A NEW REFERENCE AGENT MODEL FOR DCE-MRI THAT EXPLOITS SELECTIVE DETECTION OF TWO 19F MRI CONTRAST AGENTS

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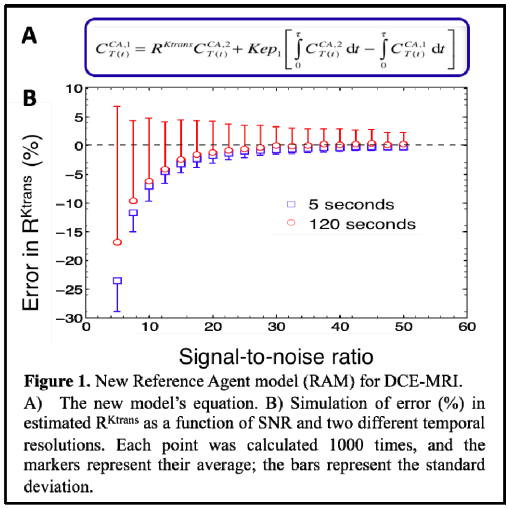

Figure 1. New Reference Agent model (RAM) for DCE-MRI. A) The new model's equation. B) Simulation of error (%) in estimated R^{Ktrans} as a function of SNR and two different temporal resolutions. Each point was calculated 1000 times, and the markers represent their average; the bars represent the standard deviation.

INTRODUCTION: Dynamic Contrast Enhancement (DCE) MRI main limitations are: 1) Identifying the Arterial Input Function (AIF), 2) Interpretation regarding blood flow and permeability, 3) Uncertainty in the value of the hematocrit in the tumor microvasculature (which can vary between 8-40%, and is known as the Fassaeus Effect) [1]. The Reference Region Model has been proposed as an alternative method for evaluating DCE-MRI results without requiring an AIF [2], yet this method cannot account for changes in blood flow and hematocrit that affect the evaluation of vascular permeability. Instead of comparing DCE of a ***single contrast*** agent (CA) in ***two tissues***, we propose a new model that compares ***two contrast agents*** in ***a single tissue***, termed the Reference Agent Model (*RAM*). This new model is independent of blood flow and hematocrit because these vascular characteristics are identical for both agents, so that RAM accurately determines the relative permeabilities of the agents, known as relative-Ktrans, defined as $R^{Ktrans=}$ $Ktrans^{CA,1}/Ktrans^{CA,2}$ = $[PS^{CA,1}F\rho(1\text{-}Hct)$ / $PS^{CA,1}F\rho(1\text{-}Hct)]$= $PS^{CA,1}/PS^{CA,2}$. To implement RAM, two MRI contrast agents must be selectively detected. Because two co-injected T_1 or T_2 MRI contrast agents are difficult to selectively detect with MRI, we have developed ^{19}F contrast agents and optimized ^{19}F MRI methods to perform simultaneous ^{19}F-DCE-MRI of two agents in a mouse model of breast cancer. **METHODS:** ***New Model and Simulations*:** The operation equation for the Reference Agent Model was derived from the standard DCE-MRI differential equations [2]; computer simulations were used to study the effect of temporal sampling, statistical noise and pharmacokinetic constants on its accuracy and precision. A series of activity curves for each agent were generated using the standard Toft's model and a range of Ktrans and kep [2]. ***Animal Model*:** Five female SCID mice were injected subcutaneously with $10x10^6$ MDA-231 breast cancer cells in the right flank; all tumors were allowed to an average volume of 250 mm^3 before initiating ^{19}F-DCE-MRI studies. ***Contrast Agents*:** Two sets of 40% v/v nanoemulsions of perfluorinated liquids with different ^{19}F MR frequencies were prepared: 1) Perfluro-15-crown-5-ether (CE), singlet (20 equivalent ^{19}F atoms) at 0 ppm. 2) Perfluorooctane (OC), triplet at 8 ppm. (6 equivalent ^{19}F atoms) and mutiplets centered at – 34 ppm (12 ^{19}F atoms). Both emulsions were extruded through a 50 nm filter and have the following composition: DPPC 85 % mol, 16:0 PEG2000 PE8.0% mol, and 7% DPPA [4]. The size of all nanoemulsions was determined by dynamic light scattering (DLS). ***^{1}H-MRI*:** Two pre-contrast 2D T_1-w and T_2-w ^1H images were acquired as an anatomical reference (FOV= 35 mm^2, matrix=128^2. Slice Thickness=4 mm, Total Slices=11). These images were rescaled to serve as an anatomical reference for ^{19}F-MRI ***^{19}F-DCE-MRI*:** A series of dynamic ^{19}F-MR images were acquired using the same geometry than the ^1H MRI anatomical reference, and the following GE pulse sequence: TR=300 msec, TE=3.09 msec, NEX= 8, alfa=42.2 deg. Geometry: FOV= 35 mm^2, matrix=64^2. Slice Thickness=4 mm, Total Slices=11). A total of 20 image sets were acquired for a total acquisition time of 51.12 min and a temporal resolution of 2.5 min/image. Two vials with each emulsion were placed next to the mouse as internal control for small differences in T1-weighting and spin density. After the first image set was acquired, a 75 µL of each agent (CE=3.5 mM,OC=4.6mM) were coinjected manually through a tail vein catheter over 35 seconds. Matlab was use to process the data and fit both activity curves to the Reference Agent Model (RAM). **RESULTS: Our computer simulations** (Figure 1B) showed that: 1) R^{Ktrans} can be calculated with only 5% error at SNR > 25, even when the sampling resolution is only 2 minutes. 2) At an SNR > 15 the precision of RAM is independent of temporal resolution (1 sec vs. 120 sec.), 3) Selection of temporal resolution greatly affect the precision of RAM at SNR < 15. **^{19}F-DCE-MRI:** The size of both nanoemulsions was 55 ±5 nm. *Both fluorinated contrast agents were simultaneously imaged in vivo* (Fig. 2A) using a GE selective excitation sequence (Fig. 3). The active curves of both agents were fitted to RAM and yielded R^{Ktrans}= 2.35. **DISCUSSION:** To the best of our knowledge, this is the first report describing the selective detection of two ^{19}F CA in a solid tissue under dynamic and multislice conditions [5]; it also opens the possibility of estimating relative permeability of two agents independent of blood flow and hematocrit. **REFERENCES: 1)** Lipowsky et al. Microvasc. Res., 1980, 19:297. **2)** Tofts P., et al. *J Magn Reson Imaging* 1999, 10:223. **3)** Yankeelov TE, et al. *Magn Reson Imaging* 2005, 23:519. **4)** Mulder W. et al. *NMR Biomed* 2006, 19:142. 5) Ruiz-Cabello J, et al. *NMR Biomed* 2010, 24:114

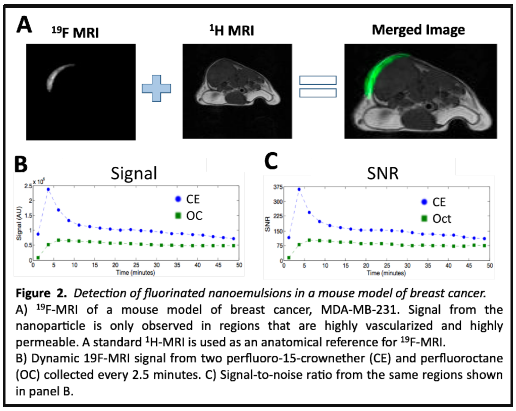

Figure 2. *Detection of fluorinated nanoemulsions in a mouse model of breast cancer.* A) ^{19}F-MRI of a mouse model of breast cancer, MDA-MB-231. Signal from the nanoparticle is only observed in regions that are highly vascularized and highly permeable. A standard ^1H-MRI is used as an anatomical reference for ^{19}F-MRI. B) Dynamic 19F-MRI signal from two perfluoro-15-crownether (CE) and perfluoroctane (OC) collected every 2.5 minutes. C) Signal-to-noise ratio from the same regions shown in panel B.

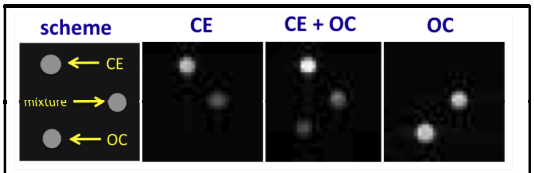

Figure 3. *Selective Detection of fluorinated nanoemulsion by ^{19}F-MRI.* The panel on the left shows a schematic representation of phantoms of 40% v/v emulsions of Perfluoro-crownether and perfluro-octane that were selectively detected by ^{19}F-MRI. The panels on the right shows the resulting images when such selective and unselective excitation pulses are used. ***This same pulse sequences were used for the data on Figure 2***