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Article

Towards Ontology-Based Integration of Biomedical Atlases

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***Abstract*— Medical imaging in clinical analysis has been the subject of significant research for many years. In many cases scan images like CT scan and MRI scan may compliment physical examinations. Linking these scan images to biomedical atlases is fundamental to facilitate analysis. Biomedical atlas provides mapping between the graphical model and the ontology. Mapping from one atlas to another corresponding atlas is complex when it involves atlases from different model organisms. For example, having a general accepted nomenclature for the components of mouse embryo which is in parallel with the human atlas nomenclature provide an efficient means for analysis and modeling in biomedicine. However, this lead to interoperability issue. Therefore, taking the advantage of Semantic Web, Intelligent Agents and Ontology, this project starts with research linking imaging data of mouse embryo MRI to a standard canonical mouse atlas as designed in Edinburgh Mouse Atlas Project and also research on spatial rules to identify matching regions in atlases and images.**

***Keywords*— Ontology; Biomedical Atlas; Data Integration.**

I. INTRODUCTION

Anatomy is the structure of biological organisms and is concerned with the study of structural and developmental relations among anatomical entities throughout the lifespan of an organism [1]. The term ontology on the other hand denotes a proper specification of a conceptualization presenting a domain modeling the entities in the domain and their relations [2]. Example on the anatomy ontology can be found in the e-Mouse Atlas Project (EMAP). The EMAP Anatomy Ontology is a hierarchically structured list of histological tissues visible at each Theiler stage of development [3]. The ontology is developed to describe normal and mutant tissue anatomy and contain a method to allow textual description of gene expression pattern. The ontology uses ‘part of’ relationships and is based mostly on anatomical structures. Composition of the ontology as a hierarchy of each developmental stage shows the structural relationships between the anatomical entities within each stage as well as throughout the whole development process. Selected anatomical terms are presented by domains in the corresponding model. These domains associate anatomical concepts with space in the embryo and therefore provide a structural description for the corresponding terms in the ontology.

Due to the few numbers of generalizable, computable representations of anatomy, developers of computable terminologies and anthologies in clinical medicine and biomedical research represent anatomy from their own perspective [1]. The resulting multiplicity cause a difficult deterrent to correlating the human anatomy, not only across computational resources, but also with the anatomy of model organisms used in biomedical experimentation [1]. When a domain is represented by numerous ontologies, there is demand for creating a mapping mechanism among these ontologies in order to assist the integration of data annotated with these ontologies and reasoning across ontologies [4].

The Foundational Model of Anatomy (FMA) ontology is designed to aid for a generalizable anatomy ontology, that can be used and adapted by any computer based application that needs anatomical information. Furthermore, it is emerging into a standard reference for numerous views of anatomy and a template for representing the anatomy of animals.

The Foundational Model of Anatomy Ontology (FMA) is concerned with the representation of classes or types and relationships primarily for the representation of the phenotype structure of the human body in a comprehensible way to humans and also navigable, and interpretable by machine-based systems. Particularly, the FMA is a domain ontology that designates an explicit declarative knowledge on human anatomy. Its ontological framework can be adapted and extended to all other species.

The foundational model of anatomy (FMA) ontology provides not only the theory of anatomy but also the ontology artefact. The theory denotes anatomy and its content domain, and therefore provides a framework to represent the nature of the diverse entities that make up the bodily structure of biological organism together with the relations that exists among these entities. In other words, FMA theory is a theory of structural phenotype. The FMA ontology artefact, on the other hand is the computable implementation of the FMA theory.

The FMA uses the Protégé environment for knowledge-based systems to deal with its anatomic concepts and relationships [5]. Protégé is an open source, extensible environment with a large user base. These features make it easy to adapt the system for special needs.

II. RELATED WORK

In image interpretation and computer vision, spatial relations between objects and spatial reasoning play crucial factors in the process of recognition and interpretation. This results in the growing of ontology based research for recognition and retrieval of biomedical information. To account for recognition of biomedical image based on spatial relations, Hudelot [6] presented fuzzy spatial relation ontology that facilitates image interpretation and identification using structural information on the spatial arrangement of structures. They enhanced the ontology by implementing fuzzy representations of concepts, which define their semantics, and allow establishing the link between these concepts and the information that can be extracted from images. In contrast, Mechouche [7] proposed an interactive system for semantic annotation of brain Magnetic Resonance Images by adapting Constraint Satisfaction Problem solving and Description Logics inference. Their works include labelling the cortical anatomical structures in MRI images based on the spatial arrangement of the gyri and parts of gyri in the brain. Based on these exemplary studies, it can be concluded that structure recognition relies on spatial relations. The approach is progressive where objects are identified sequentially and their identification makes use of knowledge about their relations with respect to other objects.

Mechouche [7] designed their application as a client-server architecture, using Web services. This provides an extension of the scientific workflow platform to facilitate interoperability. Towards a public bioinformatics resource, the proposed system must be easily accessible to researchers all over the world, both for submission and for querying data. Hence, this concerns interoperability issues. The availability of Semantic Web technologies plays a big role in the wide-scale sharing of information on the web as it enables creations and sharing of semantic annotations and their use of intelligent agents for information retrieval and reasoning. This is significant in biomedical research, particularly in the context of translational research, for facilitating the exploitation of experimental data across several disciplines and scales. More importantly, it is also applicable in the context of medical imaging as it provides the capability to describe and share additional information pertinent to the images such as their acquisition context, their content description, e.g. evidence of pathology, quantitative imaging biomarkers extracted from image data and etc [7].

Hudelot [6] demonstrates the proposed fuzzy spatial relation ontology on a medical example, dealing with knowledge-based recognition of brain structures in 3D magnetic resonance images. Similarly, Mechouche [7] also applied their method on brain structures; however, they focus specifically on the parts of sulcus and gyrus.

Mouse embryo is an excellent model to study fundamental principles that should apply similarly to human embryos. Moreover, the mouse has also been extensively used as a model for many diseases. As the mouse embryo is best genetically characterised model organism in which to study mammalian development, the development of tools that facilitates the study of mouse embryo is vital. Semantic annotation of mouse embryo images is provided in The Edinburgh Mouse Atlas Project [3]. EMAP provides a set of interoperability tools which allows users to browse text nomenclature and make queries about gene expressions that return sets of images or a list of genes expressed for a given embryo image. However, this application does not provide spatial comparison of multiple complex structures concerning topological differences between different mouse embryos images. Therefore, for this research, mouse embryo spatial relation ontology which intends to guide structure recognition of different mouse embryo images based on spatial orientation and structural information will be proposed. The ontology will be embedded in a research prototype and should support spatial reasoning, flexible structure information recognition and visualization. The new pictorial data structure based upon two-dimensional coordinate should provide an efficient means for structure equivalent verification and spatial reasoning.

Hence, there are three objectives of the research. First, to propose an ontology of spatial relations which aim to guide image interpretation and structure recognition of mouse embryo Magnetic Resonance Imaging (MRI) images. Second, to develop an application that allows spatial comparisons of multiple complex structures of mouse embryos to show similarities amongst structures. Third, to demonstrate the theoretical result in Semantic Web application.

III. METHODOLOGY

This research proposes to use Semantic Web techniques such as OWL and SPARQL to encode system metadata; the open source reasoner Pellet to provide standard reasoning services for OWL ontologies involved; the Semantic Web Rule Language (SWRL) to infer new knowledge on spatial comparisons of multiple complex structures of mouse embryos; Jena an OWL API to manipulate OWL data models and to perform reasoning based on Description Logic engines and using Tomcat as the deployment server. Overview of the proposed system architecture is shown in Figure 1.

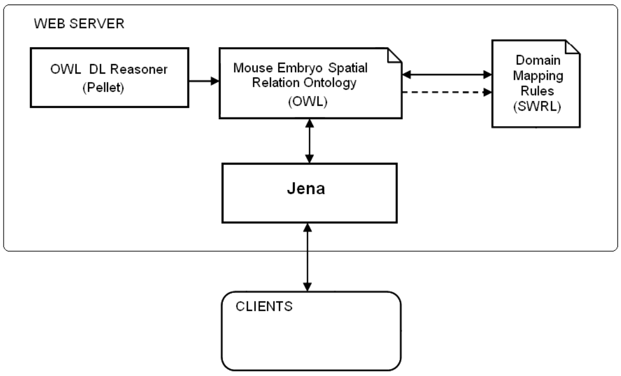


Fig. 1 The Proposed Architecture

The ontology will be constructed using OWL syntax in the Protégé-OWL tool and combined with sets of rules represented in SWRL, the Semantic Web Rule Language. Semantic web ontology language OWL has recently emerged as the de-facto standard for intelligent applications that utilize the ontologies as a knowledge formalization tool. OWL, in combination with the SWRL rule language and with domain-independent reasoners, provides a generally recognized expert system development framework. Concerning the structured knowledge of the mouse embryo anatomical structures and the classification of these structures based on partial information, OWL provides essential infrastructure concurrent with these special needs.

IV. ONTOLOGY DEVELOPMENT

The development of intelligent systems, specifically of knowledge based systems, requires the development of a knowledge based that has to include general and specific knowledge in order to solve problems in a well-defined domain of expertise. The process of knowledge based construction is identified as knowledge engineering and generally follows a specific methodology. One of the first steps of this process is ontology development. Ontologies are a central building block of the Semantic Web [8]. Ontologies describe the domain concepts and the relationships between them, and therefore present a meaningful domain language to humans and machines. Starting from the ontology it is created the knowledge based of the intelligent system.

The proposed mouse embryo spatial relation ontology is first modeled using Prolog. Later, the finalized ontology will be constructed using OWL syntax in the Protégé-OWL tool. Prolog stands for PROgramming in LOGic and it was developed from a foundation of logical theorem proving and essentially used for research in natural language processing [9]. Prolog allows for rapid prototyping of specifications, proofs and tests. As such, Prolog is chosen to demonstrate the proposed logical specification of the ideal executable mouse embryo spatial relation ontology.

For images used concurrently with the proposed ontology, the space is presented using two-dimensional coordinate system where each cell is occupied by an individual or instance. The connected individuals or instances form a structure. Several spatial integrity rules have been classified. Topological relationships are only one type of possible other types of spatial relationships that may be employed in devising integrity constraints for spatial data. Basic space rules are derived by observing properties and relationships of objects in space and the following are examples of primitive relations that have been chosen:

- T *hasPart* t – a membership relation between a continuant instance *t* and a structure *T* which it instantiates at all time
- t *hasCoordinate* c - a location relation between a continuant instance *t* and set of coordinates *c* which it holds at all time
- r1 *adjacentTo* r2 - a primitive relation of zero space between two continuants instances
- r1 *nextTo* r2 - a primitive relation between two adjacent continuants.

Inherent properties of structure derived from its elements and ordering can be expressed as constraints which those structures should conform to in space. Some examples of this type of rules for simple structure include the following:

- A structure is formed of a set of connected instances.
- Instances are adjacent if the distance between them is zero.
- Instances are adjacent if they share the same edge.
- Instances are positioned next to each other if they are adjacent to one another.

Other examples of more complex spatial data type rules include the following:

- Two structures are equivalent if they have exactly the same instances and the instances are exactly in the same adjacency.
- Two structures are next to each other, if any of their instances are next to each other.
- If instance *r1* is *nextTo* instance *r2*, and instance *r2* is part of structure *T*, then instance *r1* is *nextTo* structure *T*.
- Two structures are overlapped, if they share the same instance.

The above are examples of possible constraints that may be used to force the integrity of structures. A detailed description of the proposed mouse embryo spatial relations ontology is presented in the following section.

A. *Spatial Relations*

In this section, an overview of various kinds of spatial relations and their properties are presented. In particular, the focus is on properties of spatial relations that can be exploited for automated reasoning. The proposed framework should support terminological and spatial reasoning in a mouse embryo structure recognition application. The aim is to identify anatomical structures progressively by using spatial information between different structures.

Spatial relations include mereological relations such as parthood and overlap, topological relations such as connectedness and one-pieceness, as well as location relations. The location and the arrangement of an anatomical structure within the human body can be further specified by means of relations that express spatial orderings. The representation of spatial relations in anatomical ontologies concerns types of individuals. By an individual (also called an instance), which means an entity where at each moment of its existence occupies a unique spatial location. At the level of individuals, at least three type level relations can be distinguished which are *Parthood Relation*, *Location Relation* and *Connectedness Relation*.

Consider the following heart structure image of mouse embryo (taken at Theiler Stage 19) as shown in Figure 2, where the following *parts* are seen: *Atria*, *Atrio-venticular canal* and *Ventricles*.

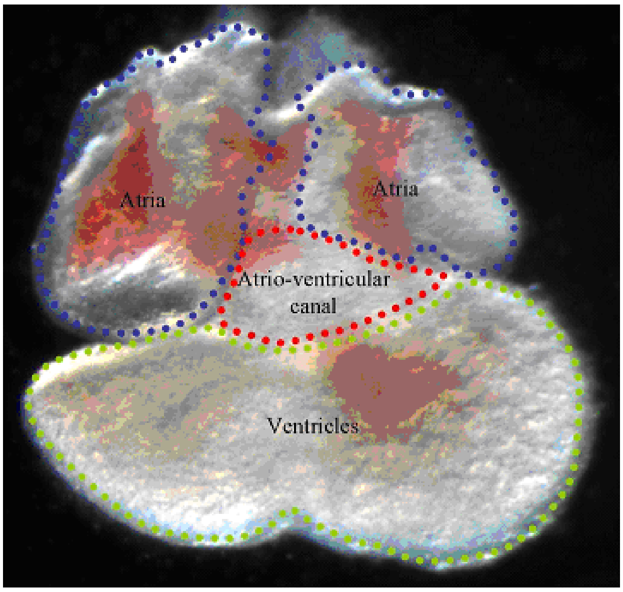


Fig. 2 Heart with outflow tract removed at Theiler Stage 19 (http://www.mouseatlas.org [10])

This heart-ventrical structure is then patterned into a set of contiguous parts in a two-dimensional coordinate system as shown in Figure 3, where P1, P2, and P3 are denoted respectively as *Ventricles*, the *Atrio-Ventricular Canal* and the *atria*. The similarity between the corresponding pattern in the two-dimensional coordinate system and gene-expression region in the scanned image is determined based on the adjacency of the contiguous element in the heart structure.

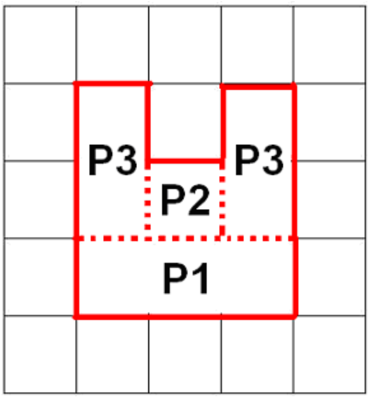


Fig. 3 Probe pattern of heart with outflow tract removed at Theiler Stage 19

B. *Parthood Relations*

Mereological essentialism is the view that objects have their parts essentially. If mereological essentialism is true, it would have the consequence that if an object would lose or gain a part, it would cease to exist (that is, the result would not be the same object anymore). Thus, mereological essentialism is about the relationship between wholes and its parts, and the conditions for their persistence.

In Prolog representation, parthood is expressed as *hasPart(Structure, Part)*. The name of the structure is represented by *Structure*, whereas, the individual which is an instance (eg. tissue, liver, brain, etc) is represented by *Part*.

To illustrate the approach, consider the situation illustrated in Figure 4. It can be seen that the following tissue are expressed: *Embryonic Tissue*, *Extra-embryonic Tissue* and *Placenta Ectoplacental Cone*. A set of “probe patterns” for this structure is illustrated in Figure 5.

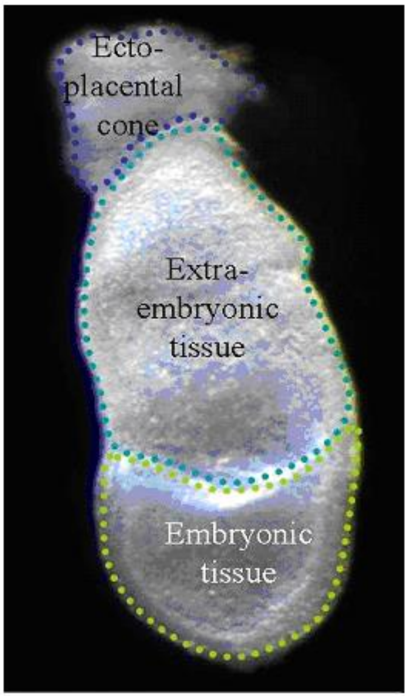


Fig. 4 Whole embryo at Theiler Stage 10 (http://www.mouseatlas.org [10])

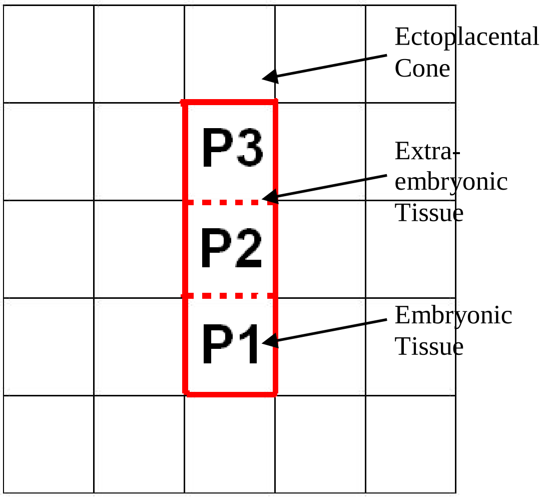


Fig. 5 Whole Embryo at Theiler Stage 10

As parthood is expressed as *hasPart(Structure, Part)*, the situation in Figure 5 and 6 correspond to the following facts in Prolog rule language:

```
hasPart(embryo, embryonicTissue)
hasPart(embryo, extraEmbryonicTissue)
hasPart(embryo, ectoPlacentalCone)
```

C. Location Relations

To be useful for anatomical ontologies, mereology needs to be further extended to include also the location among individual. The relative location of two objects using mereological relations can be expressed as follows: if structure x is part of structure y, then structure x is located in structure y in the sense that structure x's location is included in structure y's location (see Figure 6 (a)).

$$Pxy \rightarrow Oxy \qquad (1)$$

Also, if structure x and structure y overlap, then structure x and structure y partially coincide in the sense that structure x's location and structure y's location overlap (see Figure 6 (b)). If structure x and structure y overlap then structure x and structure y are partially coincide

$$Oxy \rightarrow PCoin(x,y) \qquad (2)$$

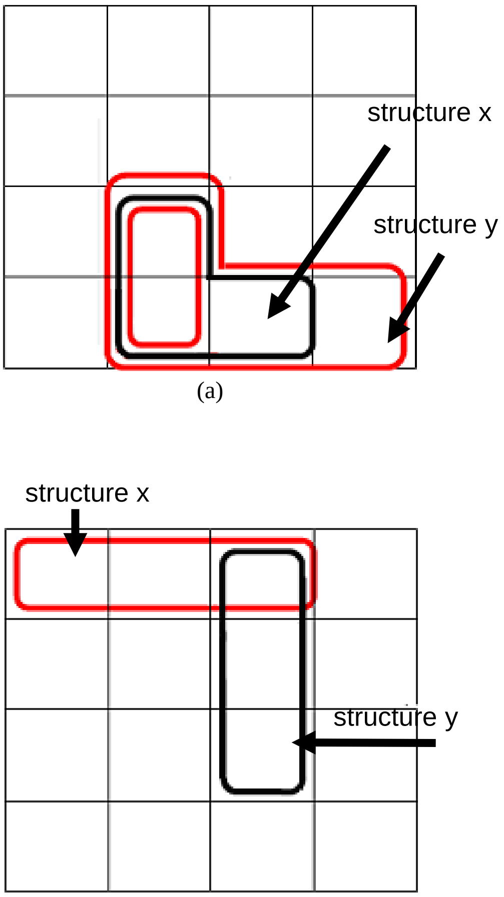


Fig. 6 (a) Wholly Coincide (b) Partially Coincide

In Prolog, the rule is expressed as follows:

```
overlaps(Structure1, Structure2) :-
                    hasPart(Structure1, Part1),
                    hasPart(Structure2,Part2),
                    (Part1 = Part2),
                    not(Structure1 = Structure2).
```

(3)

The location relations enable us to, in addition, describe the relative location of objects that may coincide wholly or partially without being part of one another or overlapping.

All location relations are introduced in terms of a region function r that maps each individual to the unique spatial region at which it is exactly located at the given moment. Spatial regions are here assumed to be part of an independent background space in which all individuals are located.

The two-dimensional coordinate system is used to indicate the location for each individual. This statement is presented through a *hasCoordinate* relation. In general, the *hasCoordinate* relation is denoted as follows:

$$hasCoordinate(Individual,\ Coordinate) \qquad (4)$$

This relation is then extended to *hasDistance* rule to indicate connectedness and one-pieceness relation as follows:

```
hasDistance(Part1, Part2, Distance) :-
          hasCoordinate(Part1, (X1,Y1)),
          hasCoordinate(Part2, (X2,Y2)),
          Distance is (ceil(sqrt(((X2 – X1) * (X2 – X1)) +
          ((Y2-Y1) * (Y2 – Y1))) – 1)),
          Distance >= 0.
```

(5)

To show space between two parts (individuals), the a *Distance* rule is derived where x and y are separated if and only if the distance between them are greater than zero.

$$SPxy \rightarrow (Dxy > 0) \qquad (6)$$

In Prolog this rule is expressed as follows:

```
separated(Part1, Part2) :-
          hasDistance(Part1, Part2, Distance),
          not(Part1 = Part2),
          not(adjacent(Part1, Part2)),
          Distance > 0.
```

(7)

D. *Connectedness Relations*

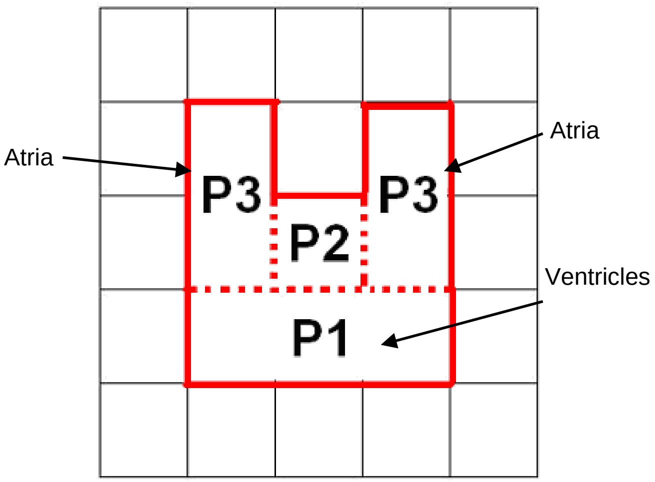


Fig. 7 Heart with outflow tract removed at Theiler Stage 19

The independent membership of each part in Figure 7 is determined through the *adjacent* rule defined as follows:

adjacentTo(Part1, Part2) :-
hasDistance(Part1, Part2, 0),
not(Part1 = Part2).
(8)

Each part may have multiple coordinates and a part cannot be adjacent to itself. Thus, the adjacent rule takes into account *not(Part1 = Part2)* as its condition to confront adjacency between different parts.

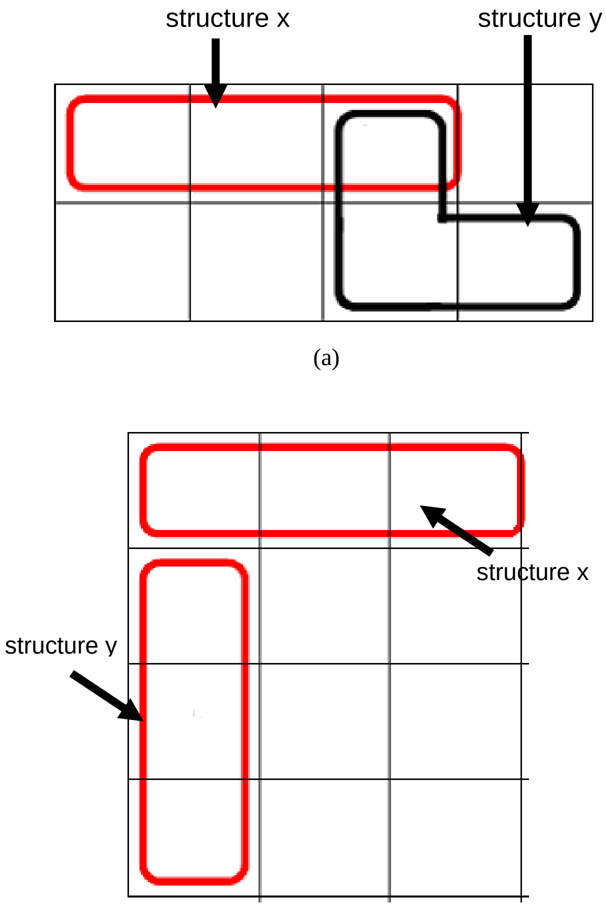
The adjacency rule is then extended into another rule named as *nextTo* rule to indicate that if *x* is connected to *y* then *y* is connected to *x*

$$Cxy \rightarrow Cyx \qquad (9)$$

The *nextTo* relation is therefore a symmetric and is written in Prolog as follows:

nextTo(X, Y) :- adjacentTo(X, Y); adjacentTo(Y, X).
(10)

Intuitively, *x* is connected to *y* if and only if *x* and *y* overlap or *x* and *y* are in direct external contact. Two regions are connected if and only if they share at least a boundary point (they may share interior points).



(a)

(b)

Fig. 8 (a) The non-transitivity of overlap. (b) Externally connected regions

Structure *x* and *y* in Figure 8(a) are connected. Similarly, the two structures *x* and *y* in Figure 8(b) are also (externally) connected.

In general, *x* and *y* are externally connected if and only if they do not partially coincide.

$$ECxy \equiv Cxy \wedge \neg PCoin(x,y) \qquad (11)$$

In Prolog, the externally connected rule is defined as follows:

externallyConnected(Structure1, Structure2) :-
hasPart(Structure1, Part1),
hasPart(Structure2, Part2),
not(Part1 = Part2),
nextTo(Part1, Part2),
not(Structure1 = Structure2),
not(overlaps(Structure1, Structure2)).
(12)

If *x* is located in *y*, then everything connected to *x* is connected to *y*.

$$LocIn(x, y) \rightarrow (\forall z)\ (Czx \rightarrow Czy) \qquad (13)$$

In Prolog, the rule is defined as follows:

nextToStructure(Part2, Structure) :-
hasPart(Structure, Part1),
nextTo(Part1, Part2),
not(hasPart(Structure, Part2)).

E. Spatial Orderings and Notion of Equivalence

Two anatomical structures are equivalent if they have exactly the same parts and the parts are structured in the same adjacency. Apparently, two anatomical structures are topologically equivalent if they can be made coincide by a transformation that involves change of shape (stretching, bending, etc) but no cutting, drilling holes, etc. Consider the Temporomandibular joint and muscle (TMJ) depicted in Figure 9 and compare it with the TMJs depicted in Figure 10. Obviously it is critical to distinguish the TMJ in Figure 9 from the TMJ in Figure 10. It is the purpose of the disc in a TMJ to be *between* the condyle and the temporal bone at all times. If the ordering relation of betweenness is taken into account, then the TMJ in Figure 9 can be distinguished from the clearly pathological TMJ in Figure 10 where the posterior attachment is between the condyle and the temporal bone and not the disc.

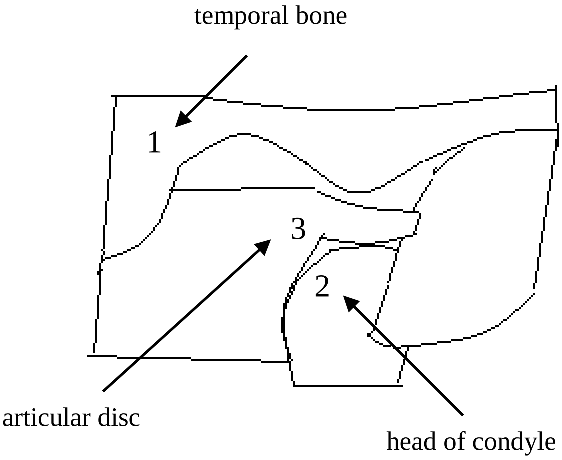


Fig. 9 Drawing of the major parts of a TMJ in an open jaw position [11]

Ordering relations like betweenness describe situations where objects are placed in a relative relation to each other. The science of anatomy has developed a whole set of ordering relation terms to describe the arrangement of anatomical parts such as superior, inferior, anterior, posterior, lateral, medial, dorsal, ventral, rostral, priximal, distal, etc. Beside betweenness, primitive ordering relations include: left-of, right-of, in-front-of, above, below, behind, etc. Therefore, one of the research questions to be examined in this study is to discover best definition to define structure equivalence. The importance behind this question is because images are traditionally visually assessed for sites of expression by a human annotator, who subsequently manually annotates an anatomy ontology to describe the parts of the tissue where expression is detected or not detected.

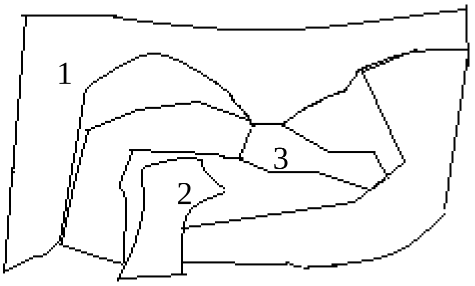


Fig.10 TMJ with disc not positioned between condyle and temporal bone [11]

This method, whilst being excellent for warehousing the data at a relatively gross level, cannot easily describe the spatial intricacies of complex gene expression patterns. In addition, this approach can be constrained by the availability of anatomical expertise and time with which to perform these manual annotations. Thus, by answering this question, the method can provide support for automated analysis of such data.

V. TOWARDS SEMANTIC WEB APPLICATION

The development of this semantic web application is a work in progress [12] and the following are examples on screenshot of the project. The ontology is constructed using OWL syntax in the Protégé-OWL tool. In its current form the ontology presents the detailed taxonomic overview of the mouse embryo domain describing mouse embryo anatomical structures related concepts. These concepts are interconnected with super-class and sub-class relations into a hierarchical treelike structure. Figure 11 presents the Protégé tool displaying some of the classes from the mouse embryo spatial relation ontology. The mouse embryo spatial relation ontology is also enriched by a set of rules, represented in SWRL, the Semantic Web Rule Language. For example, consider the rule on Figure 12, it expresses that if the distance between the coordinate value of *part1* and *part2* is zero, then *part1* and *part2* is inferred as adjacent to one another. Figure 13 presents the mouse embryo spatial relation ontology loaded in a web browser using Tomcat as deployment server. Jena API is used to manipulate OWL data models and to perform reasoning based on Description Logic engine. Based on the exemplary application, the following tasks will be solved by the proposed system: Identification of mouse embryo anatomical structure based on adjacency equivalence, identification of anatomical entity, identification of externally connected structures and identification of non-transitivity of overlapping structures. Primarily, the rational of experimenting structure equivalence based on direction is to perceive how far the functionality can go when it comes to practicality. In addition to those tasks, the following are among potential tasks to be implemented in the proposed application: Query on direction and distance; and also query on size of instances and structures.

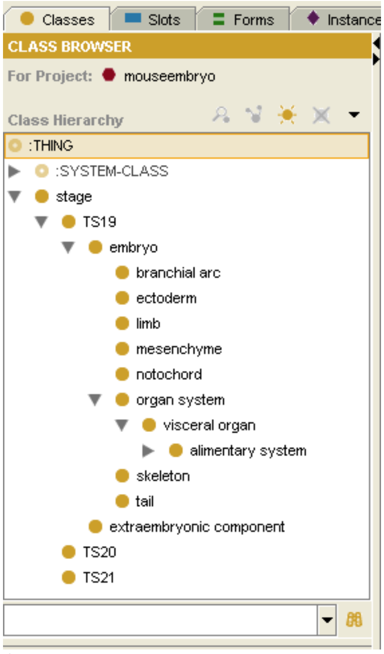


Fig. 11 Excerpt from the domain description ontology representing the class hierarchy

Name: adjacentRule

```
hasCoordinate(?part1, ?s1) ∧
hasCoordinate(?part2, ?s2) ∧
hasX(?s1, ?x1) ∧
hasY(?s1, ?y1) ∧
hasX(?s2, ?x2) ∧
hasY(?s2, ?y2) ∧
swrlb:subtract(?v1, ?x2, ?x1) ∧
swrlb:multiply(?m1, ?v1, ?v1) ∧
swrlb:subtract(?v2, ?y2, ?y1) ∧
swrlb:multiply(?m2, ?v2, ?v2) ∧
swrlb:add(?r, ?m2, ?m1) ∧
swrlm:sqrt(?m3, ?r) ∧
swrlb:subtract(?distance, ?m3, 1) ∧
swrlb:equal(0, ?distance)
 → adjacent(?part1, ?part2)
```

Fig. 12 Example of SWRL rule, edited with the SWRL plugin in Protégé

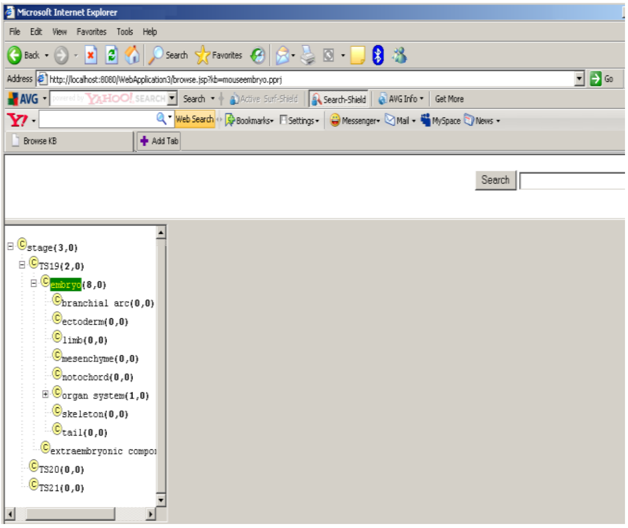


Fig. 13 Loading the OWL ontology in web browser

VI. CONCLUSIONS

Biomedical imaging informatics have become a crucial part of modern healthcare, clinical research, and basic biomedical sciences. Rapid improvement of imaging technology and advancement of imaging modalities in recent years have resulted in a significant increase in the quantity and quality of such images. Whether for epidemiological studies, educational uses, monitoring the clinical progress of a patient or translational science purposes, being able to integrate and compare such image-based data has developed into an increasingly critical component in the eHealth domain and life sciences. The work presented in this paper is rooted in the latter and uses examples from biomedical atlases. This paper explores the spatial relation-based approach to facilitate data integration across biomedical atlases.

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