Automatic prostate cancer detection through DCE-MRI images: all you need is a good normalization

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Abstract

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1. Introduction

Prostate Cancer (PCa) is the second most frequently diagnosed men cancer, accounting for 899,000 cases leading to 258,100 deaths (Ferlay et al., 2010). As highlighted by the PI-RADS Steering Committee, the two main challenges to be addressed are (Weinreb et al., 2016): (i) the improvement of detecting clinically significant PCa and (ii) an increase of the confidence in benign or dormant cases, avoiding unnecessary invasive medical exams. In this regard, multiparametric Magnetic Resonance Imaging (MRI) (mpMRI) is frequently used to build robust Computer-Aided Detection and Diangosis (CAD) systems to detect, localize, and grade PCa. In general, CAD systems are based on mpMRI which combines several of the following modalities (Lemaître et al., 2015): T_2 Weighted (T_2-W)-MRI, Dynamic Contrast-Enhanced (DCE)-MRI, Apparent Diffusion Coefficient (ADC) maps, and Magnetic Resonance Spectroscopy Imaging (MRSI).

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In DCE-MRI, a contrast media is injected intravenously and a set of images is acquired over time. Consequently, each voxel in the image is a dynamic signal which is related to the vascular properties of the tissue. In fact, these properties are automatically extracted using quantitative or semi-quantitative approaches (Lemaître et al., 2015).

The former group of approaches uses pharmacokinetic modelling based on a bicompartment model, namely Brix (Brix et al., 1991) and Tofts (Tofts et al., 1995) models. The parameters of the Brix model are found assuming a linear relationship between the media concentration and MRI signal intensity. This assumption has shown, however, to lead to inaccurate parameter calculation (Heilmann et al., 2006). In the contrary, Tofts model only requires a conversion from MRI signal intensity to concentration, which can become a non-linear relationship using specific equation of MRI sequences (e.g., FLASH sequence). Tofts modelling suffers, however, from an higher complexity (Gliozzi et al., 2011). The conversion using the non-linear approach requires to acquire a T_1 map which is not always possible during clinical examination. Furthermore, the parameter calculation require the Arterial Input Function (AIF) which is challenging to measure and can also lead to inaccurate estimation of the parameters.

The latter group of approaches are rather mathematical than pharmacokinetic modelling (Huisman et al., 2001; Gliozzi et al., 2011). These methods offer the advantages to not require any knowledge about the MRI sequence nor any conversion from signal intensity to concentration. However, the heuristic approach propose by Huisman et al. requires an estimate regarding the noise standard deviation of the signal as well as manual tuning.

Nevertheless, all presented methods suffer from two major drawbacks: (i) the inter-patient variability of the data lead to a variation of the parameters estimated and to poor classification performance while designing CAD systems, and (ii) only few parameters are used to characterize the dynamic signal implying that some information are discarded.

In this work, we propose a fully automatic normalization method for DCE-MRI that reduce the inter-patient variability of the data. Furthermore, we show

that using the full normalized signal lead to the best classification performance.

The paper is organized as follows: Section 2 outlines our normalization strategy (Section 2.1) as well as specificity regarding the state-of-the-art methods used for comparison (Section 2.2). The dataset, experiments, and results are reported in Section 3 while discussed in Section 4 followed by a concluding section.

2. Methods

2.1. Normalization of DCE-MRI images

2.2. Quantification of DCE-MRI

2.2.1. Brix and Hoffmann models

In the Brix model (Brix et al., 1991), the MRI signal intensity is assumed to be proportional to the media concentration. Therefore, the model is expressed as in Eq. (1):

$$s_n(t) = 1 + A\left[\frac{\exp(k_{el}t') - 1}{k_{ep}(k_{ep} - k_{el})}\exp(-k_{el}t) - \frac{\exp(k_{ep}t') - 1}{k_{el}(k_{ep} - k_{el})}\exp(-k_{ep}t)\right], \quad (1)$$

with

$$s_n(t) = \frac{s(t)}{S_0}, \quad (2)$$

where $s(t)$ and S_0 are the MRI signal intensity at time t and the average pre-contrast MRI signal intensity, respectively; A, k_{el}, and k_{ep} are a constant proportional to the transfer constant, the diffusion rate constant, and the rate constant, respectively. Additionally, during the injection time $0 \leqslant t \leqslant \tau$, $t' = t$ and afterwards while $t > \tau$, $t' = \tau$.

Following this model, Hoffmann et al. propose the following similar model as expressed in Eq. (3):

$$s_n(t) = 1 + \frac{A}{\tau}\left[\frac{k_{ep}\left(\exp(k_{el}t') - 1\right)}{k_{el}(k_{ep} - k_{el})}\exp(-k_{el}t) - \frac{\exp(k_{ep}t') - 1}{(k_{ep} - k_{el})}\exp(-k_{ep}t)\right]. \quad (3)$$

2.2.2. Tofts model

The extended Tofts model is formulated as in Eq. (4):

$$C_t(t) = K_{trans} C_p(t) * \exp(-k_{ep} t) + v_p C_p(t), \tag{4}$$

where $*$ is the convolution operator; $C_t(t)$ and $C_p(t)$ is the concentration of contrast agent in the tissue and in the plasma, respectively; K_{trans}, k_{ep}, and v_p are the volume transfer constant, the diffusion rate constant, and the plasma volume fraction, respectively.

Therefore, Tofts model requires to: (i) detect candidate voxels from the femoral or iliac arteries and estimate a patient-based AIF signal, (ii) convert the MRI signal intensity (i.e., AIF and dynamic signal) to a concentration, and (iii) in the case of a population-based AIF, estimate an AIF signal.

Segmentation of artery voxels and patient-based AIF estimation The AIF signal from DCE-MRI can be manually estimated by selecting the most-enhanced voxels from the femoral or iliac arteries (Meng et al., 2010). Few methods have been proposed to address the automated extraction of AIF signal. Chen et al. filter successively the possible candidates (Chen et al., 2008): (i) dynamic signals with small peak are rejecting by thresholding, (ii) voxels with a small wash-in are rejected by thresholding, (iii) a blob detector is used and large enough regions are kept, and (iv) circular and cylindricality are used to reject the last false positive. Zhu et al. propose an iterative method selecting voxels which best fit a gamma variate function (Zhu et al., 2011). However, it requires to compute first and second derivatives as well as maximum curvature points. Shanbhag et al. propose a 4-steps algorithm (Shanbhag et al., 2012; Fennessy et al., 2015): (i) remove slices with artefacts and find the best slices based on intrinsic anatomic landmarks and enhancement characteristics, (ii) find the voxel candidates using the maximum enhanced voxels and a multi-label maximum entropy based thresholding algorithm, (iii) excluding region next to the endorectal coil, and (iv) selecting the best 5 candidates which meet

enhancement characteristics and that are correlated.

All the above methods are rather complex and thus we propose a method which is based on the following simple assumptions: (i) all possible AIF signal candidates should have a similar shape, (ii) an high enhancement, and (iii) the arteries should be almost round and within a size range. Therefore, each slice is clustered into regions using K-means clustering with $k = 6$. The cluster with the highest enhancement—i.e. corresponding to the 90^{th} percentile of the maximum of each dynamic signal—contain the arteries and is selected. Finally, regions with an eccentricity smaller than 0.5 and an area in the range of $[100, 400]$ voxels are kept. Additionally, to remove voxels contaminated by partial volume effect, only the 10% most enhanced voxels of the possible candidates are kept as proposed by (Schabel and Parker, 2008) and the average signal is computed. A summary of the different segmentation steps is presented in Fig. **??**.

Conversion of MRI signal intensity to concentration To estimate the free parameters of the Tofts model (see Eq. (4)), the concentration $C_t(t)$ and $C_p(t)$ need to be computed from the MRI signal intensity and the AIF signal, respectively. This conversion is based on the equation of the FLASH sequence—see Appendix A for details—and is formulated as in Eq. (5):

$$C(t) = \frac{1}{TR \cdot r_1} \ln\left(\frac{1 - \cos\alpha \cdot S^* \frac{S(t)}{S_0}}{1 - S^* \frac{S(t)}{S_0}}\right) - \frac{R_{10}}{r_1}, \tag{5}$$

with,

$$S^* = \frac{1 - \exp(-TR \cdot R_{10})}{1 - \cos\alpha \cdot \exp(-TR \cdot R_{10})}, \tag{6}$$

where $S(t)$ is the MRI signal, S_0 is the MRI signal prior to the injection of the contrast media, α is the flip angle, TR is the Repetition Time (TR), R_{10} is the pre-contrast tissue relaxation time also equal to $\frac{1}{T_{10}}$, r_1 is the relaxitivity coefficient of the contrast agent.

T_{10} can be estimated from the acquisition of a T_1 map. However, this modality was not part of the clinical trial in this research and the value of

T_{10} was fixed to 1600 ms for both blood and prostate as stated in the literature (Fennessy et al., 2015; De Bazelaire et al., 2004; Carr and Carroll, 2011).

Estimation of population-based AIF While estimating the pharmacokinetic parameters from Tofts model, the AIF concentration $C_p(t)$ can be computed either from the patient or a population. We presented in the two previous sections the algorithms which allows to estimate the patient-based AIF concentration. To compare with the previous approach, we also computed a population-based AIF which will be also later used to compare the performance of both approaches. In that regard, the population-based AIF was estimated as in (Meng et al., 2010) by fitting the average patient-based AIFs to the model of Parker et al. (2006) which is formulated as in Eq. (7):

$$C_p(t) = \sum_{n=1}^{2} \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(\frac{-(t-T_n)^2}{2\sigma_n^2}\right) + \frac{\alpha \exp(-\beta t)}{1+\exp -s(t-\tau)}, \qquad (7)$$

where A_n, T_n, and σ_n are the scaling constants, centers, and widths of the n^{th} Gaussian, α and β are the amplitude and decay constant of the exponential; and s and τ are the width and center of the sigmoid function, respectively.

2.2.3. PUN model

Gliozzi et al. show that Phenomenological Universalities (PUN) approach can be used for DCE-MRI analysis (Gliozzi et al., 2011). The model has been successfully used in a CAD system proposed by Giannini et al. (2015). This model can be expressed as in Eq. (8):

$$s_n(t) = \exp\left[rt + \frac{1}{\beta}\left(a_0 - r\right)\left(\exp(\beta t) - 1\right)\right], \qquad (8)$$

with

$$s_n(t) = \frac{s(t) - S_0}{S_0}, \qquad (9)$$

where $s(t)$ and S_0 are the MRI signal intensity at time t and the average pre-contrast MRI signal intensity, respectively; r, a_0, and β are the free parameters of the model.

130 *2.2.4.*

3. Experiments and results

4. Discussions

5. Conclusions and future works

Appendix A. Conversion from FLASH signal to media concentration

135 In this appendix, we show the demonstration used to extract the agent concentration from the MRI signal.

The signal equation in FLASH sequence (Haase et al., 1986) is defined as:

$$S(t) = S_{eq} \sin\alpha \cdot \frac{1 - \exp\left(-TR\left(R_{10} + r_1 C(t)\right)\right)}{1 - \cos\alpha \cdot \exp\left(-TR\left(R_{10} + r_1 C(t)\right)\right)}, \tag{A.1}$$

where $S(t)$ is the MRI signal, S_{eq} is the maximum signal amplitude of the spoiled gradient at the Echo Time (TE) which is proportional to the Proton Density
140 (PD), α is the flip angle, TR is the Repetition Time (TR), R_{10} is the pre-contrast tissue relaxation time also equal to $\frac{1}{T_{10}}$, r_1 is the relaxitivity coefficient of the contrast agent, and $C(t)$ is the media concentration.

Therefore, the pre-contrast signal prior to bolus injection of the media is defined as:

$$S_0 = S_{eq} \sin\alpha \cdot \frac{1 - \exp\left(-TR \cdot R_{10}\right)}{1 - \cos\alpha \cdot \exp\left(-TR \cdot R_{10}\right)}. \tag{A.2}$$

145 To simplify the demonstration, let us define:

$$a = \exp(-TR \cdot R_{10}), \tag{A.3}$$

$$b = \exp(-TR \cdot r_1 C(t)). \tag{A.4}$$

Let us define:

$$S^* = \frac{S_0}{S_{eq} \sin \alpha}, \tag{A.5}$$

$$= \frac{1-a}{1-a\cos\alpha}. \tag{A.6}$$

Thus,

$$S^* \frac{S(t)}{S_0} = \frac{S_0}{S_{eq} \sin \alpha} \frac{S(t)}{S_0}, \tag{A.7}$$

$$= \frac{1-ab}{1-ab\cos\alpha}. \tag{A.8}$$

Now, let us define:

$$\frac{1-\cos\alpha \cdot S^* \frac{S(t)}{S_0}}{1-S^* \frac{S(t)}{S_0}} = \frac{1-\cos\alpha \left(\frac{1-ab}{1-ab\cos\alpha}\right)}{1-\frac{1-ab}{1-ab\cos\alpha}}, \tag{A.9}$$

$$= \frac{1-ab\cos\alpha-\cos\alpha(1-ab)}{1-ab\cos\alpha-(1-ab)}, \tag{A.10}$$

$$= \frac{1-ab\cos\alpha-\cos\alpha+ab\cos\alpha}{1-ab\cos\alpha-1+ab}, \tag{A.11}$$

$$= \frac{1-\cos\alpha}{ab(1-\cos\alpha)}, \tag{A.12}$$

$$= \frac{1}{ab}. \tag{A.13}$$

Thus,

$$-TR \cdot R_{10} - TR \cdot r_1 C(t) = \ln\left(\frac{1-\cos\alpha \cdot S^* \frac{S(t)}{S_0}}{1-S^* \frac{S(t)}{S_0}}\right). \tag{A.14}$$

Therefore,

$$C(t) = \frac{1}{TR \cdot r_1} \ln\left(\frac{1-\cos\alpha \cdot S^* \frac{S(t)}{S_0}}{1-S^* \frac{S(t)}{S_0}}\right) - \frac{R_{10}}{r_1}. \tag{A.15}$$

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