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Deep learning based classification of focal liver lesions with contrast-enhanced ultrasound

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ABSTRACT

Classification of liver masses is important to early diagnosis of patients. In this paper, a diagnostic system of liver disease classification based on contrast enhanced ultrasound (CEUS) imaging is proposed. In the proposed system, the dynamic CEUS videos of hepatic perfusion are firstly retrieved. Secondly, time intensity curves (TICs) are extracted from the dynamic CEUS videos using sparse non-negative matrix factorizations. Finally, deep learning is employed to classify benign and malignant focal liver lesions based on these TICs. Quantitative comparisons demonstrate that the proposed method outperforms the compared classification methods in accuracy, sensitivity and specificity.

1. Introduction

Primary liver cancer is the sixth most common cancer worldwide, and the third most common cause of death from cancer [1]. In order to increase the chances for survival by providing optimal treatments, early detection and accurate diagnosis of liver cancer is of utmost importance [2,3]. Biopsy is currently the golden standard for diagnosing cancer, but it is invasive, uncomfortable, and is not always a viable option depending on the location of the tumor [4–6]. Noninvasive diagnosis of focal liver lesions (FLLs) can be evaluated by using CEUS to determine the liver vascularization patterns in real-time, and thus, improve the diagnostic accuracy for the classification of FLLs [7].

Recently, many studies have investigated CEUS patterns of FLLs, establishing their typical behaviour in the arterial, portal and venous phases [8,9]. The normal liver is a highly vascular organ predominantly supplied by both hepatic artery (25%) and portal vein (75%) [10]. However, malignant focal liver lesions (i.e., hepatocellular carcinomas (HCCs), hypervascularity metastases) are supplied by the hepatic artery as well as tumor vessels. Therefore, the enhancement patterns of FLLs in the arterial and portal venous phases of CEUS can be used for characterizing FLLs [11]. Compared with healthy parenchyma, benign liver lesions are typically hyper-enhanced at all time, whereas malignant lesions usually present a hyper-enhanced pattern during the arterial phase and become hypoenhanced in the later portal-venous phase [12].

Time intensity curves (TICs) are a graphical illustrating representative contrast uptake kinetics represented in a CEUS investigation. Comparative TIC analysis between a tumoral region of interest (ROI) and parenchymal equivalent ROI could enhance the diagnostic accuracy of CEUS, thus establishing its role in liver cancer diagnosis [13,14]. Previous reports have shown that the analysis of TICs such as the area under the curve (AUC) and time to peak (TTP) have statistical significance between benign and malignant lesions of various types of tumors in the hemodynamic measurements [15–18].

Based on the TICs of CEUS, diagnostic systems had been developed to assist ultrasonographist in liver cancer processing to further improve the diagnostic accuracy. Casey et al. [18] extracted the TIC of each pixel within a ROI and used the measured TICs' parameters as the features to classify the benign and malignant tumors of rats by linear discriminant analysis. The problem of the method lies in that the extraction of TICs is susceptible to noise because the CEUS imaging signal is noisy due to many factors (i.e., speckle noise, fluctuations in the concentration of microbubbles) [18]. Streba et al. [19] extracted the TIC with the mean of the signal intensity within a manual drawing ROI surrounding the tumor and also used the measured TICs' parameters (i.e., AUC, TTP) as the features to classify liver tumors by artificial neural networks (ANN). The TICs obtained from ROI measurements may be composites of

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activities from different overlapping components in the selected ROI. It is the major disadvantage of ROI measurements method. Junji et al. [11] estimated TICs for an FLL by use of a series of the temporally averaged microflow imaging (MFI) images and employed a cascade of six independent ANN by use of extracted temporal and image features for classifying liver diseases.

The limitations of the above-mentioned methods were that the feature selection was determined empirically and always operator-dependent. Furthermore, the parameters setting are based on the experimental knowledge. To address the problem, we introduce deep learning [20] into the diagnostic system to classify the benign and malignant focal liver lesions. Deep learning is employed in this work because it is received much attention recently. It combines the feature extraction and recognition together perfectly. The feature extraction is implemented from low level to high level through unsupervised feature learning instead of being hand-designed [21]. Deep learning simulates the human brain to recognize objects through different layers' features.

Moreover, to overcome the subjectivity of TICs extracted with manual ROI selection and the impact of speckle noise, an automatical TICs extraction method is used. The TICs are extracted from the dynamic CEUS image sequences by Factor Analysis of Dynamic Structures (FADS) techniques. As far as we know, this is the first report combining TICs extracted automatically with deep learning to develop a diagnostic system.

The rest of this paper is organized as follows: the related works are introduced in Section 2. Section 3 describes the data acquisition and pre-processing, sparse non-negative matrix factorizations, the deep learning classifier and the framework of the classification system. In Section 4, we present the classification results and discuss the results obtained in the experiment. Finally, we give the conclusion in Section 5.

2. Related works

The TICs extracted from dynamic CEUS image sequences can be used to detect the aberrant functionality of tumor vasculature. Factor Analysis of Dynamic Structures (FADS) [22,23] is a technique used for the extraction of TICs from a series of dynamic images. The technique allows homogenous physiological structures with different temporal characteristics to be identified. Recently, FADS has been investigated in hepatic perfusion studies based on CEUS imaging [24–27]. However, one of the major drawbacks of FADS is that the solution is not mathematically unique when only non-negativity constraints are used. In order to guarantee the solution corresponding to the physiological truth uniquely, we use a sparse non-negative matrix factorizations as presented in our previous work [27] to extract the TICs.

Due to the dual blood supply from the hepatic artery and portal vein, the balance between arterial and portal blood supply is an indication of the type of lesion [26]. From a hemodynamic perspective, benign and malignant lesions in the liver differ in their respective needs in arterial blood supply [12,28]. Furthermore, most FLLs show unique enhancement patterns in the first two phases [18,29]. Therefore, in the study, we extracted the TICs of arterial and portal vein phases.

3. Materials and methods

3.1. Data acquisition and pre-processing

Ultrasound examinations were performed by an experienced ultrasonographist using a Philips iU22 equipped with a C5-1 transducer (Philips Medical Systems, Bothel, WA) and contrast specific imaging (CSI). Initially, a B-mode scan was performed to identify the best approach to the lesion. Thereafter, a bolus of 1.5–2.4 ml of Sonovue (Bracco, Milan, Italy) was injected intravenously through a cubital vein, followed by flush of NaCl 0.9% 5 ml in bolus. Real-time side by side contrast-enhanced mode continuous video clip with a mechanical index of less than 0.20 were acquired at a frame rate of 8-15 fps.

The study population comprised 22 patients with 26 lesions who underwent CEUS in Huazhong University of Science and Technology affiliated Wuhan Union Hospital between March 2012 and May 2013. Positive diagnosis was reached through a combination of other imagistic methods (CT and CE-MRI), liver biopsy in uncertain cases or followup for a minimum period of sixth months. All the cases consisted of 6 hepatocellular carcinomas (HCCs), 10 cavernous hemangiomas (CHs), 4 liver abscesses, 3 metastases (METASs), and 3 localized fat sparings (LFSs). The patients' ages ranged from 18 to 73 years (mean, 43.5 ± 9.9 years), 12 case of male and 10 case of female. The average size of the tumor was 21.2 ± 13.8 mm (size range, 10.0–56.3 mm) for benign lesions and 23.0 ± 10.3 mm (size range, 9.0–32.2 mm) for malignant tumors.

To minimize the impact of breathing motion on TICs extraction and improve the accuracy of the classification system, an image correction technique as presented in our previous work [30] that combining of template matching and frame selection was applied to compensate respiratory motion throughout each CEUS video. Respiratory motion compensation for the free-breathing data is an obligatory pre-processing step before the TICs extraction.

3.2. Sparse non-negative matrix factorizations

To extract the TICs from the dynamic CEUS image sequences, we introduce a sparse non-negative matrix factorizations (SNMF) [27,31] which uses the sparseness of each pixel in all coefficient images as a degree of the amount of mixing. The sparseness degree function is the ℓ_1-norm of each pixel. The objective function is defined by:

$$\min_{C,F} \quad \frac{1}{2}\left\|A - CF\right\|_F^2 + \alpha\sum_{i=1}^{N}\left\|C_i\right\|_1^2, \quad s.t. \quad C, F \geq 0 \tag{1}$$

where the size of matrix A is $N \times M$, N is the number of pixels in the image and M is the number of dynamic images. Matrix C and matrix F are the coefficients image and the TICs which defined in FADS model. C_i is the ith row vector of C.

In order to correct for the nonuniqueness of the solution in optimization problem (1), we use the Frobenius norm of F to constraint it. The final objective function becomes:

$$\min_{C,F} \quad \frac{1}{2}\left\|A - CF\right\|_F^2 + \alpha\sum_{i=1}^{N}\left\|C_i\right\|_1^2 + \beta\left\|F\right\|_F^2, \quad s.t. \quad C, F \geq 0 \tag{2}$$

where $\beta > 0$ is a parameter to suppress $\| F \|_F^2$, and $\alpha > 0$ is a regularization parameter to balance the trade-off between the accuracy of approximation and sparseness of C.

The objective function is solved by the alternating non-negativity-constrained least squares (ANLS) algorithm referred in [31]. The sparse NMF (SNMF) algorithm begins with the initialization of F with non-negative values. Then, it iterates the following ANLS until it is convergence:

$$\min_{C}\left\|C(F \quad \sqrt{\alpha}\boldsymbol{e}_{K\times 1}) - (A \quad \mathbf{0}_{K\times 1})\right\|_F^2, \quad s.t. \quad C \geq 0 \tag{3}$$

where $\boldsymbol{e}_{\boldsymbol{K\times 1}} \in \mathrm{R}^{\boldsymbol{K\times 1}}$ is a column vector with all components equal to one, $\mathbf{0}_{K\times 1} \in \mathbb{R}^{K\times 1}$ is a zero vector, and

$$\min_{F}\left\|F^T(C^T \quad \sqrt{\beta}\boldsymbol{I}_K) - (A^T \quad \mathbf{0}_{M\times K})\right\|_F^2, \quad s.t. \quad F \geq 0 \tag{4}$$