* in FA *IS-A neuromere* which *IS-A ganglion*, while *Ovoid* in FMA *IS-A Volume* which *IS-A Dimensional entity*. There are no dimensional concepts in FA, so by specifying that anything in FA is disjoint with the top-level concept *Dimensional entity* in FMA, the mismatch between the two concepts could be detected automatically.

Insufficient structural validation can be blamed for some false positive matches. In fact, as mentioned earlier, structural validation only requires one shared path between lexical matches across ontologies in order to validate the mapping. We noticed that, in some cases, the shared path used as positive evidence involves only high-level concepts such as the root of some hierarchy.

Take the mapping {WA: *axis*, FMA: *Axis*} for example. In WA, *axis* is defined as "spatial axis" and stands in an *IS-A* relation to *anatomy*. Its three children are: *anterior-posterior*, *dorsal-ventral*, and *left-right*. On the other hand, in the FMA, *Axis IS-A Cervical vertebra*, which *IS-A Vertebra*, which *IS-A Irregular bone*, which *IS-A Organ*, which *IS-A Anatomical structure*. The mapping received positive

evidence in the structural validation phase, because in both systems *axis* is ultimately classified under *Anatomical structure* (mapped to *anatomy* in WA). While the mapping of spatial axis to a cervical vertebra is an obvious mismatch, this false positive was not detected by structural validation. In fact, the requirement that at least one hierarchical path be shared across ontologies for this mapping is insufficient, as it should exclude trivial shared hierarchical paths such as relations to the root (or to high-level concepts) of the anatomy hierarchy.

Another such example is {ZFA: *midbrain hindbrain boundary* (synonym: *isthmus*), WA: *isthmus*} identified as a mapping through synonymy. In ZFA, *midbrain hindbrain boundary* is linked to three other concepts, *nervous system*, *compound organ*, and *anatomical structure*, all through a *PART-OF* relationship. On the other hand in WA, *isthmus* is linked to six other concepts, *pharynx*, *body region*, *Anatomy*, *digestive tract*, and *alimentary system*, also through *PART-OF* in all cases. The mapping received positive structural evidence, because both *midbrain hindbrain boundary* and *isthmus* are *PART-OF anatomical structure* (mapped to *Anatomy* in WA). Obviously, this mapping is a false positive, since *midbrain hindbrain boundary* refers to a boundary in the brain, while *isthmus* is a "section in pharynx of which muscle contract with a peristaltic motion" according to the textual definition in WA. Here again, the structural validation process failed to identify the mismatch, because one shared path to the root concept *anatomical structure* was deemed sufficient evidence for validating the lexical match. Ignoring trivial shared paths to the root would result in rejecting this mapping, which would no longer be supported by positive evidence.

The presence of **acronyms in concept names** is also responsible for some false positive mappings. For example, {ZFA: *posterior macula* (synonym: *pm*), FA: *proximal medullary amacrine neuron* (synonym: *Pm*)} were identified to be a match through synonymy. Both concepts are *PART-OF nervous system* and *whole organism*, so the mapping is supported by positive evidence. However, *posterior macula* in ZFA is defined as "patches of thickened, pseudostratified epithelium of the inner ear…" and stands in a *PART-OF* relationship to *inner ear*. In FA, *proximal medullary amacrine neuron IS-A neuron* and stands in a *PART-OF* relationship to *brain* and *nerve*. In addition to short surface forms (e.g., acronyms), shared trivial paths to root (e.g., *whole organism*) or high-level concepts (e.g., *nervous system*) are also responsible for this mismatch.

5.2 False negatives

As noted in previous studies [25], in some cases, differing knowledge representation strategies are responsible for the lack of shared hierarchical paths for equivalent concepts across ontologies. For example, {WA: *body wall musculature*, FMA: *Musculature of body wall* (synonym: *Body wall musculature*)} do not share any paths, but are nonetheless equivalent concepts. In WA, *body wall musculature IS-A muscular system*, which *IS-A Organ system*, and it has child *head muscle* and has apart *striated muscle*. In FMA, *Musculature of body wall* is *PART-OF Body wall* and *IS-A Set of muscles of subdivision of trunk*. The two concepts do not share any hierarchical links to other concepts across systems due to differences in knowledge representation. Similarly for {MA: *lip*, ZFA: *lip*}, where in MA *lip* is *PART-OF mouth*, while in ZFA *lip IS-A surface structure* which *IS-A organism subdivision*. Devising automatic methods for assessing such mappings automatically is extremely challenging.

Another example is the mapping {MA: *pancreatic duct*, ZFA: *pancreatic duct*}. In MA, *pancreatic duct* is *PART-OF exocrine pancreas* which is *PART-OF pancreas*. In ZFA, *pancreatic duct* is *PART-OF pancreatic system* which is *PART-OF endocrine system* and *digestive system*. In other words, in ZFA, both *pancreatic duct* and *pancreas* are parts of *pancreatic system*, while in MA, *pancreatic duct* is part of *pancreas* and there is no concept *pancreatic system*.

The pairs of concepts {MA: *tail*, ZFA: *tail*} (where in MA *IS-A anatomic region* which is *PART-OF adult mouse* while in ZFA *IS-A organism subdivision* which *IS-A anatomical structure*) and {MA: *lymphoid system* (synonym: *lymphatic system*), ZFA: *lymphatic system*} (where the former is *PART-OF immune system* while the latter *IS-A cardiovascular system*) also represent potential matches that could not be validated for lack of structural evidence due to differing representations.

It must be noted that tightening the structural validation process as suggested above (e.g., by ignoring the positive structural evidence solely suggested by shared path to root or high-level concepts) is likely to result in additional mapping failures due to false negatives. For example, the valid mapping {ZFA: *neuroendocrine cell* (synonym: *neurosecretory cell*), FA: *neurosecretory cell*} is only supported by one shared *PART-OF* relation to *whole organism* across two systems. These concepts do stand in other relations to other concepts, but none of these relations are shared. In ZFA, *neuroendocrine cell* is *PART-OF endocrine system*, while in FA, *neurosecretory cell IS-A neuron* and is *PART-OF brain*, *nervous system*, *ganglion* and others.

5.3 Multiple ambiguous mappings

The alignment technique we developed is expected to identify point-to-point equivalences across ontologies. Multiple mappings occur when more than one concept from one ontology is mapped to one concept from another ontology. Such ambiguous mappings are indicative of an error, because, within one ontology, concepts generally denote distinct entities. As shown in Table 3, a significant number of multiple mappings were identified in this experiment. For example, among 1,568 MA-FMA mappings, 138 MA concepts (8.80%) were mapped to more than one FMA concept and 21 FMA concepts (1.34%) mapped by more than one MA concept. Overall, the proportion of ambiguous mappings ranges from 0 to almost 10%. Mappings to the FMA tend to have higher proportions of ambiguous mappings.

Table 3. Number of ambiguous mappings in the ten pairwise alignments.

Pair of ontologies	Total # of mappings	Multiple mappings to 2nd ontology		Multiple mappings to 1st ontology	
MA-FMA	1,568	138	8.80%	21	1.34%
ZFA-FMA	522	50	9.58%	11	2.11%
FA-FMA	198	10	5.05%	1	0.51%
WA-FMA	86	8	9.30%	0	0.00%
MA-ZFA	238	4	1.68%	16	6.72%
MA-FA	90	1	1.11%	2	2.22%
MA-WA	38	1	2.63%	2	5.26%
ZFA-FA	112	3	2.68%	4	3.57%
ZFA-WA	88	3	3.41%	7	7.95%
FA-WA	88	5	5.68%	2	2.27%

Disambiguation of multiple mappings is required in order to select one valid mapping among the several mappings identified for one concept. However, disambiguation is often difficult due to a lack of detailed knowledge represented in the ontologies. For example, both *pharynx* and *esophagus* in FA were mapped to *pharynx* in WA, which has *esophagus* as a synonym. Both mappings received positive structural evidence because all three concepts are *PART-OF organ system* and *alimentary system*. In FA, both *esophagus* and *pharynx* are described as *PART-OF foregut*, while *esophagus* has one child *embryonic esophagus* and *pharynx* is a leaf concept. In WA, *pharynx IS-A organ*, *PART-OF digestive tract* and has no children. In the absence of distinctive relations to other concepts in the two ontologies, domain expertise is required to clarify the differences between esophagus and pharynx in fly and worm.

Another example of multiple mappings is {MA: *axillary vein*, FA: *axillary vein*} and {MA: *subcostal vein*, FA: *axillary vein* (synonym: *subcostal vein*)}. In FA, *axillary vein IS-A wing vein* and *PART-OF wing blade*. In MA, *axillary vein* and *subcostal vein* share the same structural specification, both simply described as a kind of *vein*. The underspecified description of two concepts in MA makes the automatic disambiguation of multiple mappings based on structural information extremely difficult.

5.4 Differences among ontologies

Differences observed among anatomical ontologies influencing the alignment include differences in granularity and in naming conventions, as well as genuine anatomical differences among species.

One of the differences explaining the limited number of equivalent concepts identified across ontologies is the **difference in granularity**. As shown in other studies [27], some 60% of the anatomical concepts in the FMA differ from their parent concept(s) solely by laterality, i.e., most often by the presence of "left" or "right" in the concepts name. Since some ontologies purposely avoid representing laterality information for paired anatomical structures, failure to identify mappings for anatomical structures represented at this level of granularity does not constitute a limitation of the alignment system. In fact, among the ontologies under investigation in this study, FMA, MA and WA represent laterality information, while FA and ZFA do not. For example, in ZFA, *nasal artery* is defined as "the nasal arteries start at the internal carotid artery and travel rostrally, passing along the right and left walls of the nasal sac at the most rostral end of the head…" but is not further classified. In MA there are two more specific nasal arteries, *dorsal nasal artery* and *ven-*

tral dorsal nasal artery. In FMA, the classification is finer-grained, further classifying *Lateral nasal artery* into *Left lateral nasal artery* and *Right lateral nasal artery*, and *Dorsal nasal artery* into *Left dorsal nasal artery* and *Right dorsal nasal artery*. Most fine-grained concepts were not identified automatically in our alignments.

The use of lexical alignment as the first step of the alignment process presupposes that concept names are amenable to natural language processing techniques, including edit distance and normalization. **Idiosyncrasies in naming** generally defeat the lexical alignment techniques. For example, concepts names specific to WA include *mu_bod* for "cell of the body wall muscles", as well as *lineage name\: MS.pppppp* and *Earaa*. In such cases, domain expertise is required to distinguish between anatomical entities for which a correspondence could be found in other ontologies under a different name, and concepts specific to a given species (e.g., specific cell lines).

Finally, there are **genuine anatomical differences among species**, including the presence of fins in fish (ZFA), wings in fly (FA) and whiskers in mouse (MA). Therefore, wing-related concepts from FA (e.g., *wing*, *dorsal wing*, *ventral wing*, *wing margin*, *wing nerve*, *wing hair*, *wing hinge*, *wing blade*) cannot be expected to be mapped to any concepts in any of the four other ontologies.

6 Conclusions

We studied the automatic alignment of anatomical ontologies for five different organisms along the evolutionary spectrum. From a quantitative perspective, only a limited number of correspondences could be identified among ontologies with an upper bound of 57% of MA concepts (followed by 24.5% of ZFA concepts) identified in FMA. In contrast, less than 5% of the concepts from a given ontology are identified in another ontology for 15 of the 20 pairs of ontologies investigated (considering the directionality of the alignment). A manual review of a limited number of the mappings revealed that, with the exception of MA-FMA, the precision and recall are generally low and might be a hindrance to data integration in the absence of manual review. One possible strategy would be to use such automatic mapping to bootstrap a mapping curated by domain experts.

The structural similarity required for the validation of lexical mappings would benefit from being tightened, for example, by ignoring shared hierarchical paths to root or high-level concepts. However, doing so will also result in increasing the number of valid mappings not supported by structural evidence. The balance between precision and recall should be considered in light of the application supported by the mapping. Semantic validation based on disjoint top-level categories was not applied in this study where only anatomical entities were to be aligned. We noticed, however, that semantic validation would have prevented a small number of mismatches. Multiple mappings to FMA are relatively frequent and require disambiguation by a domain expert. Idiosyncrasies in naming and in concept representation (including differences in granularity) account for a significant proportion of missed matches.

Overall, aligning anatomical ontologies across species remains difficult. The evaluation of such studies is difficult in the absence of gold standard alignments for most pairs of anatomical ontologies. The collaborative evaluation fostered by initiatives such as the OAEI will benefit not only the ontology alignment community, but also the biology and data integration communities.

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