LOCAL VASCULAR INPUT FUNCTION FOR PHARMACOKINETIC MODELING OF PROSTATE CANCER

Hatef Mehrabian[1,2], Masoom A. Haider[3] , and Anne L. Martel[1,2]
[1]Medical Biophysics, University of Toronto, Toronto, Ontario, Canada, [2]Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada,
[3]Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Introduction:
Multi-parametric MRI which consists of anatomical (e.g. T_2-weighted MRI) and functional (e.g. dynamic contrast enhanced and Diffusion weighted) MR imaging of a tissue (e.g. prostate) can be used for cancer detection and diagnosis[1]. Pharmacokinetic (PK) analysis of DCE-MR images of a tissue is an important component of multi-parametric imaging that provides information about tumor perfusion and vascular permeability[2]. Such information has been found to be related to prognostic factors such as tumor grade and thus, its role in assessing anti-angiogenic therapies is increasing[3]. However, the quantitative parameters derived from PK analysis (particularly K^{trans}) vary significantly between studies and needs to be improved.
Most PK models require measurement of the contrast agent concentration in the vasculature as an input. This vascular input function (VIF) is inseparable from the signal in the extravascular extracellular space (EES). Thus, it is approximated with an arterial input function (AIF) measured outside of the tissue of interest (e.g. in an artery, in a reference tissue or using a population-averaged signal). Variation and error in calculation of this AIF is one of the major sources of discrepancy between PK parameters reported in different studies. Thus, calculating the vascular enhancement locally (local VIF) at the tissue of interest rather than approximating it in a distant artery has the potential to improve PK analysis results and helps better understand contrast agent kinetics in the tissue. Such a VIF could also be used in cases there is no artery in the FOV to measure AIF or in animal studies where it is difficult to find such an artery.
We have developed an adaptive complex independent component analysis (AC-ICA) algorithm[4] for calculation of the local VIF. The algorithm uses the complex valued MR signal and applies an ICA algorithm with adaptive cost function that is learned at each iteration. The objective of this study is to validate the performance of the proposed local VIF calculation algorithm in prostate cancer studies and to compare results to the PK parameters estimated using an AIF (femoral artery). The PK parameters reflect the tissue characteristics and, for a specific tissue type, values should be independent of the AIF or VIF used in the analysis. Moreover, the method that results in a smaller variation in the calculated parameters for this tissue has a better performance.

Methods:
Adaptive Complex Independent Component Analysis (AC-ICA): Having Z, a linear mixture of source signals S that are mixed with weight coefficients A ($Z = AS$), ICA tries to identify the sources S and weights A, assuming that the sources are independent. AC-ICA algorithm assumes intravascular and extravascular MR signals are spatial independent. It also assumes the distribution of the MRI signal can be approximated with a linear combination of 3 to 5 generalized Gaussian distributions given by: $p_y(y) = \frac{\beta}{2\alpha\Gamma(1/\beta)} exp\left(-\frac{|y|^\beta}{\alpha^\beta}\right)$ where $\Gamma(\cdot)$ is the Gamma function. ACICA calculates model parameters (α, β) of the intravascular space through an expectation maximization framework at each iteration of the ICA. The ICA non-linearity is then derived from this distribution and intravascular signal is separated[4].
Pharmacokinetic modeling: The two compartmental extended Tofts model[5] was used to analyze DCE-MRI data in every voxel in the prostate. The model equations are: $v_e \frac{dc_e}{dt} = K^{trans}(c_p(t-\omega) - c_e(t))$, & $c_t = v_e c_e + v_p c_p$, where c_t, c_e and c_p are the contrast agent concentrations in tissue, EES and plasma space respectively. ω is delay, v_e and v_p are the EES and plasma fractions and K^{trans} is volume transfer coefficient representing perfusion and permeability.
Acquisition: 19 patients with biopsy proven prostate cancer were scanned using T_2W-MRI, DW-MRI and DCE-MRI on a 3T Achieva MRI scanner (Philips Healthcare) under IRB approved protocols, using a DCE sequence (3D SPGR: TR/TE=3.91/1.81 ms, FA=8°, FOV 20x20 cm, Matrix 112x112x20, slice thickness 3.5 mm) and VFA imaging with FA=5,15° for T_1-mapping prior to routine dynamic contrast enhanced imaging.
Analysis:
For every patient VIF was calculated by applying AC-ICA to the entire prostate tissue and converting the MR signal of the separated intravascular space to contrast agent concentration. This intravascular enhancement curve was then normalized with respect to its area under the curve (AUC) and was used as the input to the PK model. For comparison the femoral artery was identified in the FOV (at the central slice of the 3D volume to minimize inflow effects) and its contrast enhancement was used as AIF in the PK analysis of the prostate tissue. Normal peripheral zone tissue of the prostate was identified using the T_2w MR images and the K^{trans} value was calculated for this tissue using both AIF and VIF (both with and without normalization with AUC).

Table 1 K^{trans} value obtained using the VIF and AIF (with and without normalization) for normal PZ and tumor tissues for 19 prostate cancer patients.

Method		VIF	AIF
Normalized	Normal PZ	0.21±0.05	0.26±0.11
	Tumor	0.9±0.51	1.12±0.54
Not Normalized	Normal PZ	1.09±0.53	0.29±0.34
	Tumor	5.05±4.74	1.01±1.23

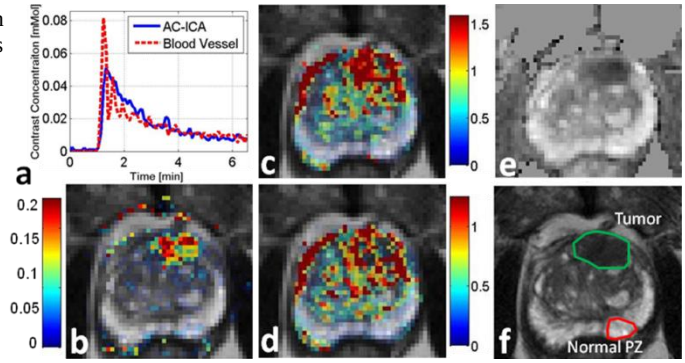

Fig.1 a) normalized VIF and AIF, b) the vascular map of AC-ICA. K^{trans} map using normalized c) VIF and d) AIF in PK analysis. e) ADC map and f) T2weighted MRI of prostate showing the tumor and the normal PZ ROIs.

Results:
The VIF (normalized) calculated for a sample slice and its AIF (femoral artery) are shown in Fig.1a. Fig.1b shows the vascular map (overlaid on the T_2w image) that is calculated using AC-ICA. This map was used as the v_p parameters VIF-based PK analyses. Fig.1c shows the K^{trans} map for the VIF-based and AIF-based PK analyses. The T_2w image of the prostate showing normal PZ tissue and tumor ROIs and ADC map are shown in Fig.1e,f. Table 1 reports the K^{trans} value for normal PZ tissue and tumor tissue, averaged over 19 patients, for VIF-based and AIF-based PK analyses (with and without normalization).
Conclusions:
K^{trans} maps show both AIF-based and VIF-based methods result in high K^{trans} values in the tumor region and their performances in detecting the tumor are similar. Table 1 shows that both methods result in similar mean values for the normal PZ tissue (ANOVA analysis showed the 2 means are from the same distributions). The normalized VIF resulted in smaller variation in K^{trans} of normal PZ tissue which shows it has a better performance compared to AIF-based (with and without normalization) and VIF-based analysis without normalization and resulted in better separation between normal PZ and tumor tissues.
Acknowledgements: The authors would like to thank Natural Sciences and Engineering Research Council of Canada (NSERC) for funding.
References: [1] Hoeks C, et al., Radiology 261 (1), 46-66, 2011. [2] Hylton N, et al., J. Clin. Oncol. 24 (20), 3293-3298, 2006. [3] Kanematsu M, et al., Am. J. Roentgenol. 184, 832-841, 2005. [4] Mehrabian H, et al., IEEE Trans. Med. Imaging 32 (4), 699-710, 2013. [5] Tofts P, et al., JMRI, 10(3), 223-232, 1999.