Towards More Accurate Modeling of DCE Data: Development of a Multi-Compartment Phantom

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Introduction: Dynamic contrast enhanced (DCE) MRI is a powerful, non-invasive tool for the detection, staging, and monitoring of cancer *in vivo*. In principle, DCE-MRI measures fundamental, physiologic parameters related to tissue microvasculature and composition that are relevant to the mechanisms of cancer proliferation. In practice, however, quantification of these parameters is hindered by image data acquisition limits *vis-à-vis* the tradeoff between spatial and temporal resolution. Additionally, there is still debate in the literature about which DCE signal model(s) best reflect(s) the image time-course data (Buckley, Yankeelov). To explore these issues, a three-compartment phantom was constructed to simulate the DCE-MRI experiment under a range of conditions and, thus, better define the relationship(s) between true parameter values and those derived from data acquired with current DCE-MRI protocols.

Materials and Methods: Semi-permeable hollow fibers were harvested from a commercial dialyzer (Fresenius Optiflux F160NR; ID = 0.200 mm; OD = 0.280 mm) and used as phantom blood vessels. Seventy-five fibers were bundled together with heat shrink tubing to minimize the mean distance between fibers. Epoxy was applied to bond the fibers together at each end of the phantom (eliminating flow in all but the lumen of the fibers) and to attach the heat-shrink shroud to luer-lock attachments. With the multi-fiber phantom in the scanner magnet, flow was driven *via* a peristaltic pump situated remote from the magnetic field. A second phantom was constructed of a single fiber suspended in a capillary tube. Again, epoxy was used to secure the ends of the fiber to the capillary and to attach the capillary to luer-lock adapters.

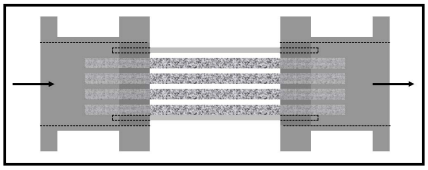

Figure 1. Multi-fiber Phantom. Schematic of the multi-fiber tissue phantom showing representative semi-permeable hollow fibers and the direction of the lumen flow.

MR experiments were performed with the long axis of the phantoms running parallel to B_0, thus minimizing susceptibility effects. All experiments were performed at 4.7 T using slice-selective imaging and spectroscopy, with the slice oriented perpendicular to B_0. Thus, time of flight effects could be used to suppress signal from media flowing through the fiber lumen. The multi-fiber phantom was filled with water and T1-weighted images of a single slice were acquired with and without media flow (TR = 500 ms, TE = 20 ms, NT = 64, data points = 128×128, FOV = 3.2×3.2 mm^2, THK = 0.5 mm; Figure 2 top). Time resolved, slice-selective spectroscopy experiments were then performed to simulate the DCE-MRI experiment under near-idealized conditions (TR = 1 s, TE = 10 ms, NT = 1, temporal resolution = 1 Hz). Under these acquisition conditions, in which signal from media in the lumen is suppressed, a controlled input function was introduced (square input function of duration = 10 min; max concentration = 1 mM MultiHance; Figure 2 bottom).

In single-fiber phantom experiments, with media absent MultiHance, T1 was measured spectroscopically (180-TI-90-TE/2-180-TE/2-collect) on a single slice with and without flow (30 TI values exponentially spaced from 0.100 to 15 s; PD = 1, 3, 5 s where PD = TR – TI; TE = 23 ms; NT = 4; PD = 1 s shown in Figure 3, top). A single slice was imaged at four TI values with flow suppression of the lumen signal (TI = 0.10, 0.91, 5.00, and 10.00 s; PD = 4 s; TE = 30 ms; NT = 32; data points= 128×32, FOV = 2.56×0.64 mm^2, THK = 2 mm; Figure 3 bottom, cropped to show only the region of interest).

Results and Discussion: Images of the multi-fiber phantom with and without flow reveal three distinct compartments (Figure 2 top). First, the lumen of the fibers where signal is effectively nulled by flow; second, the fiber "wall" where signal intensity is flow/diffusion enhanced; and third, the extra-fiber space where signal intensity is unaffected by flow in the lumen. Seventy-two of seventy-five fibers in the multi-fiber phantom show complete signal suppression in the lumen. The idealized DCE-MRI experiment, in which signal is detected by slice-selective spectroscopy (Figure 2 bottom), showed defining characteristics. The two delta spikes correspond to a loss of inline pressure (and, thus, temporary loss of lumen signal suppression) when mechanically switching the flowing media from pure water to 1 mM contrast agent. After introducing the contrast agent, the signal intensity increases rapidly, with overshoot (arrow), and then levels off. A reverse pattern is observed upon switching back to contrast-agent-free media. The distinct wash-in and wash-out kinetics and the presence of signal overshoots reflect not only the permeability of the fiber wall, but also the opposing interplay of decreasing T1 (increasing signal intensity) and T2 (decreasing signal intensity).

Inversion-recovery spectroscopy measurements were carried out, in the absence of contrast agent, in the steady state using slice-selective RF pulses. At long TI, the difference between signal intensity with and without flow accurately predicts the fractional volume of the lumen ($v_l = 0.09 \pm 0.01$; $v_{ltrue} = 0.09$) at PD = 1, 3, and 5 s (data not shown; signal has been normalized in Figure 3 to highlight R1 differences). The increase in apparent longitudinal relaxation of water in the fiber walls in the presence of lumen flow/diffusion is manifest in comparing flow *vs.* no-flow data sets (Figure 3 top; monoexponential fits with actual data points shown in the inset; $R1_{flow} = 0.49 \pm 0.01$; $R1_{noflow} = 0.449 \pm 0.001$). Subsequent imaging, under similar acquisition parameters, shows clear T1-weighted contrast between fiber wall and extra-fiber compartments (Figure 3 bottom, TI = 0.91 sec).

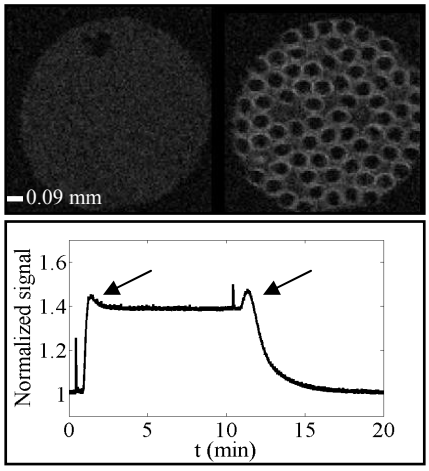

Figure 2. Multi-fiber Phantom. Top-left: no flow; top-right: with flow, lumen signal suppressed; bottom-panel: signal intensity from slice-selective spectroscopy tracking the introduction of a constant concentration of contrast agent *via* the lumen and its later removal (temporal resolution = 1 Hz).

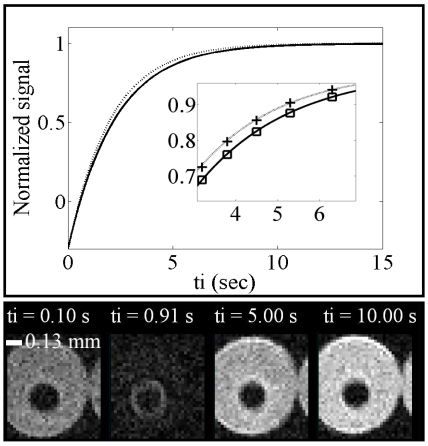

Figure 3. Single-fiber Phantom. Slice-selective inversion-recovery data at steady state. Top: spectroscopy data, PD = 1 sec, with (dotted line) and without (solid line) lumen flow. Bottom: Imaging reveals increased apparent longitudinal relaxation in the fiber wall in the presence of lumen flow/diffusion.

Conclusions: A phantom has been developed that provides a platform for carrying out DCE-MRI experiments under a variety of conditions, from near-optimal to those mimicking current *in vivo* protocols. Time-of-flight effects allow the intra-lumen signal to be suppressed in the presence of lumen flow and, thus, the kinetic characteristics defining contrast-agent diffusion through the fiber walls into the extra-lumen space to be quantitatively assessed. The phantom will provide a test bed for assessing the quantitative limits of DCE parameter estimation.

References: •Buckley DL. Uncertainty in the analysis of tracer kinetics using dynamic contrast-enhanced T1-weighted MRI. *Magn Reson Med* 2002;47:601–6. •Yankeelov TE, Rooney WD, Li X, Springer CS, Jr. Variation of the relaxographic ''shutter-speed'' for transcytolemmal water exchange affects the CR bolustracking curve shape. *Magn Reson Med* 2003;50:1151–69.