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Ultrasound-contrast-agent dispersion and velocity imaging for prostate cancer localization

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ABSTRACT

Prostate cancer (PCa) is the second-leading cause of cancer death in men; however, reliable tools for detection and localization are still lacking. Dynamic Contrast Enhanced UltraSound (DCE-US) is a diagnostic tool that is suitable for analysis of vascularization, by imaging an intravenously injected microbubble bolus. The localization of angiogenic vascularization associated with the development of tumors is of particular interest. Recently, methods for the analysis of the bolus convective dispersion process have shown promise to localize angiogenesis. However, independent estimation of dispersion was not possible due to the ambiguity between convection and dispersion. Therefore, in this study we propose a new method that considers the vascular network as a dynamic linear system, whose impulse response can be locally identified. To this end, model-based parameter estimation is employed, that permits extraction of the apparent dispersion coefficient (D), velocity (v), and Péclet number (Pe) of the system. Clinical evaluation using data recorded from 25 patients shows that the proposed method can be applied effectively to DCE-US, and is able to locally characterize the hemodynamics, yielding promising results (receiver-operating-characteristic curve area of 0.84) for prostate cancer localization.

1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer in men aside from skin cancer, and the second-leading cause of cancer death in men (Society, 2015). Given the significant risk of serious side effects associated with PCa treatment (radical prostatectomy), careful observation (termed active surveillance) instead of immediate treatment is appropriate for many patients that have less aggressive tumors. This approach requires accurate and reliable monitoring techniques. When treatment is necessary, minimally invasive methods such as focal therapy may limit side effects, which in turn requires accurate tumor localization. The current golden standard for prostate cancer diagnosis is transrectal systematic needle biopsies. However, initial biopsies miss nearly a quarter of the clinically significant cancers (Roehl et al., 2002), and provide little information regarding exact tumor locations. Moreover, being an invasive technique, it carries significant risk of infection. This requires hospitalization in up to 6% of the cases (Loeb et al., 2013), becoming even more alarming with increasing resistance to antibiotics. Although transperineal biopsy is emerging as a way to reduce this risk, it is a more complex procedure that requires high grade anesthesia (Chang et al., 2013).

Dynamic Contrast Enhanced Ultrasound (DCE-US) is a minimally invasive diagnostic tool that allows analysis of vascularization, by imaging an intravenously injected microbubble bolus. Of particular interest is the localization of neoangiogenic vascularization associated with tumor growth and metastasis (Folkman, 2002; Brawer, 1996; Weidner et al., 1993). In this paper, we aim at characterizing the microvasculature from the obtained indicator-dilution curves (IDCs) using DCE-US; each IDC represents the evolution over time of the ultrasound contrast agent (UCA) concentration in a pixel.

The microvascular structure that originates from tumor driven angiogenic growth is characterized by high microvascular density (MVD), small-diameter vessels that are highly tortuous, chaotic, irregular and have shunts. Ineffective blood flow can lead to hypoxia and deteriorated endothelial wall cells, potentially resulting in extra-vascular leakage and tumor metastases. With the aim of detecting angiogenic microvascularization, DCE-US imaging of hemodynamic features relies on the hypothesis that these features reflect changes in microvasculature associated with angiogenesis. Focusing at increased MVD, time-intensity features related to

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microvasuclar perfusion have been studied by several researchers (Lueck et al., 2008; Cosgrove and Lassau, 2010; Wei et al., 2001). However, ultrasound attenuation and scanner settings affect the estimation of local UCA concentration and the resulting amplitude based perfusion parameters. Moreover, increased tortuosity as well as increased flow resistance due to decreasing functional vascular cross-sectional area in neoplastic tissue cause lower tumor perfusion (Gillies et al., 1999), leading to perfusion heterogeneity and making localization of angiogenesis based on perfusion a challenging task. Related to this, intra-tumor vascular heterogeneity has been assessed (Cao et al., 2009), although using DCE-CT instead of DCE-US. To enhance the sensitivity of perfusion imaging, regularized deconvolution of the perfused tissue signals with the feeding-artery signal (referred to as arterial input function) is investigated for DCE-CT and DCE-MRI in Koh et al. (2004).

Alternatively, features linked to UCA bolus dispersion have been proposed (Kuenen et al., 2011; 2013a), and are instead intended to directly reflect the tortuous and chaotic structure of the tumor vasculature. Although these approaches have shown promise, independent estimation of dispersion and velocity was not possible due to the ambiguity between dispersive and convective processes reflected in the measured IDCs. Hence, so far only dispersion related parameters that represent a combination of dispersion and velocity were obtained, leaving the specific contribution of both components to the flow kinetics unassessed. Furthermore, to achieve a local estimate of the contrast kinetics, a specific spatial UCA bolus concentration profile was assumed.

Instead of modeling the individual measured IDCs, *we consider the vascular network as a dynamic linear system or channel, whose impulse response can be locally identified by input-output analysis of IDCs*. For this purpose, a Wiener filter is determined, providing an optimal (minimum mean squared error) estimation of the system impulse response. The extraction of the dispersion coefficient, velocity and Péclet number is then facilitated by employing model-based parameter estimation by least squares and Maximum Likelihood approaches.

The analytical details of the measurement model are given in Section 2.1, and an estimator for the Wiener filter is derived in Sections 2.2 and 2.3. Section 2.4 provides a model-based parameter estimator based on Least Squares minimization. Alternatively, Maximum Likelihood estimators are derived in Section 2.5. The data acquisition protocol and the validation methodology are reported in Sections 3 and 4, respectively. The method is then clinically evaluated using a dataset consisting of 61 DCE-US planes, recorded transrectally from 25 patients. A qualitative as well as a quantitative analysis is performed, and the effectiveness of Least Squares and Maximum Likelihood parameter estimators is compared in Section 5. Finally, in Section 6, the results are discussed and conclusions derived.

2. Materials and methods

2.1. Measurement model

We consider a ring shaped kernel with an inner and outer radius of 1 mm and 1.5 mm, respectively, as shown in Fig. 1. The dimensions of the kernel were selected based on the speckle-grain size (Kuenen et al., 2013b) and the scale at which early angiogenesis occurs (Brawer, 1996). The kernel should be larger than the system resolution and smaller than the scale at which angiogenesis develops. With the ultrasound system's axial resolution being approximately 0.3 mm, and the lateral resolution being approximately 0.5 mm at 5 cm from the probe, the inner radius of the kernel was set to 1 mm. Angiogenesis is required for tumors to grow beyond 2–3 mm in diameter. Although the resolution is not adequate for imaging single microvessels, it is sufficient to appreciate changes in the macroscopic hemodynamic phenomena related to early angiogenesis. The adopted kernel is used as follows. The center-pixel IDC is considered to be the local channel input, and the IDCs of the pixels in the kernel are the possible outputs of the channel. Here we assume that there are physically causal relations between the center-pixel IDC and those in the kernel pixels. Firstly, the channel impulse responses from the input to the outputs are estimated. Then, all non-causal responses are discarded (those where the output anticipates the input), after which a mean causal impulse response is obtained.

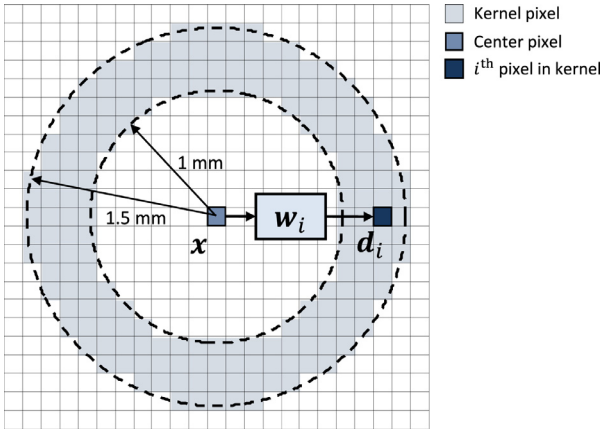

Fig. 1. Kernel for impulse response estimation, showing the Wiener system model $\vec{w}_i$ between the indicator dilution curve at the center pixel and the ith pixel within the kernel.

To accomplish this, we model the IDC of the ith pixel within the kernel $\vec{d}_i \in \mathbb{R}^N$ as a filtered version of the IDC of the pixel at the center $\vec{x} \in \mathbb{R}^N$. Minimizing the mean squared error between the desired output $d_i[n]$ and the filtered input $\sum_{m=0}^{n-1} w_i[m]x[n-m]$, the optimal Wiener filter coefficients $\vec{w}_i$ are given by the Wiener–Hopf equations (Scharf, 1991):

$$\vec{r}_{d_i x} = \mathrm{R}_x \vec{w}_i, \tag{1}$$

where $\vec{r}_{d_i x}$ denotes the cross correlation vector between $\vec{d}_i$ and $\vec{x}$ and R_x is the autocorrelation matrix of $\vec{x}$. In practice, ultrasonic IDC measurements are corrupted by multiplicative (*e.g.* speckle) as well as additive (*e.g.* thermal, electronic) noise. We first analyze their effects on the Wiener estimate, and consider noisy observations

$$\tilde{\vec{x}} = u_1 \vec{x} + v_1, \tag{2}$$

$$\tilde{\vec{d}}_i = u_2 \vec{d}_i + v_2, \tag{3}$$

with v_1, v_2 being independent and identically distributed (i.i.d.) white $\mathcal{N}(0, \sigma_v^2)$ and u_1, u_2 following i.i.d. Rayleigh distributions with scale parameter σ_u, being mutually independent and independent of the signal components. The local assumption on equal noise variances of u_1 and u_2 is reasonable given the small kernel size. A Rayleigh distribution was chosen because it captures the effects of fully developed speckle noise in ultrasound (Wagner et al., 1983). The measured cross correlation vector is then given by

$$\vec{r}_{\tilde{d}_i \tilde{x}} = \mathrm{E}[u_1]\mathrm{E}[u_2]\vec{r}_{d_i x} = \frac{\pi}{2}\sigma_u^2 \vec{r}_{d_i x}, \tag{4}$$

where $\mathrm{E}[\cdot]$ denotes the expectation. Similarly, the measured autocorrelation matrix of $\tilde{\vec{x}}$ can be derived as

$$\mathrm{R}_{\tilde{x}} = \mathrm{R}_{u_1} \mathrm{R}_x + \sigma_v^2 \mathrm{I}, \tag{5}$$

where R_{u_1} is the autocorrelation matrix of the multiplicative noise component and I denotes the identity matrix. Assuming a white