Optimized Contrast for On-Resonance Proton Exchange Processes of MRI-PARACEST Agents in Biological Systems

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Introduction: A new class of paramagnetic (PARA) agent has recently been developed for magnetic resonance imaging (MRI) that generates contrast by chemical exchange saturation transfer (CEST) [1-4]. To observe PARACEST contrast, the proton exchange between bound water or amide protons with bulk water must satisfy the slow exchange condition ($\Delta\omega \geq k_{ex}$, where $\Delta\omega$ is the chemical shift of the bound protons, and k_{ex} is the exchange rate from bound protons to bulk water). However, the on-resonance irradiation of bulk water in the presence of a PARACEST agent may also generate contrast, even if in the fast exchange regime ($\Delta\omega < k_{ex}$). The on-resonance proton exchange processes between water bound to a PARACEST agent and bulk water in solution have been thoroughly modeled by Vinogradov *et al*. using a two-pool model [5] based on the modified Bloch equations with exchange terms and incorporating the WALTZ-16 pulse train [6]. However, the model proposed by Vinogradov *et al*. is not directly applicable *in-vivo* due to the inherent magnetization transfer (MT) effect in biological systems. In this work, a four-pool model is presented that incorporates the proton exchange processes between the bulk water (pool A) and the bound water of a PARACEST agent (pool B), the amide protons of a PARACEST agent (pool C), and the exchangeable protons associated with endogenous macromolecules (pool D). The model incorporates the chemical shift, relaxation times, proton exchange rate, and concentration of each pool of spins, as well as the saturation power and the duration of the WALTZ-16 pulse train [6].

Methods: The magnetization in each pool can be described by the modified Bloch equations incorporating chemical exchange. A series of 600 ml solutions (pH 7) of Tm^{3+}-DOTAM-Gly-Lys [7] were produced with concentrations ranging from 0.05 to 5 mM. Bovine serum albumin (BSA, 98% bovine albumin, Sigma Chemical Company) was used to simulate the MT effect caused by macromolecules within tissue. Five additional 5% BSA solutions (pH = 7.0) containing different concentrations of Tm^{3+}-DOTAM-Gly-Lys (0, 0.1, 0.5, 1, and 2 mM) were prepared. Images were acquired on a Varian 9.4T small animal MRI scanner at room temperature using a two-dimensional fast low angle shot (FLASH) pulse sequence (field of view (FOV) = 40 × 40 mm^2, data matrix: 256 × 256, TR = 4.3 ms, echo time (TE) = 1.9 ms, and flip angle = 6°), preceded by a continuous presaturation pulse (saturation power = 6.35 μT = 265 Hz, saturation time = 0.24 or 0.48 s). Four images without saturation were acquired as a reference followed by four images with saturation on the bulk water protons. The results were averaged.

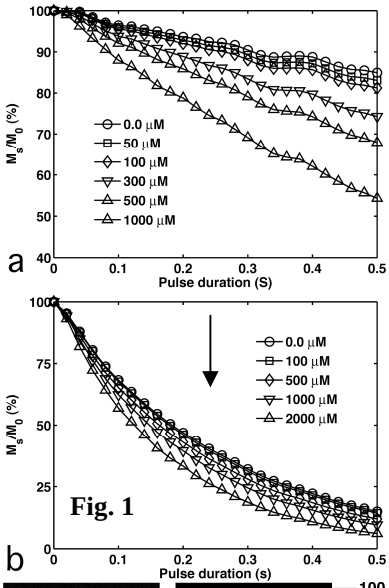
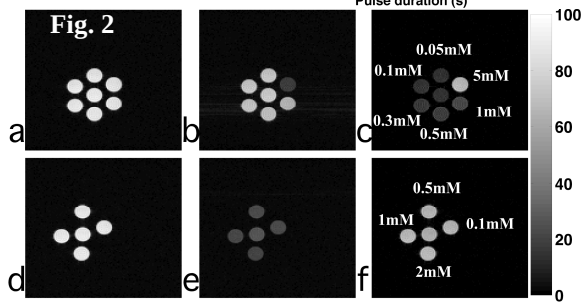


Fig. 1

Results and Discussion: The effect of saturation pulse duration on the on-resonance CEST effect was simulated for samples with different PARACEST agent concentration in the absence (Fig. 1a) and presence (Fig. 1b) of macromolecules for a given saturation pulse power (T_{1A} = 2.5s, T_{2A} = 0.5s, T_{1B} = 0.1s, T_{2B} = 0.1s, T_{1C} = 0.1s, T_{2C} = 0.1s, T_{1D} = 0.1s, T_{2D} = 0.01ms, lifetimes of bound water, amide protons, and protons associated with macromolecules are 10 μs, 2 ms, and 20 ms, 5% macromolecules, 500 ppm for bound water chemical shift, -50 ppm for amide protons chemical shift, and B_1 = 6.35-μT). The simulations demonstrate that greater contrast (difference between reference phantom (no agent) and phantom containing PARACEST agent) is achieved with longer saturation pulses for aqueous solution (Fig. 1a). However in the presence of macromolecules (Fig. 1b), an optimal saturation pulse duration exists that produces maximum contrast due to the competition between the MT effect from endogenous macromolecules and the agent-induced CEST effect. Images of the aqueous phantoms (top row) and BSA phantoms (bottom row) containing different concentrations of Tm^{3+}-DOTAM-Gly-Lys are shown in Fig. 2. The corresponding concentration of each sample is marked beside it, and the unmarked phantom in the center is the reference phantom (water or BSA). The reference images (without saturation) are given in Fig. 2a and 2d, the images following 0.48-second on-resonance saturation are given in Fig. 2b and 2e. The relative difference images are shown in Fig. 2c and 2f, respectively. The effective decrease of bulk water signal due to the presence of 300, 500, 1000, and 5000 μM Tm^{3+}-DOTAM-Gly-Lys was 2.3, 3.7, 7.7, and 52.6 % for the 0.48 s saturation and 1.0, 2.4, 5.0, and 45.6 % for the 0.24 s saturation (images not shown), respectively. The effective decrease of bulk water signal in BSA phantoms due to the presence of 100, 500, 1000, and 2000 μM Tm^{3+}-DOTAM-Gly-Lys was 2.3, 2.3, 4.6, and 5.8 % for the 0.48 s saturation and 3.2, 3.7, 5.6, and 8.0 % for the 0.24 s saturation (images not shown), respectively. Consistent with the simulated results, greater contrast was realized with the 0.48 s saturation pulse for aqueous solutions and the 0.24 s saturation pulse for BSA samples.



Conclusion: On-resonance saturation duration must be optimized to maximize on-resonance CEST contrast for *in-vivo* applications. This result was predicted using a four-pool model for the proton exchange processes of a PARACEST agent in biological systems, and verified in phantoms containing bovine serum albumin and Tm^{3+}-DOTAM-Gly-Lys.

Acknowledgements and References: Funding provided by Ontario Institute of Cancer Research and CIHR/UWO Strategic Training Initiative in Cancer Research and Technology Transfer. [1] Zhang SR *et al*, J Am Chem Soc 2005;127:17572-17573. [2] Zhang SR *et al*, J Solid State Chem 2003;171:38-43. [3] Ward KM *et al*, J Magn Res 2000;143:79-87. [4] Aime S *et al*, Magn Reson Med 2002;47:639-648. [5] Vinogradov E *et al*, J Magn Reson 2005;176:54-63. [6] Shaka A *et al*, J Magn Reson 1983;52:335-338. [7] Wojciechowski F *et al,* Bioconjugate Chem 2007;18:1625-1636.