Effect on time duration on the precision of pharmacokinetic parameters in DCEMRI

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Introduction: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is now widely accepted as a tool for non-invasive characterization of tumor vasculature. [1,2,3,4]. The reliability and accuracy of quantitative parameters derived using the pharmaco-kinetic (pK) models of DCE data are dependent on experimental settings such as the duration of the scan. The effect of duration of scan on the precision of pharmacokinetic parameters was evaluated on computer simulations by Aerts et al [6]. This effect has so far not been studied on clinical datasets, which generally provide lot more challenges in its analysis as compared to synthetic data. In this study the same effect of duration of scan on the precision of pK parameters is evaluated on clinical datasets of the prostate. We also compare our clinical findings with the synthetic data observations. **Methods and Materials** **Patient database:** Data for our study was acquired from patients at multiple centers with appropriate IRBs approving the studies. The database consists of 10 prostate cases. Imaging: The datasets were obtained on a 1.5T GE Signa (GE Healthcare, Waukesha, WI). The protocol for the DCEMRI prostate scan was : axial slices using a 3D FSPGR sequence with EIS TORSO coil, TE = 1.38- 2.1ms, TR =3.7- 4.1ms, FA = 15° - 30°, 80 bolus volumes, ~ 6 s/volume, TH = 6 mm, matrix size = 256 x256 , FOV = 260 x 260 mm2. The rate of contrast injection was 0.1 mmol/kg injections at 3-5 cc/sec. **Experimental Methodology:** The steps for this study are as follows ***A. Determination of lesion and normal voxels:*** A set of around 10-15 enhancing voxels were identified manually for each of the prostate DCE datasets. Majority of these voxels were picked from the potential lesion zones. These landmarks were marked using the VV software and co-ordinates stored in a text file. [7]. ***B. Pharmacokinetic Model***: There are two models that are routinely used in DCE-MRI. The two parameter model also known as Ketty model uses only the perfusion parameter (K^{trans}) and extra-cellular volume fraction (v_e) while modeling the flow of contrast between the two compartments [8]. It is described by $v_e \frac{dC_e(t)}{dt} = K^{trans}(C_p(t) - C_e(t))$ where C_e and C_p are concentration of the contrast agent in the extra-cellular and blood vessel compartment respectively. The three-parameter model uses the fractional plasma volume (f_{PV}) parameter in addition to the K^{trans} and ve parameter [8]. The model equation in 3-parameter model is $C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(t') \exp\left(\frac{-K^{trans}(t-t')}{v_e}\right) dt'$. ***C. Experimental setup***: Our in-house library for processing of dynamic contrast enhanced MRI (DCE-MRI) was used for the experiments. The library has modules to perform automatic AIF detection or uses population-based AIF to compute the pK model parameters using the two compartment or three compartment models. Nonlinear curve fitting using Levenberg-Marquardt algorithm was used to estimate the pK parameters from the concentration curves. The entire library was implemented using the functionality provided in Insight Toolkit. The library was adapted to compute the pharmaco-kinetic parameters at identified voxel locations. A parameter was introduced in the algorithm setup that could control the duration (seconds) of the scan that was used for the optimization algorithm. The duration of the scan for the pharmacokinetic model was dynamically varied within the toolkit implementation. For this experiment the duration parameter was set between 155 seconds to 335 seconds after the bolus arrival time (BAT). The step size was chosen as 30 seconds. As all the datasets for our study came from a single site they had similar acquisition protocols with similar injection times. Figure 1. shows the plot of the Arterial Input Function (AIF) from each of the ten datasets of our study. It demonstrates that all the datasets had similar BAT. The signal units and the time vector within this duration were used for computing the pharmacokinetic parameters. The tests were carried out using two AIF modes: Automatic AIF and Population Model based AIF [8]. The voxels were filtered where the K^{trans}, v_e and f_{PV} values were below the acceptable thresholds: $K^{trans} < 0.1$, $v_e < 0.05$, $f_{PV} < 0.001$.

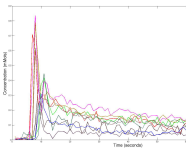

Figure 1: Plot of the AIF from the ten datasets

***D.Statistics comparison with complete duration*:** We compare the results from each of the runs with the execution when the entire time-concentration curve was used for estimation of pK model parameters. The parameters obtained from entire series are considered as gold reference and with respect to this reference, the variability associated with each parameter is computed as: var = |measured – ref|/(0.5 * (measured + ref))The Quantitative Imaging Biomarker Alliance (QIBA) specifies that the parameter values should be within 15% of the ground truth for various processing of same data to be considered comparable. We have used 15% variability as the threshold to choose the optimal time duration of DCE prostate scan.

Results and Discussion: The K^{trans}, v_e and f_{PV} maps computed using variable time duration of time-intensity curves are demonstrated in Figure 2. Two pharmacokinetic models are studied 2-Param and 3-Param model. Two modes of AIF are studied (AUTO-AIF (Left side) and Model-AIF (Right side). The Statistical analyses was performed with MedCalc®(v. 12.0) software. From the results we observe that in 2-Parameter model duration of scan up to and beyond 215 seconds after bolus arrival give reliable parameter values. Duration less than 215 seconds in 2-Parameter results in more than 15% variation in the parameter values. In the case of 3-Parameter model, especially with f_{PV} longer durations up to 305 seconds are required to achieve the required fidelity. Durations up to 305 seconds (approximately 5 minutes) seem ideal and scan longer than 5 minutes after bolus arrival do not lead to great improvement in parameters.

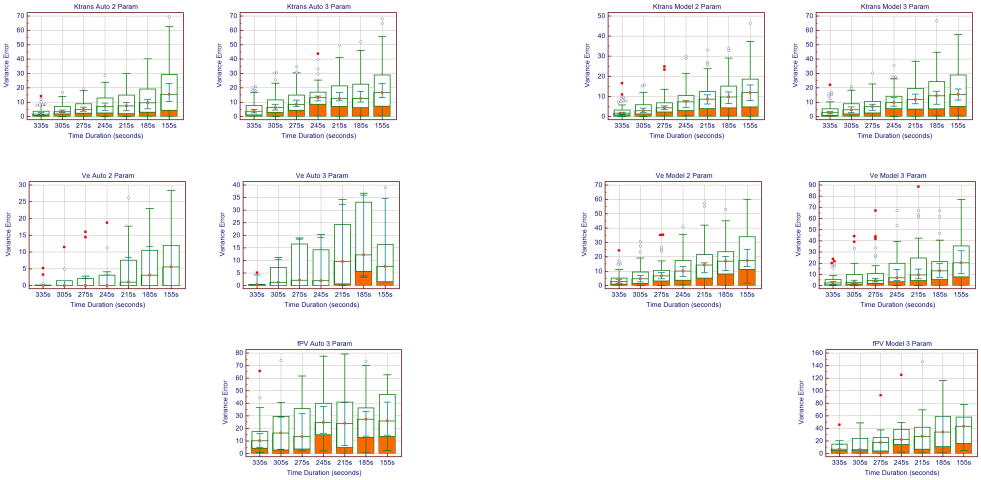

Figure 2. K^{trans}, v_e , f_{PV} maps for various time duration of time-intensity curves. Two pharmacokinetic models are studied 2-Param and 3-Param model. Two modes of AIF are studied (AUTO-AIF (Left side) and Model-AIF (Right side).

Conclusions: We have demonstrated the precision of pharmacokinetic parameters and its effect due to duration of the time-intensity signal. Our results demonstrate that for the prostate case it is preferable to have scan duration of 5 minutes. Scan durations of more than 6 minutes do not generally contribute to any further improvement in the parameters. **Acknowledgements:** "We will like to thank Dr. Fiona Fennessy (Brigham and Women's Hospital, Boston) and Dr. Adilson Prando (Ressonancia Magnetica Campinas, Brazil) for providing the data used for these experiments. **References:** [1]. Tofts et.al. JMRI 1999;10(3):223-232. [2]. Parker et.al. Proc. ISMRM 2003, p1264 [3].Padhani et al JMRI 2002;407-422 [4] Rudisch et al Eur. J. Radiol. 2005 514-9 [5] O'Connor et al Lancet Oncol. 2008, 766-776 [6] Aerts et al Phys. Med. Biol. 2011 5665-78 [7] Seroul et al MICCAI 2008 [8] A.Jackson et al DCEMRI in Oncology