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# The added value of quantitative ultrasound to shear wave elastography for assessment of steatohepatitis in a rat model

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***Abstract*—Non-alcoholic fatty liver disease is a highly prevalent condition, which may progress to non-alcoholic steatohepatitis (NASH), an advanced form found in 3 to 5% of the population. As liver biopsy is invasive, there is a need for a non-invasive technique for the assessment of NASH. Due to promising results of shear wave elastography (SWE) in staging this disease, there is a high interest in developing a multi-parametric approach for assessment of liver steatosis within the same ultrasound (US) examination. The goal of this study was to assess the added value of quantitative US (QUS) parameters to SWE, based on random forest classifiers and areas under the ROC curve (AUC). Sixty male Sprague-Dawley rats were either fed a standard chow or a methionine- and choline-deficient diet. Using a research US system (model V1, Verasonics Inc.), SWE measurements were performed while rats were under anesthesia. To generate shear wavefronts within the liver, a linear array US transducer (ATL L7-4, Philips) was used to induce three 40-V 125-µs long radiation force pushes 4 mm apart. For SW tracking, the same transducer was used to acquire plane wave radiofrequency data at a frame rate of 4 kHz; images were reconstructed using the f-k migration algorithm. QUS acquisitions were performed using the same system and transducer. One hundred frames were acquired, migrated, and the echo envelope was obtained with Hilbert transforms. The image post-processing yielded 4 homodyned-*K* parametric maps within the region-of-interest (ROI), from which 8 features were extracted. The local attenuation coefficient slope within the ROI was also computed using the spectral shift method. QUS parameters improved the classification accuracy of steatohepatitis, liver steatosis, inflammation, and fibrosis compared to SWE alone. For detection of liver steatosis grades 0 vs ≥ 1, ≤ 1 vs ≥ 2, ≤ 2 vs 3, respectively, AUCs increased from 0.70, 0.65, and 0.69 to 0.78, 0.78, and 0.75 ($p < 0.001$).**

***Keywords—nonalcoholic steatohepatitis,. non-alcoholic fatty liver disease, random forests, shear wave elastography, homodyned K-distribution***

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## I. Introduction

Non-alcoholic fatty liver disease is a highly prevalent condition, which may progress to non-alcoholic steatohepatitis (NASH), an advanced form found in 3 to 5% of the population. As liver biopsy is invasive, there is a need for a non-invasive technique for the assessment of NASH.

Due to promising results based on shear wave elastography (SWE) in staging this disease, there is a high interest in developing a multi-parametric approach for assessment of liver steatosis within the same ultrasound (US) examination. The goal of this study was to assess the added value of quantitative US (QUS) parameters to SWE, based on random forest classifiers [1] and areas under the ROC curve (AUC). More details about this study can be found in [2].

## II. METHODS

### A. Animals

This study was approved by the Institutional Animal Care Committee of the University of Montreal Hospital Research Centre. Sixty male Sprague-Dawley rats were either fed a standard chow or a methionine- and choline-deficient diet [2]. The rats were distributed into four groups of 12 rats each that were imaged and then euthanized after 1, 4, 8, and 12 weeks. A control group was constituted of twelve 11-week-old healthy rats that were euthanized after 4 weeks within the study.

### B. SWE acquisition

Using a research US system (model V1, Verasonics Inc.), SWE measurements were performed while rats were under anesthesia. To generate shear wavefronts within the liver, a linear array US transducer (ATL L7-4, Philips) was used to

induce three 40-volts 125-µs long radiation force pushes 4 mm apart. For SW tracking, the same transducer was used to acquire plane wave radiofrequency data at a frame rate of 4 kHz. Images were reconstructed using the f-k migration algorithm [3]. Further details on shear wave acquisition and analysis are presented in [2].

### C. *QUS acquisition*

QUS acquisitions were performed using the same system and transducer. One hundred frames were acquired, migrated, and the echo envelope was obtained with Hilbert transforms. The image post-processing yielded 4 homodyned-*K* parametric maps within the region-of-interest (ROI), from which 8 features were extracted [4, 5, 6]. The local attenuation coefficient slope within the ROI was also computed, using the spectral shift method [7]. See [2] for more details on the spectral and statistical QUS analysis.

### D. *Gold-standard*

Steatosis grade (0 to 3), lobular inflammation grade (0 to 3), and fibrosis stage (0 to 4) were reviewed by a hepatopathologist based on histology slides of liver specimens. The histopathology analysis and examples of images are described in [2].

### E. *Machine learning*

For each steatosis grade, inflammation grade and fibrosis stage, a dichotomic classification was performed, based on random forest classifiers [1]. Areas under ROC curves were estimated with the 0.632+ bootstrap methodology [8]. A full description of the statistical learning analysis is provided in [2].

## III. RESULTS

QUS parameters improved the classification accuracy of steatohepatitis, liver steatosis, inflammation, and fibrosis compared to SWE alone [2]. Notably, for detection of liver steatosis grades 0 vs $\geq 1$, $\leq 1$ vs $\geq 2$, $\leq 2$ vs 3, respectively, AUCs increased from 0.70, 0.65, and 0.69 to 0.78, 0.78, and 0.75 ($p < 0.001$). See Figures 1 to 3 for examples of homodyned-*K* parametric maps based on the diffuse-to-total signal power ratio in the case of a rat belonging to the control group and two rats with steatosis grade 2 and grade 3, respectively.

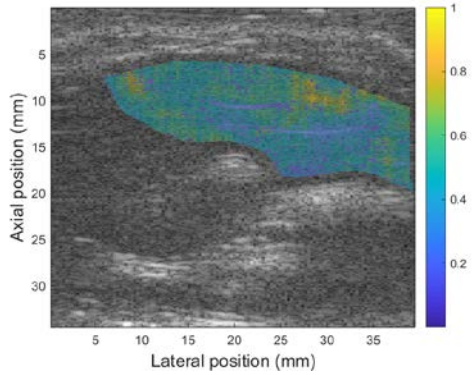


**Figure 1** : Parametric map of the homodyned-*K* parameter $1/(\kappa+1)$ (diffuse-to-total signal power ratio) in the liver region of a rat in the control group with steatosis grade 0. Inter-quartile range of $1/(\kappa+1)$ was 0.15 in this case.

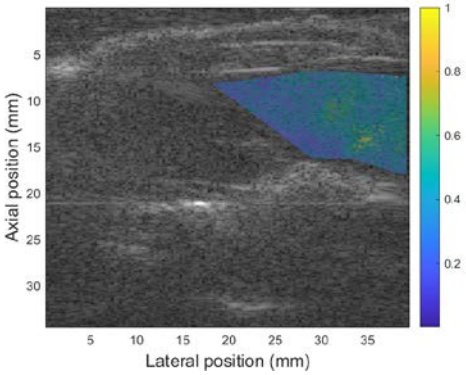


**Figure 2** : Parametric map of the homodyned-*K* parameter $1/(\kappa+1)$ (diffuse-to-total signal power ratio) in the liver region of a rat with steatosis grade 2 after 1-week of methionine-andcholine-deficient (MCD) diet. Inter-quartile range of $1/(\kappa+1)$ was 0.25 in this case, indicating a greater variability in structural organization in the steatosis case compared to the control group.

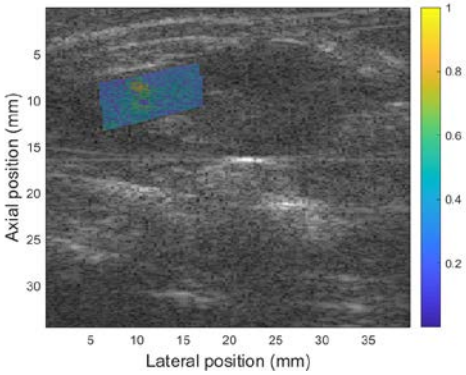


**Figure 3** : Parametric map of the homodyned-*K* parameter $1/(\kappa+1)$ (diffuse-to-total signal power ratio) in the liver region of a rat with steatosis grade 3 after 1-week of methionine-andcholine-deficient (MCD) diet. Inter-quartile range of $1/(\kappa+1)$ was 0.30 in this case, indicating a greater variability in structural organization in the steatosis grade 3 case compared to the steatosis grade 0 or grade 2 cases displayed in Fig. 1 and Fig. 2, respectively.

## IV. DISCUSSION

The inter-quartile range of the homodyned-*K* parameter $1/(\kappa+1)$ (*i.e.*, the diffuse-to-total signal power ratio) was retained in the best combination of features for each of the three dichotomous classification tasks of the steatosis grade [2]. In view of the experiments reported in [5], this finding suggests that the structural spatial organization of scatterers (assumed to be hepatocytes in this case), presents a greater variability as the steatosis grade increases. This hypothesis is illustrated in Figures 1 to 3, where one observes an increase in the inter-quartile range of $1/(\kappa+1)$ with an increase in steatosis grade.

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