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**Citation for published version (APA):**

Mischi, M., Kuenen, M. P. J., Wijkstra, H., Hendrikx, A. J., & Korsten, H. (2009). Prostate cancer localization by contrast-ultrasound diffusion imaging. In *Proceedings 2009 IEEE International Ultrasonics Symposium, 21-23 September 2009, Rome, Italy*, (pp. 283-286). Institute of Electrical and Electronics Engineers.  
<https://doi.org/10.1109/ULTSYM.2009.0070>

**DOI:**

[10.1109/ULTSYM.2009.0070](https://doi.org/10.1109/ULTSYM.2009.0070)

**Document status and date:**

Published: 01/01/2009

**Document Version:**

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

**Please check the document version of this publication:**

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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# Prostate cancer localization by contrast-ultrasound diffusion imaging

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**Abstract**—Prostate cancer is the form of cancer with the highest incidence in men. The invasiveness or low specificity of available diagnostics hampers a timely use of efficient focal therapies. New imaging techniques are therefore needed for an early prostate cancer localization. We propose a new ultrasound imaging method for prostate cancer localization based on quantification of the (intravascular) local diffusion of ultrasound contrast agents. Local diffusion is expected to correlate better than perfusion with cancer microvascular growth and, therefore, aggressiveness. Local diffusion is estimated by transrectal ultrasound imaging of an ultrasound contrast-agent bolus passing through the prostate circulation after a peripheral intravenous injection. A time-intensity curve (TIC) is measured at each pixel by acoustic quantification. The measured TICs are fitted by a modified Local Density Random Walk model, a solution of the convective diffusion equation that provides a physical representation of the diffusion process. The obtained parametric diffusion images were compared with the histology results after radical prostatectomy. The resulting receiver operating characteristics (curve area = 0.91) were superior to those obtained by estimation of perfusion related parameters. Although extensive validation is necessary, contrast ultrasound diffusion imaging is a promising method, with potential to assess cancer aggressiveness.

## I. INTRODUCTION

Prostate cancer is the form of cancer with the highest incidence in western males, accounting for 25% and 10% of all cancer diagnoses and deaths, respectively [1, 2]. Nowadays, timely-detected prostate cancer can be efficiently treated. A number of minimally-invasive focal treatments, such as cryoablation, brachytherapy, radiotherapy, and high-intensity focused ultrasound, are available. They can possibly permit avoiding a radical prostatectomy along with the related risks of the patient remaining incontinent and impotent [3].

Unfortunately, the implementation of an efficient mass screening, aimed at a systematic early localization of prostate cancer and, therefore, at a timely and efficient use of the available minimally-invasive treatments, is hampered by the limits of the available diagnostics. In fact, in the presence of a high level of prostate specific antigen in blood, the only reliable diagnostic investigation requires performing a number of systematic biopsies [3], i.e., at least 6 to 12 distributed prostate samples are taken by a core needle, according to a prescribed geometric scheme. Repeated biopsy sessions are often required to obtain a sufficient sensitivity. In retrospective, about 76% of all biopsy investigations are unnecessary [3].

A timely and efficient use of the available focal treatments requires therefore the introduction of new non-invasive diagnostic methods. To this end, extensive research has been carried out to define cancer-related features that can be detected noninvasively by imaging techniques. In this context, a major breakthrough was the discovery of a close relationship between cancer growth and angiogenesis, i.e., the formation of a dense network of microvessels. This relationship is also valid for prostate cancer, where angiogenesis correlates with cancer growth and aggressiveness [4, 5]. As a result, the histological assessment of the microvessel density has become an important prognostic indicator of prostate cancer [4, 5].

This breakthrough has opened new possibilities for prostate cancer imaging. In particular, several methods have been developed for the quantification of tissue perfusion [6, 7]. With the objective of measuring flow, the use of transrectal ultrasound (TRUS) Doppler techniques has been amply investigated [6, 7]. However, cancer microvessels cannot be accurately detected because of the low blood velocity and because of their small size, smaller than the TRUS spatial resolution [8, 9].

Alternative methods that are gaining increasing interest are based on contrast-enhanced TRUS [6–8]. These methods make use of an ultrasound contrast agent (UCA), which is a dispersion of gas microbubbles coated by a biocompatible elastic shell [10]. UCA microbubbles have a size comparable to that of blood cells, and can therefore flow through the microvasculature, backscattering acoustic energy when invested by ultrasonic waves [10].

A number of methods have been introduced to assess tissue perfusion by contrast-enhanced TRUS. In particular, intermittent imaging, based on the destruction-replenishment technique [11], has also been tested to a limited extent for prostate cancer detection [8]. However, perhaps because of the intrinsic anisotropy of the measurement and the difficulty to achieve a steady concentration level during UCA infusion, this technique has not demonstrated, so far, an ability to localize prostate cancer in a reliable way [8].

In this paper, a different approach for the localization of prostate cancer by contrast-enhanced TRUS is presented. Rather than using a destruction-replenishment approach, a peripheral intravenous injection of a small bolus of UCA is performed, followed by the echographic measurement of the

time-intensity curve (TIC) representing the bolus first pass through the prostate circulation. Although this procedure is in general not new, and has already been tested for prostate cancer detection [7, 12, 13], we introduce a new TIC analysis method: rather than aiming at the quantification of tissue-perfusion features, we aim at the quantification of the UCA diffusion dynamics through the prostate circulation. In fact, contradictory effects of angiogenesis on perfusion are reported. Low flow resistance results from a lack of vasomotor control and increase of arteriovenous shunts, but this can be counterbalanced by an interstitial pressure increase due to extravascular leaking and by the small diameter of the growing microvessels (Hagen-Poiseuille equation) [9].

Differently from perfusion, the diffusion dynamics is expected to show a better correlation with the microvascular architecture and, therefore, with cancer aggressiveness. Similarly to the characterization of flow through porous media [14], the intravascular diffusion can in fact be correlated with microvessel density, constrictivity, and tortuosity.

## II. METHODOLOGY

### A. Data acquisition

The data acquisition was performed at the Academic Medical Center in Amsterdam (the Netherlands) using an iU22 ultrasound scanner (Philips Healthcare) equipped with a C8-4v transducer, which permitted a transrectal use. An intravenous injection of 2.4 mL of SonoVue™ contrast agent (Bracco, Milan, Italy) was performed in an arm vein. TRUS imaging was performed in contrast-enhancement mode [10]. A low mechanical index (MI=0.06) was used for minimization of bubble collapse. Separate in vitro measurements at the Catharina hospital (Eindhoven, the Netherlands) using software Q-Lab™ (Philips Healthcare) for acoustic quantification confirmed the linearity of the relationship between measured acoustic intensity and UCA concentration at the adopted concentrations.

The acquired echographic image sequences were stored in DICOM (Digital Imaging and Communications in Medicine) format, which can directly be used as input to the analysis software that we implemented in Matlab™ (MathWorks, Natick, MA). In order to map the gray level image sequence stored in the DICOM file to the UCA concentration, it is necessary to compensate for the function (typically logarithmic) implemented in the ultrasound scanner for compression of the acoustic dynamic range [15]. Given the linear relationship between UCA concentration and acoustic intensity, the relationship between gray level and UCA concentration  $G(C)$  depends on three coefficients ( $a_0$ ,  $a_1$ , and  $a_2$ ) as given in (1):

$$G(C) = a_0 \ln(a_1 C + 1) + a_2. \quad (1)$$

The baseline  $a_2$  can easily be estimated from the gray level data and the coefficient  $a_1$  can be included in the concentration  $C$ , since a scale factor does not influence the estimation of the TIC-shape parameters of interest. Therefore, the compression compensation reduces to the estimation of  $a_0$ , which depends on the dynamic range of the log-compression.

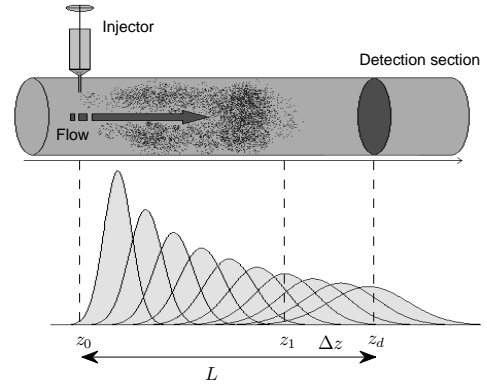


Figure 1. LDRW model together with the contrast spatial distribution for increasing time.

For a given scanner setting,  $a_0$  was estimated by fitting the compressed gray-level TICs to the same TICs measured by software Q-Lab™. After compensating for the logarithmic compression, a scaled TIC can be obtained at each pixel covering the prostate. The spatial resolution of the acquired data is therefore higher than that necessary for detection of clinically significant carcinomas (diameter of 0.5 cm [16]).

### B. Diffusion modeling

Several models are reported in the literature for the characterization of the dilution process of an intravascular indicator. In this study, we adopt the Local Density Random Walk (LDRW) model [17, 18], as it provides a physical interpretation of the diffusion process, enabling the estimation of diffusion-related parameters. Moreover, the LDRW model has been already reported as to provide an accurate interpolation of UCA TICs [19].

The LDRW model, shown in Fig. 1, characterizes the UCA dilution process in a straight infinitely-long tube of section  $A$ , in which a carrier fluid flows with velocity  $v$  [17, 18]. The main assumptions are a fast bolus injection of dose (mass)  $m$  at a certain distance  $z = z_0$ , the UCA mass conservation, and a Brownian motion of the UCA microbubbles. Given these conditions, the model is a solution of the mono-dimensional convective diffusion equation, which describes the concentration dynamics  $C(z, t)$  as

$$\frac{\partial C(z, t)}{\partial t} = \frac{\partial}{\partial z} \left( D \frac{\partial C(z, t)}{\partial z} \right) - v \frac{\partial C(z, t)}{\partial z}, \quad (2)$$

with  $D$  being the diffusion coefficient,  $z$  the distance along the tube main axis, and  $t$  the time variable.

$C(z, t)$  is therefore described as a Normal distribution moving with the carrier-fluid velocity  $v$ , with a variance that is a linear function of time. By sampling  $C(z, t)$  at  $z = z_d$ , we obtain the LDRW formalization  $C(t)$  [18, 19]:

$$C(t) = \frac{\alpha}{\mu} e^{\lambda} \sqrt{\frac{\lambda \mu}{2\pi(t-t_0)}} e^{-\frac{\lambda}{2} \left( \frac{\mu}{t-t_0} + \frac{t-t_0}{\mu} \right)}, \quad (3)$$

with  $t_0$  being the injection time and

$$\alpha = \frac{m}{vA}, \quad \mu = \frac{L}{v}, \quad \lambda = \frac{vL}{2D}. \quad (4)$$

In (4),  $L = z_d - z_0$  is the distance between injection and detection site,  $\mu$  is the mean transit time, i.e., the average time that an UCA microbubble takes to travel the distance  $L$ ,  $\lambda$  is a parameter related to the curve skewness, and  $\alpha$  is a scale parameter. The parameter  $\lambda$  is related to the diffusion coefficient  $D$  and can be interpreted as the ratio between diffusive time  $\tau_D = L^2/(2D)$  and convective time  $\tau_C = \mu$ . This parameter is therefore a key parameter for the assessment of the UCA diffusion dynamics. However, due to its dependency on the distance  $L$ , which cannot be estimated in most clinical applications,  $\lambda$  cannot be determined locally. A different diffusion-related parameter must therefore be defined that is independent of  $L$ .

Local dilution properties can be assessed by focusing on a short segment of the infinitely long tube. According to (2), and with the hypothesis of a fast bolus injection at time  $t = t_0$ , the bolus at time  $t = t_1 > t_0$  can be represented in space by a Normal distribution centered at  $z_1 = z_d - \Delta z$  and with variance  $\sigma_1^2 = \sigma^2(t_1)$ . If  $\Delta z > 2\sigma_1$ , the UCA fraction that has already reached  $z_d$  is negligible, and the boundary condition for (2) is

$$C(z, t_1) = \frac{m}{A\sqrt{2\pi\sigma_1^2}} e^{-\frac{(z-z_1)^2}{2\sigma_1^2}}. \quad (5)$$

The parameters  $D$  and  $v$  are assumed to be locally constant, i.e.,  $D(z) = D_\ell$  and  $v(z) = v_\ell$  within the tube segment  $(z_1 - \Delta z) \leq z \leq z_d$ . For  $z < (z_1 - \Delta z)$ ,  $D$  and  $v$  may take any arbitrary positive value and, in particular, they can be equal to the local values  $D_\ell$  and  $v_\ell$ . As a result, the injection time  $t_0$  can be estimated as

$$\hat{t}_0 = t_1 - \frac{\sigma_1^2}{2D_\ell}. \quad (6)$$

Since  $D(z) = D_\ell$  holds only for  $z \geq (z_1 - \Delta z)$ , while (6) assumes  $D = D_\ell$  for the entire tube length,  $\hat{t}_0$  does not reflect the real injection time  $t_0$ . However, (6) can be used to represent the TIC in the form of (3), but with local parametrization

$$\alpha = \frac{m}{v_\ell A}, \quad (7a)$$

$$\mu = t_1 - \hat{t}_0 + \frac{z_d - z_1}{v_\ell}, \quad (7b)$$

$$\lambda = \frac{v_\ell^2}{2D_\ell} (t_1 - \hat{t}_0) + \frac{v_\ell(z_d - z_1)}{2D_\ell}. \quad (7c)$$

Based on (7), we can define a new local parameter  $\kappa$ , dependent only on  $D_\ell$  and  $v_\ell$ , and given as

$$\kappa = \frac{\lambda}{\mu} = \frac{v_\ell^2}{2D_\ell}. \quad (8)$$

The TIC can then be expressed as

$$C(t) = \alpha \sqrt{\frac{\kappa}{2\pi(t - \hat{t}_0)}} e^{-\frac{\kappa(t - \hat{t}_0 - \mu)^2}{2(t - \hat{t}_0)}}. \quad (9)$$

The parameter  $\kappa$ , i.e., the local ratio between diffusive time and squared convective time, is the local diffusion-related parameter adopted for detection of cancer-related microvascularization. A small or large value of  $\kappa$  leads to a skewed or symmetrical TIC, respectively.

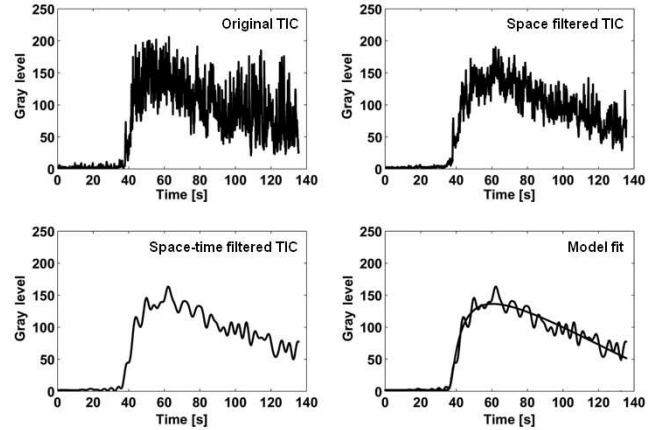


Figure 2. Filtering and fitting of a single-pixel gray-level TIC.

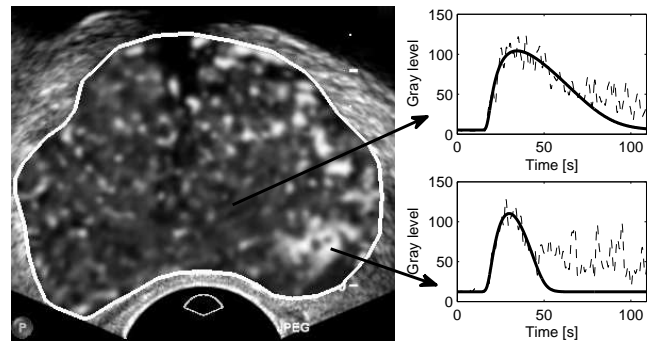


Figure 3. Example of parametric diffusion image in a defined region of interest with two fitted TICs measured from healthy (upper TIC) and cancerous (lower TIC) tissue.

### C. Parameter estimation

The estimation of the local diffusion-related parameter  $\kappa$  can be obtained by fitting (9) to the TICs measured at each pixel covering the prostate. Unfortunately, TICs measured at the image resolution can show a poor signal-to-noise ratio (SNR), making a direct model fit unreliable. However, as the image resolution is higher than the actual resolution of the ultrasound scanner, and the TIC bandwidth is limited to low frequencies ( $< 0.5$  Hz), the recorded data can be low-pass filtered in space and time domain to improve the SNR. Noise analysis was performed in space and time domain for the design of optimal filters. Due to the presence of multiplicative noise [19], filtering is applied in the logarithmic (gray level) domain, where the multiplicative noise becomes additive. Fig. 2 shows the result of the filtering steps on a TIC measured from one pixel.

The filtered TIC is then fitted with the model in (9) by a Gauss-Newton least-squares fitting as shown in Fig. 2. The fitting interval is limited in order to include only the first pass curve, while excluding the UCA recirculation. The inflection triangle method described in [18] is adopted for the parameter initialization. The complete fitting is performed on the log-compressed (gray level) TICs.

Table I  
SENSITIVITY, SPECIFICITY, AND ROC AREA ON PIXEL BASIS

Parameter	Cancerous if	Sensitivity	Specificity	ROC area
$\kappa$	$\geq 0.35 \text{ s}^{-1}$	78.1 %	92.4 %	0.91
At	$\leq 9.00 \text{ s}$	89.6 %	54.3 %	0.73
ttP	$\leq 12.20 \text{ s}$	94.1 %	56.8 %	0.73
MTT	$\leq 62.22 \text{ s}$	83.3 %	50.0 %	0.59
Pt	$\leq 19.80 \text{ s}$	93.2 %	63.2 %	0.79
Pi	$\geq 83.60$	50.0 %	52.1 %	0.53
integral	$\leq 14049$	50.0 %	57.0 %	0.54
$\lambda$	$\geq 4.45$	72.7 %	50.0 %	0.62

#### D. Method validation

A finite-element implementation of (2) was made in order to simulate variations of the diffusion parameter and the ability of the proposed method to estimate local values.

A preliminary validation of the method was then performed by analysis of data registered from two patients referred for radical prostatectomy at the Academic Medical Center (Amsterdam, the Netherlands). After radical prostatectomy, the prostate was cut in slices of 4-mm thickness and the presence of cancer was marked by a pathologist after histology analysis [16]. The slice corresponding to the ultrasound imaging plane was then selected, and the histology results were compared with those obtained by the proposed contrast ultrasound diffusion imaging method.

For each patient, the results from two areas larger than 1000 pixels containing healthy and cancerous tissue were used to estimate the receiver operating characteristic (ROC) of the parameter  $\kappa$  on a pixel basis. The tissue-classification threshold was determined by Bayes inference assuming a Gaussian distribution of the estimated parameter given a specific class (healthy and cancerous tissue). Fig. 3 shows an example of parametric diffusion image with the fit of two TICs measured from two pixels in cancerous and healthy tissue, respectively. A comparison with different TIC analysis methods proposed in the literature was also performed [12, 13].

### III. RESULTS

According to our simulations, differently from the parameter  $\lambda$ , the parameter  $\kappa$  can be estimated locally. The fitting accuracy was also evaluated. The model fits on the available dataset of measured TICs (about  $10^5$  TICs) after spatio-temporal filtering provided an average determination coefficient  $R^2 = 0.93$ , which was by 24% higher than without spatio-temporal filtering.

The average sensitivity, specificity, and ROC-curve area obtained by the parameter  $\kappa$ , based on the preliminary validation, are reported in Table I together with the results obtained by the TIC appearance time (At), time to peak (ttP), peak intensity (Pi), mean transit time (MTT), and area, as well as by the parameter  $\lambda$  of the LDRW model.

### IV. DISCUSSION AND CONCLUSIONS

A new method based on contrast ultrasound diffusion imaging is proposed for the localization of prostate cancer. The diffusion process is modeled by the convective diffusion

equation. The method provides parametric images based on the local estimation of a diffusion-related parameter that is independent on the dilution history between the injection and detection site.

A preliminary validation with two patients shows the accuracy of the method. An extensive validation, also aimed at evaluating the method potential for assessment of cancer aggressiveness (grading), is however necessary prior to the method adoption in clinical practice. To this end, an improved validation method must be implemented in order to obtain an accurate match between histology slices and ultrasound imaging planes. In this perspective, the use of three-dimensional contrast-enhanced TRUS might open new possibilities, permitting also the investigation of the entire prostate volume by a single bolus injection.

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