Introduction

Lesion detection and characterization for cancer diagnosis in e.g. liver, breast or prostate has become an important field of application in contrast-enhanced ultrasound imaging. In prostate, for example, systematic biopsy, currently still the “gold standard” for prostate cancer diagnosis, misses approximately 30% of cancers [1]. Even new biopsy strategies, such as increasing the number of cores taken during a biopsy examination, have low success rates [2]. With conventional (i.e. unenhanced) ultrasound imaging, the detection of prostate cancer, aimed at identifying hypoechoic areas in the peripheral zone, is unreliable [3]. However, studies of targeted biopsy approaches using contrast-enhanced ultrasound guidance have shown that the number of positive biopsy cores increases, and that the total number of cores normally taken with systematic biopsy approaches can be reduced [4]. Moreover, with the help of new perfusion quantification analysis methods, contrast-enhanced ultrasound may soon provide an alternative to systematic biopsy as the first choice for prostate cancer diagnosis. This could result in a major and welcome reduction in patient discomfort and morbidity, and could dramatically decrease associated costs.

In contrast-enhanced ultrasound imaging, lesion detection is typically based on differences in contrast enhancement (hypo- or hyper-enhancement) and perfusion kinetics compared to normal tissue [5][6]. Perfusion kinetics can be measured and quantified by recording so-called time-intensity curves (TIC), which represent the echo-power as a function of time and, consequently, relate to the time evolution of the local instantaneous contrast agent concentration after, for example, a bolus injection [7]. These TIC are normally analyzed after the examinations using dedicated off-line post-processing quantification software. By off-line analysis using best-fit optimization approaches, perfusion parameters, such as Rise Time (RT), Time-to-Peak (TP) enhancement, mean Transit Time (mTT), Peak Intensity/Enhancement (PI), Wash-in Rate (WiR), Wash-out Rate (WoR), etc., are extracted from sophisticated mathematical models describing the bolus kinetics of the contrast agent [8]. These perfusion parameters are typically presented as single values obtained from analyzing a pre-defined region-of-interest (ROI), or they can be presented as static parametric images showing the spatial variation of values of any parameter of interest, on a pixel-by-pixel basis [9].

For lesion characterization, benign lesions can be differentiated from malignant lesions based on differences in their vascular properties, such as microvascular density and/or structure. Thus, lesions
can be characterized by imaging and analyzing the finest details of the microvascular network, preferably on full resolution images. Capturing the complete microvascular structure of a lesion under investigation is often challenging in contrast-enhanced ultrasound imaging because the instantaneous local agent concentration can be extremely low, even to the extent that single microbubbles are imaged flowing in microvessels. This hinders the rendering of the complete microvascular structure and, therefore, limits correct lesion characterization. The microvascular structure can, however, be imaged with contrast-enhanced ultrasound using so-called maximum-hold or maximum intensity projection (MIP) imaging approaches (such as MVIT™, MFI™, CPS-capture™), especially in situations of low instantaneous local contrast agent concentrations. In MIP imaging, the absolute maximum echo value is preserved over time in each pixel. In this way, trajectories of individual bubbles flowing through microvessels are ‘projected’, and the finest details of the microvascular network can thus be imaged. However, at times beyond the initial ‘arterial’ wash-in phase, MIP images generally have become ‘diffuse’ due to perfusion of normal parenchyma tissue, and image information specific to the microvascular structure of a lesion has a tendency to fade. This limits the usefulness of MIP imaging for lesion characterization considerably. Another limitation of MIP imaging may be its high sensitivity to motion resulting in blooming artifacts.

**Real-time parametric imaging**

In this work, a new method was developed which allows for improved contrast perfusion imaging, by displaying parametric images of contrast-enhanced ultrasound sequences in real-time. The method is based on a robust smoothing algorithm, combining a maximum- and minimum-hold filter, applied on image data in real-time. The video data are linearized also in real-time (i.e. producing echo-power signals proportional to local contrast agent concentration) to revert the effects of non-linear log-compression and color rendering. In this way, images of microvascular structures are displayed in real-time during the wash-in phase after a bolus injection of a contrast agent, whereas distinct perfusion kinetics related to the wash-in phase (and/or wash-out phase) are accurately preserved and can be exploited in a rigorous way for dynamically displaying parametric images (i.e. the parametric images are created also in real-time). Because of the robustness of the algorithm, the new method can be applied on full resolution data with a low signal-to-noise ratio without the need for spatial filtering. Consequently, full resolution parametric images can be created without loss of information. Thus, differences in contrast agent perfusion between normal tissue, benign lesions and malignant lesions can be optimally exploited for improved lesion detection.

The method has been optimized for contrast-enhanced ultrasound examinations of the prostate and is implemented in a software program called *SonoProstateLive*. Because of the symmetry of the prostate gland and its zonal anatomy, lesion detection is typically based on comparing contrast perfusion kinetics in contra-lateral regions. Moreover, contrast-enhanced image sequences of prostate
examinations are convenient for real-time processing purposes since the images are relatively stable and motion artefacts are practically non-existent. In this work, lesion detection and characterization was restricted to the peripheral zone (PZ) since 80% of prostate cancer is located in the PZ [10]. Figure 1 illustrates an example of the new method applied on an image sequence recorded during a prostate examination after a 2.4 mL bolus injection of SonoVue®.

Figure 1. Prostate images obtained during real-time WiR parametric image processing at different time instants: at 25 s (A), 30 s (B), 35 s (C), 40 s (D) and 50 s (E) after a bolus injection of SonoVue®. The final WiR parametric image (E) is overlaid with 50% transparency on the B-mode image in F.

Figures 1A to 1E show the results at different time instants during real-time processing. During the early part of the wash-in phase 25 s after injection (Figure 1A), the contrast agent appears in the highly vascularized central zone (i.e. middle part) of the prostate, showing the typical symmetric enhancement of this part of the prostate. The MIP character of the method at this stage of processing enhances relatively big vessels of the vascular network already at this early part of contrast wash-in (see for example the bright ring on the right side in Figure 1A). Also, an asymmetric enhancement pattern in the right peripheral zone of the prostate (i.e. on the lower-left side in the MIP image in Figure 1A indicated by the arrow), which is absent in the contra-lateral part of the prostate, appears and suggests the presence of a suspicious region in this part of the prostate. During late wash-in of the agent at 30 s after injection (Figure 1B), the suspicious region is well delineated, enhancing branches of its vascular network, which is a clear indication of a malignancy. After the wash-out has started in the lesion and normal surrounding tissue is perfused at 35 s after injection (Figure 1C), the method switches to parametric imaging and starts to create parametric maps in real-time.

Figures 1D and 1E show examples of full-resolution parametric images (i.e. pixel-by-pixel with no spatial filtering applied) of WiR at 40 and 50 s after injection, respectively. For each pixel in the image, the WiR values are normalized to a reference value calculated globally, and are subsequently
color coded according to a predefined palette with red colors corresponding to large values and blue colors corresponding to low values of the $WiR$. The suspicious region in the right PZ of the prostate can be clearly identified against normal regions in the contralateral zone, by the relatively high density of high $WiR$ values, and remains conspicuous even during the (late) wash-out phase. Moreover, the high resolution parametric images reveal details of the microvascular system, allowing improved detection and may facilitate characterization. Functional information may be combined with anatomical information by overlaying the final $WiR$ parametric image of Figure 1E on the B-mode image. Figure 1F shows the final results, applying a 50% transparency for the $WiR$ parametric image. In this way, it can be easily recognized if a suspicious lesion is completely contained within the prostate gland or if it is extending outside the gland. This kind of information may be important as it will condition the choice of possible therapeutic strategies to follow. Note that also in the transition zone (TZ), regions with a high density of high $WiR$ values are observed, which is mainly due to the hyper vascular character of TZ tissue. However, it is anticipated that for detecting prostate cancer (PCa) in PZ this will not be a problem in practice, since in most cases PZ can be easily separated from TZ due to the zonal anatomy of the prostate.

The method was tested in a clinical context during contrast-enhanced ultrasound examinations of four patients scheduled for radical prostatectomy. $SonoProstate^{\text{Live}}$ was installed on a notebook computer, operating under MS-Windows XP, which was connected to the video output of an ultrasound scanner through a digital video frame grabber. This allowed to process the contrast sequences in real-time during the examination. The resulting $WiR$ parametric images were analyzed subjectively, and suspicious regions were identified. Their locations were compared to data available from biopsy histopathology reports, and in all four cases, the final $WiR$ parametric images allowed correct identification of PCa. Moreover, the method was validated in a qualitative way by retrospective off-line analyses on image sequences of previously recorded contrast-enhanced ultrasound examinations. Possible locations of PCa identified in the $WiR$ parametric images generated by $SonoProstate^{\text{Live}}$ were compared to histopathology data obtained after either biopsy or radical prostatectomy. The locations of PCa given by $SonoProstate^{\text{Live}}$ corresponded in all cases with the histopathology data.

Figure 2 shows an example of the qualitative validation with the overlaid $WiR$ parametric image of Figure 1F on the left-hand side and the corresponding histology section on the right-hand side. The suspicious region identified by a relatively high density of high $WiR$ values in the right PZ of the parametric image (red arrow), correctly corresponded with PCa as outlined by the pathologist in blue in the histology section. An adenoma was also present in the left TZ of the same prostate, as is indicated by the green arrow in the histology section. The same location in the $WiR$ parametric image (green arrow) corresponded to a region with a non perfused internal part (i.e. with $WiR$ values close to zero) and a hyper vascular peripheral part with a high density of high $WiR$ values. This might be a
typical characteristic of adenoma in prostate and could be used for lesion characterization, but this is subject for future studies.

Figure 2. WiR parametric image (left) and corresponding histology coupe (right). A suspicious region identified in the WiR parametric image in the right PZ (red arrow) corresponds with PCa outlined by the pathologist in blue in the histology section. Adenoma was also detected in the left TZ of the same prostate (green arrow).

Statistical analysis.

Parametric images of WiR may facilitate the identification of possible locations of a pathological condition. Indeed, the example illustrated in Figure 2 showed that a region with a relatively high density of high WiR values in the right PZ corresponded to the location of PCa, whereas normal tissue corresponded to regions of low WiR values. Therefore, distributions of WiR values were statistically analyzed based on their histograms calculated in ROI placed in the parametric images (a histogram of WiR values calculated in a ROI of a parametric image reflects perfusion information at the pixel level). Figure 3 illustrates the principle on the WiR parametric image of Figure 1. A ROI was drawn in the parametric image around the right PZ with PCa, and a histogram of all WiR values within this ROI was calculated. The graph on the right-hand side of Figure 3 shows the resulting histogram (blue bars), where WiR values are plotted on the x-axis and the corresponding normalized counts are plotted on the y-axis. The counts were normalized to the total number of counts in the ROI to make the distribution independent of the ROI size.

Next, the original histogram was smoothed (red curve shown on the right-hand side in Figure 3) with a lognormal probability density function of the form:

\[ F(x) = \frac{1}{x s \sqrt{2\pi}} e^{-\frac{[\ln(x) - m]^2}{2s^2}}, \]

where \( m \) and \( s \) are the mean and standard deviation of the natural logarithm of \( x \), respectively (\( x \) corresponds to the WiR values). Values for \( m \) and \( s \) are determined by a best-fit analysis between \( F(x) \)
and the original histogram. Smoothing the original histograms allows improved comparison between histograms obtained from different regions in the prostate. For example, Figure 4 on the left shows in red the smoothed histogram of Figure 3 calculated in the right PZ with PCa, and in green the one calculated in the contra-lateral region representing normal tissue, i.e. in the left PZ. The histogram curve corresponding to the right PZ with PCa is very different in shape compared to the one from normal tissue in the left PZ; its peak value is lower, its peak position is shifted to the right, i.e. to higher \( WiR \) values, and its peak is wider, i.e. reflecting a larger variation of \( WiR \) values.

![WiR parametric image](image1)

**Figure 3.** \( WiR \) parametric image (left) and corresponding histogram of \( WiR \) calculated in the right PZ shown in the parametric image (right). The original histogram (blue bar plot) is smoothed with a lognormal distribution function (red curve) obtained from a best-fit optimization procedure.

Shape differences between the histogram curves, corresponding to different lesions or types of tissue, may be exploited by extracting parameters from the lognormal distribution function, obtained after the best-fit optimization with the \( WiR \) histograms. Examples of such parameters are: the Mean (center of gravity of the histogram curve), Mode (value at the peak, i.e. the most frequently occurring value in the histogram), Median (middle value, i.e. the value such that an equal number of samples are less than and greater than said value), Sigma (standard deviation, i.e. the variability or dispersion around the Mean of the histogram curve) and Skewness (asymmetry of the histogram curve). These parameters can be calculated from the best-fit parameters \( m \) and \( s \) by:

\[
\text{Mean} = e^{m - \frac{s^2}{2}}, \quad \text{Mode} = e^{m - s^2}, \quad \text{Median} = e^m, \quad \text{Sigma} = \sqrt{e^{s^2 + 2m(e^{s^2} - 1)}} \quad \text{and} \quad \text{Skewness} = \sqrt{e^{s^2 - 1}((2 + e^{s^2})}. 
\]

Here, we used a combination of the Mode and Sigma parameters to compare histogram curves corresponding to different lesions or types of tissue located in the PZ. For both histogram curves shown on the left-hand side of Figure 4, the Mode and Sigma parameters were calculated. Next, a 2-dimensional (2D) map of Mode and Sigma was generated in which the Mode was plotted on the x-axis and Sigma on the y-axis, and the results are shown on the right-hand side in Figure 4; the data point corresponding to normal tissue in PZ is plotted in the lower-left region of the 2D map, whereas the one
corresponding to PCa in PZ is plotted in an upper right region relative to normal tissue. This example suggests that a 2D representation of shape parameters obtained from histogram curves of a WiR parametric image may be used to differentiate between PZ tissue with and without cancer.

![WiR histogram (PZ)](image)

**Figure 4.** Fitted lognormal histogram curves (left) calculated in right PZ with PCa (red curve) and left PZ containing only normal tissue (green curve). Corresponding Mode and Sigma were calculated from the best-fit parameters $m$ and $s$, and were plotted in a 2D map (right). Data points relating to normal tissue or PCa in PZ are plotted in very distinct regions in the 2D parametric plot.

To validate this approach, 23 DICOM image sequences of different patients were studied retrospectively off-line. The image sequences were acquired during contrast-enhanced ultrasound examinations with different ultrasound systems (18 with the Philips iU22, 4 with the Siemens Sequoia, and 1 with the Toshiba Aplio) by 5 different users. Histogram curves were calculated in 62 ROI located in PZ containing different lesions or types of tissue. For each histogram curve, the Mode and Sigma parameters were calculated and the 2D map of Mode and Sigma was generated. Histopathology data, obtained after biopsy examinations or radical prostatectomy, was available for 26 ROI in 8 patients and confirmed 14 cases of PCa, 2 cases of Prostatitis and 10 cases of normal tissue; no data was available for the remaining 36 ROI. Figure 5 shows the 2D map of Mode and Sigma calculated in all 62 ROI. Data points with known histopathology were colorized according to the type of lesion or tissue, *viz.* green for normal tissue, red for PCa and orange for Prostatitis in the PZ. Data from PCa and normal tissue in PZ are located in distinct regions in the 2D map, as was described above; normal tissue data appears to be relatively uniform distributed in the lower-left region, whereas PCa data is more dispersed and located in an upper-right region relative to normal tissue data. The dispersion observed for PCa data may be explained by a high heterogeneity in tumor development, as would be expected for different patients. Moreover, based on the results shown in Figure 5, it may be possible to differentiate Prostatitis (benign tissue) from PCa in PZ, but this should be confirmed by including more data.
Figure 5. 2D map of Mode and Sigma calculated in 62 ROI. Data points with known histopathology were colorized according to the type of lesion or tissue (see color legend).

The results shown in Figure 5 confirm the suggestion made above that the distinct regions in the 2D map of Mode and Sigma correspond to the different lesions or tissue located in the PZ, and thus that this method may be used for improved lesion characterization in PZ of the prostate. It is furthermore interesting to note that, especially for normal tissue, all results are consistent even though the data were acquired with different ultrasound systems and by different users, each with their own preferred settings. This suggests that the method is very robust and could reduce operator-dependent variability.

Conclusion
In summary, real-time WiR parametric imaging, as implemented in SonoProstateLive, is a new imaging modality which may allow improved lesion detection in PZ during contrast-enhanced ultrasound examinations of the prostate. Parametric images of WiR are generated during the examinations, mapping the spatial distributions of WiR values in the prostate as soon as 50 s after agent injection, and could be used for targeted biopsy guidance. Moreover, perfusion kinetics information is available to the examiner even after the wash-out phase of the agent, whereas in normal contrast examinations the effective observation time for lesion detection is limited to 20 to 30 s only. Since multiple foci occur in more than 85% of the cases of PCa [11], SonoProstateLive might increase chances of detecting small lesions which would have been missed during a conventional contrast examination.

The results from SonoProstateLive can be further analyzed for characterization purposes. A 2D map of Mode and Sigma of the statistical distribution of WiR in a ROI could facilitate lesion characterization
in PZ of the prostate by contrast-enhanced ultrasound. Consequently, it could lower false-positive findings in prostate cancer detection and thus would decrease overdiagnosis and overtreatment of patients with prostate cancer. However, the preliminary results of this work need to be confirmed by a prospective clinical validation study. Another interesting topic would be to see if SonoProstate live in combination with the 2D map of Mode and Sigma could aid in determining the effect of a therapeutic treatment (e.g. HIFU, brachy- or cryo-therapy), by assessing tumor response to treatment, and could identify non-responders at an early stage during therapy. Finally, the possibility of detecting cancer in highly vascular regions, such as in the TZ, should also be investigated.

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