Quantification of bound contrast agent concentration using delta relaxation enhanced MR

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Introduction Delta relaxation enhanced magnetic resonance (dreMR) is an emerging method for performing molecular imaging, which utilizes a removable electromagnetic coil to modify the strength of the main magnetic field during an MRI pulse sequence (1, 2). The purpose of this field-cycling method is to acquire information about the binding state of targeted contrast agents that is not obtainable with static-field MRI methods. Targeted contrast agents, like regular blood-pool agents, are pharmaceuticals for increasing the local relaxation rate of water hydrogen. Unlike blood-pool agents, targeted contrast agents possess a special molecular configuration, which allows selective binding to a particular biological target molecular. Generally, both the bound and unbound states will result in MR image enhancement, making it impossible to differentiate the bound and unbound agent with conventional methods.

The dreMR method has been shown to qualitatively differentiate image enhancement due to bound contrast agent form all other sources by measuring the magnetic field dependence of the relaxation rate ($R_1 = 1/T_1$) of the sample. Due to an increase in rotational correlation time following binding, the relaxivity of a bound contrast agent molecule will generally demonstrate a significant dependence upon the strength of the applied magnetic field, while the magnetic field dependence of an unbound agent molecule will be nearly field independent. Figure 1 shows the field dependence of the agent MS-325 in both the bound and unbound state.

This work describes a method for advancing dreMR from qualitative imaging to quantitative measurement of contrast agent binding. By measuring the concentration of bound agent, the corresponding concentration of the target molecule can determined.

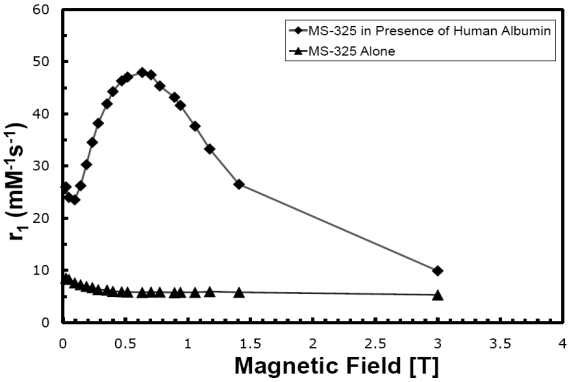

Figure 1. The relaxivity of a contrast agent indicates its ability to increase relaxation rates per milli-molar concentration (1). The contrast agent MS-325 demonstrates strong field dependence only when it has bound to it target molecule, human serum albumin, and little dependence in the unbound state.

Methods The relaxivity of a contrast agent is a measure of its ability to increase the relaxation rate of a sample. If $R_{1,pre}$ is the relaxation rate of a biological sample preceding injection of a non-targeting contrast agent of relaxivity, r_1, and concentration, c, then the measured relaxation rate post-enhancement is given by the expression, $R_{1,post} = R_{1,pre} + c \cdot r_1$. In this situation, c can be calculated provided that r_1 is known *a priori*.

When a targeted agent is used, both the bound and unbound components contribute to change the observed relaxation rate. If c_f and c_b are the concentrations of the unbound (subscripted as *f* for *free*) and bound agent respectively, and $r_{1,f}$ and $r_{1,b}$ the relaxation rates of the free and bound agents then the measured relaxation rate is; $R_{1,post} = R_{1,pre} + c_f \cdot r_{1,f} + c_b \cdot r_{1,b}$. In this situation, it is not possible to determine the concentrations of the free, c_f, and bound, c_b, agent. Mathematically, one might say that this is a case of *1* equation and *2* unknowns.

$$R_{1,post}^{1.5T} = R_{1,pre}^{1.5T} + c_b^{1.5T} \cdot r_{1,b}^{1.5T} + c_f^{1.5T} \cdot r_{1,f}^{1.5T} \qquad [1]$$

$$R_{1,post}^{1.3T} = R_{1,pre}^{1.3T} + c_b^{1.3T} \cdot r_{1,b}^{1.3T} + c_f^{1.3T} \cdot r_{1,f}^{1.3T} \qquad [2]$$

$$c_b = \frac{(R_{1,post}^{1.5T} - R_{1,pre}^{1.5T}) \cdot r_{1,f}^{1.3T} - (R_{1,post}^{1.3T} - R_{1,pre}^{1.3T}) \cdot r_{1,f}^{1.5T}}{r_{1,f}^{1.3T} \cdot r_{1,b}^{1.5T} - r_{1,b}^{1.3T} \cdot r_{1,f}^{1.5T}} \qquad [3]$$

$$c_f = \frac{-(R_{1,post}^{1.5T} - R_{1,pre}^{1.5T}) \cdot r_{1,b}^{1.3T} + (R_{1,post}^{1.3T} - R_{1,pre}^{1.3T}) \cdot r_{1,b}^{1.5T}}{r_{1,f}^{1.3T} \cdot r_{1,b}^{1.5T} - r_{1,b}^{1.3T} \cdot r_{1,f}^{1.5T}} \qquad [4]$$

$$c_b \sim \frac{R_{1,post}^{1.5T} - R_{1,post}^{1.3T}}{r_{1,b}^{1.5T} - r_{1,b}^{1.3T}} \qquad [5]$$

This situation is corrected by taking a second measure of $R_{1,post}$ and $R_{1,pre}$ at a different magnetic field strength, resulting in two equations and two unknowns as shown in equations 1 and 2. The ability to change the magnetic field strength of the MRI system in provided by the dreMR insert coil. In equations 1-5, the strength of the main magnetic field is indicated as a superscript above the relaxation rates and relaxivities. In this example, field strengths of 1.5 T and 1.3 T are used. If the relaxivity of either the bound or unbound agent varies with the strength of the applied magnetic field then it becomes possible to calculate the concentration of both the bound and unbound contrast agent as is shown in equations 3 and 4. For equations 3 and 4 the denominator will be non-zero when the relaxivity curve profiles are different for the bound and unbound agent, $r_{1,free}^{1.3T}/r_{1,bound}^{1.3T} \neq r_{1,free}^{1.5T}/r_{1,bound}^{1.5T}$. As before, it is required that the relaxivity values of the agent are known for each state and at each field strength.

By taking the approximation that, the relaxivities of the unbound agent and the surrounding biological tissue (R_1 pre-contrast) demonstrate minimal magnetic field dependence, $\left(r_{1,f}^{1.3T} \sim r_{1,f}^{1.5T}\right)$ and $\left(R_{1,pre}^{1.3T} \sim R_{1,pre}^{1.5T}\right)$, equation 3 reduces to equation 5. In equation 5, the need to measure the R_1 pre-contrast is removed, halving the total scan time. This method requires that the relaxivity values of the bound agent be different at the two magnetic field strengths of measurement, i.e. $r_{1,b}^{1.5T} \neq r_{1,b}^{1.3T}$.

Discussion We have shown how quantification of biological molecules is theoretically possible when using field-cycled MRI methods. To measure the concentrations of both bound and unbound agent, four measurements of R_1 are required. If magnetic field independence is assumed for both surrounding biological tissue and the unbound agent, then only two, post-contrast R_1 measurements are needed. Because most, if not all, targeted, T_1-shortening agents only show magnetic field dependence in the bound state, this quantification method may be applied to various molecular imaging applications.

References

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2. Alford J.K., et al., Magn Reson Med 2009;61(4):796-802.