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Background: Dynamic contrast enhanced MRI (dceMRI) has demonstrated considerable utility in both diagnosing and evaluating the progression and response to treatment of malignant tumors. dceMRI involves the periodic acquisition of T_1 -weighted images before, during and after injection of a gadolinium labeled tracer such as gadopentetate dimeglumine. The change over time in signal intensity in a voxel or region of interest in this time series can then be related to tracer concentration. By making use of a two-compartment model, with one compartment representing blood plasma and the other abnormal extra-vascular extra-cellular space (EES), the observed uptake curves in tissue and plasma can be used to estimate various physiological parameters.

One of the primary challenges in estimating perfusion parameters is identifying an accurate arterial input function (AIF). Using a theoretical curve ignores differences in injection rate and cardiac output, which can greatly reduce reproducibility. However, the MR signal in arteries is frequently corrupted by flow artifacts, with the result that regions of interest at different points in the same artery or in other nearby vessels can provide grossly different uptake curves. This problem is illustrated in Fig. 1 below:

Parameter Calculation: Uptake curves were generated for tumor tissue by averaging the uptake curves of all voxels within the tumor ROIs. Parameters were also calculated on a voxel-by-voxel basis. Uptake curves for tumor and plasma were designated $C_t(t)$ and $C_p(t)$, respectively. In the interests of noise reduction, both plasma and tumor data were fit to gamma variate curves. The vascular bed was modeled as a linear system, such that:

$$C_t(t) = C_p(t) * h(t) \quad (1)$$

with impulse response $h(t)$ given by:

$$h(t) = K^{trans} e^{-k_{ep}t}, \quad (2)$$

where K^{trans} is the volume transfer constant between blood plasma and EES, while the rate constant between EES and blood plasma is given by k_{ep} .

Abstract: A method is presented for the calculation of perfusion parameters in dynamic contrast enhanced MRI. This method requires identification of uptake curves for both tumor tissue and plasma. Inter-operator variability in the derived rate constant between plasma and extra-cellular extra-vascular space is assessed using semi-automated tumor margin identification with both manual and automated plasma identification. In addition, an assessment is made of the contribution to total variability made by differences in tumor margin identification and differences in plasma identification. Experimental results show a mean coefficient of variability (CV) for parameter measurement with manual plasma identification of 20.1%, with a mean CV for parameter measurement with automated plasma identification of 6.7%. Analysis shows that 67% of the variability in parameter measurement with manual plasma identification is attributable to differences in identified plasma signal, with the remainder attributable to differences in identified tumor margins.

Experimental Procedure: The experiments involved in this study were intended to assess the reproducibility of perfusion measurements using manual and automated plasma identification, and to determine the percentage of measurement variability due to differences in tumor margin and plasma region of interest, respectively. Experimental data were derived from three dogs with naturally occurring mammary tumors. Each animal was imaged three times over a period of 12 weeks. Images for this study were acquired using a GE 1.5T LX/CV scanner. Three slices through each tumor were acquired using a cardiac coil. Perfusion images used a GRE pulse sequence with a repetition time of 20ms, echo time of 1ms, and a flip angle of 40 degrees. Imaging time for each image set was seven seconds, with a two second scanner delay, yielding temporal resolution for the data set of nine seconds. The reconstruction matrix was 256x192, FOV was 140mm, and slice thickness was 4mm. Sample images from this data set are given in Fig. 2.

Because a primary aim of this study was the assessment of inter-operator variability, four analysts were trained in the use of the analysis software. All analysts were also trained in the appearance of canine mammary tumors and the selection of appropriate plasma regions using images from animals not included in this study. Each analyst was then asked to identify and delineate both tumor and plasma in each of the nine included data sets. When identifying plasma, the analysts had the option to view the uptake curve for the currently selected region at any time, and to erase, modify or replace the currently selected region. In this way each analyst was able to manually select a reasonably optimized plasma region.

Experimental Results: Coefficients of variability in measurement of among the four analysts, defined as measurement standard deviation divided by measurement mean, were calculated separately for manual and automatic plasma identification, and for each of the nine cases examined. For the nine manual plasma identifications, coefficients of variability ranged from 3.1% to 39.2%, with a mean of 20.1% and a median value of 21.5%.

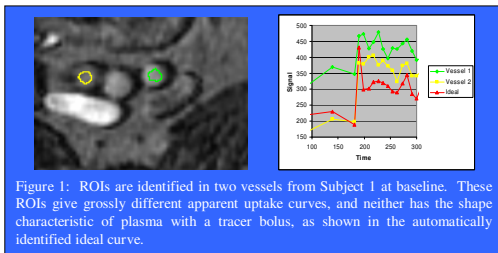
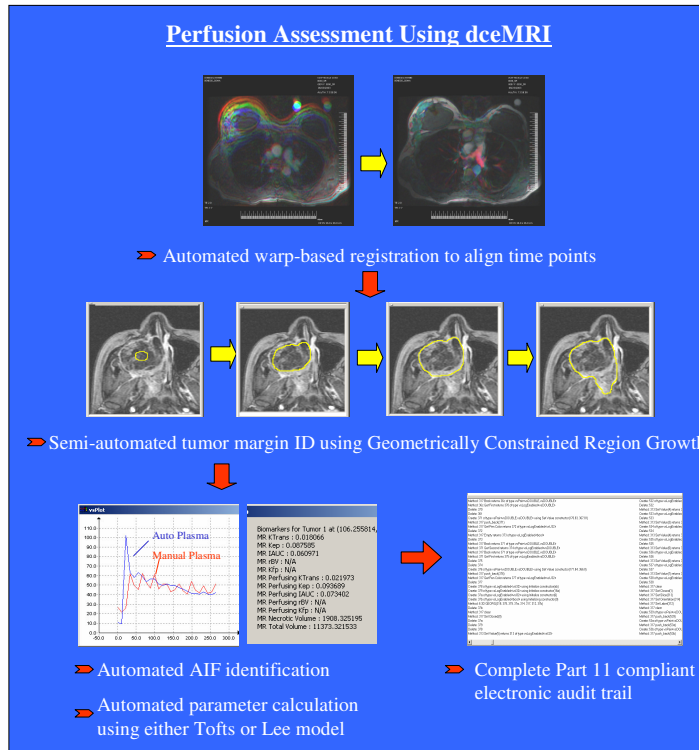


Figure 1: ROIs are identified in two vessels from Subject 1 at baseline. These ROIs give grossly different apparent uptake curves, and neither has the shape characteristic of plasma with a tracer bolus, as shown in the automatically identified ideal curve.

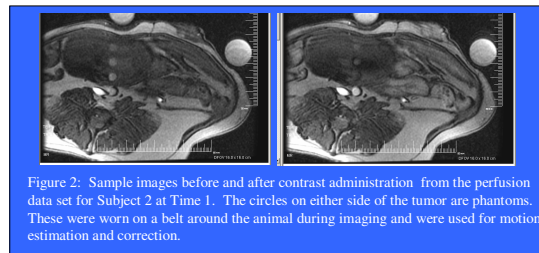


Figure 2: Sample images before and after contrast administration from the perfusion data set for Subject 2 at Time 1. The circles on either side of the tumor are phantoms. These were worn on a belt around the animal during imaging and were used for motion estimation and correction.

Given $C_t(t)$ and $C_p(t)$, K^{trans} and k_{ep} were estimated using a gradient-descent energy minimization scheme. Local minima were avoided through the use of multiple instantiations with different initial parameter settings. This method has been tested against Nedler-Mead direct search optimization and found to be equivalent where noise conditions are favorable, and to provide superior performance in cases where signal-to-noise ratios are low.

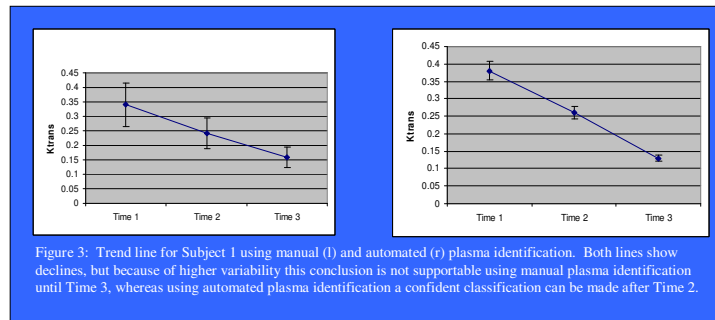


Figure 3: Trend line for Subject 1 using manual (l) and automated (r) plasma identification. Both lines show declines, but because of higher variability this conclusion is not supportable using manual plasma identification until Time 3, whereas using automated plasma identification a confident classification can be made after Time 2.

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%.

An examination of the trend over time in for Subject 1 (see Fig. 3) using manual and automated plasma identification highlights the value of the reduced measurement variability afforded by the automated process. Although both trend lines indicate that vascular perfusion for this tumor is declining over time, higher variability makes that assumption statistically insupportable at time two for manual plasma identification, and marginally supportable after time three. Using automated plasma identification, however, this subject may be confidently classified as declining after time 2.