Regional assessment of liver disease progression and response to therapy by multi-time point m-SLIC correspondence

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Abstract. Liver disease has reached worryingly high levels worldwide and there is a need for better analysis to monitor progression of disease and response to therapy. Quantitative imaging such as corrected T1 and PDFF can accurately quantify levels of inflammation/fibrosis and fat. In this study we develop a method to assess regional change throughout the liver to characterise disease change. We show that this method is stable in healthy test-retest cases but is able to characterise change in disease in autoimmune hepatitis cases.

1 Introduction

Liver disease has already reached worryingly high levels worldwide, and development of methods to assess disease early, as well as its progression and response to therapy is needed [8]. Conventional MRI imaging of the liver can be used to assess anatomical variation; but the acquired image depends on the acquisition settings and cannot be related to the underlying tissue characteristics. However, quantitative imaging of the liver is becoming increasingly commercially available, and can be used to assess pathology by measuring liver tissue characteristics. For example, Myomaps, CardiacQuant, and CardioMaps pulse sequences can be used to derive a quantitative T1 map of the liver which are related to inflammation/fibrosis [2]. First, however, the quantitative measure of T1 that is measured by these pulse sequences has to be corrected for iron levels, which can be measured separately. The corrected T1 and PDFF values are related to liver inflammation/fibrosis and fat, respectively [2]. Such quantitative MRI is one of the key modalities for non-invasive assessment of diseases such as non-alcoholic

fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [7]. These scans allow quantitative and repeatable assessments of the liver, and can be a non-invasive alternative to liver biopsies.

To monitor patient response to therapy, or the progression of disease, it is important to be able to characterise change in the relevant organ, here the liver, between two or more time points. This can be achieved by calculating change from representative regions of interest (ROI) placed in the organ, or from the change in a representative statistic from the whole organ or a chosen region. There is also value in capturing regional change across the whole biological organ or pathology. An organ or pathology can be divided into contiguous sub-regions for local analysis [5]. Various other methods such as clustering are available to assess regions of a tumour or organs at a single time point, and the change in a global description can be used to quantify longitudinal progression of disease [6] or shape change of the overall organ shape can be monitored [3].

In the study reported here, we propose an approach to assess regional change in a cross sectional slice of the liver. The method aims to capture overall change, particularly where there is disease variation, and can be applied to any set of medical images where a slice wise correspondence can be established between time points. However, this method is most valuable in quantitative imaging in order to assess meaningful change. Our method enables, in principle, local change to be captured that would be 'diluted' when calculating a summary statistic for the whole organ. An analogy to this automatic method would be manually placing corresponding ROIs at two time point across the whole organ of interest and measuring the difference. We are not aware of any methods that have been used to measure regional change in the liver across time points.

2 Methods

We develop a novel approach to quantitatively assess change in regions of the liver from quantitative corrected T1 maps (cT1), which, as described earlier, measure inflammation and fibrosis. The workflow is shown in Figure 1. Two quantitative cT1 scans of the liver are acquired at two time points with 4 or more slices that are centred on the porta hepatis. In this example, a patient with auto-immune hepatitis is scanned twice approximately 12 months apart while undergoing treatment. Corresponding liver cross sections are manually selected from the two multislice sequences; the livers are then automatically segmented and large vessels excluded. Next, the segmentations are matched and superpixel regions which are generated for the first image are mapped onto the second. This allows a region-wise metric of liver change to be calculated.

The liver segmentations were performed using a deep fully convolutional network to automatically segment the liver from the cT1 images while removing larger vessels and ducts. The network takes a quantitative map as input and comprises of 15 stacked convolutional layers with 3x3 kernels. The first half of the network includes pooling layers to create a high level representation and the second half of the network upsamples the represent to the original resolution,

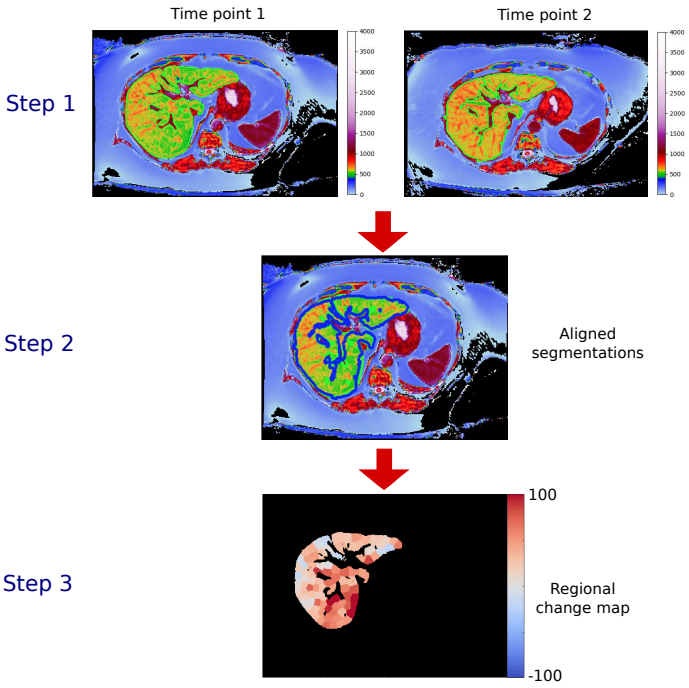


Fig. 1. The processing pipeline to measure regional change in the liver using quantitative cT1. cT1 is visualised using a specialised colour map that shows lower cT1 in the liver as green and higher levels that indicate potential inflammation or fibrosis as orange or red. Step 1: automation segmentation at two time points, Step 2: mask alignment, and Step 3: superpixel generation and measurement of regional change.

and, therefore, combining the trained high level representation with low level features for the final segmentation (further details can be found in [4]). Larger vessels and ducts are excluded so that change measurements are representative of the tissue parenchyma (Step 1, Figure 1).

The liver was parcellated into superpixels using m-SLIC [5]. As with the original simple linear iterative clustering (SLIC) superpixel method [1], m-SLIC uses a distance function (d), in the local clustering, and combines spatial and feature similarity as shown in Eqn 1.

$$d = \sqrt{(d_f)^2 + (d_s/r)^2} \tag{1}$$

Starting from seed points, this method clusters the image into regions that appear locally homogeneous, and provides an efficient coding of the image for a number of computer vision tasks. m-SLIC extends standard SLIC method and allows the creation of superpixels in an irregular mask. This method places seed points in the mask using a distance transform and a regularisation step. After the seed points are initialised correctly, standard SLIC is applied using this method

(see our previous work for further details [4]). In this study, we use superpixels of size 100 pixels, which aims to make the method robust to variation.

Next, we align the segmented liver masks from the second time point to the first using an affine registration method (Step 2) and, using this transform, propagate the superpixel regions from the first time point onto the second.

The alignment and superpixels allow direct comparison between regions of the two images, to assess local changes in cT1 (Step 3). Matching of the liver masks is more reproducible than whole slice registration because the method is not affected by variation of other organs in the image. We currently only consider alignment between single slices. The case shown in Figure 1 exhibits regional inflammation at time point one and more homogeneous inflammation at time point two – most likely due to AIH flaring – and the regional map shows a local change in inflammation in particular in the right lobe.

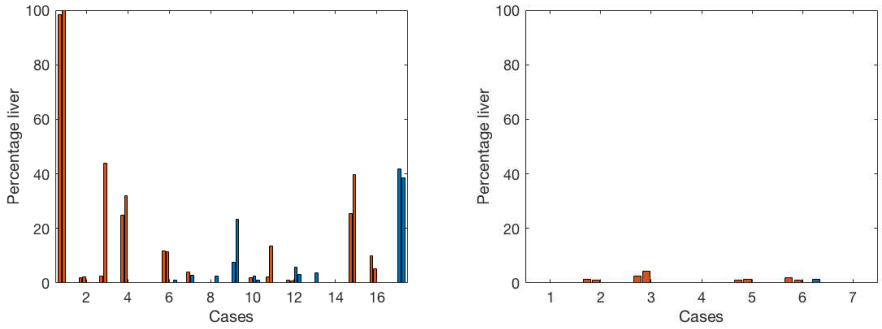
3 Data

Human volunteers were scanned at the Oxford Centre for Magnetic Resonance (OCMR) using a Siemens 1.5T Magnetom Avanto Fit equipped with Myomaps. Seven male volunteers (from the Perspectum staff) were scanned, then taken out of the scanner, then rescanned on the same scanner. Evidently, positioning varies between the scans. A second study was also performed using patients with autoimmune hepatitis (AIH) on a Siemens Magnetom Verio 3T MRI. This study is ongoing; but in this initial assessment of the method we used 17 cases. Each case was scanned and then rescanned approximately 12 months later. AIH is a relapsing/remitting disease that is not always controlled by treatment. "Flares" of inflammation are diagnosed clinically on biochemistry when they happen, however predicting those at higher risk of a "flare" using non-invasive measures is imperfect, hence there is potential for MRI to be used. We used this method to characterise regional change within the dataset in a selected and neighbouring slice.

4 Results

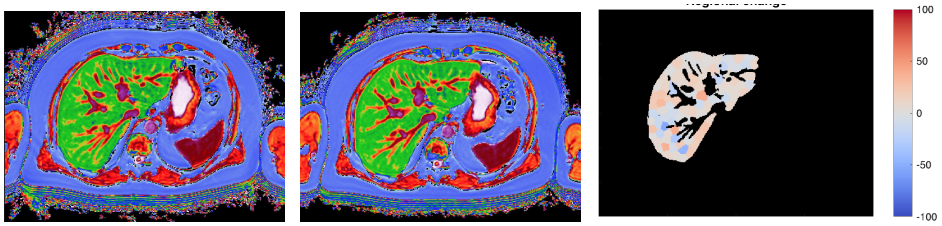
In this analysis, we defined a positive or negative change in cT1 of >75ms as being of clinical interest and calculated the percentage of the liver that showed an increase or decrease in excess of this amount, where an increase in cT1 corresponds to increase liver inflammation and fibrosis burden. This threshold was qualitatively chosen based on previous work on a fatty liver disease cohort but could be adjusted depending on the required sensitivity to change.

In the healthy test-retest cohort the mean proportion of the liver that showed positive change was 0.99 ± 1.01 % and negative change 0 ± 0% which demonstrates that the method is stable to variations in positioning as shown in Figure 2 and an example is shown in Figure 3. AIH cases showed a mean percentage increase of 10.45 ± 24.15% and the mean decrease was 3.76 ± 10.07%. The Pearson correlation between the chosen and next slice is also high 0.92.



(a) (b)

Fig. 2. Percentage of the liver showing a change above or below 75ms (red is an increase and blue shows a decrease) for a) the AIH cohort and b) the healthy test/retest cohort. This is shown for the matched slice and the following slice)



(a) (b) (c)

Fig. 3. Healthy test/retest case showing only very small regional change in cT1 (ms)

These cases were highly variable – depending on whether the patient shows improvement under treatment or flaring. The net percentage change of the liver was highly correlated to the mean liver change in cT1 (0.97) and, so for cases with large homogeneous change, a mean measurement for the entire liver suffices. However, in cases with local change such as Figure 1, the mean does not sufficiently represent the change, and measurement of regional change is also necessary. This is illustrated in Figure 4 for cases 14 and 15 (numbered from Figure 2). Case 14 shows a mean change of 32ms and case 15 shows a mean change of 57ms. However, if we consider regional change above 75ms, we see that case 14 shows no change while 25% of the liver in Case 15 shows an increase above 75ms. This highlights the value in assessing local disease change. Therefore, Case 15 has seen a considerable increase in regional disease burden while in Case 14 there is only a small homogeneous change that could be affected by other factors including diet.

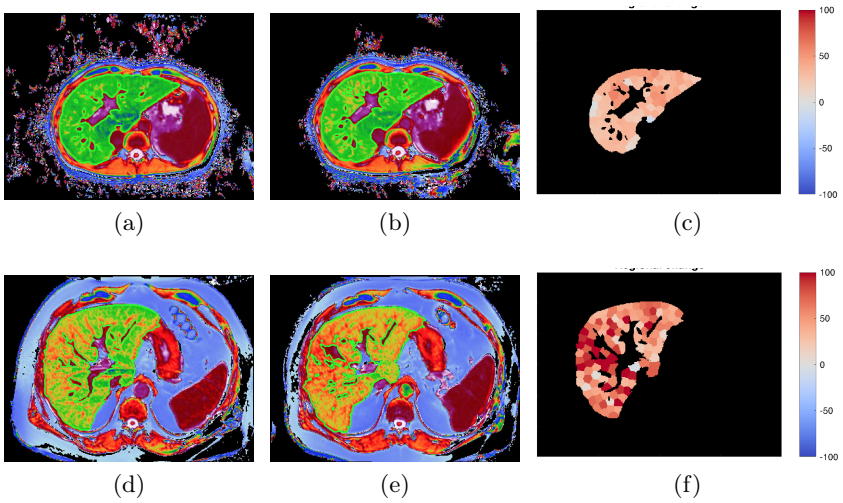


Fig. 4. Illustration of regional change measurement in cT1 (ms) in two cases (a-c and d-f). The percentage of change is shown in Figure 2, case 14 and 15

5 Discussion

In this study, we propose a novel method to measure regional change in quantitative axial slices through an organ. We show that the method is consistent across slices, and that it can be used to capture change due to pathology, and is particularly useful for assessing disease where there is regional change. This method is also robust to normal variation.

Regions are used instead of a voxelwise comparison to make the method robust to variations in position and noise. We use a threshold of 75ms to characterise clinically interesting change and this appears to be a good choice to account for normal variability as suggested by the test-retest study. However, more research is required to determine the best choice. This method also does not explicitly exclude artefacts in the image and these would need to be excluded in some cases. In future, we plan to compare changes and response to therapy to other clinical markers and end points.

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