MONTE CAROL MODELING OF THE NON-MONOEXPONENTIAL CPMG RELAXATION IN IRON OVERLOAD

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Target audience: Scientists and clinicians interested in iron quantification, relaxometry, and quantitative biomarkers.

Purpose: In patients with iron overload, the CPMG measurement in liver exhibits a non-monoexponential decay.[1] By using a theoretical model, one can decompose the decay into two major components associated with the two forms of endogenous tissue iron: ferritin and hemosiderin.[2] A separate quantification may be useful in assessing iron storage and chelation therapy,[3,4] because ferritin iron may more directly reflect iron toxicity.[5] However, the validity of the quantitative model has not been previously studied with numerical simulations of in vivo iron deposits with heterogeneous sizes and spatial distributions.[6] In this work, we investigate the model's performance in realistic tissue geometry by simulating the MR relaxation from iron spheres with statistically distributed sphere sizes. The simulated iron concentrations of ferritin and hemosiderin were varied over a clinically relevant range. As a reference, conventional bi-exponential fits to the signals were also calculated.

Methods: Simulation We developed a 3D Monte Carlo simulation of MR relaxations resulting from hemosiderin and ferritin at 1.5T. To simulate hemosiderin induced relaxation, impermeable iron spheres with a gamma distributed radius (mean ± std: 3.8 ± 2.2 μm) were randomly distributed to simulate aggregated, insoluble iron (Fig. 1a).[7,8] The volume fraction was determined from the calibrated relation with liver iron concentration.[6] 50,000 water molecules were positioned randomly and performed 3-D random walks with a step size of 0.25 μm (diffusivity = 0.76 $\mu m^2/ms$ [9]). Each molecule experienced the magnetic dipole field produced by the iron spheres with magnetic susceptibility = 8.6×10^{-6} (CGS Unit).[10] The phase accumulation of each molecule was computed by a simulated CPMG sequence with an interecho time of 4 ms and maximum echo time of 100 ms. For ferritin (dispersed, soluble iron) induced relaxation, it was modeled as a monoexponential decay with a relaxation rate determined from the calibrated relation with liver iron concentration.[4] The simulated relaxations of hemosiderin and ferritin were then combined to form the final signal (Fig. 1b). The total iron concentration was varied from 7.8 to 39.2 mg/g dry by changing the concentrations of hemosiderin and ferritin separately (Fig. 2). Each simulation was repeated five times to quantify the precision. Model fits The simulated signals were fitted with the non-monoexponential model [2]: $S(t) = \exp(-RR_2 \times t - A^{3/4}\,\Delta t^{3/4}\,t^{3/8})$, where reduced relaxation rate (RR_2) quantifies the relaxation due to ferritin, aggregation index (A) is proportional to hemosiderin concentration, and Δt is half the interecho time. The signals were also fitted with the bi-exponential model (fast R_2 and slow R_2) for comparisons. The fittings were performed using the Levenberg-Marquardt algorithm in Matlab (Mathworks, Inc.) and assessed using Bayesian Information Criterion (BIC). The BIC of two fits were compared in each experiment using the two-sample t-test with a significance level $p < 0.05$.

Results: The simulated signals deviated from the monoexponential decay (Fig. 1b). The decay were well described by the non-monoexponential and bi-exponential models, but the non-monoexponential model was a better fit (lower BIC) in 9 out of 13 total experiments ($p = 1.3 \times 10^{-6}$ to 1.3×10^{-2}). When the hemosiderin concentration was varied (Fig. 2a), the measured A and RR_2 agreed with the true A and RR_2 (deviations ΔA: 1.6×10^{-4} to 1.5×10^{-2}, ΔRR_2: 0.4 to 12.7 s^{-1}). The fast R_2 of the bi-exponential model correlated with the increased hemosiderin concentration ($r = 0.99$). The slow R_2 agreed with the true RR_2 (deviation ΔRR_2: 0.7 to 23.5 s^{-1}). When the ferritin concentration was varied (Fig. 2b), the measured A and RR_2 agreed with the true A and RR_2 (deviations ΔA: 1.2×10^{-3} to 3.6×10^{-3}, ΔRR_2: 2.4 to 4 s^{-1}). The fast R_2 correlated with the increased ferritin concentration ($r = 0.99$). The slow R_2 agreed with the true RR_2 (deviation ΔRR_2: 4.3 to 7.8 s^{-1}).

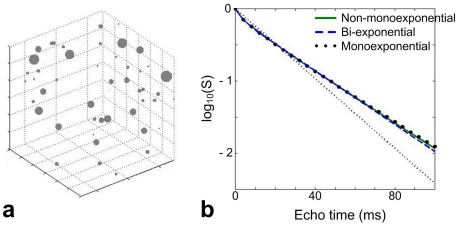

Fig. 1: a: 3-D simulation of iron deposits. **b**: An example of model fits to the simulated CPMG signals; hemosiderin/ferritin concentrations: 16.8/6.6 mg/g dry.

Discussion: The fast R_2 of the bi-exponential model was sensitive to both changes in hemosiderin and ferritin concentrations (Fig. 2). By contrast, the non-monoexponential model reflected hemosiderin and ferritin concentrations separately through the measured A and RR_2. The deviations of the measured RR_2 (ΔRR_2) were also smaller than those of the slow R_2 of the bi-exponential model. Nonetheless, the deviations (ΔA, ΔRR_2) of the measured A and RR_2 apparent at high iron concentrations may be related to the increased diffusion effects that violate the model's assumptions.[10]

Conclusion: We simulated the CPMG relaxation in realistic tissue geometry of iron overload. We demonstrated that the non-monoexponential model accurately described the signal relaxation and enables a separate quantification of the two major forms of tissue iron storage. These results support the model's potential for accurate in vivo assessments of ferritin, hemosiderin, and total iron storage.

References: [1]. Thomsen C, et al, MRI (10), 867-79, 1992. [2]. Jensen JH, et al, MRM (63), 1201-9, 2010. [3]. Kim D, et al, NMR Biomed (24), 771-7, 2011. [4]. Tang H, et al, JMRI (39), 307-16, 2014. [5]. De Domenico I, et al, EMBO J (25), 5396–5404, 2006. [6]. Ghugre NR, et al, J Microsc (238), 265-74, 2010. [7]. Weisskoff RM, et al, MRM (31), 601-10, 1994. [8]. Ghugre NR, et al, MRM (65), 837-47, 2011. [9]. Yamada I, et al, Radiology (210), 617-23, 1999. [10]. Jensen JH, et al, MRM (47), 1131-8, 2002.

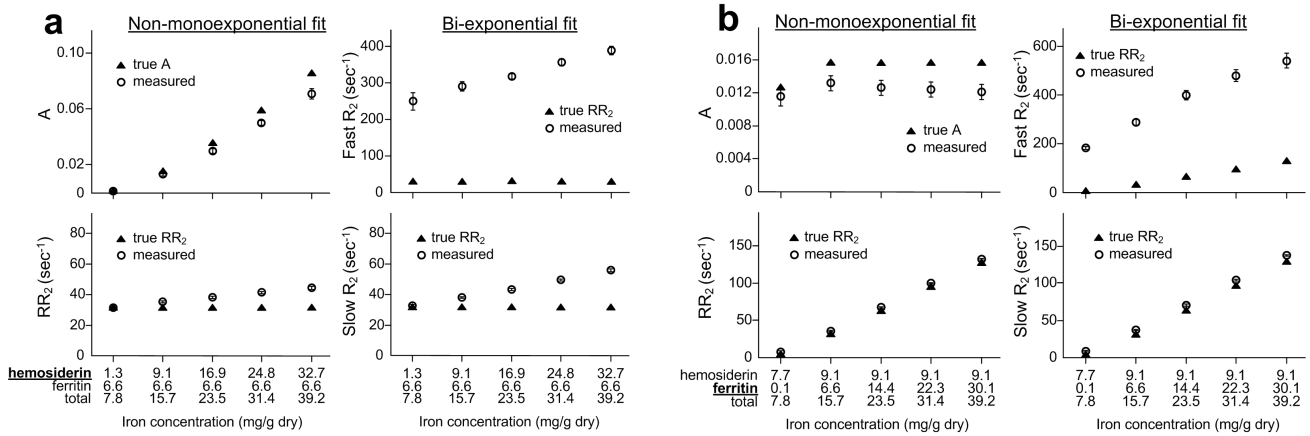

Fig. 2: Variations of the fitted parameters with increased hemosiderin (**a**) and ferritin (**b**) concentrations separately. The analytical A and RR_2 were determined from the calibrated relations with iron concentrations in liver. [4,6] Error bars indicate SD from the repeated experiments.