The Challenges of Representing Anatomical Spatial Relations

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1. Introduction

Puget, Mejino, Detwiler, Franklin and Brinkley introduce their article "Spatial-symbolic Query Engine in Anatomy" [1] by posing a seemingly straightforward anatomy question: "what vital organs would potentially be impacted by a bullet wound to the abdomen?" More than 50 years ago, such a question may well have been included at the end of a yearlong anatomy course in an essay exam. Such an open-ended question would have been intended as an invitation to my fellow medical students and me to engage in thought experiments, requiring us to impose various constraints and specifications on such a broad question in order to pursue cogent spatial reasoning. Confronted with such a question, today's student would most likely turn to the computer. However, he or she would find it challenging, if not impossible, to construct a satisfactory answer. A survey of 100 on-line anatomy information resources [2] found that they were lacking in sufficient quality and depth for levels of learning beyond the memorization of structure names. Despite the growing emphasis on web-based "distance learning" during the intervening 10 years, today it would still be essentially impossible for a student to launch a query such as the question posed by the authors (hereafter the SQE team), let alone find satisfactory answers. The team implies that, by proposing the prototype of a spatial-symbolic query engine (SQE) as a proof of concept, they will, in the long run, make such a task more readily feasible.

After the paper was reviewed and accepted, the editor of *Methods of Information in Medicine* solicited comments from eight additional experts (hereafter commentators) in various fields of biomedical informatics and medical image computing. I am honored to have been invited to introduce the paper along with the experts' comments, all of which appear in the current issue. I do so as an anatomist, who has taught many generations of young health care professionals, ranging from nursing and medical students to surgical residents. During the last phase of my academic career this experience was enriched by new insights into the time-honored discipline of anatomy through stimulating and productive collaborations with investigators and graduate students in computer science, biomedical informatics and philosophy.

2. The Paper's Contributions

The authors' claims about the significance of the prototype SQE are realistic and rather modest compared to the potential significance several of the commentators perceive in the prototype SQE. The prototype translates location information obtained from an annotated 3D dataset into symbolic assertions, which can be integrated into an established computational ontology. The 3D dataset used was that of the *Visible Human* [3], and the ontology, the *Foundational Model of Anatomy* (FMA) [4]. The paper defines some spatial relations current in anatomical discourse and couples them with a method for defining query volumes in the image dataset. The team proposes a query formalism and processing methods for expressing and answering queries regarding spatial relationships among internal body parts. Such spatial query processing is implemented by the SQE. A web interface is also provided, enabling exploration of the computed spatial relationships by domain experts. Together these support evaluation and, in a longer term, may help build consensus on the definitions and representations of spatial relations between anatomical entities. The authors recognize that the evolving SQE in its current state may not qualify as an end-user application; rather, they propose it as a framework for the development of applications and the enhancement of he spatial information content of ontologies. The FMA is envisaged as the repository for such newly generated information.

The following remarks pertain to some of the desirable enhancements of the SQE suggested by the commentators and, perhaps more importantly, the envisaged challenges and benefits the continued development of the SQE could meet and realize. It is always a compliment for any work if its potential applications can be anticipated in several user domains beyond its own which, judging by the comments, is the case for this paper.

3. A Gold Standard of Anatomical Spatial Relations

Basing the development of the SQE on a 3D image dataset derived from a single individual is perceived as the main limitation of the work. Another is the difference between the evaluation results recorded by two domain experts. Most of the other comments follow from these observations. Underlying these perceptions – explicitly stated or not – is the need for a *gold standard* of anatomical spatial relations, which could serve as a reference for detecting and representing anatomical variations. The notion of a gold standard in anatomy invokes the distinction between canonical anatomy (a generalized mental image of the body described in anatomy textbooks and hard-copy atlases, and taught in anatomy courses), and instantiated anatomy (encountered in individual patients in clinical practice). Such a distinction is key to the context in which the FMA has been created [5]. The fact that the FMA has evolved into a widely used *reference ontology* for anatomical information called for by a variety of *application ontologies* and end-user programs, which are intended for assisting specific diagnostic and therapeutic tasks [e.g., 6–8], argues for the usefulness of a *canonical human*, not only in an ontological but also in a 3D graphical representation. I pose some questions relevant to this proposition.

4. Is a 3D Graphical Canonical Human Feasible?

The canonical human of the FMA is not the result of statistical averaging of anatomy for individuals of the species. Rather, the FMA's approach takes for granted the highly conserved nature of the morphogenetic processes that operate during prenatal and postnatal development. Provided that gene expression and other developmental processes proceed without interference, the result will be a fully formed, mature individual. Although such an idealized individual may only rarely or never exist in reality, its postulation is indispensable as a gold standard, or a universal reference. Anatomical and pathological variations in the structure of organisms, or that of their parts, and the relations among these parts, can be comprehended most readily through reference to such an idealized conceptualization: the *canonical human*. The canonical human of the FMA neglects to take into account the sequential morphologic and structural changes that distinguish stages of development, growth, aging and senescence. I venture to suggest, however, that the canonical human of the FMA could serve as a template reference for the creation of canonical humans at different phases of the life cycle, and also, as it has been used to a greater or lesser extent, for some other vertebrate species [9, 10].

Is it possible to create an atlas equivalent to a canonical human visualized in 3D? How could it be obtained and is there a need for it?

Several 3D datasets are now available from serially sectioned human cadavers, in which many anatomical entities have been segmented and annotated (e.g. [3, 11]). It is not clear, however, to what extent the size, shape and spatial relations have been distorted in these specimens as a result of the varying status of health at the time of death, the causes of death, and the post-mortem infusion of large amounts of preservatives and colored contrast media.

Were it ethically justifiable, could comprehensive datasets obtained from a male and a female individual of average body build and in a proven perfect state of health serve as a 3D graphical gold standard?

The commentators may have their own cogent reasons for not considering such an option. They advocate instead statistical approaches, which make use of advanced 3D visualization methods for clinical imaging. Their primary interest seems to be in individual variations of anatomy. Evidently, for the SQE to realize its potential in clinical imaging, it should represent ranges of variation in the query volumes it specifies in terms of qualitative anatomical coordinates.

5. What Is the Nature of Individual Anatomical Variation?

Anatomy education, textbooks and hard copy atlases pay little or no attention to variation, which is consistent with their mission. Variations in the body's structure assume importance, however, in fields such as clinical practice and industry that deal with individuals. Leaving aside space-occupying pathological entities that may cause significant changes in the shape and relations of otherwise normal anatomical structures, variations in the body's structure fall into different categories: anatomical variants and congenital abnormalities, as well as variations in the size and shape of whole individuals or of their selective body parts.

Anatomical variants and congenital abnormalities result from some infidelity in, or disruption of, the morphogenetic program. The distinction between them is fuzzy, depending on whether or not there is a resulting functional impairment. For example, a 13th pair of ribs in the lumbar region will be detected only as an incidental radiological finding. However, if the supernumerary rib is located in the neck, it may give rise to compression of neurovascular structures leading to functional impairment in the upper limb. Although the mechanism for generating these extra pairs of structures is likely to be quite similar, should one be regarded as an anatomical variant and the other a congenital abnormality? The author of an ontology may well have to make such a decision. Also, there is variation in the spatial relations of thoracic, abdominal and pelvic viscera not only in cases of curvatures of the spine, but also resulting from movements of the diaphragm and the degree of distension of the bladder or the pregnant uterus. Should a gold standard, ontological or graphical, account for such displacements?

The commentators, however, do not seem to be concerned with such variations; their primary focus of interest is person-to-person variations attendant on differences in gender, age and body size. Although they are of obvious importance in the construction of prostheses, for instance, such variations seem inconsequential to an anatomist. This assertion is by no means intended to belittle the focus in the discussion; rather it is meant to highlight the complexity of dealing with variations. Perhaps the need for addressing person-to-person variations is best illustrated by the call for refinements in the methods for defining a target volume for radiation therapy.

The needed information is most likely to be generated by advanced methods of 3D visualization and medical image computing. Statistically averaged anatomical representations, such as shape models, are already employed for improving segmentation and intraoperative cortical mapping of functional sites [see comments by Handels and 12]. Although they smooth out much anatomical detail of interest to anatomists, such statistical models also hold promise for capturing the range of variation in the extent of the image volumes in which a particular spatial relation holds between a query or target structure and its referent. This kind of information would be impossible to obtain through other means. Yet, once obtained by some method, ranges in the variation of the size, shape and spatial disposition of anatomical entities can be readily accommodated in ontologies such as the FMA.

There are multiple advantages of representing such information with the machinery of ontology. Although the apprehension of spatial relations among anatomical and pathological entities may be more intuitive from 3D data than from ontological assertions, discourse and records in clinical domains demand that such relations observed in images be expressed semantically using terminology that accommodates the different naming conventions of diverse fields. The facility exists in the FMA for associating image equivalents with their preferred terms as well as their synonyms [13]. Moreover, information pertaining to the spatial disposition of anatomical entities needs to be correlated with other structural relations better captured in an ontology than in a 3D visualization. These relations include parthood, containment, boundaries, attachments and continuities of cavitated and solid anatomical structures. Also, some anatomical entities defy visualization by current imaging modalities. An ontology can represent such structures and insert their graphically generated 3D models among the visualizable entities in concordance with appropriate relations defined by an ontology.

6. What Are the Challenges of Defining Anatomical Spatial Relations?

The definitions of anatomical spatial relations are ambiguous and more problematic than that of physical anatomical entities, a point noted for example by Pommert. Yet, a critical requirement for a gold standard is the elimination of ambiguity in the meaning of the terms that it employs as identifiers for the entities under the purview of its domain. Such semantic consistency is assured through principled definitions (14, 15) and the correlation of synonyms associated with the defined entities. The requirement applies equally to gold standards of text-based and image-based information resources. In order to allow evaluation of the validity of definitions, their authors must declare the principles and methods according to which they have constructed the definitions. Schulz's comments pertain to this point. I will deal in some detail with Schulz's reservations because of their importance in general and in particular for the current paper. Also, Schulz is a careful and critical thinker who has contributed extensively to ontological considerations of anatomical location, and is well positioned for criticizing the spatial definitions created for the SQE. First I establish the background with some general comments.

Anatomy texts intended for different user populations vary in the emphasis they place on spatial relations. Among those structured vocabularies and ontologies in the biomedical domain that include anatomical information, the FMA was the first to take account of structural and spatial relations other than *part_of* [16, 17]. Indeed, it was this work that sparked the motivation for the establishment of a high-level *Relation Ontology* [15] which, as well as encompassing domains other than anatomy, transcribed selected FMA definitions as axiomatic assertions. Currently the FMA includes a detailed ontology of structural relations in section 4.9 of [4], which distinguishes between a variety of location relations[a]. One of these relations, '*relative anatomical position*', asserts the relative position of a target entity to a referent entity. For example, the relative position of target structure esophagus *has_location_posterior_to* the referent structure heart. This relation may hold true in the same query volume for more than one target structure (e.g., vertebral column, in the current example). Of all spatial relations in the FMA, at present, '*relative anatomical position*' is the least adequately defined and instantiated. A motivation for the development of the SQE by the Structural Informatics Group was the development of semi-automated methods to relieve the burden of manually instantiating pair-wise relations among the vast number of spatially related anatomical entities. Although data entry with the use of SQE has not yet begun, the prototype SQE was submitted

[a] A similar ontology has been recently proposed by Coulter and Leopold [18].

for publication with the intent of stimulating interest in collaborative, online data entry. The input gleaned from the invited discussion comes as an unexpected bonus.

Schulz takes issue with the SQE's method for defining the query volume in which a particular '*relative anatomical position*' relation holds. The difference between him and the SQE team can be accounted for by the different assumptions each party makes. Schulz approaches the definition of the query volume from the point of view of an observer. Consequently the query volume would vary according to the distance of the observer from the query object (hereafter 'referent') and according to the perceived angle between the referent and target objects. My contention, along with that of the SQE team, is that in a reference ontology (e.g., FMA) or in a reference 3D dataset (e.g., by default, the Visible Human), the query volume for any anatomical entity should be invariant for any given relative anatomical position relation. We eliminate reference to any observer and any perceived angle between referent and target objects. We justify our assumptions based on the following considerations.

The first line or reasoning takes for granted the highly conserved nature of morphogenetic regulation. In a vertebrate organism location relations of its anatomical entities, including relative anatomical position, are constant, regardless of the orientation in 3D space of the organism itself or that of its observer. Anatomical relations are established during the process of gastrulation in the early embryo, as a result of the coordinated expression of groups of genes involved in morphogenesis. Cohorts of cells migrating through the primitive node (a morphogenetic organizer) spread out in different directions: those that form the notochord establish the organism's axis and thus determine the embryo's rostral, or cephalic pole (corresponding to the vertex), and the caudal pole (corresponding to the tip of the tail or the coccyx). The primitive node also influences which of the laterally migrating cells should spread out to the right or the left of the notochord, determining left and right sidedness. The body surface of the embryo overlying the notochord (presumptive vertebral column) specifies the dorsal aspect of the embryo; the surface overlying the developing heart and gut the ventral aspect. This highly conserved *Bauplan* establishes the foundation for virtual planes and qualitative coordinates which serve for conceptualizing the relative position of other developing entities that are likewise determined by coordinated gene expression.

These planes and coordinates, designated by time-honoured usage, are employed for the spatial subdivision of pre- and postnatal vertebrates. Sagittal planes parallel the one that transects the notochord longitudinally and also passes through the rostral and caudal poles of the embryo. Transverse planes, positioned at right angles to sagittal planes, divide the notochord and body into rostral and caudal portions; and coronal planes, at right angles to both sagittal and transverse planes, into dorsal and ventral portions.

Terms such as ventral and dorsal (equivalent in some anatomical usage to the terms anterior and posterior, respectively) are regarded in conventional anatomical discourse as location descriptors; hence the designation of the class these terms instantiate as 'qualitative anatomical coordinates'. In terms of the constraints of a principled ontology, however, they serve as qualifiers or attributes of some location relation. To help us disambiguate the current semantic inconsistencies, let us regard qualitative anatomical coordinates as vectors, each having an origin, directionality and target. A referent object serves as the origin of a vector, which ultimately intersects some point of the body surface. This point, as well as any other entity (anatomical, pathological or foreign) intersected by the vector is regarded as the target of the vector. Reversing the role of target and referent reverses the direction of the vector and accounts for the inverse of the relation. For example, in a vertebrate embryo, the target developing sternum *has_location_ventral_to* the referent developing heart; inversely, the target heart *has_location_dorsal_to* the referent sternum. The terms designating these coordinates are used not only for indicating directions, but also as adjectives to distinguish similar anatomical entities (e.g., the ventral pancreatic bud from the dorsal pancreatic bud; right humerus from left humerus). Similarly, these terms also serve for distinguishing different surfaces and parts of an anatomical structure.

We now proceed to a thought experiment and equate qualitative anatomical coordinates (vectors) with parallel rays in a beam of light – such as those emanating from the sun – that run at right angles to one of the three kinds of virtual cardinal planes. Then, for example, the rays that intersect a coronal plane can be defined as ventral and dorsal coordinates respectively, depending on whether the beam illuminates the dorsal or ventral body surface of a vertebrate embryo. The other coordinates can similarly be defined with reference to virtual planes other than coronal.

Cardinal virtual planes and qualitative coordinates, most readily defined in an embryo, are renamed in postnatal vertebrate anatomy. The inconsistency alluded to above is introduced largely by this naming convention. For example, in human anatomy the equivalent term for ventral becomes anterior (meaning toward the front) whereas the same vector in quadrupeds points not ventrally but toward the head (vertex), as in the embryo. The inverse term 'posterior' corresponds to 'dorsal' in bipeds, but to 'caudal' in quadrupeds. Thus the assertion sternum *has_location_anterior_to* heart is valid in human beings but not in a rat or a mouse. Such inconsistencies in terminology impact on the determination of phylogenetic equivalents of anatomical structures in humans and other vertebrates (e.g. [9]), which can be of concern when drawing conclusions from experimental models of human disease. Also, because of these inconsistencies, the formulation of ontologically sound definitions for these qualitative coordinates becomes particularly challenging.

The second line of reasoning extends our thought experiment more directly to Schulz's concerns about the SQE team's definition of a query volume. We adopt the notion of shadow volume, introduced in computer graphics to denote a technique used for adding shadows to a rendered scene [19]. By shadow volume we mean the umbra of the shadow cast by an anatomical structure illuminated by imaginary parallel rays of light, under the same conditions described above. (The umbra is that part of the shadow space which receives no light from the source.) We assume all anatomical entities intercepted by the beam of light to be transparent, except the referent object. Then the shadow volume of the referent will be bounded by the shadowed surface of the referent, the area of the body surface intercepted by the umbra, and the interface between the umbra and the illuminated region around the umbra. We can then declare that any of the parts, or the whole, of a 3D anatomical entity that are encompassed within (in other words, overlapped by) the umbra be regarded as having a 'relative anatomical position anterior_to the referent, if the beam of light illuminates the posterior body surface. (Posterior body surface can be defined as the subdivision of the body surface that overlies the vertebral column and its associated structures and is illuminated by parallel rays of light that intercept a coronal plane.) Since '*has_location*' is an ontological ancestor of the '*relative anatomical position*' relation cl*ass, the assertion* '*has_location_anterior_to*', or even '*anterior_to*' are equally valid, and may be preferred by those users who have no need for expressing the relation with maximum semantic specificity. However, such semantic specificity is a requirement in a reference ontology. Other relative location relations can be readily defined by orienting the light rays perpendicular to any of the other cardinal virtual planes, or to any oblique plane intermediate between them.

With respect to Schulz's reservation, we can note that viewed in any plane, the boundaries between the umbra cast by a referent and the surrounding illuminated (or transparent) region will be parallel. Definitions will be introduced in the FMA for the classes and ontological descendants of '*qualitative anatomical coordinate*' and '*relative anatomical position*' in accord with the above considerations.

It is perhaps pertinent to note here that the SQE team sets a threshold for including an entity in a particular query volume. This facility may be useful for certain applications. However, as proposed in the foregoing, an ontology or a 3D dataset that serves as a general reference should include the target entity in the set of entities related to the referent if any part of that target entity falls within its shadow volume. After all, although the resulting injury may be of different degrees of severity, the heart will be injured regardless of whether 1% or 50 % of its volume has been damaged by a projectile. Also, the discrepancy in the raters' scoring may be largely attributed to the predilection of anatomists to think in terms of whole anatomical entities when it comes to satisfying a particular spatial relation. Experts though they may be, they may find it difficult to reason with percentages in contexts, such as the evaluation of the SQE.

7. Concluding Remarks

The significance of a scientific publication may be judged not only by the discoveries it reports, but also by the perspectives it opens up for shedding new light on, or improving, existing knowledge. The comments by the invited experts along with my own remarks suggest that the paper by Puget et al. [1] satisfies the latter criterion.

In the Discussion following this editorial, Kulikowski relates the SQE team's contributions to the work pursued by the Structural Informatics Group at the University of Washington over more than three decades. This work has been motivated since the inception of the Group by the hypothesis that biological structure provides an organizational framework for the computable representation of all biomedical entities [20, 21], since anatomical structures are the independent continuants on which, in an ontological context, physiological and pathological processes depend [22]. With the Digital Anatomist atlases [23] the Group has pioneered the rendering, in high fidelity 3D, of anatomical structures and regions, which motivated the National Library of Medicine's *Visible Human* project [3], as well as the prototype of the FMA ontology [24] as the anatomical enhancement of NLM's Unified Medical Language System.

The SQE prototype is a significant milestone in the pursuit of the Group's motivating hypothesis because, as Blake points out, it provides a so-called *mashup* for linking up independent and public domain spatial (image-based) and symbolic databases. It also enables access to these novel *knowledge spaces* over a web-service through which such 'spaces' can be enriched as well as queried. In the broadest sense, Moura envisages in the Discussion the potential contributions the SQE can make in "eHealth" by starting out with a seemingly simple problem, and then revealing how the unexpectedly complex solution can be approached by an innovative strategy.

Having been closely associated with the Structural Informatics Group and being aware of the genesis of the SQE, I would like to highlight the benefits of handing a thorny problem to a group of budding investigators and supporting them in coming up with unanticipated solutions. After decades of promoting spatial reasoning by generations of students and trainees in the health profession, the SQE initiative gave me the impetus to rethink and clarify the ontology of anatomical spatial relations, which I discuss in this editorial.

At a time when the teaching of anatomical reasoning through student-teacher interactions is being replaced by independent learning through interacting with a computer, it is critical that online educational resources go beyond fostering rote memorization and promote reasoning. The SQE could be the first step toward such an objective. Indeed, as a result of its foreseeable evolution, the SQE may promote the interactive construction of a 3D anatomical scene, a reverse exercise to dissection. Such an exercise could make use of a knowledge space that can access realistic 3D models of anatomical entities and enable corrections in faulty reasoning about anatomical relations supported by computational ontologies within the space. Students learning anatomy with the aid of such resources should have no problem reasoning their way along the track of a bullet passing through the abdomen.

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