Closing up on pharmacokinetic modeling – Exploring the limits of the Tofts model for DCE-MRI analysis using intravital microscopy

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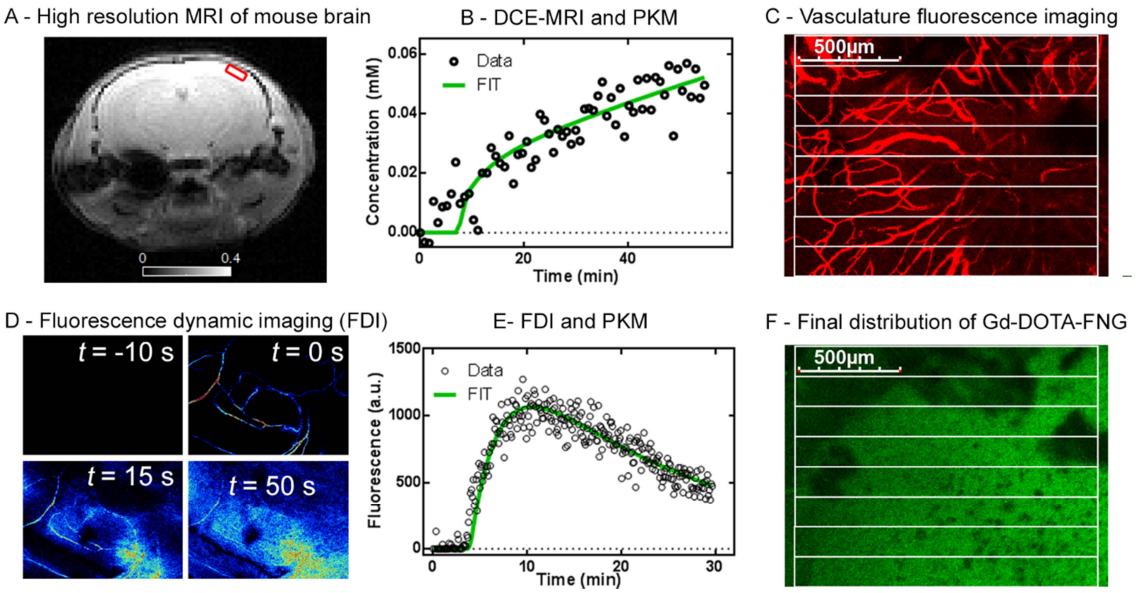
Purpose: Pharmacokinetic modeling (PKM) is used to characterize the perfusion of tissues and the permeability of blood vessels. In the MRI community, the Tofts model (TM) and its extended version (ETM) are commonly used for this purpose. This compartmental model depicts a system in which a contrast agent is transferred at a rate set by K^{Trans} from the vascular volume (v_p) to tissues and accumulates in the accessible space of tissues, often referred to as the extracellular extravascular space, and which is tentatively modeled as v_e. However, it is not known how well these parameters reflect the quantities they describe. Characterizing tissues using alternate methods would improve our understanding of the applicability of the Tofts model. We characterised tissues using MRI and intra-vital microscopy using a multimodal, fluorescein-labeled contrast agent (Gd-DOTA-FNG456) and a vasculature restricted dextran labeled with TRITC.

Methods: *In vivo microscopy*. Female Balb/c mice (n = 2) were imaged through a cranial window using a confocal microscope (FV1000, Olympus). To visualize cerebral vessels, we injected 2.25 mg of TRITC-labeled dextran (155 kDa) into the tail vein of the mouse, and acquired 1 × 1 × 14 μm images from the surface of the brain to a depth of 300 to 400 μm. We then performed dynamic fluorescence imaging (1.88 × 1.88 × 14 or 28 μm). For this purpose, Gd-DOTA-FNG456 was injected and its fluorescence monitored over 30 minutes (temporal resolution of 5.94 s). *In vivo MRI.* MR imaging was conducted in a small animal 7T scanner (Varian) with a dedicated mouse head-coil. Pre-contrast T_1-weighted imaging with an array of flip angles was performed to acquire a T_1 map, and T_1-weighted DCE-MRI was then performed before, during and after the injection of Gd-DOTA-FNG456 (field of view (FOV) = 20 × 20 × 15 mm^3, slice thickness = 1.5 mm).



Results. Fig. 1 – (A) Dynamic T_1-weighted MRI was performed with Gd-DOTA-FNG456. The red rectangle represents the FOV for fluorescence imaging through a cranial window (not implanted on this particular animal). (B) DCE-MR images were analysed voxel-wise using the ETM – the data presented here correspond to a voxel inside the red rectangle of (A). (C) The vasculature of the cortex was imaged using a large fluorescent dextran molecule. This data set was used to measure the vascular volume in the cortex, v_p. The white rectangles (150 μm x 1500 μm) correspond to axial MR voxels superimposed on the sagittal fluorescence image (the third dimension is 150 μm as well). (D) Gd-DOTA-FNG456 was injected – a 5-s time resolution allowed to visualize the bolus (t = 0 s) and the initial dispersion of the agent in the surrounding tissues. (E) Individual voxels were fitted with the TM using the same algorithm as in (B); such a fit for a representative voxel is shown. (F) After 30 minutes, the distribution of Gd-DOTA-FNG456 was found to be fairly homogeneous between the vasculature and surrounding tissues.

The v_p of the cortex modeled in DCE-MRI was volatile but remained below 0.15 ± 0.07% (N=2), while the vascular volume fraction as measured by fluorescence imaging was 4.8 ± 0.6%. Note that the shape of the dynamic curves found in DCE-MRI and FDI are not in accordance. Absolute parameter values for K^{Trans} and v_e could not be extracted in FDI due to the lack of calibration, further work will be required for this particular aspect. Nevertheless, tissue/blood equilibrium was reached very quickly in FDI (~ 5 min post-injection), suggesting a high K^{Trans}, while equilibrium was not reached after 60 minutes of DCE-MRI, suggesting a low K^{Trans}. The tissue and vasculature yield very similar fluorescence intensity at t = 30 min. This suggests that the accessible volume for the contrast agent is similar in the tissues and in the blood (v_e ~ 0.45, the hematocrit) - although heterogeneities are observed in the tissue.

Discussion and conclusion. Our results suggest that the pharmacokinetic parameters derived from DCE-MRI might not be representative of the underlying physiology. Optimization of fluorescence imaging to highlight cell membranes would be desirable. It has not yet been determined whether our multimodal compound Gd-DOTA-FNG456 can enter into cells. The lack of correspondence between dynamic fluorescence imaging and DCE-MRI using the same compound suggests caution should be exerted when interpreting pharmacokinetic modeling results.