Delta Relaxation Enhanced MR: Experimental Validation

J. K. Alford[1], B. K. Rutt[1,2], T. J. Scholl[1], W. B. Handler[1], and B. A. Chronik[1]

[1]Physics and Astronomy, The University of Western Ontario, London, Ontario, Canada, [2]Imaging, Robarts Research Institute, London, Ontario, Canada

Introduction: Magnetic resonance molecular imaging enables the high-resolution *in vivo* study of molecular processes, frequently utilizing gadolinium-based probes [1] that specifically bind to a particular biological molecule or tissue. Few MR probes are inactive when unbound and produce enhancement only after binding, instead they are typically nonspecific and cause enhancement in either state. Accumulation processes are then required to increase probe concentration in regions of the target molecule/tissue. Herein, a method referred to as **d**elta **r**elaxation **e**nhanced **MR** (**dreMR**) is used to create image specificity for a probe that would typically cause image enhancement in either state [2, 3]. dreMR utilizes magnetic resonance field-cycling methods [4] to produce MRI contrast related to the dependence of T_1 upon magnetic field. The partial derivative of T_1 with respect to magnetic field strength, referred to here as T_1-slope, can be used as an unambiguous measure of probe binding. As experimental validation of this technique, T_1 weighted images and T_1-slope weighted images were produced for a phantom having regions with both magnetic field dependent and magnetic field independent T_1 values.

Methods: There are multiple methods that can be employed to generate dreMR contrast. The simplest involves the weighted subtraction of two T_1 weighted images, each image acquired with a slightly different sequence. These sequences, referred to as the T_{1+} and T_{1-} sequences, both resemble T_1 weighted sequences; however, in the T_{1+} sequence a field increasing ΔB pulse is applied during longitudinal relaxation, while in the T_{1-} sequence a field decreasing ΔB pulse is used. In Fig. 2 the T_{1+} and T_{1-} sequences are shown. Each sequence contains a relaxation period where the static magnetic field strength (B_0) is either increased or decreased by an amount ΔB, as well as an acquisition sequence, which may be a conventional imaging sequence such as gradient recalled echo, spin echo, fast spin echo, etc. In this experiment a spin-echo acquisition sequence was used. Subtraction of the images produced by the T_{1-} and T_{1+} sequences would result in an image where the only intensity would be due to magnetic field dependent tissue. Non field dependents source of contrast are suppressed.

To demonstrate the feasibility of field-cycled imaging in clinical MRI systems, a phantom was constructed that would exhibit both field-independent and field-dependent T_1 profiles. The field-dependent component was the contrast agent Vasovist (Bayer HealthCare Pharmaceuticals, gadofosveset trisodium, 0.25 mmol/mL). In its unbound form this agent acts to shorten the T_1 of nearby water, largely independent of magnetic field strength; however, upon binding to the protein albumin its relaxivity becomes highly field dependent. See Figure 1. The particular choice of the Vasovist and albumin was based on the availability of the contrast agent and its well-documented relaxivity mechanisms. The phantom consisted of two columns of liquid samples. The left column contained phosphate buffered saline solution (PBS) with graded concentrations of the contrast agent Vasovist. Neither the PBS nor the Vasovist demonstrated a strong dependence on magnetic field. In this column the samples spanned a range of T_1 values; the shortest T_1 values were found in samples with the highest concentration of Vasovist. The right-hand column contained a biologically significant concentration of rabbit serum albumin (RSA) dissolved in PBS, again with varied concentrations of Vasovist. Vasovist bounding to the rabbit serum albumin created a range of samples exhibiting varying T_1 and T_1-slope; the shortest T_1 as well as largest T_1-slope seen in samples with the highest concentration of contrast agent. Therefore the right column was expected to demonstrate a measurable change in MRI image intensity when imaged at different magnetic field strengths.

Results: For T_1 images (Figure 3a,b), samples with low concentrations of Vasovist in an albumin solution could not be differentiated from samples with higher concentrations of Vasovist in buffer. Conversely in Figure 3c, the T_1-slope weighted images showed high specificity to albumin (right column enhanced, left column suppressed). Albumin samples with a 10 µM concentration of Vasovist were enhanced over buffer samples containing up to 16 times more Vasovist. While the signal to noise ratio has been measurably decreased by the subtraction process, the trade-off is a significant improvement in contrast. This method has succeeded in producing contrast that is linearly related to the concentration of Vasovist that was bound to albumin – all samples without albumin have been suppressed.

Discussion: dreMR imaging is a method for producing image contrast proportional to the magnetic field dependence of T_1 as a mechanism for imaging endogenous molecules. One primary application is the significant improvement in specificity to binding state of gadolinium based agents that preferentially bind to targeted molecules or proteins such as EP-2104R (Epix) and Vasovist (Bayer). The appeal of dreMR contrast is that it can be used with any contrast agents that cause a change in the local T_1-slope upon binding.

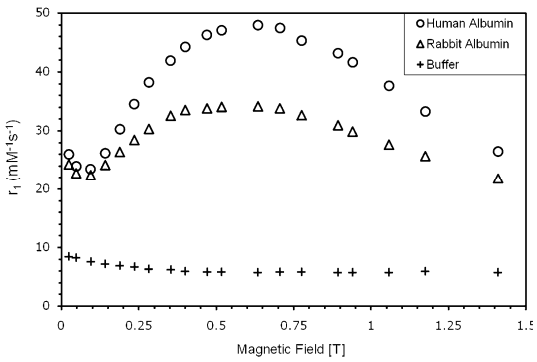

Figure 1. Relaxivity (ability to shorten T_1) is plotted as a function of field strength for 0.1 mM of Vasovist (MS-325) in phosphate buffered saline PBS; alone (+), in 4.5% (wt/vol) human (○) or rabbit serum albumin (Δ). The relaxivity of the agent after albumin binding is highly magnetic field dependent while the relaxivity of the unbound agent demonstrates very little field dependence. Data provided by Dr. Peter Caravan, Massachusetts General Hospital [1].

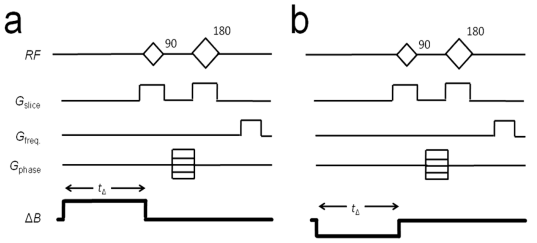

Figure 2. a) The field-increasing pulse sequence used a ΔB pulse to increase the field during the longitudinal relaxation. b) A magnetic field pulse of opposite polarity was applied during the field-decreasing pulse sequence. A typical spin echo pulse sequence followed approximately 10 ms after the end of the magnetic pulse.

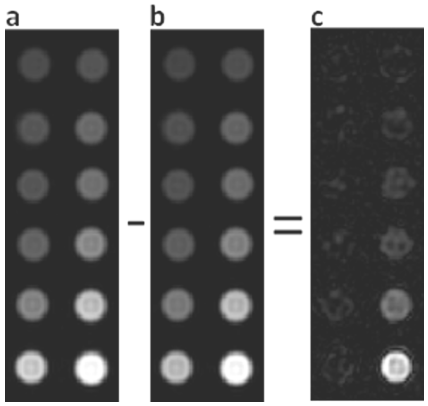

Figure 3. Images a and b show the T_1 weighted spin-echo images in which the main magnetic field was first increased and then decreased by 70 mT respectively. Image c shows the absolute difference of these images. The left column of samples, those having T_1 values which are independent of magnetic field are suppressed in intensity while in the right column samples (those with a strong magnetic field dependence) remain bright.

References:

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