

Multi-atlas Approaches for Image Segmentation across Modality, Species and Application Area

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Abstract

This paper introduces multi-atlas segmentation (MAS) methods, including considerations for reference library generation, image registration algorithms, and voxel voting strategies. MAS has the flexibility to achieve high segmentation accuracy, even in the presence of pathology and anatomical variation. It has become one of the most widely-used and successful segmentation techniques and Invicro's unique implementation is utilized across a wide variety of therapeutic area and applications. Several case studies are presented, spanning different application areas, modalities, and species. Case study examples include magnetic resonance imaging (MRI) for human brain region volume estimation, ultrasound for mouse cardio-physiology, computed tomography (CT) for monitoring tooth development in non-human primates, and whole organ segmentation across multiple species. The case studies describe how the segmentation approaches strengthen image quantification in support of studies of neurodegeneration, radiation dosimetry, cardiac function, and musculoskeletal development. Furthermore, this approach significantly improves speed and reliability of organ segmentation compared to traditional manual delineation approaches.

1 Introduction

Volumetric measurements derived from non-invasive medical imaging data provide valuable biomarkers for drug discovery and development. While human observers can segment regions-of-interest from an individual scan using manual approaches, this process is slow and prone to inter- and intra-observer variability. Given the size of many clinical and preclinical studies, semi-automated segmentation approaches are necessary to match research timelines and minimize costs. Additionally, one of the largest challenges facing machine-learning and artificial intelligence tasks is the ability to efficiently and accurately generate labels (identify anatomical structures) for pre-existing and new data. Tools that are capable of such labeling in 2D and 3D data sets across a variety of anatomical structures and imaging modalities are indispensable for the downstream generation of features utilized in machine learning pipelines.

A MAS tool is presented to accurately and reproducibly segment image data. MAS methods utilize image registration techniques to map a population of reference subjects and their associated subject-specific region segmentations to a test subject. The tool leverages linear and non-linear registrations of a reference library of gold-standard segmentations to a test dataset, building a probabilistic atlas that is mapped to a determined region of interest (ROI) [1,2].

2 Methods

The following describes the steps utilized to implement a MAS routine. The majority of the described steps are general to the MAS technique while certain deployment details are specific to Invicro's implementation. The Invicro MAS routine has been developed, evaluated and applied in a uniquely diverse collection of data that spans imaging modalities, species, organ systems and resolution levels.

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2.1 Generation of reference library

Reference images, i.e. labeled training images, form the foundation of MAS algorithms [3]. They are obtained by selecting a sample data set from a representative study population, usually a few tens of data sets. To construct the reference library from this sample data set, training images are manually segmented by a domain-specific expert who relies on an interactive visualization software. Invicro's implementation uses Invicro's VivoQuant™ for manual labeling as it has been developed with a variety of 2D and 3D region generation tools to aid this task. Representative data and gold standard segmentations are stored in an accessible data storage repository to enable downstream processing. Invicro's iPACS® data management tool is used internally for this task as it is capable of supporting multiple data formats and is directly linked to the VivoQuant, enabling ease of data and region access as well as segmentation execution.

2.2 Registration

Generally, MAS routines utilize a sequence of image registration steps to map reference library data and segmentations to a test data set. Invicro's MAS implementation utilizes a series of linear and nonlinear geometric transformations to map a reference library into the space of a new and previously unseen data set. A combination of rigid and affine transformations is computed, first, to generate a bounding box specific to each target ROI. Invicro MAS then efficiently refines the accuracy of the mapping within this bounding box by using deformable registration. The non-linear registration is performed using a high dimensional Symmetric Normalized (SyN) registration [4], or a fast-symmetric demons deformable registration [5]. The optimal choice of algorithm depends on the biomedical application, its goal, and operational constraints, such as available computational resources, desired accuracy, and restrictions on time [3]. Future work will accelerate these procedures through the application of deep learning.

2.3 Label fusion

The final step of general MAS methodologies is the combination of mapped reference segmentations into a final region segmentation, associated with the test data set. In the Invicro implementation, once registration of all the reference images to the subject space is completed, the resulting spatial transform from a subset of the best-registered datasets, according to a registration quality metric, are used to map

the corresponding labels to the coordinates of the input image. The propagated labels are combined using a label fusion algorithm [6, 7]. The simplest fusion method is to average the propagated labels to form a probability map and to threshold this map at a fixed cutoff to generate the final ROI in the subject space. More sophisticated label fusion approaches are commonly used, particularly maximum likelihood-based methods which will be implemented in the future [6, 7].

Fig. 1 illustrates the workflow by way of an example application in lung MRI.

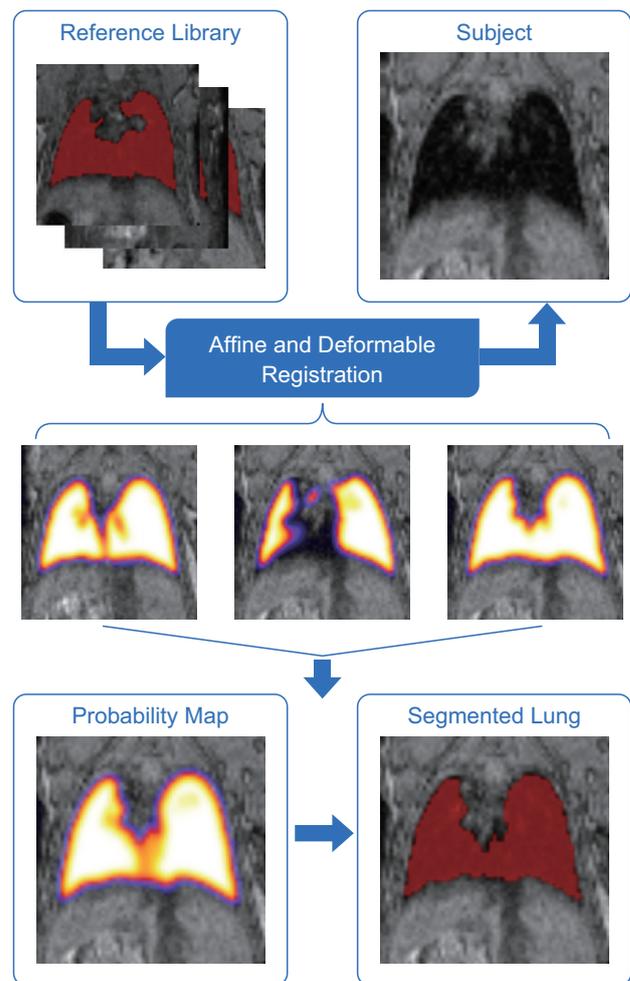


Fig. 1 Workflow for application of MAS tool in lung MRI. Images generated using VivoQuant™.

3 Applications

The MAS methods are used across a wide range of applications. Several case studies are presented below that describe how the specific Invicro MAS segmentation approach strengthens quantitative image estimates in support of studies of neurodegeneration, radiation dosimetry, cardiac function, and musculo-skeletal development.

3.1 Rhesus Teeth

A multi-resolution MAS-based pipeline was developed for tooth segmentation in CT images of rhesus monkeys. The four teeth that were segmented include the left incisor, the left canine, and two molars on the left side of the subject. Manually segmented ROIs for each of the four regions were created for twelve subjects and used as the reference library. Secondary reference libraries were also created for each individual tooth at a higher resolution but limited to a small region extracted around each tooth. An input image was evaluated with the MAS tool at low resolution (0.5 mm isotropic voxels) to detect the approximate locations of each of the teeth. The individual teeth were extracted from the original image at full resolution (0.1 mm isotropic voxels). The MAS tool was run again on each of the extracted teeth at full resolution to determine the final segmentation for each tooth. Fig. 2 shows an example pipeline for a single tooth (incisor) from input image to segmentation.

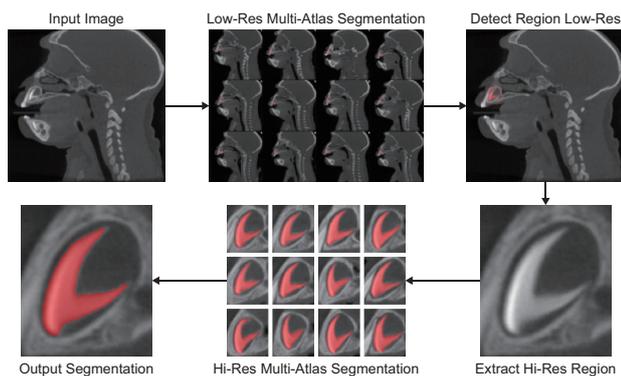


Fig. 2 Pipeline of MAS-Based Rhesus Tooth segmentation.

Leave-one-out validation was implemented using each of the data sets in the reference library. The performance metrics calculated were the Dice coefficient, Jaccard index, accuracy and precision of the output region against the gold-standard hand segmented ROI. The metrics were used to validate that the tool was performing correctly and to aid the optimization of settings. Dice coefficient overlap between gold standard segmentation and tool segmentation was 0.94 ± 0.02 for the canine, 0.96 ± 0.01 for the incisor, 0.96 ± 0.01 for the first molar, and 0.95 ± 0.02 for the second molar (Mean \pm SD).

3.2 Brain Volumetric

MRI-derived hippocampal and ventricular volumes are widely used as key biomarkers as well as to aid the quantitative analysis of amyloid/tau PET scans for normal aging and Alzheimer's Disease (AD). Here

we present an example of the Invicro MAS tool which is implemented in Invicro's VivoQuant™ software platform for fully automated hippocampus, ventricle and whole brain segmentation [8]. The performance of MAS on these data is evaluated against manual tracing and FreeSurfer (a standard software in the field of human brain mapping for automated volumetric of T1-weighted neuroimaging [9]).

Preprocessing steps include denoising, bias field correction, anterior commissure/posterior commissure alignment [10,11], and intensity normalization. Labeled MRIs (reference library) were affinely-registered to target images and a bounding box was generated around each ROI. Regions within the bounding box of the reference MRIs were warped to the target image using deformable registration. The warped labels corresponding to the best fourteen reference MRIs are fused to produce example output as shown in Fig. 3.



Fig. 3 Example outputs from VivoQuant™-MAS tool.

Automated segmentation was compared with manual segmentation for the hippocampus, which is the most challenging region in the data set. The Dice index between VivoQuant™-MAS derived segmentation and manual tracings is 0.81 ± 0.05 and 0.82 ± 0.05 for left and right hippocampus.

Normal aging and disease progression-related reduction in hippocampus and whole-brain volume in tandem with increase in ventricle volume is observed. Using the VivoQuant™-deployed MAS method, the AD group exhibited a greater atrophy of a) left hippocampus relative to MCI, LMCI and Normal groups and b) right hippocampus relative to MCI and Normal groups. In contrast with another widely used segmentation software, only the comparison of left hippocampus atrophy in AD and Normal groups reached statistical significance, suggesting that Invicro's segmentation strategy improved power in distinguishing atrophy rates between subjects from different disease populations (Fig. 4).

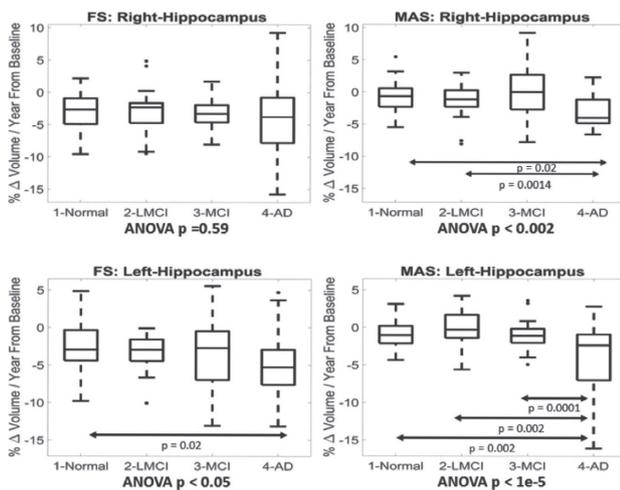


Fig. 4 Atrophy rate: FreeSurfer v.s. VivoQuant™-MAS.

VivoQuant™-MAS, a fully automated segmentation tool, achieved high overlap with the EADC-ADNI validation dataset and performed favorably relative to FreeSurfer in sensitively quantifying regional brain volume changes. VivoQuant™-MAS has been deployed in a CFR21-Part11 compliant manner to support clinical trials.

3.3 Ultrasound Echocardiography

Echocardiography is a widely used and clinically translatable imaging modality for the evaluation of myocardial structure and function in preclinical drug discovery and development. The objective of this study was to develop a robust analysis workflow for semi-automated segmentation of left ventricle (LV)

ultrasound mice images. This was done using Invicro's VivoQuant™ MAS tool to automate the otherwise lengthy manual image analysis and reduce intra- and inter-operator variability.

Following the manual selection of a diastole and systole frame, the reference library images (containing 25 manually segmented subjects) were registered to the two selected frames respectively. The subjects were affinely-registered with normalized mutual information (NMI) as the objective function. Following registration, the labels of the five registrations with the highest NMI were mapped and averaged to create a probability map that was then thresholded to generate the final segmentation used for LV analysis.

The MAS approach was tested and validated on three different data sets (1 control and 2 disease mouse models, see Fig. 5) for a total of 90 subjects ($n=30/\text{group}$). Dice coefficients from comparisons of semi-automated and manual segmentations ranged from 0.85–0.98 with an average of 0.93 ± 0.03 . The approach reduced user analysis time by approximately half in comparison to manual segmentation.

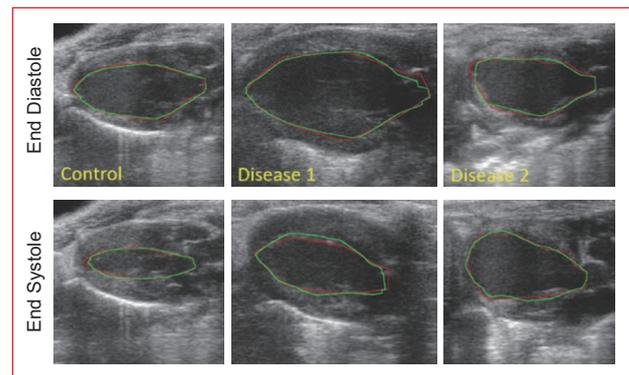


Fig. 5 Comparison between manual (red) and automatic (green) segmentations of selected diastole and systole frames.

3.4 Whole-Body Segmentation

The most widely used application of MAS techniques is in regional brain segmentation of structural MRI data. In brain segmentation, the skull provides a natural boundary that aids in registration. Extension of these techniques to segmentation of organs outside of the brain introduces complexity, owing to the lack of rigidity of the body in the vicinity of these regions.

To achieve success in this more complex task, a few criteria are required in algorithm development. The identification of the reference library is critical and population demographics must be considered to ensure that the variability among subjects is well represented. As a result, the required reference library is large and fast initial screening of best matched

reference library data sets is critical to processing in a reasonable amount of time. Additional preprocessing steps are utilized to harmonize anatomical orientation and field of view. Finally, a sophisticated optimizer that is particularly robust to parameter settings is utilized to improve whole body image registration.

This methodology has been utilized for both whole body CT and MRI data. One of the primary applications for this whole-body segmentation approach has been in dosimetry studies in rats, non-human primates, and humans where radiation dosimetry estimates require whole organ estimates of uptake. This step is often the most time consuming in the radiation dosimetry analysis process. MAS enables automated segmentation of brain, liver, lungs, heart, and kidneys, requiring minimal manual intervention. See Fig. 6 for an example of an automated CT segmentation of heart, lung, liver, and kidneys.

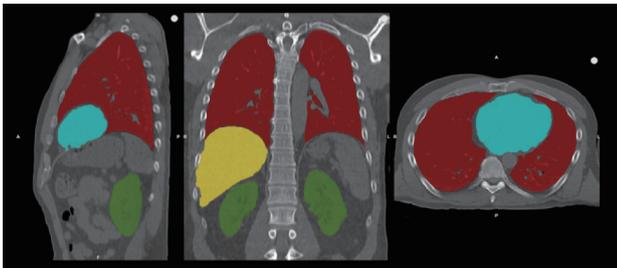


Fig. 6 Example whole organ segmentation of clinical CT data. Grayscale is the CT data. Red is lung, cyan is heart, yellow is liver, and green is kidneys.

4 Conclusions

In vivo's MAS techniques are powerful and general, enabling automated segmentation across multiple modalities, species, and therapeutic areas. By utilizing these tools in 2D & 3D datasets to segment a large array of anatomical structures, labels are automatically and accurately generated for large sets of data, resulting in measurable time savings and decreased region variability. Features, such as those used in radiomics methods, may then be automatically extracted from the regions, unlocking many machine learning options. Additionally, these labeled data can become valuable source data for deep learning techniques. Given the large amount of pre-existing data from many preclinical and clinical imaging trials as well as the continued growth of imaging, these techniques are of paramount importance to enable streamlined and accurate analysis workflows that do not rely on large amounts of human resource to achieve their goals.

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