

A System for Tumor Perfusion Assessment in Clinical Trials using dceMRI

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Dynamic contrast enhanced MRI (dceMRI) has demonstrated considerable utility in both diagnosing and evaluating the progression and response to treatment of malignant tumors. By making use of a two-compartment model, with one compartment representing blood and the other abnormal extra-vascular extra-cellular space (EES), the observed uptake curves in tissue and blood can be used to estimate various physiological parameters relating to tumor vascularity [1]. In a clinical trial setting it is critical to be able to accurately measure the change in these parameters over time due to disease progression or response to therapy. Measurement reproducibility must therefore be of primary concern when designing a system for perfusion assessment in clinical trials. Reproducibility can be adversely impacted by random noise introduced at many stages in the measurement process, from data acquisition to final report generation. It was the goal of this work to design an end-to-end analysis system for tumor perfusion assessment which would provide maximum measurement reproducibility through the elimination of as many of these noise sources as possible.

There are several major sources of variability in perfusion parameter measurements using dceMRI. The first, and most difficult to control, is in the data acquisition process. Subject cardiac output, motion both during and between time points, and inconsistency in acquisition protocol can all adversely affect scan/rescan reproducibility. Cardiac output and patient motion are not directly controllable. However, we have found that variability in these factors can be minimized through careful subject preparation, including instruction in breath-hold or shallow breathing techniques and a walk-through of the imaging process. Protocol variability can be minimized through in-person training of all technologists who will be involved in scanning subjects. We have also found that there is significant value in the use of T1 and linearity phantoms in order to ensure that the MRI systems used in the trials are properly maintained.

During the analysis process, major sources of variability are subject motion between time points, variation in identification of tumor margins, and variation in identification of arterial input function (AIF). Our system compensates for subject motion through the use of a warp-based registration algorithm that aligns structures in all subsequent time points to those in the first [2]. Variability in tumor margin identification is minimized through the use of a semi-automated volume segmentation system [3]. This system combines statistical information with a 3D surface model to approximate optimal tumor margins. The results of this algorithm are then reviewed by a radiologist for accuracy and corrected if necessary. Variability in identification of AIF is the most significant detriment to analysis reproducibility, accounting for as much as 67% of all variability at this stage of the processing chain. Our system minimizes this variability through the use of an automated matched-filter based algorithm that identifies an ideal AIF for each subject [4].

The final source of variability in the analysis chain is human error in the recording and transcription of results. This is eliminated in our system through the use of a database script which directs each step in the process from data ingestion to report generation. Human interaction is limited to identifying regions of interest in the data and reviewing results for accuracy.

This system has been tested using dceMRI data taken from both human and canine subjects. The statistic of interest in both experiments was coefficient of variability for multiple measurements of a single data set by multiple operators. In the animal experiment the rate transfer constant between plasma and EES (K^{trans}) for three subjects over three time points was measured by four independent analysts (a total of 36 analyses) using both manual and automated AIF identification. Using manual AIFs, coefficients of variability ranged from 3.1% to 39.2%, with a mean of 20.1% and a median value of 21.5%. For the nine automated plasma identifications, coefficients of variability ranged from 3.1% to 11.8%, with a mean of 6.7% and a median value of 6.2%.

In the human experiment K^{trans} was measured for 12 subjects over two time points (24 image data sets measured once each by four independent operators, for a total of 96 analyses). Using manual AIFs, coefficients of variability ranged from 1% to 43%, with a mean of 13.1% and a median value of 11%. Using automated AIFs, coefficients of variability ranged from 1% to 38%, with a mean of 9.8% and a median value of 6%. Note that the variability results for humans using automated AIFs are very similar to those seen in the canine experiment, while the variability results for humans using manual AIFs are significantly better than those for canines. This is as expected, since the smaller vessel sizes and significantly higher blood velocity in canines make identification of arterial signal that is uncorrupted by artifacts much more difficult in canines than in humans.

References: [1] Tofts P, Brix G, *et al.*, JMRI, pp. 223 – 232, 1999. [2] Lester H, Arridge S, Pattern Recognition, pp. 129 – 149, 1999. [3] Ashton E, Du T, Proc. of SPIE-MI 2004. [4] Ashton E, Proc. of ISBI 2004.