ULTRASONIC FATTY LIVER IMAGING

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ABSTRACT

Fatty liver disease is a prevalent condition which may result in serious liver complications and is currently lack of an effective and efficient approach for its quantification. In the paper, we propose to directly image the fat content distribution in liver based on ultrasound echo radio-frequency signals. In the proposed method, spectral difference is utilized to represent the small pieces of liver tissues. Then the connection between the data representation and liver tissues is directly established by an elaborately designed learning process in the high-dimensional feature space, which includes comprehensive hyper-parameter learning and model learning. Experimental results demonstrate the effectiveness of the proposed method which is able to visualize the fat distribution and has a 0.93 correlation coefficient with the fat-percentage quantification results of doctor's pathological analysis.

Index Terms— Fatty liver, Quantification, Imaging, Ultrasound echo signal, Machine learning

1. INTRODUCTION

Fatty liver, or liver steatosis, is the buildup of triglycerides in the form of lipid droplets in the liver which can be a result of several causes such as alcohol consumption, viral hepatitis or metabolic dysfunction [1, 2]. If fat proportion in the liver is larger than 5~10%, it is considered as fatty liver disease which is highly reversible when the extent of fatty change is not high [2]. However with further progress associated with inflammation, the disease becomes much irreversible and may result in severe conditions such as steatohepatitis, liver cirrhosis and hepatocellular carcinoma [1]. Since the prevalence of fatty liver disease is as high as around 30% of the population [3], an efficient and accurate method for diagnosing fatty liver extent is important for the clinical practice.

Nowadays liver biopsy is the golden standard to evaluate patient's fat fraction. Histopathological analysis is reliable on tissue characterization. However the approach may encounter the problem of limited tissue sampling [4]. It is also an invasive method and patients may suffer from serious complications. These significantly restrict the application of liver biopsy in fatty liver quantification.

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Ultrasound as a diagnostic imaging is widely used due to its noninvasive nature, real-time imaging and low cost. In ultrasound echo images, fatty liver disease manifests as increased echogenicity and signal attenuation. Experienced doctors may diagnosis the existence of fatty liver disease, but it is subjective, operator-dependent and not quantitative. Research on quantitative ultrasound has demonstrated the capability for the diagnosis of fatty liver disease to some extent [5, 6].

As liver fat content results in increased attenuation, conventional echo signal based attenuation estimation is one major research direction for fatty liver disease diagnosis [5, 7]. These methods assume total attenuation as a function of attenuation coefficient in an exponential form. Then an echo signal from a well-characterized reference target is utilized and the attenuation coefficients can be estimated for the processed target [8]. However, parenchyma heterogeneity may negatively impact these methods. Meanwhile, signal beamforming for the processed and reference data is required to be consistent. There also exist approaches without using the reference signal [9, 10]. But they are often based on strong assumptions or require additional signal information to constrain the estimation performance. Recently shearwave-based parameter estimation methods [11, 12] demonstrate the potential for a reliable output however they are still in the preliminary research phase. Other acoustic parameters like thermal stain [13], acoustical nonlinear parameter, etc. [14] manifest the variation due to the change of fat content. For the practical estimation of these parameters, rigorous approaches are required for specific signal acquisition.

For fatty liver quantification, the parameter-based methods need to further establish a connection between different parameter values and the corresponding fatty liver extents. The above mentioned ultrasound parameters often approximately demonstrate a linear relationship with the extent of fat content. However the exact relationship is still not fully understood yet. Also since fatty liver tissue is fundamentally a synthetical configuration, the estimated ultrasound parameters manifest interacted impacts with each other. Such interaction may significantly affect the diagnosis of fatty liver disease and is still under research.

Another research direction for fatty liver quantification is the learning-based discrimination between fatty liver and normal liver. Authors in [15, 16] developed a classifier based on fuzzy similarity measures with the features of statistical image features and RF acoustic parameters. Experiments on 150 cases achieved 91% sensitivity. Abou

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zaid *et al* [17] did a study on distinguishing the normal, fatty, cirrhosis and carcinoma cases. A neural network with two hidden layers is applied with the features of image statistics and the total accuracy is 96% as reported. These methods highly depend on device settings due the utilization of echo images. Meanwhile, binary classification of normal and fatty patients is the concerned problem. The quantification of fatty liver extent is beyond the scope of these methods.

In the paper, we propose to directly image the fat content distribution in liver based on ultrasound echo radio-frequency (RF) signals. With the visualized fat distribution, doctors may conveniently identify the fatty liver extent of one patient. In the proposed method, to represent one small piece of liver tissue, the spectrum difference is simply derived based on the RF signal around the small piece of liver tissue and directly used as one sample. With a large number of such liver samples, a learning process is performed to directly model the connection between the samples and their corresponding histopathological analysis results. The learning process is based on the utilization of an elaborately designed machine learning approach which includes comprehensive hyper-parameter learning and model learning. The histopathological results for every ultrasound data are based on the analysis of tissue slices that are obtained from the corresponding patient's liver surgery. With the established learning-based model, fatty liver tissues can be directly identified in real time. The imaging of the visualized fat distribution in liver is termed as ultrasonic fatty liver imaging in our paper.

2. PROPOSED METHODS

2.1 Data representation

When an ultrasound echo signal is transmitted to a small piece of liver tissue, the signal will be interacted with the small piece of liver tissue. Such interaction is a complex process. Generally, the signal "before" entering the small piece of liver tissue will be different from the signal "after" the interaction with the small piece of liver tissue. In the proposed method, one fundamental assumption is that the difference between the "before" and "after" signals contains the related characteristic information of the small piece of liver tissue and may be used to represent the small piece of liver tissue. Therefore to denote such "difference", it is heuristically proposed to apply the following equation for the characteristic representation of the small piece of liver tissue:

$$S = |F(S_{\text{after}})| - |F(S_{\text{before}})| \qquad (1)$$

where S is the representation for one small piece of liver tissue, which is considered as one sample in the following learning process. S_{before} and S_{after} are the "before" and "after" RF signals in time domain, respectively. $F(\cdot)$ denotes the Fourier transform and the result is a vector of the corresponding complex coefficients. $|\cdot|$ denotes the norm calculation for each frequency component.

The design of such signal representation is based on the following considerations. First, for ultrasound RF signals, the Fourier transform could be applied to represent the signal with a basis of frequency components. Therefore it can be seen that one sample S as calculated in (1) has the form of a high dimensional vector. The elements in the vector are obtained based on the Fourier frequency components which are perpendicular with each other. Considering the elements as features from the learning point of view, such property is important for sample representation in the following learning process. Secondly, it is straightforward to apply the "minus" operation to denote the "difference". With such operation, signal information in the data representation part is supposed to be "complete" for the following process. Thirdly, for one sample S, the "before" and "after" signals are the portions of the received RF signal around the corresponding small piece of liver tissue. The calculation of the spectrum difference as (1) can be directly and simply performed. The following processes are based on such generated samples. No other assumption that is related with any ultrasound signal property or further signal processing settings of ultrasound machine is taken. This design avoids the further requirement of signal or machine constraints like other methods as mentioned in section 1. Fourthly, the following process is to directly link the samples with their corresponding histopathological analysis results. The relationship between the ultrasound RF spectrum difference and the fat content is directly established without any intermediate calculation. Therefore the application for the fat-extent quantification can be straightforward and conveniently performed.

Now the question is, does such data representation really contains enough or correct signal information for the objective of fatty liver quantification? Will any other ultrasound signal property change impact the final model output? In the proposed method, the questions are not straight or theoretically answered from the signal itself. Instead, a learning process is proposed and applied to first learn the connection between the data representation and the fat-content quantification and later validate whether such a connection can be found and robustly established. The impacts from other ultrasound signal properties are designed to be handled by the learning process and the learned connection is supposed to be intrinsic for the application. The learning is proposed to be directly per-

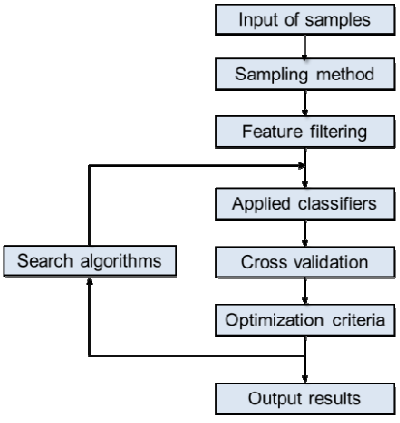


Fig. 1. Diagram of the model-learning framework

formed in the high-dimensional space of the data representation, which strongly enhances the learning's potential capability. An elaborately designed machine learning approach is correspondingly proposed, which will be described in details in the next section. Since the small pieces of liver tissues (not the patients) are the processed objects, the number of samples for the learning could reach the level of hundreds of thousands even with a limited number of patients. This further guarantees the feasibility of the proposed method. Experimental results preliminarily validated the effectiveness of the proposed data representation, which will be detailedly described in section 3.

2.2 Learning process

The proposed learning process consists of two parts. The first one is the hyper-parameter learning which is to understand the proper biological representation of liver fatty and normal content for the spectrum difference and adjust the appropriate number of samples for the following process. The second part is to learn the optimal model for connecting the samples with the corresponding histopathological results. To achieve the real-time imaging, the classifier which is as the core part of the learned model is restricted to the ones with an appropriate complexity. Meanwhile, the computational complexity for the optimization of model is deliberately and tremendously increased to achieve the high performance for the entire learning process.

2.2.1 Hyper-parameter learning

For one sample as defined by (1), there are two hyper-parameters related with the biological representation. The first one is the RF signal length for either S_{before} or S_{after}, which denotes the choice of information quantity that is interacted with the liver tissue. Large length may benefit the sufficiency of the considered signal information. However it may also lead to the loss of localization for the data representation. The second hyper-parameter is the interval length between the "before" and "after" signals, which is related with the appropriate tissue size for representing the liver normal or fatty content.

Since the number of samples for the learning process could be extremely large which may not be suitable for some kinds of models, it is necessary to optimize the number of samples in an appropriate level considering the different computing capabilities of the following learning models. Therefore the sample-density coefficient is the third hyper-parameter required to be optimized, which denotes the region size for selecting one small piece of liver tissue and generating the corresponding one sample as defined by (1). It is noted that the "sample" and the related descriptions here and as followed are for the term from the learning point of view, which has nothing to do with the sampling notion when receiving the RF echo signal.

For the described three hyper-parameters, an intensive grid search is applied for their learning. In the entire learning process, the hyper-parameter learning is used as the wrapper for the following model learning.

2.2.2 Model learning

This study focuses on identifying the liver fat tissue in the liver normal parenchyma which is technically considered as a binary classification problem and supervised learning is utilized in the proposed method. The ground truth is from the histopathological analysis results. However the histopathological analysis result for each fatty liver case is a percentage of fat content. It doesn't denote the exact correspondence between every small piece of liver tissue and its histopathological analysis result, which is impossible to be realized in practice even with the large histopathological slice. To handle this problem, the fatty liver cases with a high percentage of fat content are selected in the proposed method to extract the fatty liver training samples which are given with the ground truth as complete fatty tissue. Correspondingly, normal liver samples are extracted from normal liver cases. It can be seen that for fatty liver samples, an unknown proportion of them is given with the incorrect ground truth. However since the majority of the samples is with the correct ground truth, it is assumed that such majority could dominate the determination of the hyper-plane for the binary classification problem. The impact from the incorrect ground truth is left to be handled by the model learning itself in the sample space. The feasibility of such assumption has been validated by experimental results.

Based on the extracted training samples and the corresponding ground truth, a learning framework is established to perform the model learning. The diagram of the framework is demonstrated as Figure 1. The features for one sample are the frequency components of the spectrum difference as calculated in (1). Sampling method first deals with the number imbalance of fatty and normal samples. Then feature filtering is applied to preselect the relatively significant features and preliminarily reduce the feature dimension. Optimization criterion is further used to measure the performance for the cross validation results and guide the learning within the search algorithms. When every step of the framework selects one specific method,

Framework Step	Applied methods
Sampling method	None-sampling, over-sampling, under-sampling [18]
Feature filtering	None-filtering, T-test [19], Wilcoxon rank-sum test [20], Kolmogorov-Smirnov Test [21], MR-MR [22], KL Divergence, Rf-Gini Importance, Rf-Mda Importance [23], ReliefF [24]
Applied classifiers	KNN, SVM, linear discriminant analysis [25], logistic regression [26], AdaBoost [27], Random forests [28]
Optimization criteria	Accuracy, g-mean sensitivity, AUROC [29]
Search algorithms	Grid search, stepwise optimization, constrained stepwise optimization, genetic algorithm [30], simulated annealing [31]

Table 1. Detailed methods of the model learning framework.

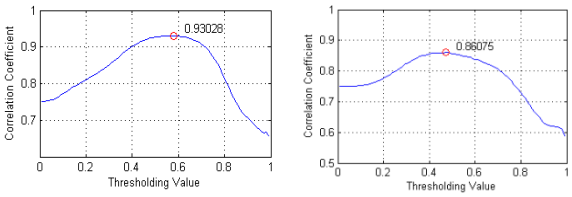
the whole framework can be performed once and the specific learning will stop after the convergence. In the proposed method, we make several different methods available for each step of the framework. Different methods may take different assumptions or have different computational advantages for classification problem. The detailed methods for each step are listed in Table 1. Then the model learning based on the framework is performed by exhaustively running all the combinations of all different essential methods for every step. Meanwhile we extremely increase the number of optimized parameters and their optimization ranges for different methods. The search algorithms are simultaneously performed in both feature and parameter space. Considering the grid search of hyper-parameter learning as the wrapper of the model learning, it can be seen that the computational cost for the entire learning process is extremely large. This may guarantee the learning process converged at the optimal model for representing the intrinsic connection between the data representation and the histopathological results. Meanwhile, after the entire learning process, the main computational cost for the imaging application of the learned model mainly comes from the classifier complexity. As previously mentioned, the applied classifiers are constrained with the ones of an appropriate complexity. Therefore the extremely high complexity of the learning process will not affect the imaging cost and the real-time imaging can be still guaranteed.

3. EXPERIMENTAL RESULTS

Ultrasound RF signals were collected on liver parenchyma regions with patients' consent by Philips iU22 system with a L9-3 transducer before surgery. The corresponding liver parenchyma slices were obtained during surgery and the pathologic analysis were further performed by at least two experienced doctors. In this study, normal liver cases are from the patients whose parenchyma is pathology confirmed with no fibrosis and no inflammation. For fatty liver cases, the patients are also not fibrotic or inflammatory and the fat-content percentage is quantified by the doctors. Totally, there are 16 normal cases from 9 patients and 11 fatty cases from 6 patients.

For the hyper-parameter learning, the RF signal length, the interval length and the sample-density coefficient are in the range of 0.62mm to 2.46mm, 0.39mm to 1.54mm and 0.0706mm^2 to 0.1413mm^2, respectively. Training samples are generated from 5 normal cases and 4 fatty cases for which the two patients' fat-content percentages are 40% and 60% respectively. Generally the number of the generated training samples is in the level of 30,000 for one specific set of hyper-parameters. All the remained samples are used as the testing samples. The output of the learned model is a normalized score in the range of 0 to 1. For one processed small piece of liver tissue, the higher value denotes higher probability to be a fat content.

The tremendous learning process in the proposed method is automatically performed with parallel computing, which totally takes 27 days. Based on cross validation results, a model with Random forests as the applied classifier is selected for the further testing. For one testing case, it takes around 0.3 second for realizing the ultrasonic fatty liver imaging. It can be seen that the elaborate design for the real-time imaging is realized.



(a) (b)

Fig. 2. Correlation results with pathologic analysis results by (a) the proposed method and (b) the model with the compared parametric data representation

For the experimental results, the reasonable and meaningful way to evaluate the model performance for the fat content quantification is to directly correlate the model's fat-percentage estimation results on the testing fatty liver data with the percentage estimation results from the pathologic analysis. A thresholding value is required to determine whether a small piece of liver tissue is fat-content by its model score. Figure 2(a) demonstrates the results of the calculated correlation coefficients. With the thresholding value as 0.58, the correlation coefficient could be 0.93 which verifies the effectiveness of the proposed method to some extent. The corresponding fat-percentage estimation on the testing normal liver data is 0.9±2%, which is also consistent with the pathologic analysis results.

For the further comparison, we used the parametric methods including attenuation [9], envelope statistics, peak-to-peak imaging, frequency shift, Nakagami parameter [32] to substitute the part of data representation in the proposed method. Every sample becomes a 16 dimensional vector and the related other processing is as same as in the proposed method. For the correspondingly learned model, the correlation result with the pathologic analysis is shown as Figure 2(b) and the correlation coefficient may achieve 0.86. On one hand, it manifests the effectiveness of the learning process in modeling the connection between ultrasound echo signal and liver tissue. On the other hand, it denotes that the proposed spectral difference is superior for the proposed method in data representation mainly due to its "complete" information.

The generated fatty liver images by the proposed method are demonstrated as Figure 3 where red denotes high probability to be fat content. The fat distribution can be clearly visualized. It also can be seen that for Figure 3(d) and 3(e), the fat-percentage should be both 5% since they come from the same patient. However Figure 3(d) denotes more fat content. The discrepancy might be possibly due to the limited scope of its pathologic slice.

4. CONCLUSION

In the paper, we propose a method to model the connection between ultrasound echo signal and fatty liver tissue. Instead of explicit description or theoretical proof, the connection is directly established by learning in the high-dimensional space. Experimental results manifest the

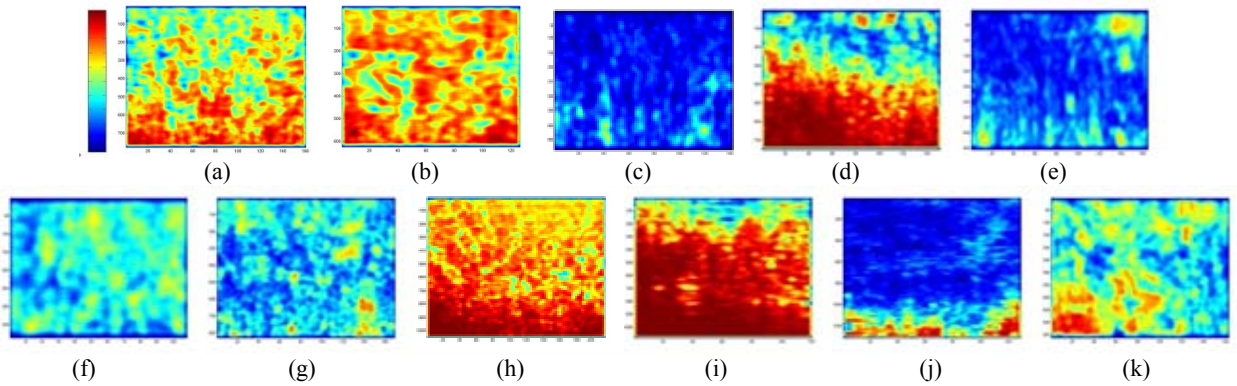


Fig. 3. The generated fatty liver images by the proposed method for which the fat-percentage results of the pathologic analysis are 40%, 40%, 15%, 5%, 5%, 10%, 10%, 60%, 60%, 8% and 8% for (a) to (k) respectively.

correlation coefficient as high as 0.93 between the proposed method and the pathologic analysis in quantifying the percentage of fat content. The in-vivo nature and visualized fat distribution make the proposed method superiorly suitable for widely and regularly screening in fatty liver quantification.

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