Estimation of the Arterial Input Function in a Mouse Tail from the Signal Phase of Projection Profiles

Jennifer Moroz[1], Andrew Yung[1], Piotr Kozlowski[1], and Stefan Reinsberg[1]
[1]*Physics and Astronomy, University of British Columbia, Vancouver, British Columbia, Canada*

Introduction: Quantitative analysis of a dynamic contrast-enhanced MRI (DCE-MRI) data set requires an accurate measure of the arterial input function (AIF) [1,2]. Due to rapid contrast kinetics, the AIF should be measured at a high temporal resolution [3,4]. However, this is challenging in mice owing to their small size and rapid heart rate. The purpose of this work is to establish a high temporal resolution AIF for use in DCE-MRI experiments in mice. A projection based technique was used to significantly improve the temporal resolution and to allow the concurrent acquisition of AIF and DCE-MRI data. The difference in signal phase was used to measure the concentration of Gd-DTPA. Phase data was chosen for its inherent insensitivity to B_1 inhomogeneities, coil sensitivity, and T_2* relaxation effects, its improved signal to noise ratio over signal magnitude and its known linear relationship with concentration of contrast agent [3,5].

Methods: All experiments took place on a Biospec 70/30 Bruker 7.0 T MRI system. A birdcage coil (inner diameter 7.0 cm) was used for signal excitation, and an actively decoupled surface coil (width 7 mm, length 18 mm) was used for data collection. An earlier experiment verified that the signal phase varied linearly with concentration over the range of 2-10 mM. From the slope of the phase vs. concentration curve, a calibration factor, converting signal phase to a concentration of contrast agent, was determined. A phantom mimicking a mouse tail – a capillary tube (inner diameter 0.4 mm) placed within a glass tube (internal diameter 3.7 mm) – was used. Gd-DTPA solutions in dH_2O were injected into the capillary tube while a 1-D FLASH experiment (TR/TE = 150/5.399, 2x2 cm2 FOV, 256x1 matrix size) was performed. The experiment was performed in static and dynamic (injection rate 0.603 ml/min representing a flow rate of 8 cm/s) conditions with flow compensation applied for the dynamic case.

AIF measurements took place in the tails of NOD/SCID mice. 30 mM Gd-DTPA was injected at a rate of 1.00 ml/min with a kd Scientific power injector (model 780220) to a dose of 5 µl Gd-DTPA / g mouse. The Gd-DTPA bolus was preceded by 25 µl saline and followed by a 40 µl saline flush. Premature mixing of solutions in the catheter was investigated and shown not to be an issue. The tail was aligned along B_o [6] and the imaging plane was oriented such that slice selection was perpendicular to the tail vessel. Projections were acquired with a FLASH experiment (phase-encoding turned off) utilizing flow compensation (TR/TE = 100/3.92 ms, 15x15 mm^2 FOV, 256x1 matrix size). A total of 2560 projections were acquired with approximately 256 projections acquired before injection. The Gd-DTPA bolus was injected over a period of 6.3-8.4 s. A 2-D FLASH image, using the same scanning parameters, was acquired before injection to establish a baseline profile for the surrounding tissue.

A baseline reference profile was defined as the mean of all pre-injection profiles. To extract the phase information corresponding only to the desired vessel, a tissue baseline profile was constructed from the 2-D FLASH image, after removal of the vessel data. The tissue baseline was then subtracted from all projections. The difference in phase between each post-injection profile and the reference profile was determined and converted to a concentration using the calibration factor. The AIF was calculated for each pixel in the profile corresponding to the vessel. The curves were later averaged to improve the SNR. Phase wrapping was investigated and the phase unwrapped (adding or subtracting 2π) when required.

Results: The results from the calibration experiments (static and dynamic) were equivalent, thus indicating that a phase-based approach may be applied to the mouse tail if flow-compensation is used. AIF's, with a temporal resolution of 100 ms, were constructed from the signal phase data of projection profiles. Figure 1 shows one in-vivo AIF with a function form of $[Gd\ (mM)] = (0.875\ e^{-0.075t} + 0.370) / (1 + 3.316\ e^{-0.873t})$. The average pre-injection profile of the tail and the temporally acquired phase data are also displayed. The curve shows a rapid increase in concentration, followed by a rapid decrease. It levels out as the inflow and outflow of contrast agent in the tissue approaches equilibrium (approximately 50 s after start of injection). It is expected that the recirculation peak (4.8-6.5 s) is masked by the injection (6.3-8.4 s), based on an assumed blood volume of 6-8% body weight and a cardiac index of 0.73 ± 0.19 ml/min/g [7].

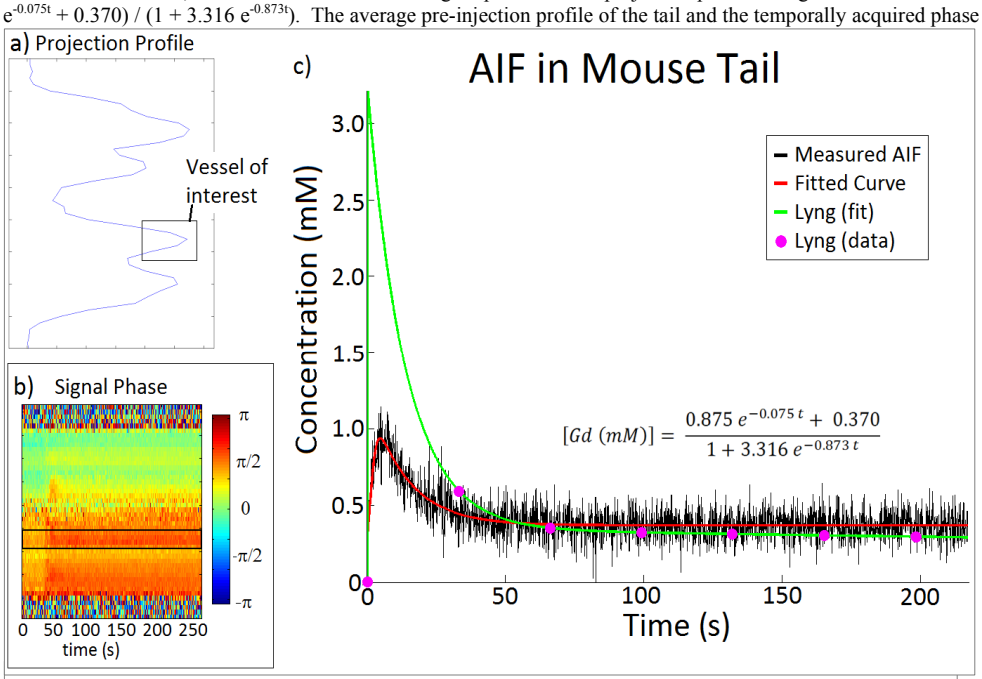

Figure 1: a) Average projection profile for all pre-injection scans. The magnitude data was plotted for identification of tail vessels. b) Signal phase of mouse tail over the time course of the experiment. The vessel of interest is outlined and corresponds with the vessel indicated in a). c) AIF in a mouse tail with a temporal resolution of 100 ms. At this temporal resolution, the shape of the curve is well characterized.

Discussion/Conclusions: Accurate characterization of tissue vasculature requires the measurement of an AIF during the experiment. Most published AIF's have temporal resolutions on the order of seconds, with Lyng et al, having a temporal resolution of 33 s [8] – this curve is commonly used for DCE-MRI analysis in mice. The AIF must be measured at a sufficiently high temporal resolution to capture the contrast agent kinetics, but the temporal resolution is often limited by the need for a sufficiently high spatial resolution to visualize the vessel when an imaging based method is used [2,9]. The use of projection profiles requires that only one line of k-space is acquired at a time, thus dramatically increasing the temporal resolution. Our experiments represent a proof of concept that AIF data can be acquired at a site distant to the tumour site and could be interleaved with the DCE acquisition. Our current temporal resolution exceeds the actual needs and could justifiable be reduced to accommodate the concurrent DCE experiment.

One limitation of this work is the assumption that the contrast agent remains intravascular. Leakage of agent into the surrounding tissue will result in tissue enhancement, which will affect the measurement of the AIF. However, tissue enhancement is expected to occur at a slower rate compared to changes in the vessel concentration [2], so it may be possible to correct the AIF while maintaining a high temporal resolution. Future work will focus on quantitatively evaluating the degree of tissue enhancement and developing a protocol to correct for it.

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