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Atlas-based liver segmentation for nonhuman primate research

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Abstract

Purpose—Certain viral infectious diseases cause systemic damage and the liver is an important organ affected directly by the virus and/or the hosts' response to the virus. Medical imaging indicates that the liver damage is heterogenous, therefore quantification of these changes requires analysis of the entire organ. Delineating the liver in preclinical imaging studies is a time consuming and difficult task that would benefit from automated liver segmentation.

Methods—A nonhuman primate atlas-based liver segmentation method was developed to support quantitative image analysis of preclinical research. A set of 82 computed tomography (CT) scans of nonhuman primates with associated manual contours delineating the liver was generated from normal and abnormal livers. The proposed technique uses rigid and deformable registrations, a majority vote algorithm, and image post-processing operations to automate the liver segmentation

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Declarations

Conflict of interest The authors (Jeffrey Solomon, Nina Aiosa, Dara Bradley, Marcelo Castro, Syed Reza, Christopher Bartos, Philip Sayre, Ji Hyun Lee, Jennifer Sword, Michael Holbrook, Richard S. Bennett, Dima Hammoud, Reed F. Johnson, Irwin Feuerstein) declare that they have no conflicts of interest.

Ethics approval: Human and animal rights The animals were housed in an Association for Assessment and Accreditation of Laboratory Care-International-accredited facility. All experimental procedures were approved by the NIAID Division of Clinical Research (DCR) Animal Care and Use Committee and were in compliance with the Animal Welfare Act regulations, Publish Health Service policy, and the Guide for the Care and Use of Laboratory Animals recommendations.

Consent to participate N/A

Availability of data and material Imaging data is sensitive and a data transfer agreement with the NIH/NIAID/IRF is needed to access anonymized CT scans.

Code availability MIM Software (Cleveland, Ohio) is commercially available.

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process. This technique was evaluated using Dice similarity, Hausdorff distance measures and Bland-Altman plots.

Results—Automated segmentation results compare favorably with manual contouring, achieving a median Dice score of 0.91. Limits of agreement from Bland-Altman plots indicate that liver changes of 3 Hounsfield units (CT) and 0.4 SUVmean (positron emission tomography) are detectable using our automated method of segmentation, which are substantially less than changes observed in the host response to these viral infectious diseases.

Conclusion—The proposed atlas-based liver segmentation technique is generalizable to various sizes and species of nonhuman primates and facilitates preclinical infectious disease research studies. While the image analysis software used is commercially available and facilities with funding can access the software to perform similar nonhuman primate liver quantitative analyses, the approach can be implemented in open source frameworks as there is nothing proprietary about these methods.

Keywords

Atlas-based segmentation; liver; computed tomography; nonhuman primate research

Introduction

Animal models facilitate preclinical viral studies of natural history and tests of novel anti-viral therapy efficacy. Nonhuman primate (NHP) imaging is used to model high consequence infectious diseases such as filovirus and Nipah virus diseases in a biosafety level 4 (BSL-4) environment. Information gleaned from multimodality medical imaging of NHPs at a BSL-4 laboratory complements clinical evaluation, virology screening, and pathological analysis during the course of disease. Advanced imaging modalities include computed tomography (CT) and magnetic resonance imaging (MRI) for morphologic detail and positron emission tomography (PET) to detect physiologic changes. Typically, these viral infections and their subsequent host responses cause injury to multiple organ systems including liver, spleen, lungs, kidneys and lymphatic systems [1–3]. Analysis of the liver using ^{18}F -fluorodeoxyglucose (^{18}F -FDG)-PET/CT scanning has demonstrated heterogeneous glucose uptake changes within the organ [4]. Due to this heterogeneity of uptake, single small regions of interest are not sufficient to analyze the extent of disease in the liver. Segmentation of the entire liver from whole-body CT scans is required and facilitates tracking of physiologic changes with the co-aligned PET images.

The liver is a spatially complex three-dimensional structure as seen in CT scans. Whereas manual delineation of the liver is considered a gold-standard, the technique is time consuming and fatiguing and prone to intra- and inter-rater variability [5]. Contrast-enhanced CT scans during the infectious disease state are not well tolerated by our experimental subjects and, therefore, are not routinely possible. On non-contrast CT scans, the liver is isodense compared to nearby tissues, such as muscle and kidney (Fig. 1), making margin decisions difficult [6]. Automated methods to segment the liver have recently been shown to be effective [7–9], however, most of the work involves segmentation of human liver. NHP livers are significantly smaller, can have a different shape, and the fat tissue

composition and distribution around the organ are different from human cases. Therefore, our contribution is to develop a digital atlas composed of manually segmented NHP livers on CT scans that can be used with post-processing techniques to automatically segment normal and abnormal livers of NHPs of different species and varying sizes.

Methods

A total of 82 whole-body CT scans from 37 NHPs (31 rhesus [*Macaca mulatta*] and 6 cynomolgus macaques [*Macaca fascicularis*]) were used in this experiment for creation of the digital liver atlas. These macaques weighed from 3 kg to 14 kg, and 10 macaques were female and 27 were male. In addition, we chose CT scans from a combination of infectious disease experiments conducted at our facility. The scans include baseline scans (no disease) and post-exposure scans from NHPs challenged with Ebola virus, Marburg virus and Lassa virus.

For imaging procedures, 37 subjects were anesthetized with ketamine (15 mg/kg, intramuscularly) first, and anesthesia was maintained using aerosolized isoflurane (2–2.5%), placed on the scanner bed in supine position, and continuously monitored during anesthesia. CT scans were obtained using a Philips Gemini 16-slice CT scanner and a Philips Precedence 16-slice CT scanner (Philips Healthcare, Cleveland, OH, USA) in helical scan mode with the following parameter settings: 140 kVp, 250 mAs/slice, 1-mm thickness, and 0.5-mm increments. PET imaging was performed using a Philips Gemini scanner, and attenuation-corrected images were reconstructed with voxel sizes $2 \times 2 \times 2 \text{ mm}^3$. Of the 82 CT scans used to create the liver atlas, 46 had associated PET scans.

Manually segmented livers in all slice planes (3-D) of 64 non-contrast and 18 contrast-enhanced CT scans were generated to build up a large heterogeneous database of cases that could be generalizable to our population of NHPs. This database of manually defined liver contours and associated CT scans were combined into a digital liver atlas using the commercial MIM software (MIM Maestro version 6.9 Cleveland, Ohio) [10,11].

The livers on all NHP CT scans were manually traced by a single individual (NA) experienced in abdominal organ anatomy and use of MIM contouring. These liver contours were randomly reviewed by a CT body radiologist (IF) who previously trained NA performing the manual contouring. Contours were drawn in the axial plane using the liver window available on the MIM software. The contours were created at the superior extent of the liver, located using the sagittal and coronal planes, and continued to the inferior aspect utilizing the 2D brush, Contour Copilot, and interpolation tools within MIM. The Copilot tool copies the contour from the previous slice and uses deformable registration to place the contour onto the current slice. When visible, the gallbladder was excluded from the liver contour. If breathing motions were observed, the contour was drawn halfway through this expansion of the liver tissue. Once a 3-D contour was initially drawn from top to bottom, a review process ensured that each slice transition was seamless.

The following sections describe the methods to i) create the digital liver atlas, ii) perform automated liver segmentation using this novel atlas and iii) analyze accuracy of the

segmentation technique. The image processing operations were performed with MIM version 6.9.

Creation of liver atlas

A high-resolution CT scan with a manually defined liver contour was resampled to $3.0 \times 3.0 \times 3.0\text{-mm}^3$ resolution and used as the atlas template. This CT scan was chosen as the template because it was representative of the population of NHPs in this study with respect to animal age, size and normal shape of the liver. Resampling reduces the image registration time and computer memory required during atlas creation and automated atlas segmentation. This image serves as the template for all subsequent image registrations. Next, 82 high resolution CT scans with associated manual liver contours were co-registered to the atlas template, and transformation matrices were stored. The transformation performed was a rigid body, six-parameter registration which included three rotations around the x,y,z axes and three translations in the x,y,z axes. Of these 82 CT scans, 49 scans were acquired from healthy NHPs, and 33 scans were acquired from virally infected NHPs (i.e., Ebola, Marburg, or Lassa virus).

Segmentation using liver atlas

The automated segmentation algorithm takes as input a high-resolution CT scan of the body of an NHP. This input CT scan is registered to the template scan using six degrees of freedom (translation and rotation in three spatial dimensions). Rigid alignments are checked by calculating normalized mutual information (NMI) as a cost function [12], and the user is prompted for intervention if the NMI value falls below a threshold of 0.15. This intervention involves manual translations of the input CT scan to match the template CT scan.

The five atlas images with the closest matching rigid registrations are automatically selected and deformably registered to the input CT scan. The transformation obtained from this constrained intensity-based, free-form deformation [12] is applied to the contours associated with the top 5 CT scans. The free-form registration process is a non-linear and more accurate than the rigid body linear registration as each voxel in the image may be translated independently, which allows for proper matching of the CT scans when local displacement including scaling, rotations, translations is required to match the template CT scan. A majority vote algorithm further defines the liver contour. If a voxel is within at least 3 of the 5 aligned contours, then it is classified as liver. To improve the accuracy of the liver contour, post-processing steps are then performed. The median radiodensity (Hounsfield unit, HU) and standard deviation (stdev) values within the liver contour are computed. Voxels are included in the liver contour if their intensity value meets the following criteria:

$$(median - 2 * stdev) < voxel\ value < (median + 2 * stdev) \quad (1)$$

A hole-filling algorithm is applied to include in the contour small missing holes in the liver. Finally, a size threshold is applied to remove any objects less than 50 mL in volume.

Evaluation of the accuracy of the automated atlas-based liver segmentation

A leave-one-out analysis was performed. The subject's scans(s) and contour(s) were removed from the atlas, and this scan was input for automated segmentation. This process was repeated for each of the 82 scans in the atlas. The Dice similarity coefficient (DSC) and the Hausdorff distance measures were used to evaluate the accuracy of the automated atlas-based liver segmentation. The DSC (2) is a measure of 3-D spatial overlap of voxels segmented as liver from the atlas segmentation (V_{atlas}) versus voxels segmented as liver from manual tracing (V_{manual}).

$$DSC = 2 \frac{|V_{atlas} \cap V_{manual}|}{|V_{atlas}| + |V_{manual}|} \quad (2)$$

The Hausdorff distance considers the difference in contours representing the margin of the liver. The distance is defined as

$$h(C_{atlas}, C_{manual}) = \max\{\min\{d(a, b)\}\} \quad (3)$$

in which a and b are points of sets C_{atlas} and C_{manual} , that are the contours from the atlas-based liver segmentation and manual tracing, respectively, and $d(a, b)$ represents the distance between points. In other words, $h(C_{atlas}, C_{manual})$ is the greatest of all the distances from a point in one contour from atlas-based segmentation to the closest point in the other contour from manual tracing.

In addition to these measures of contour similarity, we quantitatively measured the agreement in segmentation using morphologic, density, and physiologic analyses. These measures include liver volume, average HU, and average PET standard uptake value (SUVmean).

Results

The time required to manually segment the liver on non-contrast CT scans of NHPs averaged 60 minutes per CT scan. When running the atlas-based segmentation in our leave-one-out analysis, a manual adjustment of the initial rigid registration was required in 49 of the 82 scans. This adjustment occurred in cases where the size of the NHP was different from the size of the NHP whose CT scan was used as the template (NHP weight ranged from 3 kg to 14 kg). This adjustment also occurred when the field of view of the input CT scan differed from the field of view of the template (e.g., head or legs not included). Manual translation of the input CT scan to overlay the liver took approximately 2–5 seconds per scan, resulting in a significant reduction in processing time compared to manual tracing. The runtime of the processing was assessed by using a low-end Windows Intel Core i5 laptop system with 8GB of RAM. The total processing time for the atlas-based segmentation on a whole-body CT scan was less than 5 minutes. Performance can be increased with addition memory and faster CPU. The average DSC across 82 scans using a leave-one-out strategy was 0.89 with standard deviation of 0.05 and median of 0.91. The average and standard deviation of the maximum and average Hausdorff distance was 18.24 mm (0.90 mm) and 1.56 mm (0.10 mm), respectively. Table 1 breaks down the DSC and Hausdorff distance by

category of (pre-infection, post-infection with infectious disease (ID), Ebola virus, Marburg virus, Lassa virus). The atlas-based liver segmentation performed better on pre-infection CT scans than on post-infection CT scans from NHPs with infectious disease and this was statistically significant for DSC and Hausdorff distance as assessed by the unpaired t-test ($p < 4.5E-09$, $p < 6.8E-06$, respectively).

The average volume of livers as estimated by the manual contours and atlas-based segmentation was 143.60 mL and 129.89 mL, respectively. The average radiodensity of the liver were 71.10 HU and 71.75 HU for manual and atlas-based segmentation, respectively, which is a 0.91 % difference.

The average SUVmean values for manual and atlas-based segmentation were 2.44 and 2.45, respectively. Bland-Altman plots show agreement between the manual and atlas-based segmentation methods for liver density, SUVmean, and percent volume change (Fig. 2). The Bland-Altman plot (Fig. 2A) shows excellent agreement between the density of the liver as measured with the manual and atlas-based segmentation. Considering the limits of agreement (upper and lower dotted lines) seen in the Bland-Altman plot of the SUVmean, detectable changes of less than 0.4 SUV are possible (Fig. 2B). Changes of SUV greater than 3.0 between pre- and post-exposure ^{18}F -FDG scans were measured in this data set. The average percent volume difference in liver volumes between manual and the fully automated segmentation method was 8.57% (Fig. 2C). As measured from our manual tracings, increased liver volume due to viral infection reached 45%.

A variable that affects atlas-based liver segmentation is the presence of viral infection (Fig. 3). The overlap of the atlas-based liver segmentation with the manual contour was studied in an uninfected NHP (Fig. 3A) and an Ebola virus-infected NHP (Fig. 3B,C). Agreement of manual and atlas-based segmentation in the uninfected NHP (Fig. 3A) is good, as indicated by a DSC of 0.94. In an NHP infected with Ebola virus, the agreement between manual segmentation and atlas-based segmentation is lower (DSC = 0.72) and is primarily due to an enlarged Ebola virus-infected left lobe that is not well represented in the atlas.

To assess the generalizability of this novel liver segmentation technique to additional NHP species and lower resolution CT scans, a CT scan of an African Green Monkey (*Chlorocebus aethiops*) with 2-mm slice thickness was processed. Whereas this analysis did not include a ground truth manual tracing for direct comparison, the accuracy of this automated liver segmentation is illustrated in this anecdotal case (Fig. 4).

The accuracy of automated segmentation is compared to manual segmentation on an axial CT scan, in which the manual contour is displayed in blue and the atlas-based segmentation contour in red (Fig. 5). Obtaining physiological information is possible by fusing a co-registered ^{18}F -FDG PET image to the CT image (Fig. 5B). Heterogeneity of the PET signal within the liver is evident. To minimize bias when quantifying physiological change in the liver, this heterogeneity requires segmentation of the entire organ instead of a small region of interest.

Discussion

The measured Dice similarity coefficient of mean (0.89), median (0.91) is in agreement with previous automated human liver segmentation efforts [7,11]. Published methods applying automated liver segmentation to CT scans of NHPs are not available. This level of agreement between atlas-based automated segmentation and manual traced ground truth contours of the liver is sufficient for uses such as post-processing radiomics analysis, global density measurements (HU) of the liver and placement of liver contour on co-registered PET scan for global liver SUV measurements. The Bland-Altman plot (Fig. 2A) shows excellent agreement between the density of the liver as measured with the manual and atlas-based segmentation. Based on the 95% limits of agreement, detectable changes in radiodensity of less than 5% is possible. In the infectious disease state, we have seen changes in radiodensity in the images used to create this atlas on the order of 20%. The Bland-Altman plot of the SUVmean indicates that detectable changes of 0.4 SUV are possible (Fig. 2B). Changes of SUV greater than 3.0 between pre- and post-exposure ^{18}F -FDG scans were measured in this data set.

The average percent volume difference in liver volumes from 82 scan between manual and the fully automated segmentation method was 8.57%, where the manual volumes were larger than the atlas-based volumes on average (Fig. 2C). This bias towards larger livers with the manual method is due to a number of factors, such as an enlarged left lobe of the liver and part of the caudate lobe not always included by the atlas-based method. The left lobe appears to grow faster than the right lobe in response to viral infection (Fig. 3B). Increased liver volume due to viral infection, as measured from our manual tracings, reached 45%. However, improvement in our method will be required to precisely detect small liver volume changes.

The generalizability of the atlas-based segmentation was tested with input CT scans not used in the creation of the atlas. Although a high-resolution CT scan was primarily used as input to the automated segmentation technique, we tested resampled versions with 2-mm slice thickness. Results on a small sample size were comparable with the high-resolution CT scans (data not shown). We also performed atlas-based liver segmentation of African green monkeys (not used in atlas creation) and achieved similar results to that observed with tested rhesus and cynomolgus macaques.

Limitations

If the shape and radiodensity of pathologic liver is not well represented in the atlas, misclassification will occur. Examples include an enlarged left lobe of liver (Fig. 3B). In this case, the constrained deformable registration does not align the abnormal left lobe well with the left lobe of the majority of the 5 closest matching atlas scans. Another example where registration has limitations is when the field of view differs significantly (Fig. 3A). Since the head and legs are not included in the field of view, yet are included in the atlas template, manual rigid alignment was required.

Our accuracy measures assume a perfect ground truth. Due to the lack of contrast between the liver and nearby tissues, there are limitations with manual tracing. The shape and

location of the gallbladder varied among NHPs and changed post-exposure to Ebola virus. The deformable registration algorithm did not always register the input gallbladder to the gallbladders of the atlas subjects, which caused a reduction in our accuracy metrics. Also, the portal hepatis and caudate lobe are complex regions and variation occurs in this anatomy. Whereas our automated method used the majority vote algorithm to minimize false positives, the method was too conservative if only 2 of 5 subjects had the correct overlap between manual and atlas-based segmentation.

Conclusions

Infectious disease from various viruses including Ebola, Marburg, Nipah and Lassa cause organ damage through the viral infection and/or host response. Evaluating vaccines and therapeutics are possible when using advanced medical imaging of animal models that can be tracked over time. In some cases, organs such as the liver have a spatially heterogeneous response, and, therefore, the entire organ must be delineated. Our atlas-based liver segmentation tool simplifies this process and adds to our toolkit of image analyses for infectious disease imaging in preclinical studies. Our implementation of this technique is conducive to use by other research institutions performing CT and PET imaging of nonhuman primates. The 82 NHP CT scans and associated binary image masks, derived from the manual tracings of the livers which were used as ground truth in our comparisons, have been made publicly available for researchers to download at <https://www.synapse.org/#!/Synapse:syn22174612/wiki/604069>.

Future work

To address these limitations, additional cases will be added to the liver atlas that represent the diseased state (e.g., hepatomegaly). The same methods described herein will be used to include the spleen and create a multi-organ segmentation. Finally, we will investigate state-of-the-art deep learning algorithms to improve the overall segmentation performance, such as shape-based machine learning to improve detection of complex liver geometry including the caudate lobe.

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Figure 1.

(a) Coronal view of a whole-body CT scan. (b) Liver and nearby tissues such as muscle and kidney are shown.

Figure. 2.

Bland-Altman plots showing level of agreement between manual and atlas-based liver segmentation for (A) radiodensity, (B) SUVmean, (C) percent change in volume between the expert and atlas-based segmentations. The level of bias as well as the 95% limits of agreement are displayed in dashed lines.

Figure. 3.

Manual contour of the liver is shown in blue and atlas-based segmentation is shown in red. (a) Atlas-based segmentation overlaps closely to ground truth (manual tracing) with a DSC of 0.94 in this uninfected NHP. (b and c) In an NHP infected with Ebola virus, The DSC measure of overlap between manual and atlas-based segmentation of 0.72 is due to an enlarged left lobe induced by infectious disease but that is not well represented in the atlas.

Figure. 4.

Atlas-based liver segmentation shown in red on a 2-mm thick slice CT scan of an African Green Monkey (AGM) in the axial, sagittal, and coronal views. The AGM is a different species of NHP than used in the creation of the atlas. The images demonstrate efficacy of segmentation across NHP species and resolution of CT scan.

Fig. 5.
(A) CT scan with manual (blue) and atlas-based (red) liver segmentation. (B) ^{18}F -FDG PET scan fused with CT scan depicting the heterogeneity of the PET signal within the liver. Spillover effect of PET image is indicated by detection of signal beyond the margin of the liver segmented in the CT scan.

Table 1.

DSC and Hausdorff distances (cm) for pre-infected and post-infected cases. EBOV is Ebola virus, MARV is Marburg virus, LASV is Lassa virus.

	Pre-infection	Post-infection	EBOV	MARV	LASV
DSC	0.918 (0.020)	0.850 (0.070)	0.852 (0.073)	0.861 (0.054)	0.833 (0.089)
Hausdorff Distance	1.455 (0.721)	2.326 (0.915)	2.408 (0.963)	2.065 (0.659)	2.302 (1.222)