Modeling MRI contrast enhancement with exogenous T_2 agents

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Introduction: Superparamagnetic contrast agents are the most widely studied class of agents for emerging cellular-molecular applications. Rational development of new generations of contrast agents requires a computational scheme for predicting contrast enhancement *in vivo*. A general theoretical model is presented to evaluate the minimal concentration of T_2 contrast agent required for satisfactory MRI contrast in tissues. Our tissue contrast model requires only a few key parameters that are readily evaluated. The model is applicable to a wide range of T_2-type agents and delivery scenarios. Previous strategies for predicting contrast enhancement have been based largely on empirical results for specific systems. We apply our model to Feridex, which is a clinical superparamagnetic iron-oxide (SPIO) agent, and ferritin, an iron storage protein that has attracted recent interest as a novel intracellular contrast agent (1,2). For other applications, a set of general analytic expressions are provided that are applicable to range of vascular, extracellular, and intracellular agent types.

Model: The model starts with the general non-linear equations describing the MRI intensity using the spin-echo (3). T_2-weighted imaging is used to obtain a satisfactory contrast-to-noise ratio (CNR) between a region of interest (A) and its background region (B), with mean T_2-values given by T_2^A and T_2^B, respectively. Typically a *CNR* >5 is easily discernible by eye (4), and we use this criterion in order to estimate the minimal agent concentration. *CNR* can be maximized by setting TE to an optimal value, which can be explicitly calculated (3,5). Manipulations to the MRI intensity equations result in the relation $5/\lambda = \alpha^{\alpha/(1-\alpha)} - \alpha^{1/(1-\alpha)}$, where $\alpha = T_2^A/T_2^B$, $\lambda = k\sqrt{NEX}/N$, k is a constant specific to the imaging system, *NEX* is the number of averages, and N is the average image noise. We solve for the ratio $\alpha = T_2^A/T_2^B$ numerically over the range $7 < \lambda < 1000$; the result is $\alpha = 1.70689\lambda^{\lambda/(1-\lambda)} + 4.13406\lambda^{1/(1-\lambda)} - 3.09337$. Different contrast agent uptake and activation mechanisms affect the ratio $\alpha = T_2^A/T_2^B$. Below we classify agents into three categories, where in all cases [M] (or $[M]_A$) is the minimum agent concentration needed in region A to produce satisfactory contrast. The results are:

(i) Functional & Polymerized Agents

The agent is present in both regions at equal concentrations, and the agent's relaxivity in the target of interest (i.e., region A) is modified *in situ* by some active means.

$$[M] = \frac{1-\alpha}{t_2(\alpha r_2^A - r_2^B)}$$

(ii) Selective & Targeted Agents

The contrast agent has a fixed relaxivity, however the agent selectively accumulates in, or binds to, a region of interest at higher concentrations than background regions.

$$[M]_A = \frac{1-\alpha}{\alpha t_2 r_2} + \frac{[M]_B}{\alpha}$$

(iii) Highly Localized Agents

Here, the contrast agent has fixed relaxivity and is introduced into a region of interest by direct injection, implantation of labeled cells, or using nucleic acid-based intracellular MRI reporters (1). No agent is present in the background region.

$$[M] = \frac{1-\alpha}{\alpha r_2 t_2}$$

In all three cases, α is evaluated using the numerical expression shown above, t_2 is the background T_2 value for regions A or B in the absence of any agent, and r_2 is the agent's T_2 relaxivity.

Results & Methods: As an example of the applicability of the model, Figure 1 shows the model-predicted concentrations of Feridex and ferritin needed to get different levels of contrast. Also shown in Fig. 1 is the minimum 'satisfactory' contrast (i.e., *CNR*>5) threshold (dashed line). These predictions assume *NEX*=1 and the relaxivities of Feridex (145 ± 9 s^{-1} mM^{-1}[Fe]) and Ferritin (1900 ± 200 s^{-1} mM^{-1}[protein]) measured at 500 MHz and 37°C. The system-specific value of the *k/N* ratio was found by acquiring an image in phantoms (details below) and then solving for the ratio using the general spin-echo intensity equations (3). The model predicts that under these conditions, to obtain satisfactory contrast a minimum concentration of 0.043 mM Fe contained in Feridex and 2.9 μM ferritin protein is required.

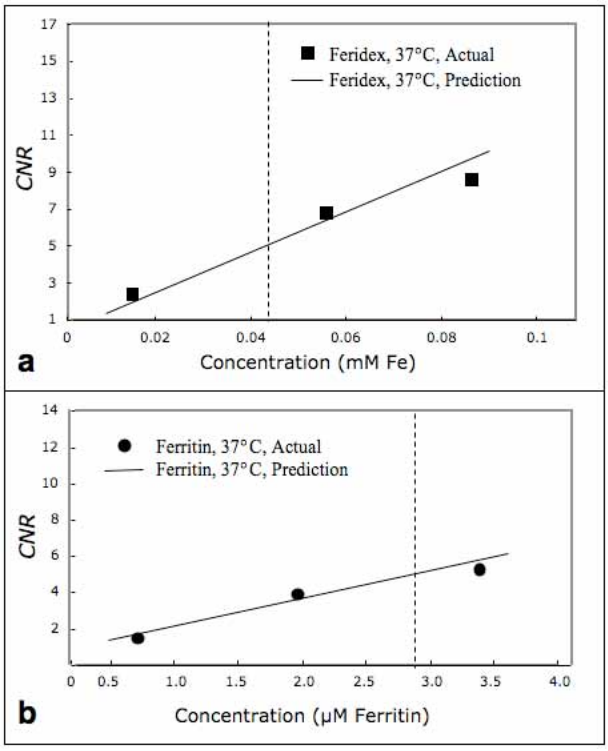

FIG. 1. Plot comparing model-predicted and actual *CNR* values for different concentrations of **(a)** Feridex and **(b)** ferritin in water at 500MHz. The dashed line indicates 'satisfactory' contrast (CNR>5).

As a simple test of this model, T_2-weighted spin echo images were acquired in phantoms containing different contrast agent concentrations in H_20. The model was used to calculate the concentrations of Feridex (Berlex Imaging, Wayne, NJ) and horse spleen ferritin (Sigma-Aldrich) that should result in *CNR* = 2, 5, and 8. Capillary tubes were filled with these concentrations and imaged at 37°C in an 11.7 T, 89-mm Bruker AVANCE micro-imaging system. Contrast agent T_2 values were verified for each sample using a CPMG sequence and used to calculate the optimal-contrast TE value (3). T_2-weighted SE images were then acquired for each sample using the parameters TE=optimal, TR = 10 s, and *NEX*=1. The *CNR* was calculated between the capillary containing contrast agent and those with pure water. Figure 1 demonstrates the model's accuracy by comparing predicted and observed *CNR* values. Predicted *CNR* values are within 2-13% of actual *CNR* observed in images.

Discussion: When developing new types of contrast agents it is important to have an understanding of the minimum agent concentration and relaxivity needed to provide detectable contrast as part of an overall design strategy. The tissue contrast model presented here can provide accurate estimates to these questions. Furthermore, the ability to predict the minimal concentration can also be used to avoid excess contrast agent, which may result in adverse biological effects such as cytotoxicity. We note that a comparable model for T_1-type agents has been previously described (4).

References:

1. Genove G, DeMarco U, Xu HY, Goins WF, Ahrens ET. A new transgene reporter for in vivo magnetic resonance imaging. Nature Medicine 2005;11(4):450-454.
2. Cohen B, Dafni H, Meir G, Harmelin A, Neeman M. Ferritin as an endogenous MRI reporter for noninvasive imaging of gene expression in C6 glioma tumors. Neoplasia 2005;7(2):109-117.
3. Hendrick RE. Image Contrast and Noise. In: Stark DD, editor. Magnetic Resonance Imaging. 3rd. ed. Volume 1. St. Louis: Mosby; 1999. p 43-67.
4. Ahrens ET, Rothbacher U, Jacobs RE, Fraser SE. A model for MRI contrast enhancement using T-1 agents. Proceedings of the National Academy of Sciences of the United States of America 1998;95(15):8443-8448.
5. Haacke EM, Brown RW, Thompson MR, Venkatesan R. Signal, Contrast and Noise. In: Haacke EM, editor. Magnetic Resonance Imaging: John Wiley & Sons, Inc; 1999. p 331-380.