

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
5 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 Diagnosis (CAD) systems to detect, localize,
10 and grade PCa. In general, CAD systems are based on mpMRI which combines several of the following modalities (Lemaître et al., 2015): T₂ Weighted (T₂-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
15 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
20 bicompartiment 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 as-
sumption has shown, however, to lead to inaccurate parameter calculation (Heil-
mann et al., 2006). In the contrary, Tofts model only requires a conversion from
25 MRI signal intensity to concentration, which can become a non-linear relation-
ship 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
30 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 pharmacoki-
netic modelling (Huisman et al., 2001; Gliozzi et al., 2011). These methods
offer the advantages to not require any knowledge about the MRI sequence nor
35 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
40 estimated and to poor classification performance while designing CAD systems,
and (ii) only few parameters are used to characterize the dynamic signal imply-
ing 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

45 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
50 section.

2. Methods

2.1. Normalization of DCE-MRI images

2.2. Quantification of DCE-MRI

2.2.1. Brix and Hoffmann models

55 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 $0 \leq t \leq \tau$, $t' = t$ and afterwards while $t > \tau$, $t' = \tau$.

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

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

2.2.2. Tofts model

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

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

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 cylindricity 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.

95 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
 100 with $k = 6$. The cluster with the highest enhancement—i.e. corresponding
 to the 90th 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%
 105 most enhanced voxels of the possible candidates are kept as proposed
 by (Schabel and Parker, 2008). A summary of the different segmentation
 steps is presented in Fig. ??.

Conversion of MRI signal intensity to concentration

2.2.3. PUN model

110 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. (5):

$$s_n(t) = \exp \left[rt + \frac{1}{\beta} (a_0 - r) (\exp(\beta t) - 1) \right], \quad (5)$$

with

$$s_n(t) = \frac{s(t) - S_0}{S_0}, \quad (6)$$

115 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.

2.2.4.

3. Experiments and results

120 4. Discussions

5. Conclusions and future works

Appendix A. Conversion from FLASH signal to media concentration

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

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

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

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 (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 relaxativity coefficient
130 of the contrast agent, and $C(t)$ is the media concentration.

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

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

To simplify the demonstration, let us define:

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

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

Let us define:

$$S^* = \frac{S_0}{S_{eq} \sin \alpha}, \quad (\text{A.5})$$

$$= \frac{1 - a}{1 - a \cos \alpha}. \quad (\text{A.6})$$

Thus,

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

$$= \frac{1 - ab}{1 - ab \cos \alpha}. \quad (\text{A.8})$$

135 Now, let us define:

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

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

$$= \frac{1 - ab \cos \alpha - \cos \alpha + ab \cos \alpha}{1 - ab \cos \alpha - 1 + ab}, \quad (\text{A.11})$$

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

Thus,

$$-TR \cdot R_{10} - TR \cdot r_1 C(t) = \ln \left(\frac{1 - \cos \alpha \cdot S^* \frac{S(t)}{S_0}}{1 - S^* \frac{S(t)}{S_0}} \right). \quad (\text{A.13})$$

Therefore,

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

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