3-D multi-parametric contrast-enhanced ultrasound for the prediction of prostate cancer

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● *Original Contribution***3-D MULTI-PARAMETRIC CONTRAST-ENHANCED ULTRASOUND FOR THE PREDICTION OF PROSTATE CANCER**ROGIER R. WILDEBOER,^{*} RUUD J.G. VAN SLOUN,^{*} PINTONG HUANG,[†]
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Abstract—Trans-rectal ultrasound-guided 12-core systematic biopsy (SBx) is the standard diagnostic pathway for prostate cancer (PCa) because of a lack of sufficiently accurate imaging. Quantification of 3-D dynamic contrast-enhanced ultrasound (US) might open the way for a targeted procedure in which biopsies are directed at lesions suspicious on imaging. This work describes the expansion of contrast US dispersion imaging algorithms to 3-D and compares its performance against malignant and benign disease. Furthermore, we examined the feasibility of a multi-parametric approach to predict SBx-core outcomes using machine learning. An area under the receiver operating characteristic (ROC) curve of 0.76 and 0.81 was obtained for all PCa and significant PCa, respectively, an improvement over previous US methods. We found that prostatitis, in particular, was a source of false-positive readings. (E-mail: r.r.wildeboer@tue.nl) © 2019 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Prostate cancer, Systematic biopsy, Dynamic contrast-enhanced ultrasound, Contrast ultrasound dispersion imaging, 3-D, Machine learning.

INTRODUCTION

Minimally invasive diagnosis of prostate cancer (PCa) is still a fundamental challenge in biomedicine in spite of being the most prevalent non-skin malignancy among Western men (American Cancer Society 2017). Therefore, according to the most recent guidelines (Mottet et al. 2017), patients with suspicious prostate-specific antigen blood levels and/or suspicious digital rectal examination must undergo a non-targeted 10- to 12-core systematic biopsy (SBx) under ultrasound (US) guidance (Ukimura et al. 2013). In the United States alone, an estimated number of 1.3 million men receive SBx annually (Hutchinson et al. 2016) against an expected 164,690 actual PCa diagnoses in 2018 (Siegel et al. 2018). Unfortunately, this procedure is associated with complications like hematuria, hematospermia and inflammation (Loeb et al. 2013); around 25% of the patients report lower urinary tract symptoms after biopsy, and in up to 6% of the patients, post-biopsy infection leads to hospitalization. Moreover, there is a well-reported risk of under-diagnosis of

significant and over-diagnosis of insignificant disease (Loeb et al. 2014), as classified by Gleason scoring of histopathology (Gleason 1992). Hence, there is a high clinical demand for imaging methods that allow biopsy targeting of only significant PCa-suspicious areas, reducing the number of negative biopsies.

Over the last decades, the limited PCa detection accuracy of classic medical imaging modalities has spurred the development of multi-parametric scoring strategies for magnetic resonance imaging (MRI) and US (Barentsz et al. 2016; Postema et al. 2015), as well as the introduction of novel modalities, such as quantified dynamic contrast-enhanced US (DCE-US) (Halpern 2006; van Hove et al. 2014) and shear-wave elastography (Correas et al. 2014). These technologies are still very much in development. In particular, benign prostatic hyperplasia (BPH) and prostatitis are often mentioned as causes for false-positive PCa reading on MRI (Barentsz et al. 2016; Panebianco et al. 2018; Wang et al. 2018) and US (Gao et al. 2016; Halpern 2006; Zhao et al. 2013).

One of the recent developments in PCa imaging is contrast-US dispersion imaging (CUDI) for DCE-US quantification (Kuenen et al. 2011; Kuenen M et al. 2013;

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Mischi et al. 2012; van Sloun et al. 2017b). These techniques are designed to characterize the kinetic behavior of a bolus of intravascular US contrast agents (UCAs) employed to visualize vascularity (Cosgrove 2006). PCa is typically associated with angiogenic processes that affect the vascular architecture (Russo et al. 2012). As CUDI is designed to quantify abnormalities in dispersion and perfusion, we found that the extracted CUDI parameters were indeed valuable biomarkers for PCa diagnosis. In 2-D, parametric maps resulting from these analyses were shown to have a higher diagnostic performance than heuristic features, such as maximum intensity projection; and a multi-parametric approach combining complementary CUDI parameters was shown to enhance the diagnostic performance even further (Wildeboer et al. 2017).

3-D DCE-US recordings that allow the visualization of the entire prostate with only one bolus injection have recently become available. Moreover, 3-D imaging alleviates the need for assumptions on out-of-plane kinetics when modeling a 3-D process in 2-D. So far, similarity-based CUDI was successfully expanded to 3-D despite lower temporal and spatial resolution (Schalk et al. 2015b, 2018), and a new algorithm exploiting the full 3-D convection-dispersion equation was developed (Wildeboer et al. 2018). With the 3-D implementation of all CUDI algorithms, formerly only available in 2-D, we strived to estimate a full set of complementary 3-D CUDI features that could be used for whole-gland multi-parametric imaging.

The aim of this work was to evaluate and compare 16 individual 3-D DCE-US/CUDI model-based parameters for the detection of PCa, as well as to examine the technical feasibility of combining their information to more accurately predict individual SBx outcomes. To this end, we describe the implementation and validation of both a single-parametric and a multi-parametric approach in the remaining sections of this paper.

MATERIALS AND METHODS

Clinical data acquisition

The 3-D DCE-US recordings were carried out at the Second Affiliated Hospital of Zhejiang University (Hangzhou, China). The study was approved by the Institutional Review Board. Participants were scheduled for standard 12-core SBx and signed an informed consent. Before biopsy, 2-min contrast imaging was performed using a RIC5-9 probe connected to a LOGIQ E9 ultrasonic scanner (GE HealthCare, Wauwasota, WI, USA). To this end, a 2.4-mL SonoVue (Bracco, Milan, Italy) contrast-agent bolus was intravenously administered. The volumetric cine-loops were acquired with a "low" image quality setting to maximize the frame rate, and UCA disruption was avoided by limiting the output power (AO%) to 10. The

data were then projected to Cartesian coordinates with a voxel size of 0.25 mm and the frame rate was maximized by choosing the field-of-view as narrow as possible, overall being 0.27 Hz on average.

A total of 58 3-D DCE-US recordings were performed, but 15 acquisitions were excluded based on protocol violations (seven), technical complications (six) or an inconclusive biopsy report (two). In the remaining set, a total of seven biopsy cores could not be scored (in three patients) and were left out of the analysis. All other biopsy cores were histopathologically examined (Montironi et al. 2005) and marked as benign (B), BPH, prostatitis (P), Gleason score 3+3 insignificant prostate cancer (iPCa) or Gleason score $\geq 3+4$ significant prostate cancer (sPCa). Cores that contained both tumor and BPH were classified as malignant, whereas cores that contained BPH as well as P were classified as P.

CUDI

On a fundamental level, CUDI is based on the notion that the behavior of blood in the prostatic (micro)vasculature can be modelled by anisotropically dispersive, multi-trajectory fluid flows in porous media. As a consequence, the kinetics of the UCA concentration (referred to as C) obey the 3-D convection-dispersion equation (Ewing and Wang 2001; LaBolle et al. 1998; Whitaker 1967)

$$\partial_t C = \nabla \cdot (\mathbf{D} \nabla C) - \mathbf{v} \cdot \nabla C, \quad (1)$$

where we assume the convective 3×3 dispersion tensor ($\mathbf{D}$) and the 3×1 velocity vector ($\mathbf{v}$) to be locally constant.

There are several ways to exploit this theoretical framework to quantify the local convective-dispersive behavior in tissue, but all CUDI algorithms essentially rely on the voxel-specific contrast-intensity evolution over time (*i.e.*, time-intensity curve [TIC]) to describe the UCA concentration at each voxel as the bolus passes. In a model-fit approach, each individual TIC is fitted by a local-density random walk (LDRW) model to quantify the local convective dispersion (Kuenen et al. 2011). Alternatively, the similarity in TIC shape between a voxel and its neighbors can serve as characterization of the dispersion in the vessel architecture connecting those voxels (Kuenen MPJ et al. 2013; Mischi et al. 2012; Schalk et al. 2017). In addition, a system identification approach can be employed to quantify this transition in terms of apparent velocity and dispersion in the underlying convective-dispersion system (van Sloun et al. 2017b). These approaches will be discussed more elaborately in the remaining sections of the materials and methods.

Data pre-processing

Because of the low frame rate of volumetric acquisitions, it is more difficult to suppress noise before analysis and to mitigate the effect of UCA recirculation. Nevertheless, it was shown that volume rates of approximately 0.25 Hz

were sufficient to resolve clinically relevant contrast-agent kinetics (Schalk *et al.* 2015b). To prevent noise and motion artefacts from obscuring the recordings, we performed signal spatiotemporal subspace selection through singular value decomposition (Demené *et al.* 2015) after spatial filtering (performed block-wise, isolating the first four signal components) and spatial downsampling, as described by Schalk *et al.* (2015b) for the model-fit and system identification approaches.

Model-fit analysis

The 1-D formulation of the convective-dispersion eqn (1) gives rise to the LDRW model (Mischi 2003; Mischi *et al.* 2003; Strouthos *et al.* 2010), that is, the shape of TICs was considered to be the result of a UCA dispersion process in a flowing carrier fluid (*i.e.*, the blood flow). Assuming that the conversion from the video quantization levels (Q) to the actual UCA concentration was known and given by a logarithmic compression based on the dynamic range (DR) factor $A = 255 \log_{10}(e)(10/DR)$, the TIC could be described by a modified LDRW model (Kuenen *et al.* 2011)

$$Q(t) = A \ln \left(\alpha \sqrt{\frac{\kappa}{2\pi(t-t_0)}} e^{-\frac{\kappa(t-t_0-\mu)^2}{2(t-t_0)}} + 1 \right). \quad (2)$$

In this formulation, t_0 is the theoretical injection time, α is the area under the TIC, κ is a dispersion-related parameter and μ is the mean transit time. These parameters were estimated by fitting the actual TIC by this model through a mean squared error minimization over the time interval $[T_0, T_{\text{end}}]$

$$\{\hat{\alpha}, \hat{\kappa}, \hat{\mu}\} = \min_{\alpha, \kappa, \mu} \left(\sum_{t=T_0}^{T_{\text{end}}} \left(Q_{\text{LDRW}}(t) - Q(t) \right)^2 \right). \quad (3)$$

The minimization procedure initializes with the naïve (*i.e.*, recirculation-free) maximum-likelihood estimates of μ and κ (Kuenen *et al.* 2014); and $\hat{\alpha} = 10 \max [Q(t)]$ was empirically chosen as a good initial guess for the area under the TIC curve. To avoid artefacts caused by recirculation, the fitting procedure was subsequently carried out only from 8 s after injection to 12 s after reaching the peak intensity (PI) in the five-element moving-average filtered TIC.

Similarity analysis

In addition to the LDRW variables, the spatiotemporal correlation (r), spectral coherence (ρ) or mutual information (MI) between the voxel of interest and its neighbors in a shell-shaped kernel were considered to be a measure of convective dominance over the dispersion. The shell-shaped kernel included all pixels between a minimum and maximum distance from the center pixel,

defined by the imaging system resolution and desired resolution of the parametric analysis, respectively. For the 3-D implementation of these analyses, we referred to the previously published works on the subject (Schalk *et al.* 2015a, 2015b, 2018). Taking into account the resolution of the imaging system employed in this study, the analysis was carried out with an inner kernel radius of 1.0 mm and an outer kernel radius of 2.5 mm.

System identification analysis

The transition of concentration evolution from voxel to voxel could also be considered governed by a convective-dispersive *system*. As such, eqn (1) in 1-D gave rise to the following Green's function representing the system's spatiotemporal impulse response mapping the TIC at the center voxel to that of another voxel, n , at distance L_n (Mischi 2003; van Sloun *et al.* 2017b)

$$w_n(t|L_n, v, D) = \frac{H(t)}{\sqrt{4\pi Dt}} \exp \left(-\frac{(L_n - vt)^2}{4Dt} \right), \quad (4)$$

provided that v and D are locally constant and homogeneous. $H(t)$ is the Heaviside step function.

Based on the TICs measured at the center voxel (c_0) and voxel $n(c_n)$, the local values of v and D could be estimated by system identification. In contrast to the Wiener filter maximum-likelihood implementation in 2-D, we used a direct model-based least-squares minimization procedure (van Sloun *et al.* 2017b),

$$\{\hat{v}, \hat{D}, \hat{B}\} = \min_{v, D, B} \left(\sum_{n=1}^N \left(B c_n(t) - c_0(t) * w_n(t|L_n, v, D) \right)^2 \right); \quad (5)$$

where B is an arbitrary scaling factor and $*$ is a convolution in time. The minimization procedure was carried out over N voxels in a shell-shaped kernel with an inner and outer radius of 1 and 2 mm, respectively.

In the (very probable) case that v and D were not radially isotropic, these values were only valid for voxels in a certain direction from the center. As we were primarily interested in the dominant v and D , we enforced causality by only including kernel-voxels that showed a positive cross-correlation at $t \geq 1$ s (van Sloun *et al.* 2017b). The Péclet number (Pe) is a common fluid-dynamic quantity used to characterize convective-dispersion; for the dilution system in eqn (4), we could define $Pe = L_n \hat{v} \hat{D}^{-1}$.

3-D convective dispersion modelling

The most recent addition to CUDI was spurred by the availability of 3-D DCE-US, allowing a full evaluation of the 3-D convective-dispersion equation (Wildeboer *et al.* 2018). In this approach, $\mathbf{D}$ and $\mathbf{v}$ were assumed locally constant and could thus be directly estimated by solving

eqn (1) as a linear system of first- and second-order concentration gradients in a sufficiently small volumetric kernel. Accordingly, the local least-squares problem was solved in a l_2 -regularized fashion using a moving spherical kernel with a diameter of 7 voxels.

To mitigate the effect of high-frequency noise in estimating the gradients, these were computed by convolution between the concentration data and derivatives of the Gaussian function (Blom et al. 1993). The Gaussian standard deviations, σ and σ_t , defined the scale of the assessed gradients in space and time, respectively. These gradients were computed in the Fourier domain, using Gaussian functions with $\sigma = 1$ mm and σ_t equal to the inverse of the frame rate. Finally, the estimates of $\mathbf{D}$ and $\mathbf{v}$ were expressed in terms of the apparent dispersion coefficient and the magnitude of the velocity, which were defined as $D_{CD} = |\text{Tr}(\mathbf{D})/3|$ and $v_{CD} = |\hat{\mathbf{v}}|$, respectively, where $\text{Tr}(\bullet)$ is the trace operator.

Fractal dimension analysis

Fractal dimension (FD) modelling of flow patterns obtained by CUDI analyses could serve as a geometric measure of vascular structures (Saidov et al. 2016). Essentially, FD quantified the rate at which the level of detail changed for different scales of reference; in this work, we assessed the change in blood flow patterns within kernels of an increasing size. In 2-D as well as in 3-D, there was a relation between the FD and relative dispersion (RD) of the regional blood flow distribution (Qian and Basingthwaihte 2000). As the PI was shown to reflect properties of blood flow, we define RD as σ_{PI}/μ_{PI} , that is, the ratio between the standard deviation and the mean of the PI as derived by the LDRW model-fit analysis. This was related to FD through (Qian and Basingthwaihte 2000; Saidov et al. 2016)

$$\frac{RD(m)}{RD(m_{\text{ref}})} = \left(\frac{m}{m_{\text{ref}}} \right)^{1-\text{FD}}. \quad (6)$$

Here, m is the number of zones into which the initial kernel was divided. We used a cubic kernel of $6 \times 6 \times 6$ voxels, which was split into eight $3 \times 3 \times 3$ zones and, analogously, in 27 $2 \times 2 \times 2$ zones. In addition, the kernel could be divided in 12 equally sized $3 \times 3 \times 2$, $3 \times 2 \times 3$ or $2 \times 3 \times 3$ zones, etc. We took eight zones as m_{ref} , the initial division reference. To assess the vascular heterogeneity, we successively evaluated the model in our kernel for eight, 12 ($3 \times$), 18 ($3 \times$), 27, 54 ($3 \times$) and 216 equally sized zones. As a result, the FD reflected the rate at which the level of detail was lost when assessing the blood flow at an increasingly larger scale. For each kernel, the FD-value was estimated by linear regression of the log-linearized relation that follows from eqn (6) (Mischi et al. 2015; Saidov et al. 2016).

Single-parametric performance

To assess the correlation between a parameter value and the presence of benign or malignant prostatic disease, the 3-D prostate was delineated and divided into 12 regions (i.e., four regions from left to right for the apex, mid- and base parts of the gland). The regions extended approximately 22 mm in the anterior direction (i.e., the length of the biopsy needle) and were constructed under slight lateral angles to conform to the SBx template shown by Ukimura et al. (2013). An inter-region margin of 5 mm was adopted. This template was registered to the outer contours of each individual prostate in order to reach an as high as possible level of reproducibility. An additional advantage of this approach was that the validation was less sensitive to motion artefacts, which could complicate voxel-to-voxel matching.

Correspondence between parameters was assessed by generating all 3-D parametric maps and post-processing with a 1.5-voxel (i.e., approximately 1.13 mm) Gaussian spatial filter. Subsequently, we calculated the median, 10th percentile, 90th percentile, mean, skewness, kurtosis, variance and entropy (van Sloun et al. 2017a) of the parametric distributions in each region. The linear correlation between every pair of parameters was assessed in terms of the linear Pearson correlation coefficient; any correlation with p value above 0.05 was not deemed to significantly reflect the relation between parameters. Moreover, as our distributions were not necessarily Gaussian, we employed a Wilcoxon rank sum test to assess the level of significance of each feature to distinguish benign (diseases) from PCa or sPCa.

Then, in order to obtain the single-parametric performance, receiver operating characteristic (ROC) curves were acquired to assess each parameter's power to discriminate benign and malignant regions or benign and significantly malignant regions (van Erkel and Pattynama 1998). The performance was quantified by the area under the ROC curve (ROC-AUC).

Multi-parametric performance

After a full set of CEUS/CUDI features was established, we exploited a support vector machine (SVM) and a Gaussian mixture model (GMM) as a discriminative and generative machine-learning strategy, respectively, to combine potential complementary information. An SVM essentially distinguished two classes by computing a hyperplane in multi-parametric space, which maximized the margin between the training-set different-class instances that were closest to it (i.e., the support vectors) (Cortes and Vapnik 1995). New instances were subsequently classified depending on their position relative to this hyperplane. Analogously, supervised GMM algorithms identified each class's multi-parametric distribution based on the training set and then classified each test instance as the class for which it had the highest probability (McLachlan 1992).

The machine-learning approaches were implemented in the Matlab (Version 2015b, MathWorks, Natick, MA, USA) environment and their feasibility was assessed by evaluating their performance in a leave-one-prostate-out cross-validation procedure to be least sensitive to training-set imbalances. To avoid overfitting, we selected the region-mean as the most representative feature for all parameters. Parameter selection was subsequently performed on each training set through a backward feature elimination ranking procedure (Guyon and Elisseeff 2003), again in a leave-one-prostate-out fashion. This way, the best-suited feature set was specifically determined based on the training set of each cross-validation fold specifically, without observing the samples of the test patient.

For the SVM, a radial-basis kernel was adopted. Furthermore, the misclassification penalty for negative and positive instances was weighted in the training phase to compensate for the training-set unbalance. Other hyperparameters were tuned in each training fold. The GMM robustness was improved by adding 0.01 to the diagonal elements of the covariance matrices, and the benign- and malignant-class distributions were fitted with 2 and 1 Gaussian(s), respectively. Each parameter was normalized by the 95-percentile value over the entire set to make the training invariant to parameter scale while preventing outliers from affecting the scaling. The multi-parametric performance was assessed by computing ROC curves based on the double-logit distance to the SVM-hyperplane (*i.e.*, $1/[1+\exp(2x)]$ with x as the distance) or the GMM-confidence scores as defined by Wildeboer *et al.* (2017). These performance measures were also used for the feature selection during training.

Research framework

The research framework is summarized in Figure 1. Single parameters were extracted from 43 3-D DCE-US videos of the prostate, and in total, 509 biopsy cores were matched to specific regions in the 3-D parametric maps to evaluate their value as biomarker of PCa. Subsequently, machine learning by means of an SVM and a GMM was examined for the prediction of SBx outcomes. Its performance was cross-validated in a leave-one-patient-out fashion.

RESULTS

Single-parametric performance

An example of all 3-D parametric maps in a prostate harboring sPCa is depicted in Figure 2. The inter-parameter correlations are shown in Figure 3, revealing strong positive and negative correlations in bright green and blue, respectively. In particular, parameters extracted using the same algorithm tended to be more correlated. As for the correlation with the presence of sPCa, in total, 85 parameters showed significant differences in distribution and thus potential as a biomarkers.

As the mean value was generally the most meaningful feature (with 14 of the 16 mean parameter distributions being significant biomarkers), this measure was more elaborately examined. In Figure 4, the per-region-mean parameter distributions are depicted using a boxplot with each region displayed as gray dots. The number of regions of each class are shown above the boxplot. Significant or highly significant differences are connected by a line, either marked by * or ** for $p < 0.05$ and $p < 0.005$, respectively.

Fig. 1. Schematic overview of model-based machine-learning strategy, consecutively showing (1) 3-D DCE-US data acquisition, (2) model-based feature extraction, (3) region-wise feature extraction and (4) both discriminative and generative machine-learning with ROC-AUC-based feature selection to be validated in a leave-one-patient-out fashion; (5) SBx cores ($n = 509$) served as ground truth. BPH = benign prostatic hyperplasia; DCE-US = dynamic contrast-enhanced ultrasound; PCa = prostate cancer; ROC-AUC = area under the receiver operating characteristic curve; SBx = systematic biopsy.

Fig. 2. Example of all 16 3-D parametric prostate maps in the same patient with PCa; the biopsy revealed significant (Gleason 4 + 5) prostate cancer in all three left lateral SBx cores. PCa = prostate cancer; SBx = systematic biopsy; TIC = time-intensity curve.

To obtain the level of significance, a Wilcoxon rank sum test was employed.

In terms of the ROC-AUC, the diagnostic potential to distinguish between either benign tissue (*i.e.*, B, BPH or P) and PCa or benign tissue and sPCa is listed in Table 1 for all of the single parameters. The wash-in time (WIT) and the convective velocity were the best performing single parameters.

Multi-parametric performance

The results of the multi-parametric approach are also shown in Table 2, alongside each classifier's performance using only a single parameter. For comparison, the two best performing single parameters for PCa and sPCa were chosen, WIT and v_{CD} , respectively. The GMM especially showed a superior performance compared with the single parameters. As the feature selection

Fig. 3. Color-coded inter-parameter correlation matrix of all model-based features, grouped per model parameter; Pearson correlation coefficients with $p > 0.05$ are not considered to significantly reflect linear correlation and are marked with a •. The two right columns show the Wilcoxon rank sum test's p value for the association of the features with the presence of PCa or sPCa. α = area under the time-intensity curve; AT = appearance time; D_{CD} = convective dispersion; D = dispersion; FD = fractal dimension; κ = dispersion parameter; MI = mutual information; PCa = prostate cancer; Pe = Péclet number; PI = peak intensity; r = spatiotemporal correlation; sPCa = significant prostate cancer; μ = mean transit time; v_{CD} = convective velocity; V = velocity; WIR = wash-in rate; WIT = wash-in time; ρ = spectral coherence.

was incorporated in the training folds, there was no single multi-parameter set. However, as depicted in Figure 5a, the selection of the parameters clearly favored a specific order of combination. Ultimately, only the GMM and SVM with combinations of respectively three and eight parameters were included in the analysis. Figure 5b shows the distribution of the GMM scores for all pathologies.

DISCUSSION

In the past decade, CUDI has been shown to be a promising tool for the characterization of prostatic tissue based on 2-D DCE-US recordings (Kuenen *et al.* 2011; Kuenen M *et al.* 2013; Misch *et al.* 2012; van Sloun *et al.* 2017b). 3-D analysis does not only mitigate the risk of missing PCa lesions outside of the conventional 2-D field of view but the clinical work flow is also substantially sped up because of the need for only one bolus injection.

Prompted by the introduction 3-D DCE-US imaging, 3-D CUDI similarity analysis has recently been developed and validated against the presence of PCa in SBx cores (Schalk *et al.* 2018). Moreover, a novel method for 3-D convective-dispersion modelling was developed (Wildeboer *et al.* 2018). This work elaborates on the expansion of all CUDI algorithms into 3-D. Moreover, we assessed the correspondence of the 3-D CUDI parameters as well as their ability to discriminate sPCa from benign prostatic tissue.

Interestingly, most 3-D parameters from different analyses had only a low to moderate correlation on a voxel-to-voxel value basis. There are however some distinctive resemblances between μ and WIT, as well as between r , ρ and MI, which follow from sharing a common underlying model and physical principles. Convective dispersion and system-identified dispersion seem remarkably uncorrelated. As hypothesized by Wildeboer *et al.* (2018), this might be the consequence of the former reflecting spatial dispersion, whereas the latter primarily captured

Fig. 4. Distributions of region-mean parameter values for benign (B), benign prostatic hyperplasia (BPH), prostatitis (P), insignificant (*i.e.*, Gleason 3 + 3) PCa and significant (*i.e.*, Gleason $\geq 3 + 4$) PCa. The gray dots depict data points, the boxplots reflect their distributions and the lines connect distributions that are significantly (*) or highly significantly (**) different. B = benign; BPH = benign prostatic hyperplasia; P = prostatitis; PCa = prostate cancer; iPCa = insignificant prostate cancer; sPCa = significant prostate cancer; TIC = time-intensity curve.

temporal dispersion of the contrast bolus. We speculated that the moderate correspondence between v and v_{CD} might be caused by spatial convection being partly captured by both v_{CD} and D_{CD} .

PCa-induced angiogenesis has been considered a key discriminating factor for PCa imaging (Padhani et al. 2005) and, indeed for CUDI, to distinguish cancer from healthy tissue. However, benign prostatic diseases, such as

BPH and prostatitis, are also associated to some extent with angiogenesis (Sandhu 2008; Shih et al. 2003). Although BPH often exhibits an increase in microvascular density (Deering et al. 1995), also reflected by BPH having a significantly higher α in Figure 4, other parameters do not generally show suspicious values. In terms of molecular angiogenic activity, BPH + P has been observed to have significantly elevated levels of vascular endothelial

Table 1. 3-D contrast-enhanced ultrasound parameters and their full-set single-parametric performance for both benign tissue versus PCa and benign tissue versus sPCa

Symbol	Parameter Name	Unit	PCa	sPCa
Model-Fit Analysis				
κ	Dispersion Parameter	s^{-1}	0.68	0.66
μ	Mean Transit Time	s	0.72	0.79
α	Area Under The TIC	a.u.	0.57	0.58
Similarity Analysis				
r	Spatiotemporal Correlation	-	0.70	0.71
ϱ	Spectral Coherence	-	0.63	0.64
MI	Mutual Information	-	0.62	0.60
System Identification				
Pe	Péclet Number	-	0.67	0.65
v	Velocity	$mm \cdot s^{-1}$	0.52	0.72
D	Dispersion	$mm^2 \cdot s^{-1}$	0.57	0.67
3-D Convective-Dispersion Modelling				
v_{CD}	Convective Velocity	$mm \cdot s^{-1}$	0.74	0.80
D_{CD}	Convective Dispersion	$mm^2 \cdot s^{-1}$	0.73	0.77
Heuristic Parameters				
WIT	Wash-In Time	s	0.75	0.78
WIR	Wash-In Rate	$a.u. \cdot s^{-1}$	0.64	0.68
PI	Peak Intensity	a.u.	0.59	0.62
AT	Appearance Time	s	0.58	0.63
Fractal Dimension Analysis				
FD	Fractal Dimension	-	0.53	0.52

PCa = prostate cancer; sPCa = significant prostate cancer; TIC = time-intensity curve.

The highest performances for PCa and sPCa are indicated in boldface.

Table 2. Leave-one-patient-out cross-validated ROC-AUC performance of v_{CD} , WIT and a multi-parametric approach for both benign (disease) versus PCa and benign (disease) versus sPCa

Parameter	PCa	sPCa
GMM		
v_{CD}	0.72	0.78
WIT	0.73	0.75
multi	0.76	0.81
SVM		
v_{CD}	0.71	0.78
WIT	0.70	0.72
multi	0.73	0.77

GMM = Gaussian mixture model; PCa = prostate cancer; ROC-AUC = area under the receiver operating characteristic curve; sPCa = significant prostate cancer; SVM = support vector machine; v_{CD} = convective velocity; WIT = wash-in time.

The highest performances for PCa and sPCa are indicated in boldface.

growth factor compared with BPH alone (Huang *et al.* 2018), for example. This might explain why especially regions whose biopsy cores contain prostatitis seem to mimic those with PCa. For this study, it should be underlined that the 17 cores carrying prostatitis were taken from only four patients in total. It is also worth mentioning that prostatic inflammation is considered a distinctive feature for risk of PCa development (Sandhu 2008).

Another trend discernible for almost all parameters was a persistent difference in variance among regions with iPCa

and sPCa. Whereas sPCa is strongly characterized by elevated levels of r , Pe and v_{CD} , for example, and reduced WIT and μ , a number of iPCa regions exhibit values comparable to those containing BPH or no disease at all. As iPCa is generally not associated with life-threatening risks, showing a very low probability of metastasis (Kryvenko and Epstein 2015; Ross *et al.* 2012), this might not pose a problem. The management of Gleason 3 + 3 disease in the diagnostic process and treatment strategy, however, is still a matter of debate among urologists (Mottet *et al.* 2017). In a more extended set, a grade-weighted or three-class classification approach (*i.e.*, B, iPCa and sPCa) could be considered.

In this paper, we also evaluated the feasibility of an SVM-based and a GMM-based machine learning approach to classify biopsy regions. The multi-parametric performance based on GMM outperforms single parameters. Likely, this is because the parameters that are consecutively selected are different in underlying physical meaning; whereas κ , r and MI are related to UCA dispersion, μ , α , v_{CD} and WIT reflect perfusion. The single-parametric evaluation as well as the feature selection order (see Fig. 5) showed that flow-related parameters (*i.e.*, v_{CD} and WIT) contribute most to the classification. Interestingly, α dominantly featured in the best performing multi-parametric sets even though its individual performance was poor. This might indicate that the number of microbubbles passing a certain voxel (*i.e.*, α) only became important once the TIC shape (*i.e.*, μ or WIT) and dispersive fingerprint (*i.e.*, r) were known. Another interesting observation was that, in general, parameters from different analyses were combined. These parameter differed not only in physical quantities that were estimated or the underlying models that were exploited but also in the scale these processes were assumed to be present. Hence, these analyses could be regarded to carry complementary information useful for the detection of PCa.

Because of the limited number of patients in our data set, the learning was restricted to the region-mean values of the parameters. In radiologic practice, however, the spatial appearance of lesions, such as tissue heterogeneity or abnormal spiculation, is also often assessed. Radiomic features allow quantitative extraction of temporal and spatial information from (parametric) images and look beyond the plain voxel-specific parameter or gray-scale values (Aerts *et al.* 2014; Lambin *et al.* 2012; Larue *et al.* 2017). Therefore, the extensive set of features described in this work (such as the maximum value or entropy) might become very useful when applying machine learning in a more extended data set. The same holds for information from other vascular US imaging techniques (*e.g.*, molecular imaging [Turco *et al.* 2017], ultrafast Doppler [Provost *et al.* 2015], super-resolution US [Couture *et al.* 2018] or acoustic angiography [Gessner *et al.* 2013]), other

Fig. 5. (a) Parameter selection frequency over all cross-validation folds shown as bar height with the selection order depicted in color; (b) The GMM score distribution over benign and malignant diseases, similar to Figure 4. α = area under the time-intensity curve; AT = appearance time; B = benign; BPH = benign prostatic hyperplasia; D_{CD} = convective dispersion; D = dispersion; FD = fractal dimension; GMM = Gaussian mixture model; iPCa = insignificant prostate cancer; κ = dispersion parameter; MI = mutual information; P = prostatitis; Pe = Péclet number; PI = peak intensity; r = spatiotemporal correlation; sPCa = significant prostate cancer; μ = mean transit time; v = velocity; v_{CD} = convective velocity; WIR = wash-in rate; WIT = wash-in time; ρ = spectral coherence.

imaging modalities or even blood tests and other clinical data that could provide useful complementary features on a patient level.

Unfortunately, SBx is known to sometimes misrepresent the actual histopathologic fingerprint because of sampling errors (Eichler et al. 2006; Graif et al. 2007; Ukimura et al. 2013) due either to a mismatch between the template and actual location or to missing the region's cancer hotspot. This study might therefore wrongly assume regions to be true negative or false positive. As our analysis was based on the entire region surrounding the biopsy location, we expected that in particular some false positive regions would have been upgraded in a more rigorous histologic examination. As these errors in the ground truth could have potentially impacted both the training and testing, their effect might be significant. In the future, a radical-prostatectomy reference study would enable us to assess the presented (multi)parametric maps value for the localization of PCa. However, such a data set would be severely biased toward PCa presence because healthy, BPH-only or prostatitis-only prostates, which coincidentally comprise a large part of the biopsy population, cannot be represented. A prospective targeted-biopsy study with 3-D-CUDI guidance might eventually help determine its PCa-detection ability. In the last two approaches, we envision the use of a 3-D multi-parametric map (similar to those displayed in Fig. 2) rather than biopsy-region-based assessment.

CONCLUSIONS

This study revealed the potential of a multi-parametric combination of 3-D CUDI parameters, either as single parameters or in a multi-parametric approach through

machine learning by a Gaussian mixture model. We envisage additional optimization of 3-D algorithms and expansion of the data set to prompt further development of this technique (e.g., toward deep learning approaches). Eventually, we believe these approaches might allow reliable imaging of PCa for targeted biopsy procedures.

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