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Pharmacokinetic analysis of prostate cancer using independent component analysis

Hatef Mehrabian [a,b,*], Michael Da Rosa [c], Masoom A. Haider [c], Anne L. Martel [a,b]

[a] Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada
[b] Department of Physical Sciences, Sunnybrook Research Institute, Toronto, ON, Canada
[c] Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

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ABSTRACT

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 K^{trans} 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 K^{trans} values obtained from the un-normalized input functions with the K_N^{trans} values obtained after normalizing the AIF and local VIF. Normalization of the input function resulted in smaller variation in PK parameters (K_N^{trans} vs. K^{trans} 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 K_N^{trans} vs. K^{trans} was 0.89 vs. 0.75 for local VIF and 0.94 vs. 0.41 for AIF). The AC-ICA and AIF-based analyses provided similar (K_N^{trans}) 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.

* Corresponding author at: 2075 Baview Ave, Room M6-623f, Sunnybrook Research Institute, Toronto, Ontario, M4N 3M5, Canada. Tel.: +1 416 480 6100.
E-mail address: hatef.mehrabian@sri.utoronto.ca (H. Mehrabian).

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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 T_1 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, Onmiscan) 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]:

$$\begin{aligned} \mathbf{c}_t(t) &= v_p\mathbf{c}_p(t) + v_e\mathbf{c}_e(t) \\ v_e\frac{d\mathbf{c}_e(t)}{dt} &= K^{trans}\left(\mathbf{c}_p(t) - \mathbf{c}_e(t)\right) \end{aligned} \tag{1}$$

where $\mathbf{c}_t$ is the concentration of the contrast agent in the tissue (entire voxel), $\mathbf{c}_e$ is the concentration in the EES, $\mathbf{c}_p$ is the concentration in the plasma pool, K^{trans} is the volume transfer constant describing the rate by which the contrast agent diffuses from the plasma space into the EES, v_e is the EES per unit volume of tissue, and v_p 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, ω, in the bolus arrival time has to be introduced ($\mathbf{c}_p(t) = \mathbf{c}_a(t-\omega)$) as the contrast agent does not arrive in the TOI ($\mathbf{c}_p$) and the artery ($\mathbf{c}_a$) 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.