R2* Reference Phantoms for Longitudinal Research Studies

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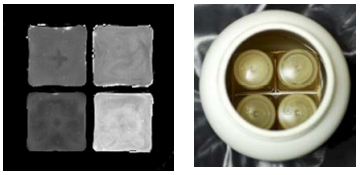
PURPOSE Calibration reference phantoms exhibiting long-term chemical stability and temperature-insensitive R2*/T2* relaxation are needed in longitudinal research studies employing quantitative R2* methods to improve the sensitivity and reproducibility of R2* measurements, to detect and correct bias, and to decrease the variance of pooled study data. The relevant literature is sparse.[1-4] This project aims to design and evaluate a R2* phantom that is stable over time and temperature, and mimics organ tissue T1 and T2.

METHODS The temperature dependence of T1 relaxation varies for different paramagnetic cations, with Cu^{2+}, Mn^{2+}, Fe^{3+}, and Gd^{3+} exhibiting greater dependence than Ni^{2+}, Co^{2+}, Fe^{2+}, and Nd^{3+} in aqueous solution.[5-6] $NiCl_2$ was selected as a T1 modifier to maximize thermal stability. Addition of a gelling agent can mimic a target tissue's T1 and T2. SPIO readily precipitates from aqueous solution.[7] Thus, the gelling agent is needed to fix the SPIO for long-term stability. Agarose was used to modify T2 and promote gel formation. Carrageenan aids the formation of a strong tissue-like gel. The combination of a fixed quantity of carrageenan (3%) with a variable quantity of agarose was used to achieve the desired T2 relaxation.[8] A gel mixture of $NiCl_2$ (1.1 mM) and agarose (1.2%) matching the T1 (~900 ms) and T2 (~62 ms) of pediatric brain at 0.35T[9] was doped with SPIO nanoparticles (Feridex I.V.) to produce phantoms with 63.6, 72.7, 90.9, 127 μM Fe in four 200 mL bottles. A methylisothiazolinone-based preservative (Kathon CG/ICP II) provides long-term antimicrobial protection. The phantom was scanned on 4 different GE MR scanners having B_0 field strengths of 0.35T, 0.7T, 1.5T, 3.0T, using multi-echo GRE pulse sequences at 1.5T and 3.0T, else separate single-echo GRE acquisitions for each TE were acquired at constant receiver gain. Custom MATLAB (The MathWorks) software was used to generate the R2* maps via voxel-wise nonlinear least squares fitting to $S(TE)=S_0e^{-R2^* TE}$, and ROI statistics obtained.[10] Phantoms were immersed in a tap water bath for constant temperature during scanning. Fig. 1A shows a computed 3T R2* map of the phantom apparatus shown in Fig. 1B.



A B

Fig. 1 R2* Map at 3.0T and Phantom Apparatus

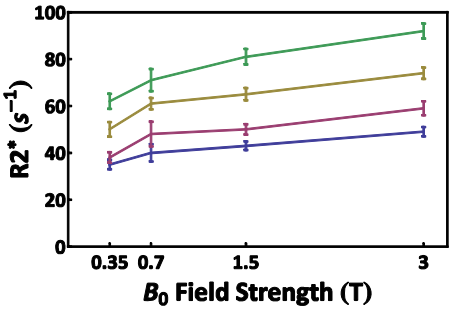


Fig. 2 Phantom R2* vs. B_0 and [SPIO] at Room Temperature

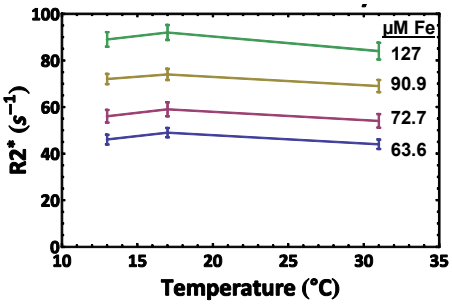


Fig. 3 Phantom R2* Thermal Dependence at 3.0T

RESULTS AND DISCUSSION Average T1 and T2 for the SPIO-free gel at 0.7T was 838 ms and 89.5 ms respectively. The formulation of the gel mimicking pediatric brain consisted of 1.1 mM $NiCl_2$, 1.2% agarose, and 3% carrageenan. R2*([SPIO]) at 0.35T was 34.6±1.9 s^{-1} at 63.6 μM, 37.9±2.1 s^{-1} at 72.7 μM, 49.7±3.1 s^{-1} at 90.9 μM, and 61.7±3.2 s^{-1} at 127 μM Fe, acceptably close to the design goals. Fig. 2 plots the measured R2* of each of the 4 bottles at the 4 B_0 levels. The R2* of a mixture behaves linearly from ~1T to 3T. Below 1T, the rate of decrease of R2*(B_0) steepens. Fig. 3 plots the phantom R2* values over the temperature range from 13ºC to 33ºC. There appears to be a gentle hump in R2* in the range of room temperature. Multiple phantom copies were fabricated in April 2009 and we will continue to periodically rescan the phantoms to track their R2*(t) to detect if any degradations appear. No evidence of microbial growth or other degradation of the phantoms has been seen during the 6 months since fabrication, suggesting that methylisothiazolinone has been an effective preservative agent. Refinement of the method for transferring the hot liquid gel mixture into the phantom mould is needed to improve the homogeneity of the gel by preventing small air bubbles.

CONCLUSIONS Implementation of a stable SPIO-doped gel phantom to enable reliable R2* measurements within longitudinal research studies is demonstrated. The SPIO gel formulation is adequately insensitive to temperature variations near room temperature (20ºC). Due to nonlinear interdependence of the phantom's T1 and T2 relaxation properties on the concentrations of both $NiCl_2$ and agarose, use iterative design to adjust the formulation to obtain the desired relaxation behavior.

REFERENCES **1.** MacMillan B, et al. Solid State Nucl Magn Reson, 2005; 28:106-110. **2.** Howseman AM, et al. MRM, 1999; 41:368-374. **3.** Hines CD, et al. JMRI, 2009; 30:1215-1222. **4.** Virtanen JM, et al. Magn Reson Imaging, 2008; 26:1175-1182. **5.** Kraft KA, et al. MRM, 1987; 5:555-562. **6.** Waiter GD, et al. Magn Reson Imaging, 1997; 15:929-938. **7.** Latourette MT, Siebert JE. Proc. ISMRM, 2008; p. 1422. **8.** Yoshimura K, et al. MRM, 2003; 50:1011-1017. **9.** Holland BA, et al. Am J Neuroradiol, 1986; 7:201-208. **10.** Siddique MK, et al. J Investigative Medicine, 2006; 54(2):S344.