Pharmacokinetic analysis of prostate cancer using independent component analysis

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A B S T R A C T

Dynamic contrast enhanced (DCE)-MRI combined with pharmacokinetic (PK) modeling of a tumor provides information about its perfusion and vascular permeability. Most PK models require the time course of contrast agent concentration in blood plasma as an input, which cannot be measured directly at the tissue of interest, and is approximated with an arterial input function (AIF). Variability in methods used in estimating the AIF and inter-observer variability in region of interest selection are major sources of discrepancy between different studies. This study had two aims. The first was to determine whether a local vascular input function (VIF) estimated using an adaptive complex independent component analysis (AC-ICA) algorithm could be used to estimate PK parameters from clinical dynamic contrast enhanced (DCE)-MRI studies. The second aim was to determine whether normalizing the input function using its area under the curve would improve the results of PK analysis. AC-ICA was applied to DCE-MRI of 27 prostate cancer patients and the intravascular signal was estimated. This signal was converted into contrast agent concentration to give a local vascular input function (VIF) which was used as the input function for PK analysis. We compared Ktrans values for normal peripheral zone (PZ) and tumor tissues using the local VIF with those calculated using a conventional AIF obtained from the femoral artery. We also compared the Ktrans values obtained from the un-normalized input functions with the Ktrans values obtained after normalizing the AIF and local VIF. Normalization of the input function resulted in smaller variation in PK parameters (Ktrans vs. Ktrans for normal PZ tissue was 0.20 ± 0.04 mM min⁻¹ vs. 0.87 ± 0.54 min⁻¹ for local VIF and 0.21 ± 0.07 mM min⁻¹ vs. 0.25 ± 0.29 min⁻¹ for AIF) and better separation of the normal and tumor tissues (effect-size of this separation using Ktrans vs. Ktrans was 0.89 ± 0.25 vs. 0.75 for local VIF and 0.94 vs. 0.41 for AIF). The AC-ICA and AIF-based analyses provided similar (Ktrans) values in normal PZ tissue of prostate across patients. Normalizing the input function before PK analysis significantly improved the reproducibility of the PK parameters and increased the separation between normal and tumor tissues. Using AC-ICA allows a local VIF to be estimated and the resulting PK parameters are similar to those obtained using a more conventional AIF; this may be valuable in studies where an artery is not available in the field of view.

1. Introduction

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) involves intravenous administration of a bolus of low molecular-weight contrast agent, followed by imaging the tissue of interest repeatedly to monitor the passage of the bolus through its vasculature. Combining DCE-MRI with pharmacokinetic (PK) modeling of the tumor tissue, which models the exchange of contrast agent between blood plasma and the extracellular extravascular space (EES), provides information about tumor microvasculature, perfusion, and capillary permeability [1–3]. These quantitative parameters have been shown to be related to prognostic factors, and can be used to differentiate normal tissue from malignant tumors [4,5], and also to assess tumor response to therapy [2,6–8]. However, accurate calculation of PK parameters is subject to several measurement and analysis errors and inconsistencies (particularly in AIF measurement) that have limited their application to research environments [9] and well-controlled clinical trials [10–12] rather than common clinical practice [13]. Other factors that have limited the application of PK analysis are un-standardized imaging protocols, the fact that most models provide parameters that represent a combination of blood flow and permeability, lack of ground truth and proper validation for models.

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There exist several PK models such as the Tofts–Kety (TK) model, the extended Tofts–Kety (ETK) model [3,14], and the adiabatic approximation to tissue homogeneity (AATH) model [15] that are commonly applied to DCE-MRI of tumors. These pharmacokinetic models, which are derived from the theory of tracer–kinetics in linear and stationary systems [16–18], require information about the time course of contrast agent concentration in blood plasma at each voxel of the tissue of interest (TOI). Identifying and separating the intravascular signal in each voxel of the TOI from the signal in the extravascular space is very difficult due to the low spatial resolution (relative to the size of the capillaries) and low signal to noise ratio of DCE-MRI (resulting from requiring high temporal resolution), indirect effect of contrast agent molecules in MRI signal, flow effects (this effect is small as the flow in small vessels in the tumor is very slow), etc. Therefore the time course of intravascular contrast agent concentration is usually approximated outside of the TOI using an arterial input function (AIF). The AIF represents the time course of contrast agent concentration in blood plasma and is used as an input in pharmacokinetic modeling of contrast agent kinetics in the TOI.

Many approaches for estimating the AIF have been introduced. The most common method is to measure the AIF from signal enhancement of a region of interest over an artery. This has been shown to provide good results in PK analysis and if it is performed carefully can provide consistent PK parameters [19,20]. However it assumes that an artery close to the tissue of interest and of sufficient size is present in the field of view (FOV). Finding an artery is often difficult in animal studies and alternative methods are desired.

If no major artery is available, then reference region (RR) methods may be used [21]: these require either prior knowledge about PK parameters of a normal tissue (using parameter values reported in previous studies) [22], or use the signal of a small blood vessel to first calculate the PK parameters of the reference tissue [23]. The rate of change of contrast concentration in the RR is slower compared to an artery which means that some RR techniques are able to work on data with lower temporal resolution [21]. However small signal enhancement in the RR often leads to low signal to noise ratio and makes the analyses prone to error [21].

In the dual-bolus method, a low dose bolus is injected before the main bolus to measure the AIF with high temporal accuracy; however the first bolus affects the PK analysis results of the main bolus (due to first injection which affects the pre-contrast T₁ of the tissue and thus MRI signal to contrast agent concentration conversion process) [24,25]. This problem could be solved by waiting for a long time (9–15 min in rabbits) between the two injections which is not practical in clinical settings [24,25]. Population-average [26] and theoretical bi-exponential [27,28] AIFs may be used in cases where no other technique can be used. If the imaging protocols are kept the same, these methods have the potential to provide reliable PK parameters [26,27], but they do not account for patient variability [25]. Furthermore, in all of these methods there is a delay between arrival of the contrast agent in the TOI and the site of AIF measurement which makes PK analysis more complex.

We hypothesize that using an intravascular input function that is calculated locally at the TOI, which we will refer to as the local vascular input function (VIF), can provide more accurate PK parameters with consistent values for a specific tissue type (normal peripheral zone tissue in this study) between different subjects, and results in a better separation of the normal and malignant tissue types. An independent component analysis (ICA)-based algorithm was developed to indentify and separate the intravascular signal in DCE-MRI, which was capable of estimating the intravascular signal accurately both spatially and temporally [29–31]. This algorithm, which we refer to as adaptive complex ICA (AC-ICA), uses complex-valued DCE-MRI data (magnitude and phase), estimates the spatial distribution of the intravascular signal, and calculates the signal enhancement in the intravascular space of the TOI. The algorithm only requires the DCE-MRI signal within the TOI and does not need a major feeding artery in the FOV, or any prior information about a normal tissue close to the TOI. It also does not require the presence of a small blood vessel close to TOI, or a second contrast agent injection.

In this study we first address the problem of scaling ambiguity in the AC-ICA analysis by developing a method of converting the calculated intravascular MR signal into a normalized contrast agent concentration time course to obtain the local VIF. In a cohort of prostate cancer patients (27 patients), we then compare the PK analysis results obtained using the local VIF generated by the AC-ICA algorithm, to the conventional method in which the contrast agent concentration time course at the femoral artery is used as the AIF.

Prostate cancer is used for evaluating the performance of the AC-ICA algorithm since the multi-parametric MR imaging of prostate cancer provides sufficient adjacent information for tumor detection, diagnosis and also PK analysis [32]. Moreover, there exist several major arteries in the FOV of prostate MR images (e.g. femoral artery) that have been used in the literature for PK analysis extensively [5,19,20,33,34], and will be used in this study to assess the performance of the local VIF calculation algorithm in PK analysis. If the proposed algorithm provided acceptable pharmacokinetic parameters in the analysis of prostate DCE-MRI (in which an alternative analysis technique is available for comparison), then its use could be extended to the pharmacokinetic analysis of tumors in cases where an AIF is not available or is difficult to measure, for example small animal studies or breast imaging.

2. Materials and methods

2.1. Pharmacokinetic modeling

Pharmacokinetic (PK) modeling provides quantitative information about the exchange of substances between blood plasma and extravascular space. In clinical DCE-MRI studies the injected Gadolinium-based contrast agent (e.g. Magnevist, Omniscan) has low molecular weight and can diffuse through the vessel walls into the extravascular space. However, these contrast agent molecules do not cross the cell membrane [35] and thus, can only diffuse into the extravascular extracellular space (EES). In PK modeling it is assumed that the rate by which the contrast agent diffuses from blood plasma into the EES is determined by the blood flow, vascular permeability, and surface area of the vessel. The ETK model is used in this study, whose governing equations are given in Eq. (1) [3,14,36]:

\[
\frac{\partial c_e(t)}{\partial t} = \frac{\partial}{\partial t} \left( v_p c_p(t) + v_e c_e(t) \right),
\]

where \( c_e(t) \) is the concentration of the contrast agent in the tissue (entire voxel), \( c_p(t) \) is the concentration in the EES, \( v_p \) is the concentration in the plasma pool, \( v_e \) is the volume transfer constant describing the rate by which the contrast agent diffuses from the plasma space into the EES, \( v_p \) is the EES per unit volume of tissue, and \( v_e \) is the blood plasma space per unit volume of tissue. If the signal of an artery outside the TOI is being used as the plasma pool concentration, a delay term, \( \omega \), in the bolus arrival time has to be introduced (\( c_p(t) = c_p(t - \omega) \)) as the contrast agent does not arrive in the TOI at the same time. However, it is zero (\( \omega = 0 \)) when using the local VIF calculated using the AC-ICA algorithm.

It is necessary to know the plasma pool concentration (local VIF) in order to calculate the ETK model parameters; however, this signal is combined with the EES signal and cannot be measured directly. It is therefore approximated using an arterial input function [23,24,27,37–41] which is usually calculated outside of the TOI.
An ICA-based algorithm (AC-ICA) was introduced [29–31] to calculate the local VIF at the TOI and to separate it from the EES signal. This signal does not have the problems of AIF based techniques and also simplifies the PK model by eliminating the delay parameter, and directly calculating the \( \nu_p \) parameter. The next section briefly explains the AC-ICA algorithm, and the methods used to generate a normalized local VIF.

### 2.2. Adaptive complex independent component analysis (AC-ICA)

Having a time series signal \( Z = [z_0, z_1, ..., z_N-1]^T \) (e.g. the DCE-MRI data comprised of N frames), which can be represented as a linear combination of M (usually M ≤ N) spatially independent components (IC) \( S = [s_0, s_1, ..., s_M-1]^T \) (e.g. the spatial images of the intravascular space, extravascular space, etc.), the relationship between \( Z \) and \( S \) could be written as:

\[
Z = AS
\]  

(2)

where \( A \in \mathbb{R}^{N \times M} \) is the mixing matrix. Independent component analysis (ICA) is a statistical signal processing algorithm that, having the mixed signal \( Z \), identifies the underlying independent components \( S \), and the mixing matrix \( A \), without making any assumption about their underlying physiology or mixing processes. In linear ICA algorithms Eq. (2) is reformulated as:

\[
Y = WZ
\]  

(3)

where \( W \in \mathbb{R}^{M \times N} \) is the unmixing matrix and \( Y = [y_0, y_1, ..., y_N-1]^T \) is a scaled and permuted version of \( S \) [42].

Deflationary linear ICA, which estimates the ICs one by one, is used in the AC-ICA algorithm. The algorithm uses the complex-valued MRI data rather than the magnitude of MRI data in which the linear mixture assumption of intravascular and extravascular signals is violated. Details of the AC-ICA algorithm have been published in previous studies [29,43]: in brief AC-ICA models the spatial distribution of each IC (intravascular, EES, etc.) with a linear combination of 3 to 5 random variables whose probability density functions (pdf) have the form of generalized Gaussian distributions (GGD) [29,43]. An expectation maximization framework is used at each iteration of the AC-ICA algorithm to calculate the membership probabilities of these GGDs and their model parameters. The GGD with highest membership probability is used to derive the AC-ICA non-linearity function [29,43]. This adaptive non-linearity function is used in the fixed point update rule for complex ICA [29,43], and the ICs are estimated.

For each DCE-MRI dataset, dimensionality reduction is first performed by calculating the eigenvalues of the covariance matrix of the data and then keeping the \( k \) largest eigenvalues (significant eigenvalues) such that \( \sum_{i=0}^{k-1} \lambda_i / \sum_{i=0}^{N-1} \lambda_i \geq 0.01 \) where \( \lambda \) represents the eigenvalues of the covariance matrix of DCE-MRI data and \( N \) is the total number of eigenvalues. Such dimensionality reduction keeps 99% of the variance in the data. The data is also whitened [44] to make it zero-mean and unit variance. The AC-ICA algorithm is then applied and the number of ICs extracted is equal to the number of eigenvalues that were kept in the dimensionality reduction step.

The intravascular components are selected heuristically (based on previous studies [29,30] and also examining several prostate DCE-MRI data), such that the IC curves with a uniform pre-contrast uptake phase, an uptake phase in which the intensity increases rapidly and a washout phase in which the intensity drops to less than 60% of the peak value after 4 min are selected as the intravascular components [29,30].

### 2.3. Conversion of AC-ICA result to local VIF

The intravascular IC image and corresponding time–intensity curve that are calculated using the AC-ICA algorithm have to be converted into contrast agent concentration before being used in PK analysis. In order to convert the signal intensity of a voxel at time \( t = \tau \) into contrast agent concentration, both the pre-contrast signal intensity and the MR signal intensity at \( t = \tau \) are required. As ICA is a data-driven algorithm which does not make any assumption about the physiology of the data it is processing, some structures, e.g. intravascular space, might split into several ICs. These ICs have to be first combined to represent the entire intravascular signal. We can rewrite Eq. (2) in expanded form as follows:

\[
\sum_{i=1}^{k} \lambda_i > 0.01 \begin{bmatrix} z_0 \\ \vdots \\ z_{N-1} \end{bmatrix} = \begin{bmatrix} a_0 \\ \vdots \\ a_M \end{bmatrix} \begin{bmatrix} s_0 \\ \vdots \\ s_M \end{bmatrix}
\]  

(4)

where \( a_i \) is a column of mixing matrix \( A \), and \( L \) is the number of ICs that are identified as intravascular. The time series data corresponding to the intravascular signal, \( Z_{IV} \), can be written as:

\[
Z_{IV} = \begin{bmatrix} z_{IV0}, z_{IV1}, ..., z_{IVN-1} \end{bmatrix}^T = a_{IV}^T s_{IV} + \cdots + a_{IVL}^T s_{IVL}
\]  

(5)

where \( z_{IV,\tau} \) is the signal enhancement in the intravascular space at time \( \tau \) (i.e. \( t = \tau \)). The change in the intravascular signal that is generated by the contrast agent in the intravascular space between \( t = 0 \) and \( t = \tau \) is:

\[
\Delta z_{IV,\tau} = z_{IV,\tau} - z_{IV0}
\]  

(6)

adding \( \Delta z_{IV,\tau} \) to the pre-contrast MR image corresponding to \( t = 0 \) (which is \( z_0 \)), results in an MR image in which the only enhancement is generated by the contrast agent in the intravascular space. The signal intensity is the magnitude of the complex-valued MRI signal and thus we have:

\[
S_{IV}(\tau) = \left| S_{IV}(0) + \Delta z_{IV,\tau} \right|
\]  

(7)

Once \( S_{IV}(0) \) and \( S_{IV}(\tau) \) are calculated, the intravascular concentration is calculated using the standard conversion method for spoiled gradient recalled (SPGR) pulse sequence [45]. The pre-contrast T1 (T10)-map of the prostate, which is needed for this conversion, is calculated using two pre-contrast images of the prostate with flip angles 5, and 15 degrees (FA = 5°, 15°). In order to obtain accurate T10 the flip angle correction method introduced by Fennessy et al [46] was applied which uses the known T10 value of the pelvic muscle (1420 ms at 3 T) to correct for the difference between the applied and the actual flip angle. This correction however, does not account for the inhomogeneities across the field of view and only applies an overall scaling factor to the T10 values.

### 2.4. Normalizing the local vascular input function

Calculating the absolute value of the PK parameters requires calculating the absolute value of the input function (local VIF or AIF) locally at the voxel level which is not possible with the currently used methods. There is an arbitrary scaling of the input function, which varies depending on the manual ROI that is drawn around a large artery (in AIF-based analyses), or the ROI that is being used for ICA analysis (in the proposed algorithm). It is common to normalize
the input function by dividing it by the number of voxels in the ROI [47,48], which is operator-dependant and varies between measurements and thus introduces variation in the calculated PK parameters. Such normalization becomes more problematic when ICA-based local VIFs are being used as the input function, since the region used for ICA analysis may vary significantly.

If the input functions (local VIF or AIF) were scaled similarly, the values of their corresponding PK parameters could be compared between subjects. We can reformulate the ETK model equations [see Eq. (1)] as follows:

$$v_e \frac{d(c_p(t))}{dt} = K^{trans} \left[ \frac{c_p(t) - (1/v_e) (c_p(t) - c_{VN}(t))} \right]$$

(8)

calculating the integral of both sides of Eq. (8) we have:

$$v_e \int \frac{d(c_p(t))}{dt} dt = K^{trans} \left[ \int (1/v_e) c_p(t) dt - \int \frac{1}{v_e} c_{VN}(t) dt \right]$$

(9)

The above equation can be simplified as:

$$v_e c_p(T) = K^{trans} \left[ \int_0^T \frac{1}{v_e} c_p(t) dt - \int_0^T \frac{1}{v_e} c_{VN}(t) dt \right]$$

(10)

where T is the time point for the last acquired DCE-MRI frame. At time T the system has reached steady state where intravascular, $c_p(t)$ and extravascular extracellular, $c_{VN}(t)$ concentrations of contrast agent can be assumed to be equal. Thus we have $c_p(T) = c_{VN}(T) / (v_e + v_p)$, and therefore the area under the curve (AUC) of the input function is given by:

$$\int_0^T c_p(t) dt = \left( \frac{v_e}{v_e + v_p} \right)^2 \frac{c_{VN}(T)}{K^{trans}} + \frac{1}{v_e + v_p} \int_0^T c_{VN}(t) dt$$

(11)

Since the PK parameters are characteristics of the tissue and $c_p(t)$ is derived directly from MRI measurements, they do not depend on the input function calculation method (if the injection dose and procedure as well as imaging protocol are kept the same). Therefore, if two local VIFs satisfy Eq. (1), their AUCs have to be equal. We therefore propose normalizing the input function with respect to its AUC and we represent the normalized PK parameters with $K^{trans}_{VN}$ (normalized $K^{trans}$), $v_{pN}$ (normalized $v_p$), and $v_{VN}$ (normalized $v_e$), with units mM-min$^{-1}$, mM, and mM respectively (these parameters have no physical interpretation and represent the PK parameters when the local VIF is normalized with respect to its AUC). Note that these normalized parameters do not represent the same physical properties as the conventional PK parameters generated from un-normalized input functions, for instance the $v_{VN}$ does not represent the EES fraction of the voxel. We hypothesize that such normalization has the potential to enable comparison between AIF-based and local VIF-based PK parameters, and also provide more consistent inter-subject PK parameters if the dose per kilogram-of-body-weight of injected contrast agent is kept constant between patients.

2.5. Patient population and clinical study

Approval for this retrospective study was obtained from the institutional research ethics board. A cohort of 27 prostate cancer patients, where both the magnitude and the phase images of the DCE-MRI data were available, was identified and included in this study. The patients had elevated PSA readings and had undergone transrectal ultrasound (TRUS)-guided biopsy before imaging or were biopsied after imaging. Details of the patients’ age, PSA reading and biopsy results (tumor location and Gleason score) are given in Table 1. The biopsy results for prostate cancer were positive for 16 patients and were negative for the remaining 11 patients.

2.6. Multi-parametric MR imaging

Multi-parametric MR imaging containing (T2-weighted MRI, diffusion weighted MRI and DCE-MRI) is commonly used in clinical practice for detection and localization of prostate cancer [49]. These MRI sequences provide complementary information and facilitate clinical decision making process. MR imaging was performed on a 3 T Achieva Philips scanner (Philips Medical Systems). A set of MR images was first acquired to localize the prostate, followed by anatomical imaging using T2-weighted spin echo (SE) sequence acquired in sagittal, axial and coronal planes. The T2-weighted imaging was followed by axial diffusion weighted imaging (DWI) to generate maps of apparent diffusion coefficient (ADC), and multiple flip angle T1-weighted images to generate the pre-contrast T10-map of the prostate. The final step of the MR imaging was DCE-MRI, which was performed using a 3D SPGR sequence where the contrast agent, Magnevist, was injected intravenously with a dose of 0.1 m-kg$^{-1}$.

For each MRI sequence a total of 20 axial planes through the prostate were acquired. DCE-MRI was performed for approximately 6 min with a temporal resolution of approximately 4.8 s. Details of imaging parameters used for each MR sequence are given in Table 2. Details of MRI sequences used in T2-weighted, DW and T1-weighted MR imaging of the prostate are shown in Fig. 1 along with its T2-weighted MRI and ADC map.

2.7. Data analysis

For each patient, the slices in which the prostate was visible were first identified (out of the 20 slices in each dataset), and a rectangular

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE (ms)</th>
<th>FA (°)</th>
<th>b-value (s/mm$^2$)</th>
<th>FOV (cm)</th>
<th>Slice thickness (mm)</th>
<th>Reconstructed Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2w-axial</td>
<td>6800/120</td>
<td>90</td>
<td>–</td>
<td>15 ± 5</td>
<td>3.5</td>
<td>224 × 224</td>
</tr>
<tr>
<td>T2w-sagittal</td>
<td>3000/120</td>
<td>90</td>
<td>–</td>
<td>15 ± 5</td>
<td>3.5</td>
<td>224 × 224</td>
</tr>
<tr>
<td>T2w-coronal</td>
<td>3000/120</td>
<td>90</td>
<td>–</td>
<td>15 ± 5</td>
<td>3.5</td>
<td>224 × 224</td>
</tr>
<tr>
<td>DWI</td>
<td>4120/60</td>
<td>90</td>
<td>0 &amp; 1000</td>
<td>24 × 24</td>
<td>3.5</td>
<td>144 × 144</td>
</tr>
<tr>
<td>Multi-FA (SPGR)</td>
<td>10/1.81</td>
<td>5 &amp; 15</td>
<td>–</td>
<td>20 ± 20</td>
<td>3.5</td>
<td>112 × 112</td>
</tr>
<tr>
<td>D C E – M R I (3D-SPGR)</td>
<td>3.51/1.81</td>
<td>8</td>
<td>–</td>
<td>20 ± 20</td>
<td>3.5</td>
<td>112 × 112</td>
</tr>
</tbody>
</table>

* FA: Flip Angle.
A region of interest (ROI) was selected around the prostate tissue (yellow box in Fig. 1a). Two radiologists (one senior radiologist and one radiology resident in his final year of residency program) examined the MRI images of the patients and identified the tumor boundaries (by drawing a contour around the tumor region) in the 16 biopsy-positive patients, and also identified suspicious lesions in 5 out of 11 biopsy-negative patients (in 6 patients no suspicious lesion was detected by the radiologists).

ROIs were also identified on the normal peripheral zone (PZ) tissue of the prostate gland. Normal PZ tissue appears as a high intensity region on the PZ of the prostate (Fig. 1c), and was identified using T2-weighted MRI (except for 7 cases where no normal PZ

![Image](image_url)

Fig. 1. (a) The full FOV of the DCE-MR images which shows the prostate region used in ICA analyses (yellow box) and the femoral artery (blue arrow) that is used to measure AIF, (b) the ADC map, and (c) the T2-weighted image of the prostate. The tumor in the central gland of the prostate which appears as a hypo-intense region in T2-weighted MRI and ADC map is identified. An ROI in the normal PZ tissue is also shown in the T2-weighted MRI in green (hyper-intense region in PZ).

![Image](image_url)

Fig. 2. (a) The independent component corresponding to the prostate vasculature separated by the AC-ICA algorithm in a) spatial domain, and b) temporal domain. c) The intravascular space in spatial domain, obtained by converting the intravascular component into contrast agent concentration, showing the intravascular concentration in every voxel of the prostate tissue at peak bolus enhancement. d) The local VIF curve generated by averaging the contrast agent concentration of each frame in the intravascular space.
tissue was present). PK parameters for both the tumor region and the normal PZ tissue were calculated using 3 different methods:

1- Using the ICA-derived vascular signal (Eq. (7)) to calculate the intravascular contrast agent concentration and subtracting the $v_{p,N}c_{p,N}(t)$ term from the contrast agent concentration of the tissue ($c(t)$), and then fitting the remainder of the tissue concentration curve (using the local VIF as the input function) to the Tofts–Kety model equations with 2 model parameters $K_{N}^{trans}$ and $v_{p,N}$.

2- Fitting the tissue concentration curve ($c(t)$), to the ETK model equations (using the local VIF as the input), and calculating the three model parameters.

3- Fitting the tissue concentration curve ($c(t)$), to the ETK model equations using an AIF measured at the femoral artery as the input.

Methods 1–3 were used to calculate model parameters for every voxel in the prostate region for all DCE-MRI datasets. For each 3D DCE-MRI dataset the analysis was performed on the slices that were identified as containing the tumor or suspicious lesion. Results of model fitting with and without normalizing the input functions were compared. We have compared the performance of local VIF-based methods with AIF-based methods in two different aspects:

a) The ability of the method to provide consistent PK parameters for normal PZ tissue. Considering that PK parameters are characteristics of the tissue, the method that provides smaller variation in these parameters (for a specific normal tissue) has a better performance.

b) The ability of the method to separate normal tissues from tumor tissues. The method that provides better separation of these two tissue types has a better performance.

2.8. Statistical analysis

In order to assess whether the $K_{N}^{trans}$ values calculated for the normal PZ tissue in the local VIF-based and AIF-based methods belonged to two different distributions one-way ANOVA (analysis of variance) analysis was performed. The number of voxels in the normal PZ tissue region for each patient was different, which would bias the distribution toward the patients with more voxels in their normal PZ region. In order to have a population of $K_{N}^{trans}$ or $K_{N}^{trans}$ values in which different patients had the same weight, distribution of the mean-values of the $K_{N}^{trans}$ parameter for each patient were used in the analysis. The distribution of the mean-values has normal distribution (according to central limit theorem) and is suitable for ANOVA analysis.

In order to assess the separation of the $K_{N}^{trans}$ or $K_{N}^{trans}$ values for normal PZ tissue from the tumor/suspicious tissue, p-value was calculated using a two-sample t-test to determine if the two groups were different, and the effect size was calculated using Cohen’s-d method to determine how well the two groups were separated. Bootstrapping was performed (10^5 times) and the mean-value of the bootstrapped effect-size values is reported.

3. Results

3.1. Local vascular input function calculation

The AC-ICA algorithm was applied to each dataset and the intravascular component was separated. The separated intravascular component for the sample prostate slice (shown in Fig. 1a) is shown in Fig. 2a–b in spatial and temporal domains respectively. Once the intravascular component was identified and separated, the signal intensity in each voxel of the intravascular signal was converted into
contrast agent concentration to generate the local VIF curve. The results of this conversion (for the slice shown in Fig. 1) in the temporal domain (representing the local VIF curve), and in the spatial domain (representing the prostate vasculature), are shown in Fig. 2c–d. The AIF measured at the femoral artery and the local VIF calculated using the AC-ICA algorithm were normalized with respect to their AUC and are shown in Fig. 3a.

### 3.2. Pharmacokinetic parameters for extended Tofts–Kety model

PK analysis was performed using all three methods for all patients and the model parameters were calculated. The \( v_{p,N} \) maps calculated for each method are shown in Fig. 4 (for the prostate slice that was shown in Fig. 1a). It can be seen in this figure that the maps are visually similar, and that the tumor has the highest \( v_{p,N} \) value as expected. For this patient \( v_{p,N} \) tumor value was 0.58 [0.46 0.74] mM for Method 1, 0.50 [0.42 0.65] mM for Method 2 and 0.53 [0.43 0.69] mM for Method 3. These values and the color bars in this figure show that the \( v_{p,N} \) ranges calculated with different methods are similar, i.e. there were no statistically significant differences between the values generated for each tissue type by different methods (according to Wilcoxon rank sum test on each pair). Fig. 4 also demonstrates that the \( v_{p,N} \) map can be used as reference for tumor and normal PZ tissue detection.

Similar results for \( v_{p,N} \) were observed in each patient, where the ranges for \( v_{p,N} \) of the normal PZ tissue were close to each other using the three methods and also the \( v_{p,N} \) ranges for the tumor tissue were also close to each other for all three methods. However, summary statistics for \( v_{p,N} \) could not be provided for the entire patient population as the plasma fraction is patient dependant and changes between patients.

As can be seen in this figure, in local VIF-based and AIF-based \( k^{\text{trans}} \) maps, the voxels of the normal PZ tissue have small values and the tumor/suspicious lesions have large values, which show the performances of the methods in detecting the suspicious region are similar (quantitative values about this separation are reported in Table 4). This figure also shows the \( T_2 \)-weighted MRI and ADC map of the prostate slice which were used as reference for tumor and normal PZ tissue detection.

The mean \( k^{\text{trans}} \) and mean \( k^{\text{trans}}_t \) value for normal PZ tissue of each patient and the standard deviation of the mean values (as explained in statistical analysis section) were calculated and reported in Table 3. These values were calculated for the entire patient population with normal PZ tissue which included 20 datasets (in 7 patients there was no visible normal PZ tissue). These results (Table 3) show that \( k^{\text{trans}}_t \) value of the normal PZ tissue has smaller variation compared to its \( k^{\text{trans}} \) value (\( k^{\text{trans}}_t \) vs. \( k^{\text{trans}} \) for normal PZ tissue was 0.20 ± 0.04 mM.min\(^{-1}\) vs. 0.87 ± 0.54 min\(^{-1}\) for local Method 1, 0.19 ± 0.04 mM.min\(^{-1}\) vs. 0.81 ± 0.52 min\(^{-1}\) for Method 2 and 0.21 ± 0.07 mM.min\(^{-1}\) vs. 0.25 ± 0.29 min\(^{-1}\) for Method 3).

Fig. 6a illustrates the box-plot of the \( k^{\text{trans}}_t \) values for the normal PZ regions in each patient. The box-plot shows the median (horizontal line) and the 25 percentile to 75 percentile range (box) for all slices in which a normal PZ region was identified (for \( k^{\text{trans}}_t \) maps of all 3 methods). Note that, we have used box-plots in this figure to demonstrate the distribution of \( k^{\text{trans}}_t \) parameter for each patient since these distributions were non-normal.

As can be seen in this figure, the \( k^{\text{trans}}_t \) maps that were calculated using the local VIF (Methods 1–2) generally resulted in smaller variation in normal PZ tissue compared to the maps calculated using the AIF (Method 3). Comparing the results of Method 1 with Method 2 shows that their performances in calculating the \( k^{\text{trans}}_t \) value of the normal PZ tissue were similar (quantitative values of this comparison are reported

### Table 3

<table>
<thead>
<tr>
<th>Method</th>
<th>Method 1 (local VIF)</th>
<th>Method 2 (local VIF)</th>
<th>Method 3 (AIF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k^{\text{trans}}_t ) mM.min(^{-1})</td>
<td>0.20 ± 0.04 ( ^a )</td>
<td>0.19 ± 0.04 ( ^a )</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>( k^{\text{trans}} ) min(^{-1})</td>
<td>0.87 ± 0.54</td>
<td>0.81 ± 0.52</td>
<td>0.25 ± 0.29</td>
</tr>
</tbody>
</table>

\( ^a \) One-way ANOVA failed to show a significant difference (p-value = 0.4) between the \( k^{\text{trans}}_t \) values for Method 3 and Method 1.

\( ^b \) One-way ANOVA failed to show a significant difference (p-value = 0.1) between the \( k^{\text{trans}}_t \) values for Method 3 and Method 2.
The distribution (using all patients) of all voxels in normal PZ and tumor regions (both distributions were positively skewed). The Ktrans and KN values in suspicious tissues of each method. From the literature, effect size is calculated using the distributions of normal PZ and tumor tissue. Table 4 reports the median and inter-quartile ranges of Ktrans and KN values of the normal PZ and tumor region (Ktrans ranges were [0.06 0.23], [0.06 0.22], and [0.06 0.26] in normal PZ tissue vs. [0.42 1.32], [0.31 0.87] and [0.40 1.15] in tumor, for Method 1, Method 2, and Method 3 respectively), while there is large overlap between their distributions when Ktrans is being used (Ktrans ranges were [0.18 1.07], [0.17 0.97], and [0.02 0.19] in normal PZ tissue vs. [1.01 5.36], [0.72 3.81] and [0.13 0.77] in tumor for Method 1, Method 2, and Method 3 respectively).

The reported p-values for both normalized and not-normalized parameters show that in both cases the tumor and normal PZ tissues have separate distributions, however there is significant increase in the effect size when normalization is applied (the larger the effect size, the better the separation of the distributions). Table 4 also reports Ktrans values for a number of studies reported in the literature. These literature values are reported here as a reference to demonstrate that the Ktrans values that we obtained without normalization are similar to those previously reported. They also show that, as with our results, there is large overlap between the Ktrans values for normal PZ and tumor tissue that were calculated in previous studies.

### Table 4

<table>
<thead>
<tr>
<th>Method</th>
<th>Tissue</th>
<th>Method 1 (Local VIF)</th>
<th>Method 2 (Local VIF)</th>
<th>Method 3 (AIF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ktrans</td>
<td>Normal PZ</td>
<td>0.14 [0.06 0.23]</td>
<td>0.13 [0.06 0.22]</td>
<td>0.14 [0.06 0.26]</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>0.76 [0.42 1.32]</td>
<td>0.53 [0.31 0.87]</td>
<td>0.69 [0.40 1.15]</td>
</tr>
<tr>
<td>Effect-Size</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ktrans</td>
<td>Normal PZ</td>
<td>0.44 [0.18 1.07]</td>
<td>0.41 [0.17 0.97]</td>
<td>0.46 [0.22 0.75]</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>2.45 [1.01 5.36]</td>
<td>1.68 [0.72 3.81]</td>
<td>2.92 [1.13 0.77]</td>
</tr>
<tr>
<td>Effect-Size</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ktrans</td>
<td>Normal PZ</td>
<td>0.07 ± 0.047</td>
<td>0.07 ± 0.047</td>
<td>0.07 ± 0.047</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
<td>0.14 ± 0.071</td>
<td>0.14 ± 0.071</td>
<td>0.14 ± 0.071</td>
</tr>
<tr>
<td>Effect-Size</td>
<td>0.29 [0.09 0.67]</td>
<td>0.29 [0.09 0.67]</td>
<td>0.29 [0.09 0.67]</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic analysis of tumors using DCE-MRI requires information about the time course of contrast agent concentration in the intravascular space. However, it is not possible to separate the signal enhancement due to intravascular contrast agent from the MR images in DCE-MRI using currently available techniques and thus, it is approximated using an AIF. The aim of this study was to determine whether the AC-ICA algorithm, developed to calculate the intravascular signal locally at the tissue of interest, could be used to calculate the local VIF. We carried out this evaluation using DCE-MRI of the prostate as it allows us to compare the AC-ICA results with a commonly used approach in which the AIF is measured from the femoral artery.

A normalization step was also introduced which normalized the input function (local VIF or AIF) with respect to its AUC. Note that the
PK parameters of the two input functions (AIF and local VIF) could not be compared before normalization as these two curves had different scales. The normalization step improved the results of both the local VIF (Methods 1–2) and the AIF (Method 3) approaches. Firstly it significantly reduced the variability in the PK parameters calculated from normal PZ tissue as reported in Table 3 ($K^\text{trans}$ vs. $K^\text{trans}$ for normal PZ tissue was $0.20 \pm 0.04 \text{ mM min}^{-1}$ vs. $0.87 \pm 0.54 \text{ min}^{-1}$ for Method 1, $0.19 \pm 0.04 \text{ mM min}^{-1}$ vs. $0.81 \pm 0.52 \text{ min}^{-1}$ for Method 2 and $0.21 \pm 0.07 \text{ mM min}^{-1}$ vs. $0.25 \pm 0.29 \text{ min}^{-1}$ for Method 3).

Secondly, the normalization resulted in better separation of normal PZ tissue and tumor tissue as reported in Table 4 (the inter-quartile ranges were better separated and the effect sizes were larger for $K^\text{trans}$ compared to normal tissue. The normalization scheme proposed in this investigation, we performed a proof of concept to assess reproducibility of $K^\text{trans}$ measurements. Lastly, although our method was evaluated using prostate cancer DCE-MRI, it is a general method and has the potential to be applied to other cancers as well. The AC-ICA based method provided similar results to the conventional AIF-based method in prostate. This suggests that the algorithm could be used for PK analysis in cases where it is difficult (if not impossible) to find an artery for AIF measurement, such as small animal studies or in studying breast tumors.

5. Conclusions

In this study we presented the steps required for generating local VIF curves from an intravascular signal separated by the AC-ICA algorithm. A normalization step was also introduced and explained. This local VIF was then used in PK analysis of DCE-MRI images of a cohort of 27 prostate cancer patients and the results were compared to the commonly used AIF-based analyses. It was shown that normalization resulted in better separation of normal PZ and tumor tissues in local VIF-based and AIF-based methods compared to their $K^\text{trans}$ values, and also compared to AIF-based $K^\text{trans}$ values of several previous studies. Additionally, all 3 methods provided similar $K^\text{trans}$ values and separations for normal PZ and tumor tissues ($K^\text{trans}$ ranges were [0.06 0.23], [0.06 0.22], and [0.06 0.26] in normal PZ tissue vs. [0.42 1.32], [0.31 0.87] and [0.40 1.15] in tumor, for Method 1, Method 2, and Method 3 respectively).

These results show that the proposed algorithm has the potential to replace AIF-based analyses and is capable of providing equivalent results ($K^\text{trans}$ vs. $K^\text{trans}$ for normal PZ tissue was $0.20 \pm 0.04 \text{ mM min}^{-1}$ vs. $0.87 \pm 0.54 \text{ min}^{-1}$ for Method 1, $0.19 \pm 0.04 \text{ mM min}^{-1}$ vs. $0.81 \pm 0.52 \text{ min}^{-1}$ for Method 2 and $0.21 \pm 0.07 \text{ mM min}^{-1}$ vs. $0.25 \pm 0.29 \text{ min}^{-1}$ for Method 3). The algorithm also provides the prostate vasculature map without PK modeling ($K^\text{trans}$ for tumor tissue was $0.50 [0.42 0.74] \text{ mM for Method 1, 0.50 [0.42 0.65] mM for Method 2 and 0.53 [0.43 0.69] mM for Method 3}$.

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