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Convective-Dispersion Modeling in 3D Contrast-Ultrasound Imaging for the Localization of Prostate Cancer

R. R. Wildeboer¹, R. J. G. van Sloun¹, S. G. Schalk, C. K. Mannaerts, J. C. van der Linden, P. Huang, H. Wijkstra, and M. Mischi²

Abstract—Despite being the solid tumor with the highest incidence in western men, prostate cancer (PCa) still lacks reliable imaging solutions that can overcome the need for systematic biopsies. Dynamic contrast-enhanced ultrasound imaging (DCE-US) allows us to quantitatively characterize the vascular bed in the prostate, due to its ability to visualize an intravenously administered bolus of contrast agents. Previous research has demonstrated that DCE-US parameters related to the vascular architecture are useful markers for the localization of PCa lesions. In this paper, we propose a novel method to assess the convective dispersion (D) and velocity (v) of the contrast bolus spreading through the prostate from three-dimensional (3D) DCE-US recordings. By assuming that D and v are locally constant, we solve the convective-dispersion equation by minimizing the corresponding regularized least-squares problem. 3D multiparametric maps of D and v were compared with 3D histopathology retrieved from the radical prostatectomy specimens of six patients. With a pixel-wise area under the receiver operating characteristic curve of 0.72 and 0.80, respectively, the method shows diagnostic value for the localization of PCa.

Index Terms—Prostate cancer, dynamic contrast-enhanced ultrasound, convection, dispersion, 3D.

I. INTRODUCTION

THE most recent cancer statistics list prostate cancer (PCa) as the most common non-cutaneous malignancy among American men, and the third most occurring cause of cancer-related death [1]. To date, however, there is no imaging modality considered to be sufficiently reliable for the diagnosis of PCa. This leaves the ≥ 10 -core systematic biopsy procedure as the guideline-recommended strategy for detection and grading of PCa [2]. Due to the focal, heterogeneous nature of PCa, this procedure has a known risk of missing significant PCa lesions or underestimating its aggressiveness [3]. Conversely, the associated detection of pathologically insignificant PCa leads to overdiagnosis [4]. Reliable imaging is considered key for the reduction of the number of needle-cores by targeted biopsy [5], reduction of low-grade PCa detection, planning and monitoring of focal therapy, and [6] follow-up in active surveillance [7].

Currently, multiparametric magnetic resonance imaging (MRI), ultrasound shear-wave elastography, ultrasound spectral analysis and dynamic contrast enhanced ultrasound (DCE-US) are studied as advanced imaging tools for the localization of PCa with increasingly promising results [5], [8]–[10]. In this work, we focus on DCE-US, in which $\sim 10\text{-}\mu\text{m}$ -sized gas-filled microbubbles (ultrasound contrast agents, or UCAs) are specifically imaged by exploiting their non-linear response [11]. Since UCAs do not leave the blood stream, a DCE-US video of their wash-in and wash-out in the prostate can be used to characterize the underlying vasculature [12]. This is particularly important, as clinically-significant PCa lesions alter the vascular architecture due to angiogenesis [13], [14]. UCA transport kinetics have therefore been studied thoroughly as markers for the localization of PCa [15].

Whereas one might expect a PCa lesion being characterized by a simple increase in perfusion due to increased microvascular density, the effect of cancer growth on the vasculature appears to be more ambiguous and heterogeneous in nature [14], [16]; for instance, a higher fraction of tortuous vessels and raised interstitial pressure might

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just have the opposite effect on perfusion. By viewing the multi-trajectory spreading of the bolus through the prostate as dispersion, the UCA behavior can be modeled as a convective-dispersion process. The essence of contrast-ultrasound video quantification is the extraction of physical parameters underlying this type of processes.

For instance, it was shown that fitting a modified local density random walk model to the measured time-intensity curve (TIC), diagnostically-useful parameters related to perfusion and dispersion could be derived [17]. In another approach, the similarity between TICs was successfully used as a dispersion-related measure for the localization of PCa [18], [19]. In particular, the spatiotemporal correlation (referred to as r) between the TIC of a single pixels with its neighbors in a ring-shaped kernel provided a good quantification of this similarity [20]. Dispersion and velocity were also directly calculated by system identification and their value as markers of PCa imaging has been shown [21]. Whereas the model-based approach characterizes the contrast-agent behavior at each pixel individually, the spatiotemporal approaches quantify the contrast kinetics between multiple pixels.

Until recently, these techniques were limited to a two-dimensional (2D) imaging plane. Three-dimensional (3D) DCE-US acquisitions enable tissue characterization of the entire gland with just one UCA-bolus injection. As a result, the risk of missing lesions is reduced and the procedure time is shortened. Another advantage is that the assumptions on blood flow directionality needed for the evaluation of the UCA kinetics in 2D data are alleviated, enabling full 3D modeling of the kinetic behavior of UCAs in the prostate. The similarity analysis has already been extended to 3D [22], [23]. A systematic-biopsy validated study showed that especially r exhibits a good performance in the localization of PCa [24]. For this, similar to the 2D implementation, the TIC from each voxel is compared to the TICs from surrounding voxels in a shell-shaped kernel and the degree of similarity, r , is seen as a measure for the dispersion within the kernel.

In this work, in contrast to similarity assessment as a measure for dispersion, we aim at estimating convective dispersion and velocity by directly modeling the 3D behavior of the UCA bolus spreading through the prostate as a convective-dispersion process. Different from the 2D analysis, we do not have to make assumptions on out-of-plane kinetics; therefore, we can solve the convective-dispersion equation through least-squares optimization to quantify the local contributions of convective dispersion and convection to the UCA transport kinetics. We analyzed the resulting 3D parametric maps in a multiscale fashion and validated their ability to locally detect PCa by comparison with histopathology.

II. MATERIALS AND METHODS

A. Convective-Dispersion Modeling

1) *Definition of the Least-Squares Problem:* The transport kinetics of the UCA concentration, $C(x, y, z, t)$, which henceforth will be referred to as C for notational convenience, are considered to be governed by the convective-dispersion equation in three dimensions [25], [26],

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

for which we define $\mathbf{D}$ as the locally-constant convective dispersion tensor,

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}, \quad (2)$$

and $\mathbf{v}$ as the locally-constant velocity vector,

$$\mathbf{v} = [v_x, v_y, v_z]^T. \quad (3)$$

By modeling the concentration kinetics as such, we consider a macroscopic, spatially-averaged transport process through the vascular bed rather than the kinetics of individual UCAs. This approach is similar to the treatise of multi-trajectory, anisotropically diffusive flow in porous media [25]–[27].

Since $D_{xy} = D_{yx}$, $D_{xz} = D_{zx}$, and $D_{yz} = D_{zy}$, and the remaining six independent convective dispersion and three independent velocity elements were assumed to be locally constant, the convective-dispersion equation expands to [28]:

$$\begin{aligned} \partial_t C = & D_{xx} \partial_{xx} C + 2D_{xy} \partial_{xy} C + 2D_{xz} \partial_{xz} C \\ & + D_{yy} \partial_{yy} C + 2D_{yz} \partial_{yz} C + D_{zz} \partial_{zz} C \\ & - v_x \partial_x C - v_y \partial_y C - v_z \partial_z C. \end{aligned} \quad (4)$$

High-frequency noise is amplified during the computation of derivatives. This effect is mitigated by computing the concentration gradients through convolution between the data and Gaussian derivatives in space and time [29]. Defining σ and σ_t as the standard deviations in space and time, respectively, we generate the required four-dimensional derivatives of the Gaussian function

$$g(x, y, z, t) = \alpha \exp \left(-\frac{x^2 + y^2 + z^2}{2\sigma^2} - \frac{t^2}{2\sigma_t^2} \right), \quad (5)$$

in which α is a normalization constant such that the area under the function is equal to 1.

The nine elements that define the convective-dispersion process can be calculated by solving the least-squares problem based on Eq. 4:

$$\hat{\beta} = \arg_{\beta} \min ||\mathbf{y} - \mathbf{X}\beta||_2^2. \quad (6)$$

with

$$\mathbf{y} = (\partial_t g) *_{\mathbf{x},t} C, \quad (7)$$

$$\mathbf{X} = \begin{bmatrix} (\partial_{xx} g) *_{\mathbf{x},t} C \\ 2(\partial_{xy} g) *_{\mathbf{x},t} C \\ 2(\partial_{xz} g) *_{\mathbf{x},t} C \\ (\partial_{yy} g) *_{\mathbf{x},t} C \\ 2(\partial_{yz} g) *_{\mathbf{x},t} C \\ (\partial_{zz} g) *_{\mathbf{x},t} C \\ -(\partial_x g) *_{\mathbf{x},t} C \\ -(\partial_y g) *_{\mathbf{x},t} C \\ -(\partial_z g) *_{\mathbf{x},t} C \end{bmatrix}^T, \quad (8)$$

and

$$\beta = [D_{xx}, D_{xy}, D_{xz}, D_{yy}, D_{yx}, D_{zz}, v_x, v_y, v_z]^T. \quad (9)$$

Here, $*_{\mathbf{x},t}$ is the convolution in space and time, and $\hat{\beta}$ is the least-squares estimate of β .

The inference of convective-dispersion coefficients from experimental concentration measurements is an inverse problem which is notoriously ill-conditioned, as discussed in [30]. Therefore, we add an l_2 -norm regularization term to the minimization problem:

$$\hat{\beta} = \arg_{\beta} \min ||\mathbf{y} - \mathbf{X}\beta||_2^2 + \lambda ||\beta||_2^2. \quad (10)$$

This strategy penalizes extreme values in the β -estimate, $\hat{\beta}$, to an extent that is controlled by the regularization parameter λ .

As the size of $\mathbf{y}$ might change, either due to a longer acquisition time (i.e., more frames) or a change in the number of voxels over which the least-squares problem is evaluated, we define a size-independent regularization parameter λ_0 . This parameter relates to λ through $\lambda = \lambda_0 n$, in which n is the number of elements in $\mathbf{y}$.

We successively perform the minimization procedure (i.e., Eq. 10) in a moving, spherical kernel around each voxel of interest. The size of the kernel is defined by its diameter, s . The problem is solved by an elastic-net approach [31]

$$\hat{\beta} = \frac{1}{\sqrt{1+\lambda}} (\mathbf{X}^{*T} \mathbf{X}^*)^{-1} \mathbf{X}^{*T} \mathbf{y}^*, \quad (11)$$

where

$$\mathbf{X}^* = \frac{1}{\sqrt{1+\lambda}} \begin{bmatrix} \mathbf{X} \\ \sqrt{\lambda} \mathbf{I} \end{bmatrix}, \quad (12)$$

$$\mathbf{y}^* = \begin{bmatrix} \mathbf{y} \\ \mathbf{0} \end{bmatrix}, \quad (13)$$

in which $\mathbf{I}$ is a 9×9 -identity matrix and $\mathbf{0}$ is a 9-element zero-vector.

The regularized minimization procedure is performed using QR factorization as implemented in MatlabTM (MathWorks, Natick, MA, USA). To limit computation time, the necessary convolutions are carried out in the frequency domain, using Gaussian functions spanning 24 mm in each direction and 32 s in time. This spatiotemporal support was sufficiently large for the largest-scale Gaussian function.

Finally, we condense the estimates of $\mathbf{D}$ and $\mathbf{v}$ into a scalar convective-dispersion and velocity-specific parameter, respectively. The estimate of the dispersion tensor will be presented in terms of the apparent dispersion coefficient, D_{ADC} , similar to the apparent diffusion coefficient in diffusion-weighted MRI [32], [33]. The degree of dispersion will therefore be defined as the magnitude of the trace $\text{Tr}(\mathbf{D})$ divided by three,

$$D_{ADC} = \frac{1}{3} (D_{xx} + D_{yy} + D_{zz}). \quad (14)$$

The velocity vector will be quantified by the magnitude of its coefficients,

$$v = \sqrt{v_x^2 + v_y^2 + v_z^2}. \quad (15)$$

2) Multiscale Analysis: At a specific time scale (i.e., σ_t), we expect the highest speed that can be captured for a certain spatial support (i.e., a certain choice of σ) to scale with σ/σ_t . Since we consider a macroscopic view of the vascular network, any change in σ would make the analysis become sensitive to different physiological scales in speed and size.

For example, we expect feeding vessels to be more dominant over microvasculature when the range over which the spatial gradients are calculated increases. Therefore, we hypothesize that taking the mean over several scales that are sensitive to the microvasculature could improve the characterization of the underlying tissue.

B. Validation Methodology

1) Simulational Validation: As a first step in the validation of convective-dispersion modeling, we generated a dataset simulating contrast boli traveling or dispersing for a range of velocities and dispersion coefficients, respectively. For the velocity estimation, nine boli traveling at speeds equidistantly ranging from 0.25 mm/s to 2.25 mm/s in the y -direction were simulated at different locations (x_i, z_i) following

$$C(x, y, z, t) = C_0 \exp \left(- \frac{(x-x_i)^2 + (y-v_y t)^2 + (z-z_i)^2}{\gamma} \right). \quad (16)$$

Here, we used $C_0 = 400$ a.u. and $\gamma = 8$ mm². The concentration units correspond to those of the linearized log-compressed data; these values were chosen to reflect the signal intensities observed in clinical DCE-US recordings. To simulate typically-encountered noise, we added Rayleigh-multiplicative noise [34] and convolved with a Gaussian point-spread-function of 1.1 mm, which is the lateral resolution of our system at 25 mm [23]. Subsequently, we added Gaussian-distributed noise with a standard deviation of $C_{noise} = 10$ a.u.

Analogously, we simulated nine concentration sources at different locations (x_i, y_i, z_i) that diffuse equivalently in all directions. To this end, we used the Gaussian probability function that is the solution to Eq. 1 with $\mathbf{v} = \mathbf{0}$ and a uniform diffusion tensor with all its diagonal components equal to dispersion coefficient D , ranging equidistantly from 0.2 mm²/s to 1.8 mm²/s [33], [35]:

$$C(x, y, z, t) = \frac{C_0}{\sqrt{(4\pi Dt)^3}} \exp \left(- \frac{(x-x_i)^2 + (y-y_i)^2 + (z-z_i)^2}{4Dt} \right). \quad (17)$$

Here, C_0 of $5 \cdot 10^8$ a.u. was chosen. Analogously to the simulation highlighting different velocities, noise was added. For both simulations, the simulation space spans $55 \times 55 \times 55$ cubic voxels of 0.75-mm size across 20 frames at a frame rate of 0.25 Hz. Fig. 1 depicts an impression of the simulated videos. In order to appreciate the effect of scale selection for the analysis, σ was varied from 0.75 mm to 3 mm. The analysis was run using $\lambda_0 = 0.1$ and $\sigma_t = 4$ s in a moving spherical kernel with $s = 7$ voxels.

To investigate the combined impact of velocity and dispersion on the estimation, we separately simulated all nine combinations of $D = 0.33, 0.66$ and 1.0 mm²/s with $v = 0.5, 1.0$ and 1.5 mm/s. For this, the convection-term in y -direction has been added to Eq. 17.

Moreover, to determine the optimal settings for the convective-dispersion analysis, we systematically evaluated the impact of different values of λ_0 (i.e., 0.01, 0.05,

Fig. 1. Evolution of concentration over time for the simulation of (a) traveling boli, and (b) dispersive boli, respectively.

0.1, 0.5 and 1) and the diameter of the evaluation kernel s (i.e., 3, 5, 7, 9, and 11 voxels). A σ_t equal to 4 s and σ equal to 3 mm were used as default, so that the entire range of dispersion coefficients and speeds were covered. The performance for each pair of λ_0 and s is quantified by the absolute value of the mean percentage error (AMPE) between estimation and ground truth of v_y and D in the respective simulations. This measure was chosen as it also penalizes systematic under- or over-estimation.

2) Experimental Validation: Two-minute 3D DCE-US acquisitions were performed at the Second Affiliated Hospital of Zhejiang University (Hangzhou, Zhejiang, China) in six patients that were referred for radical prostatectomy. Written informed consent was obtained. Patients received an intravenous 2.4-mL bolus injection of Sonovue® (Bracco, Milan, Italy) and were subsequently scanned in contrast mode with a LOGIQ E9 scanner (GE HealthCare, Wauwasota, WI, USA) equipped with an RIC5-9-D endocavitary transducer driven at 4 MHz. The volume rate was maximized by setting the image quality ‘B’ to ‘low’ and the output power, AO%, was kept at ‘10’ to avoid disruption of microbubbles. Two-minute recording time captures the full wash-in and wash-out of microbubbles and is therefore sufficiently long for our analysis. Furthermore, in a previous publication it was shown that the volume rate (~ 0.25 Hz) is still sufficient to resolve clinically-relevant contrast-agent kinetics [23].

Preprocessing of the DCE-US loops comprised the linearization of the data and the spatial downsampling to a voxel spacing of $0.75 \text{ mm} \times 0.75 \text{ mm} \times 0.75 \text{ mm}$, as described in [23]. The video frame rates remained ~ 0.25 Hz. Using the same range of scales σ_s , our method was applied to the experimental data; gradients were calculated in the Fourier domain and the least-square minimization procedure was performed for each pixel within the prostate with $\lambda_0 = 0.1$ and $s = 7$ voxels. The σ_t was set to the frame rate of the video. The resulting 3D parametric maps were post-filtered using a Gaussian spatial filter with a standard deviation of 1.5 mm (i.e., $2\Delta x$, approximately half the kernel radius).

The radical prostatectomy specimens were sectioned, haematoxylin and eosin-stained and histopathologically examined [36] by an experienced uropathologist, marking tumor surface and Gleason Score [37]. Subsequently, the histopathologic data were digitally reconstructed in 3D using radial-basis functions [38], and registered to the 3D in-vivo prostate with a surface-based algorithm [39]. Tissue with a Gleason Score equal or higher than $3+3$ was considered to be malignant. The dataset consisted of radical prostatectomy specimens with PCA

of Gleason Score $3+3=6$ ($1\times$), $3+4=7$ ($3\times$), $4+5=9$ ($1\times$) and $5+4=9$ ($1\times$).

Based on the 3D histopathology, voxels were assigned to either the benign or the malignant class. In light of known registration errors in 3D reconstruction, 1.5 mm [38], and registration, 2.1 mm [39], we did not take into account voxels within a 3.6-mm error margin from the region boundaries. To assess the diagnostic value of our method, Receiver Operating Characteristic (ROC) curves were generated using the parametric values in the included voxels. The number of benign voxels was downsampled to the size of the malignant set prior to the ROC analysis (i.e., $\sim 15 \cdot 10^3$ voxels). The optimal operating point in the ROC-curve (i.e., the point closest to the one with ideal sensitivity and specificity) allowed us to extract the optimal threshold-value for each parametric map.

III. RESULTS

A. Simulation Results

In Fig. 2, we present the proposed method’s performance in capturing the transport kinetics of the simulation containing nine traveling non-dispersing contrast boli. Its ability to resolve different speeds has been visualized by depicting v_y , v_x , and D_{ADC} along three cross-sectional lines perpendicular to the trajectory of the boli. The graphs show the mean values along these lines over 11 x, y -planes in the middle of the simulation domain. The results per value of σ are depicted in horizontal rows, showing that a larger σ highlights higher velocities. In a similar fashion, the simulation results with nine non-moving dispersive boli are depicted in Fig. 3.

The simulations shown in Fig. 4 demonstrate the method’s ability to assess a process with both dispersion and velocity, using the same settings for λ_0 , s and σ_t . The figure should be read as a table; the degree of dispersion grows with each row, whereas the simulated velocity increases column-to-column. It can be seen that all values of D and v can be resolved, irrespective of their combination.

B. Optimization Results

In Fig. 5, the performance of different combinations of λ_0 and s are depicted. Taking into account that v_y and D should be equally well estimated, the simulations reveal that a λ_0 of 0.1 provides the most balanced trade-off between accuracy in the v and D_{ADC} estimates. As the size of the kernel also affects computation time, the validity of the locally-constant assumption and the final resolution of the maps, we set a small s of 7 voxels (i.e., kernel radius = 2.6 mm)

Fig. 2. Simulation results for nine boli convecting at different speeds: (a) y -velocity maps for $\sigma = 1$ mm and $\sigma = 2$ mm in the center of the simulation space; (b) estimation of the y -velocity and x -velocity as well as (c) the apparent dispersion coefficient, respectively, for multiple scales σ measured at three lines shown in (a). The ground truth velocities and dispersions are appended at the bottom of (b) and (c), respectively, displayed in red.

Fig. 3. Simulation results for nine boli dispersing at different rates: (a) dispersion maps for $\sigma = 1$ mm and $\sigma = 2$ mm in the center of the simulation space; (b) estimation of the y -velocity and x -velocity as well as (c) the apparent dispersion coefficient, respectively, for multiple scales σ measured at three lines shown in (a). The ground truth velocities and dispersions are appended at the bottom of (b) and (c), respectively, displayed in red.

for the remaining part of the paper. This value also provides the best trade-off between v and D_{ADC} in Fig. 5.

C. Experimental Results

The 3D DCE-US videos of six patients were preprocessed and analyzed using the described method. In Fig. 6, the

registered parametric maps of D_{ADC} and v of one prostate are shown, alongside an illustration of the 3D histopathology and a parametric map of r , generated following [23], that underwent the same post-filtering procedure. In Table I, the area under the ROC curves is used as a measure for the diagnostic performance in distinguishing voxels that harbor benign and

Fig. 4. Simulation results of boli that both disperse and travel with different combinations of dispersion coefficient and speed: average result in y -direction for v_y and D_{ADC} in the 21 x,z -planes after the “injection site” to ensure the bolus has not dispersed below the noise floor within the measurement area.

Fig. 5. (a) The absolute value of the mean percentage error (AMPE) between estimation and ground truth along the three center lines in the velocity- and dispersion-based simulations for different combinations of the l_2 -norm regularization parameter, λ_0 , and kernel diameter, s ; the colors depict the mean value between the dispersion and the velocity simulation, whereas the numbers indicate the dispersion / velocity AMPE, respectively. (b,c) Visualization of the AMPE dispersion vs. velocity trade-off for $s = 7$ and $\lambda_0 = 0.1$, respectively.

malignant tissue. The ROC-optimal thresholds are tabulated between brackets. A similar analysis shows that r achieves an area under the ROC curve of 0.78 (≥ 0.29). Fig. 7 depicts this result alongside the best performing scale of D_{ADC} and v , that is, $\sigma = 1.5$ mm. In a multiscale approach, which we implemented by taking the average value of $\sigma = 0.75$ mm, $\sigma = 1$ mm, $\sigma = 1.5$ mm, we were able to achieve a minor improvement in performance. Any other combination of scales yielded a lower performance.

IV. DISCUSSION

The diagnosis of PCa still lacks an imaging solution that is sufficiently reliable for a shift from systematic biopsy towards image-targeted biopsy [2]. In this paper, we propose

TABLE I
AREA UNDER THE ROC CURVE FOR D_{ADC} AND v
(OPTIMAL THRESHOLD) AT DIFFERENT SCALES

scale	D_{ADC}	v
$\sigma = 0.75$ mm	0.68 (≥ 0.009 mm ² /s)	0.77 (≥ 0.11 mm/s)
$\sigma = 1.0$ mm	0.70 (≥ 0.027 mm ² /s)	0.79 (≥ 0.20 mm/s)
$\sigma = 1.5$ mm	0.70 (≥ 0.092 mm ² /s)	0.79 (≥ 0.42 mm/s)
$\sigma = 2.0$ mm	0.65 (≥ 0.18 mm ² /s)	0.75 (≥ 0.57 mm/s)
$\sigma = 2.5$ mm	0.57 (≥ 0.19 mm ² /s)	0.70 (≥ 0.69 mm/s)
$\sigma = 3.0$ mm	0.52 (≥ 0.21 mm ² /s)	0.68 (≥ 0.97 mm/s)
multiscale	0.72 (≥ 0.04 mm²/s)	0.80 (≥ 0.24 mm/s)

a method to quantify the transport kinetics of a UCA bolus in a 3D DCE-US video by solving the convective-dispersion equation in a spherical kernel around each voxel in the

Fig. 6. Exploded view example of 3D parametric maps with the tumor delineations in red based on the 3D histologic model shown in (i); (a,e) D_{ADC} and v for $\sigma = 1$ mm, respectively, (b,f) D_{ADC} and v for $\sigma = 2$ mm, respectively, (c,g) the mean D_{ADC} and v over $\sigma = 0.75$ mm, $\sigma = 1$ mm, and $\sigma = 1.5$ mm and (g) the corresponding map of spatiotemporal correlation, r . For each image, the color bars range from 0 to the 97th percentile of the value distribution. In (h) a few B-mode cross-sections of the same prostate are shown.

Fig. 7. The distribution of (a) D_{ADC} , (b) v , and (c) r among benign (light gray) and malignant (dark gray) voxels visualized in a boxplot and corresponding histogram for the multiscale approach. Inserted in the histograms, the ROC curves are depicted with the area under the curve.

imaging domain. We assume the dispersion and convection parameters to be constant within said kernel, compute smooth concentration gradients using Gaussian derivatives, and, subsequently solve the regularized least-squares problem of the equation.

In the first part of this work, we demonstrated the method's ability to retrieve the convective-dispersive behavior of contrast distributions from simulated DCE-US recordings.

We clearly find that larger scales enable us to resolve larger speeds or higher rates of convective dispersion. Indeed, as the scale of concentration gradients in time remains constant, larger spatial support is required to capture these effects, especially at low volume rates. However, larger scales reduce the spatial resolution of the parametric maps; this is why σ was only chosen sufficiently large to resolve the convective behavior of interest.

Although only dispersive processes were simulated in Fig. 3, also large speed values were obtained. This might be partly explained by the nature of the simulation, where the contrast kinetics in between two boli dispersing at a different rate might be perceived as flow, and partly because of the large intensity gradients in the vicinity of the dispersive cores. Still the magnitude of D_{ADC} is shown to scale accurately with the degree of dispersion along the boli.

In clinical data, the spatial distribution and perceived values of D_{ADC} and v also vary with the chosen scale (See Fig. 6). Over the years, the modeling of macroscopic behavior of microvascular beds has received quite some attention [27], [40]. Pries *et al.* [41] modeled the blood flow in the microvasculature as a function of the blood vessel generation (i.e., the number of branches between the vessel and the feeding vessel), finding blood flow velocities from roughly 2 mm/s for 5th generation vessels to 0.5 mm/s at the 20th generation. This order of magnitude has been confirmed in the measurement of skin capillary blood flows, in which an average flow of 0.47 mm/s was obtained [42]. We hypothesize that by increasing σ and thus the scale over which contrast gradients have to persist, increasingly larger vascular structures will become dominant in the estimation. As angiogenesis primarily affects the microvasculature [13], we aimed at the highest achievable resolution; therefore, we may prefer lower scales that are sensitive to velocities in the range of 10th to 20th generation vessels, between 0.5 mm/s and 1 mm/s [41]. Taking into account the maximum resolvable speeds in the simulations, this might explain why the lower scales yield the highest tumor classification performance.

As stated in the methods, we regard the obtained convective-dispersion effects as the spatially-averaged behavior of UCAs, similar to the analysis of flow in porous media [25]–[27]; we cannot distinguish the behavior in the subresolution-sized microvasculature (which have lengths ranging from 0.3 to 0.5 mm [40]), but rather the average flow dynamics over all pathways within the voxels of interest. In contrast to dispersion of TICs, of which lower values were shown to be a marker of malignancy [17], [19], [21], convective dispersion seems to be increased in PCa regions. This intuitively corresponds to the heterogeneous nature of the angiogenic vascular bed [16] and thus the variety of pathways in cancerous regions. Previously reported parameters related to dispersion (i.e., κ [17], r [18] and the Péclet number [21]) reflect the point-to-point effect of UCA dispersion and velocity. Whereas r quantifies the average impact of the multi-trajectory path from the inner voxel to all voxels in its surrounding kernel, it does not take into account the directional effects within the kernel. These effects are captured by D_{ADC} and v , which might explain why v seems to be a more indicative parameter for PCa with respect to r for the scales of interest.

Furthermore, the parametric maps do not show a clear, clean-cut border between malignant and benign tissue, which might indicate that angiogenesis-like vasculature is not strictly confined to malignant tissue but spreads out into the vicinity of the tumor, and vice versa [43]. As we have used

a histopathologic rather than an immunohistologic reference, this remains to be tested.

The parametric maps show some false positive areas that might depict other perfusion-increasing pathology. Benign prostate hyperplasia (BPH), for instance, was also found in the prostates during initial biopsy. Similar to PCa, BPH is known to prompt angiogenic growth of vessels [44]. Moreover, malignant tissue is heterogeneously perfused [16], a phenomenon which might reflect in higher values for convective dispersion. The diagnostic potential of a measure for perfusion heterogeneity has also been demonstrated by quantifying the entropy of 2D DCE-US velocity fields [45].

Linear combination of different scales is a first, crude multiscale approach. Taking into account the relatively minor improvement with regard to single-scales and the diversity of information among scales, such an analysis might be better performed in a machine-learning context [46] albeit this would require a larger number of prostates. Since D_{ADC} and v cannot be combined in the Péclet number [21] as D_{ADC} seems to reflect spatial rather than temporal spreading, such a machine-learning approach could also be used to combine the information of D_{ADC} and v in a single parametric map. In 2D, the multiparametric combination of dispersion and velocity-related parameters was shown to improve diagnostic performance [47].

It should be noted that one of the limitations of this work is that we present a pixel-wise ROC analysis. For targeted biopsy, detection rate and negative predictive value of the index lesion might be more indicative for this method's value in clinical practice. At this stage of development, our preliminary number of patients does not allow such analysis and, therefore, we plan to expand the clinical dataset. Moreover, this would allow us to assess the diagnostic ability to distinguish significant and non-significant PCa.

Current guidelines on PCa diagnosis only recommend imaging (in the form of mpMRI) in biopsy-negative patients with persistent suspicion [2]. Large clinical trials on mpMRI show increasingly promising results for high-grade PCa detection, even though the optimal mpMRI procedure is still matter of debate; the use of dynamic contrast-enhanced MRI, for instance [48], [49]. Different from our technique, MRI contrast agents do not necessarily remain in the vasculature [13] and cannot be modeled as a mere convection-dispersion process as proposed in this paper [50]. In light of PCa localization with ultrasound, the attained ROC-curve areas (ROC-AUC) using our method are comparable to other techniques such as elastography (per-patient ROC-AUC of 0.8, [51]) and ultrasound spectral analysis (per-biopsy-core ROC-AUC of 0.81, [8]). The reported ROC-AUCs are also in line with those obtained by other DCE-US based quantification techniques, albeit in 2D [17], [19], [21]. As for 3D, this work reports on the improvement of the current method over r , which was shown to be the 3D DCE-US measure with the best performance [24]. Further research might reveal how this translates to DCE-US-guided biopsy performance, e.g. as studied by Postema *et al.* [52], [53], Xie *et al.* [54] and Frauscher *et al.* [10].

V. CONCLUSIONS

In conclusion, we have shown that quantification of convective dispersion (i.e. by D_{ADC}) and velocities (i.e. by v) of the UCA bolus in DCE-US videos provides valuable maps for the localization of PCa. This method would be particularly useful, since full analysis of the entire gland with only a single bolus alleviates some substantial limitations of current 2D DCE-US analysis techniques.

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