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Ontological labels for automated location of anatomical shape differences

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ABSTRACT

A method for automated location of shape differences in diseased anatomical structures via high resolution biomedical atlases annotated with labels from formal ontologies is described. In particular, a high resolution magnetic resonance image of the myocardium of the human left ventricle was segmented and annotated with structural terms from an extracted subset of the Foundational Model of Anatomy ontology. The atlas was registered to the end systole template of a previous study of left ventricular remodeling in cardiomyopathy using a diffeomorphic registration algorithm. The previous study used thresholding and visual inspection to locate a region of statistical significance which distinguished patients with ischemic cardiomyopathy from those with nonischemic cardiomyopathy. Using semantic technologies and the deformed annotated atlas, this location was more precisely found. Although this study used only a cardiac atlas, it provides a proof-of-concept that ontologically labeled biomedical atlases of any anatomical structure can be used to automate location-based inferences.

1. Introduction

The past several years have seen tremendous advances in cardiovascular imaging [1,2]. Multimodality imaging has permitted characterizing myocardial shape and function in different disease states. Integrating information from these modalities can potentially enhance understanding of cardiovascular morphological and functional response to pathology. As an example, high resolution computed tomography coronary angiography provides detailed information about the vessel anatomy that can be combined with the myocardial perfusion positron emission tomography (PET) or single-photon emission computed tomography (SPECT) scans to evaluate regional blood flow. Integration of data across multiple imaging modalities would benefit from methods that can provide annotations using a consistent nomenclature, as it provides a systematic tool to share information among specialists from different disciplines.

The ability to describe the anatomical structures and their related functions in a formalized manner is critical for sharing data and integrating information across studies. Development of standard anatomical and functional terms and their relationships in a formalized language has been the focus of biomedical ontology. Ontology, traditionally the subfield of philosophy focused with questions about the nature of being, now refers to a mode of formal knowledge representation in the informatics world. In formal ontologies, knowledge about a specific domain can be given to a machine in subject–predicate–object triples so that the machine may perform automated inferences using these statements. Because ontology engineering often requires a well-known and stable body of knowledge to be useful, ontologies have found adoption of varying degrees in a variety of biomedical domains. Ontologies have been designed to describe genes [3], diseases [4], proteins [5], and anatomy [6], among many others. Additionally, an open-access repository of biomedical ontologies called BioPortal [7] has been established by The National Center for Biomedical Ontology [8].

Annotation of medical imaging data is a challenging task as the anatomical information is represented indirectly as image data. Images must be interpreted either manually or automatically to associate image regions with anatomy or physiology. This

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segmentation and labeling process can be done per-subject or using a pre-labeled atlas [9,10]. In the atlas-based approach, annotated structures are mapped to a specific study via registration. For instance, in a study of brain activation in schizophrenic subjects (SZs) and healthy volunteers (HVs), ontological labels from the Foundational Model of Anatomy (FMA) were used to annotate neuroimages [9]. Subject images were first coarsely registered to the Talairach atlas [11]. After performing statistical analyses on regions of brain activation, the maximal voxel in each significant cluster was labeled with the appropriate anatomical term from the FMA. These labels were then used to answer questions like, 'Which parts of the precentral gyrus are active in SZ and HV in these data?'. This and other related work showed how such labels can be used to query the results of neuroimaging studies. Similar approaches can be adapted to annotate imaging data of structures other than the brain in order to perform the same kind of queries.

Despite the healthcare impact of cardiovascular disorders, there have not been many reported studies regarding the annotation of cardiac imaging data. In one study, a diagrammatic representation of congenital heart defects was developed [12]. However, this model is limited to a particular disease state and does not address the integration of information across different studies and imaging modalities. The present study demonstrates a general method for using ontological labels to locate regions of statistical significance in any (including non-brain) anatomical structure. In particular, an annotated atlas of the left ventricle of the human heart was created and combined with the Large Deformation Diffeomorphic Metric Mapping (LDDMM) algorithm [13] to generate diffeomorphic (smooth, invertible, one-to-one, differentiable) transformations which are thought to be superior to other registration techniques [14,15]. Such diffeomorphisms preserve certain topological features like smoothness, connectedness and disjointedness which ensure that all anatomical substructures and many important features are faithfully transferred from one image to the other [16]. For instance, in a segmented image such as an anatomical atlas, all segments are mapped onto the corresponding locations in the target image.

In particular, this study extends the work by Ardekani et al. [17] which used LDDMM and statistical analyses to characterize left ventricular remodeling in the hearts of patients with ischemic cardiomyopathy (ICM) versus nonischemic cardiomyopathy (NICM). The study revealed that nonischemic population had, on average, larger regional myocardial volume relative to the ischemic population. Creating a reference atlas of the left ventricle (LV) with ontological labels provides both a complete automation of the identification of the region of significant tissue volume expansion and a standard frame of reference for future research. More generally, using LDDMM with ontologically labeled biomedical images is shown to provide a fruitful way to automatically locate regions of statistical significance in any anatomical structure.

2. Materials and methods

2.1. Computational cardiac anatomy

Ardekani et al. [17] analyzed *in vivo* multi-detector computed tomography (MDCT) images of 25 human subjects at both end systole (ES) and end diastole (ED) phases of the cardiac cycle. Of these 25 subjects, 12 had nonischemic cardiomyopathy (NICM) and 13 had ischemic cardiomyopathy (ICM). An average template image at each of ES and ED was generated and then mapped using LDDMM to each target image. Although other results were shown in this previous study, the focus is on the voxel-based Jacobian analysis done using a non-parametric randomized permutation test on all 25 subjects. This Jacobian map encodes local volume difference; a value of 1 indicates none, a value greater than 1 indicates expansion, and a value less than 1 indicates compression. The present study used both a binary version of the ES template and this same template with corrected *p* values as intensities.

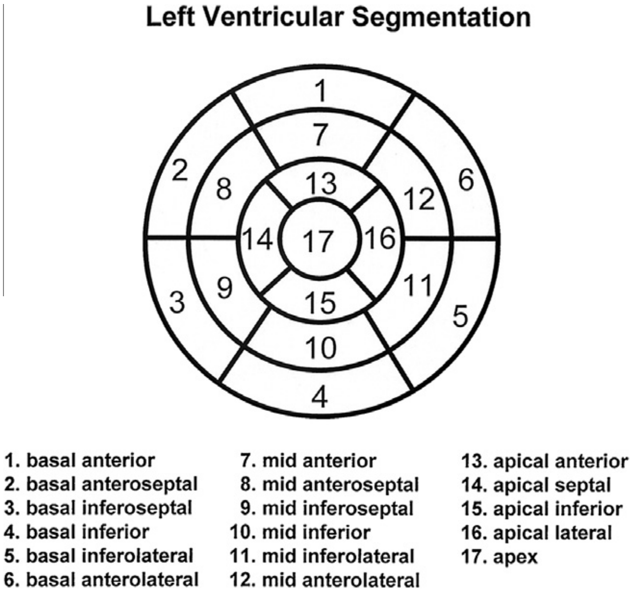

Fig. 1. The 17 myocardial parcellation of the left ventricle recommended by the American Heart Association [22] which was used to segment the atlas.

2.2. Ontology extraction

The Foundational Model of Anatomy (FMA) [6] served as our reference ontology. First, the subclass hierarchy of the term `Region_of_myocardium` was extracted from the full ontology. This extraction was performed using the Jena[1] implementation of vSPARQL [18–20], an extension to the ontology query langauge SPARQL that allows for recursive and sub-queries. In addition to this extraction, a complete set of terms pertaining to the cardiovascular system in the FMA and other biomedical ontologies has been identified for future extraction.

2.3. Atlas generation

The construction of the imaging atlas for this study began with an *ex vivo* magnetic resonance image (MRI) of a human heart's myocardium obtained from the Center for Cardiovascular Bioinformatics and Modeling (CCBM) at Johns Hopkins University (JHU). The imaging protocol was the same as for the canine hearts as detailed in [21].[2]

The image data was converted to ANALYZE7.5 format and hand segmented by a trained clinician according to the 17 parcellation recommendation of the American Heart Association (AHA) [22]. In the AHA parcellation, the left ventricle is divided along the long axis into apical, mid, and basal regions as well as an apex. The apical region is divided along the short axis into four regions, while each of the mid and basal regions is divided into six regions. Fig. 1 shows a schematic of this segmentation.

The hand segmented binary masks were recombined into a single label map image volume, with intensities at each voxel

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[1] http://jena.sourceforge.net.

[2] Although the data has not been published, the file `Null_Intensity.mat` at http://www.ccbm.jhu.edu/research/canine_heart_1_060904_normal.php contains the human heart geometry data.