

Introduction

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 widespread adoption in biomedical domains. While uses of biomedical ontologies run from experimental setup description to psychiatric diagnosis, this project uses ontologies to annotate biomedical images in order to use these images to automate diagnosis.

In particular, we used ontologies in conjunction with the tools of computational anatomy to provide a method for automatically diagnosing left ventricular remodeling, a key biomarker for heart failure. In this paradigm (see [3]), anatomical variability is understood by studying diffeomorphisms (smooth, invertible, one-to-one, differentiable) mapping anatomical manifolds to one another. Formally, anatomy is modelled as the quadruple $(\Omega, \mathcal{G}, \mathcal{I}, \mathcal{P})$, where Ω is the background space (i.e. subsets of \mathbb{R}^3), \mathcal{G} is a group of diffeomorphisms on Ω , \mathcal{I} is the orbit of a template I_0 under \mathcal{G} , and \mathcal{P} is a family of probability measures on \mathcal{G} . Geodesic paths, $\phi_t \in \mathcal{G}$ for $t \in [0, 1]$, are used to evolve a template according to $I_0 \circ \phi_t^{-1}$, and a mapping to a target I_1 is defined when $I_1 = I_0 \circ \phi_1^{-1}$. The Large Deformation Diffeomorphic Metric Mapping algorithm (LDDMM; see [4] for details and further references) generates such diffeomorphisms between two images.

This project builds on a project carried out by Ardekani et al. [1] which used LDDMM and statistical analyses to diagnose left ventricular remodeling in patients with ischemic cardiomyopathy (ICM) versus nonischemic cardiomyopathy (NICM). In particular, by creating a reference atlas of the left ventricle (LV) with ontological labels, we both provide a complete automation of the diagnosis process and a standard frame of reference for future research.

Methods

Image Acquisition. The image that was segmented into our atlas (see below) is a 3D MRI image from the JHU Center for Cardiovascular Bioinformatics and Modeling (CCBM). For the original LV study [1], 25 patients were scanned using CT and split into a training and a testing set.

Template Generation and Shape Analysis. From the training set, end systole (ES) and end diastole (ED) (i.e. beginning and end of cardiac cycle) images of each patient were selected and an average template for both ES and ED was generated. Using LDDMM, these templates were mapped to the ES and ED image of each of the training patients. The Jacobian map, which encodes local volume expansion or contraction, was calculated at the voxel level. A non-parametric randomized permutation test was performed on all 25 subjects at both ES and ED and p values were corrected using family wise error method.

Significant tissue volume expansion was found in the mid anterior region in the NICM group when compared to ICM at ES. This region of statistically significant tissue volume expansion is shown superimposed on the averaged ES template in the figure below.

Ontology Extraction. We used the foundational model of anatomy (FMA) [5] as our reference ontology. Using vSPARQL [6]—an extension to the

standard RDF query language SPARQL which allows for recursive and sub-queries—we extracted all the information from the subclass hierarchy surround the term `Region_of_myocardium`. A complete set of terms pertaining to the cardiovascular system in the FMA has been identified for extraction along with relevant terms in other biomedical ontologies.

Atlas Generation. The CCBM image was hand segmented by an anatomically savvy clinician according to the 17 parcellation recommendation of the American Heart Association [2]. The hand segmented binary masks were recombined into one image, with intensities at each voxel corresponding to 10 times the zone number for the particular region of myocardium. We stored the atlas as a NIFTI image with intent code 1002 (i.e. label map). The header field `aux_file` points to a text file that maps each intensity to the appropriate term in the FMA (a sample line being “10 http://sig.biostr.washington.edu/fma3.0#Myocardial_zone_1”).

Mapping. This atlas was first coarsely aligned with the ES template using FSL’s affine registration tool FLIRT. Then a four-stage cascading LDDMM mapping was used to diffeomorphically register the atlas to the template as depicted below. Because diffeomorphisms send submanifolds to submanifolds, the segmented regions of myocardium in the atlas are sent to the corresponding regions on the ES template.

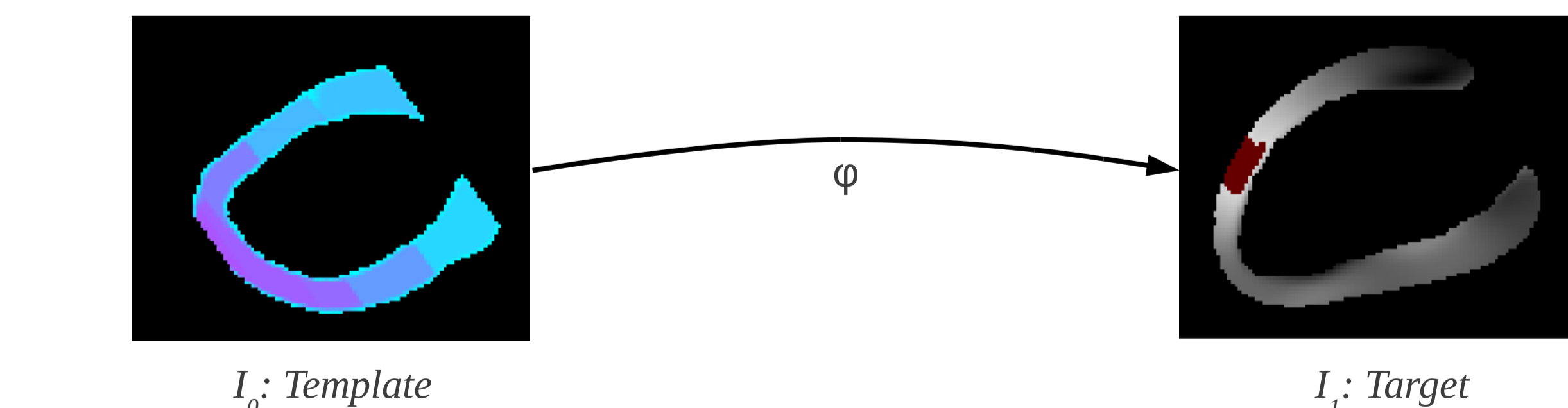


Figure: We mapped an ontologically labeled atlas onto the ES average template, shown here on the right with the region of significant tissue volume expansion colored.

Querying. Once we mapped the atlas onto the averaged ES template, we used the ontological labels in the atlas to ask three (of many possible) questions: what regions of myocardium are annotated in the atlas? what was the average T value of the Jacobian map per region of myocardium? in which region was significant tissue volume expansion observed? This last question represents the key to completely automating the diagnosis process in this particular case.

Results

Q. What regions of myocardium are annotated in this atlas?

A. Myocardial_zone_1, ..., Myocardial_zone_17

Q. What is the average T value for each region of myocardium?

Region	Average T value
Myocardial_zone_13	3.401515481
Myocardial_zone_14	2.8456438
Myocardial_zone_7	1.7604088
⋮	⋮

Table: Average T value by Region

Q. Where is the region of statistically significant tissue volume expansion located?

Region	# Voxels
Myocardial_zone_13	696
Myocardial_zone_10	3
Myocardial_zone_9	2
Myocardial_zone_7	1
⋮	⋮

Table: Number of ROI Voxels per Region of Myocardium

A. Myocardial_zone_13 = apical anterior



Figure: Because diffeomorphisms preserve submanifolds, the atlas registered to the ES template can be used to locate the region of significant tissue volume expansion.

Discussion

Our results show that biomedical atlases with ontological labels can reliably be used in conjunction with shape analysis algorithms like LDDMM to automatically locate regions of shape difference in anatomical structures. Although we focused on remodeling of the left ventricle, this project provides a proof-of-concept because the methods are general and could easily be adapted to other anatomical structures.

Mid versus apical anterior. As mentioned above, Ardekani et al. [1] concluded that the region of interest was in the mid anterior while our ontological methods concluded that this was the apical anterior. One first thinks to ask: which region is it in fact? But this question is misguided. The original placement of the region of interest was done by visual inspection. What we have done in this project is provided a method and standard frame of reference from which to make such inferences to location. In one sense, neither answer is right; but our answer is “more right” because the same methods we used can be used in other experiments.

Further work. There are many dimensions along which this project can be extended. It should be possible to perform a fuller ontology extraction, including also terms from more ontologies than just the FMA (i.e. Radiology Lexicon). This fuller extraction will be used to ask more meaningful questions in an automated manner. It will also help to engineer an ontology for describing the meta-data generated by LDDMM. Most importantly, the pipeline used in this project can be integrated into software like Slicer3D which has some of the infrastructure in place. This would allow clinicians to take images, send them off to a computational pipeline, and receive a diagnosis when the work was done.

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