Sufficiency of Two-Pool Model for Quantitative Magnetization Transfer Imaging in Tumors

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Target Audience: Investigators who are interested in quantitative magnetization transfer (qMT) imaging in cancer.

Purpose: QMT provides measurements of macromolecular content in biological tissues, and has been widely implemented to assess, for examples, neurological disorders and cancer. For simplicity, qMT data are usually modeled with a two-pool (free water and macromolecules) model[1]. However, this is an oversimplification because real biological tissues usually contain multiple water/macromolecular pools. To improve accuracy of model fits, more sophisticated four-pool models have been developed, but these models are impractical for in vivo applications. Tumors are multi-pool systems containing significant intra- and extracellular components[2] for which accurate qMT data could provide valuable information. Although cell membranes provide a spatial barrier between the intra- and extracellular spaces, when water exchange is intermediate to fast (e.g. a few Hz, larger than R_1 relaxation rate which is < 1 Hz) the water pools in different compartments become well mixed, so the composite MR signal can be approximately regarded as from a single water pool. In such circumstances, a two-pool model may be sufficient to describe qMT data in tumors. To test this hypothesis, Gd-DTPA was injected in tumor bearing animals to selectively alter extracellular relaxation properties without changing macromolecular contents. Both off-resonance (pulsed saturation[3]) and on-resonance (selective inversion recovery (SIR)[4]) qMT methods were implemented and compared and compared with numerical simulations and in vivo experiments.

Methods: Numerical simulations: Two-, three- and four-pool models were simulated in Matlab by numerically solving the Bloch equations. The three-pool model includes intracellular and extracellular water pools, and a single macromolecular pool. The four-pool model includes an additional extracellular macromolecular pool. The water exchange rates between the intra- and extracellular water was varied at 0, 1, 5, and 10 Hz. The fractions of the extracellular water were set as 25% of overall water in the multi-pool models. To mimic the injection of Gd-DTPA, the T_1 of the free water in the two-pool model and the extracellular water in the three- and four-pool models were varied between 0.3 s and 3 s, stepped by 0.2 s. The sampling schemes are the same as those used in the experimental data collection, as described below. All simulated pulsed-MT and SIR data were fitted to corresponding two-pool models[5,6].

MRI: All experiments were performed on a 9.4T Agilent MRI scanner. Six male Fischer 344 rats (290-310 g) bearing 9L brain tumors were imaged. In the baseline period, B_1, B_0, T_2, pulsed-MT, and SIR data were acquired. B_1 maps were determined with a double-angle method. B_0 map were determined with a multi-echo gradient-echo sequence. Pulsed-MT data were acquired with a MT-weighted spoiled gradient echo sequence, with two irradiation powers (220° and 820°, pulse width/TR = 14.6/28.0 ms) and ten frequency offsets (1-100kHz, logarithmically spaced). SIR data were acquired with a customized EPI sequence[7], with an optimized 7-point acquisition scheme using the algorithm developed in our previous work[6]. These imaging acquisitions were interleaved and repeated 10 times during and after the Gd-DTPA injection, with the acquisition time ~ 5 minutes for each dynamic.

Data analysis: The T_2 data were fit to a mono-exponential decay model. The pulsed-MT data were fit to Ramani's model[6]. The SIR data were fit to both mono-exponential[4] and bi-exponential models[2,4,5] for T_1 and qMT parameters, respectively. Dynamics 2 and 3 were excluded from statistical comparison due to rapid T_1 variation within each acquisition. A linear mixed-effects model was used to compare the dynamics 4-11 to the baseline and to check the differences between the qMT methods.

Results and Discussion: Numerical simulations indicated that in the two-pool model, PSR is independent of the T_1 of the free water pool. For the three- and four-pool models, the simulated data can be well described by the two-pool qMT models. The obtained PSRs are close to expected PSRs (< 10%) and independent of the T_1 of the extracellular component, when the water exchange is in the intermediate to fast range, as shown with an example four-pool model in Fig. 1.

Fig. 2 shows the mean measured R_1 (=1/T_1) in the tumor regions-of-interests (ROIs). Compared to the baseline, the peaks of R_1 in most rats were ~ 1.2 s^{-1}. T_2 was found to vary between 20 and 36 ms. The corresponding mean pool size ratios from the SIR method (PSR(SIR)) in the tumor ROIs are plotted in Fig. 3. Across all six rats, for dynamics 4 to 11, the mean differences in both PSR(SIR) and PSR(pulsed) are less than 0.01. Statistical analyses indicated that there was no significant changes in PSR(SIR) and PSR(pulsed) for dynamics 4-11, and there was no significant difference between PSR(SIR) and PSR(pulsed) across all dynamics.

Conclusion: Tumors have been demonstrated to be more complex system than normal tissues. This work demonstrated that when there is intermediate to fast water exchange between the intra- and extracelluar water spaces in tumors, consistent PSR values were observed in a broad range of observed R_1. Therefore, the two-pool model is sufficient to describe qMT data in tumors. This is encouraging since two-pool qMT models are readily implemented in practice. Similar to phantom studies[4], this work also demonstrated that PSR is independent of proton relaxation even if the observed R_1 varied over a broad range of 0.4 to 1.2 s^{-1}, indicating that PSR is potentially a specific biomarker to quantify the macromolecular content in tumors. Moreover, our results indicate that the on-resonance SIR method is equivalent to the off-resonance pulsed saturation method in quantifying PSR.

References: (1) Henkelman, MRM, 2003. (2) Tofts, JMRI, 1999. (3) Sled, JMR, 2000. (4) Gochberg. MRM 2007. (5) Ramani, MRI, 2002. (6) Li, MRM, 2010. (7) Xu, NMR Biomed, 2014.

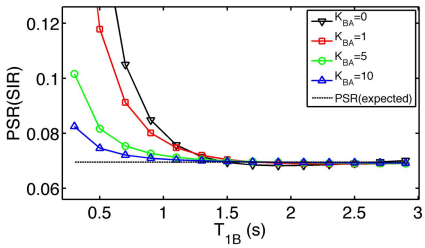

Fig. 1. Example simulation for a four-pool model with different compartmental PSR.

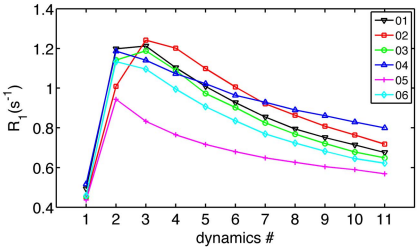

Fig. 2. R_1 in the tumor ROIs vs. dynamics.

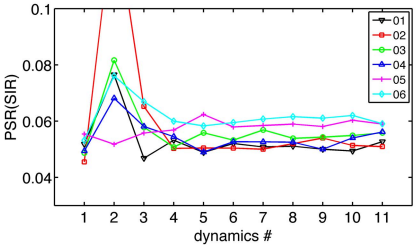

Fig. 3. PSR(SIR) in the tumor ROIs vs. dynamics.