Multiparametric approach for Dynamic Contrast-Enhanced Ultrasound imaging of prostate cancer

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed type of non-cutaneous cancer in American men [1]. A sufficiently reliable PCa imaging method is currently not available, leaving systematic biopsy as the guideline-recommended technique for PCa diagnosis [2]. Dynamic Contrast-Enhanced Ultrasound (DCE-US) is currently being studied for the characterization of prostatic tissue, since it might prove able to reveal the vascular changes associated with (PCa) angiogenesis [3]. The effect of PCa on blood flow, however, is ambiguous [4]; assessment of the contrast agent kinetics that is more objective than the visual inspection of the contrast video is therefore required.

In recent years, parametric analysis of DCE-US recordings has shown promising results in distinguishing benign and malignant tissue. The pixel-specific evolution of contrast intensity over time, referred to as the time-intensity curve (TIC), can be used to extract valuable heuristic parameters: the peak intensity (PI), the peak time (PT), the appearance time (AT, where the TIC reaches 5% of the PT), the wash-in time (WIT, from the AT to the point where the TIC reaches 95% of the PI), and the full-width half maximum (FWHM). Analysis of the TIC by fitting the data by a local density random walk model also allows for the extraction of physics parameters such as the mean transit time ($\mu$), the skewness parameter ($\kappa$), and the ratio between the diffusive and convective time ($\lambda = \mu \kappa$) [5]. Lastly, the TIC similarity between each pixel and its neighbours can be quantified by the spectral coherence ($\rho$) or spatiotemporal correlation ($r$), providing a measure of contrast dispersion [6].

The mentioned parameters can be viewed as related to dispersion or perfusion. Therefore, we hypothesize that they exhibit complementary information. A combination of parameters might thus improve the accuracy of PCa localization in DCE-US images. We tested three supervised machine learning strategies to combine individual parameters in a multiparametric approach.

Materials & Methods

At the Academic Medical Center, University of Amsterdam, DCE-US recordings were performed in 19 patients that were referred for radical prostatectomy. The procedure was carried out using a 2.4 mL SonoVue\textsuperscript{\textregistered} (Bracco, Milan) bolus that was intravenously injected and imaged with an iU22 ultrasound scanner (Philips, Bothell; equipped with a C10-3v or C8-4v probe). Histopathological analysis allowed us to draw $\sim$0.5-cm\textsuperscript{2} regions of interest (ROIs) on the B-mode images, depicting 43 benign and 42 malignant areas on 45 DCE-US images in total. From the pixels in these ROIs, all parameters mentioned in the introduction were extracted following the methods in [5, 6]. Subsequently, these parameters were individually evaluated using the optimum threshold based on their Receiver Operating Characteristics (ROC) curve.

The accuracy of the multiparametric classification was evaluated in each prostate using the other prostates as a training set following a leave-one-out approach. Values were normalized to their 90\textsuperscript{th}
percentile. Due to the ease of its implementation, the $k$-Nearest Neighbour ($k$-NN) approach is often used as the benchmark for other machine learning approaches [7]. This algorithm classifies each pixel in the test set by assessing the most represented class in the $k$ pixels with the shortest distance in multiparametric space ($k = 5$, Euclidean distance). Furthermore, we evaluated a Support Vector Machine (SVM) algorithm that defines a hyperplane separating benign and malignant pixels in the training set [7]. Subsequently, each pixel in the test set is classified depending on its location with respect to this decision boundary. A nonlinear hyperplane based on a radial basis function (i.e., Gaussian) was adopted and the pixels in the training set were downsampled by a factor 30 to reduce computation time. In addition, a Gaussian Mixture Model (GMM) approach was performed [8]. For this, the same-class pixels are described by Gaussian probability distributions in multiparametric space, allowing us to classify each test pixel as the class for which it has the highest probability ($p_A$). Moreover, we defined a confidence level of the classification based on the ratio of the two probabilities ($p_A$ and $p_B$) via $P = 2p_A / (p_A+p_B) – 1$. The analyses were performed in Matlab® (MathWorks, Natick, MA).

<table>
<thead>
<tr>
<th>Parameters:</th>
<th>ROC: single parameters</th>
<th>$k$-NN</th>
<th>SVM</th>
<th>GMM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>WTT</td>
<td>$\mu$</td>
<td>$\kappa$, $\lambda$, $r$</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>73</td>
<td>72</td>
<td>72</td>
<td>78 (65–91)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>71</td>
<td>75</td>
<td>74</td>
<td>74 (64–96)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>75</td>
<td>68</td>
<td>70</td>
<td>72 (62–92)</td>
</tr>
</tbody>
</table>

![Fig 1. Performance of the best-performing single parameters as well as the best-performing multiparametric sets using the three machine learning approaches. The mean of the multiparametric sets as well as the median (10%–90% range) are reported. Below the table, the multiparametric maps of overlaying two imaging planes are shown alongside histopathology. Suspicious regions are shown in red, whereas non-suspicious areas are depicted in green. The transparency of the GMM images scales with the confidence level.](image)

**Results**

For each classification algorithm, the multiparametric set consisting of one to four parameters with the highest average accuracy over all prostates was selected. The table in Fig. 1 reports the classifier performance as well as the best performing single parameters from similarity analysis, curve assessment, and model-based analysis, respectively. The multiparametric results of the $k$-NN algorithm are an improvement as well as those of the SVM and, in particular, the GMM, which outperforms the single parameters over all performance measures.
In Fig. 1, full-plane multiparametric maps are shown alongside the histopathology to give an impression of the classifiers’ results. Generally, \(k\)-NN algorithms yield images in which classes are somewhat scattered instead of delineated in specific malignant and benign areas. Furthermore, the GMM algorithm allows the definition of a confidence level that enables us to assess the likelihood of misclassification. Exclusion of low-confidence pixels was shown to result in an increased accuracy.

**Discussion and Conclusion**

In this work, we evaluated the performance of multiparametric DCE-US for the localization of PCa using several machine learning approaches. Due to the underlying design of the \(k\)-NN, SVM, and GMM algorithms and the differences in parameter distributions, each method yields a different best-performing parameter set. However, all approaches demonstrate that a combination of dispersion and perfusion related parameters mostly improves the accuracy of classification, that is, all of them select both \(r\) and \(\mu\) or \(\lambda\). In comparison, the SVM and the GMM seem more suitable for this technique than the \(k\)-NN algorithm.

Validation in an extended patient group and further optimization of the classification algorithms are recommended. Nevertheless, the results obtained by multiparametric classification of DCE-US are promising and suggest that this technique might become useful in targeted biopsy or the planning of focal therapy.

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**References**