Estimating Microvessel Spacing or Cell Sizes Using $R_{1\rho}$ Dispersion

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Target Audience: Investigators interested in quantitative tissue characterization and measurements of vessel spacings by MRI.

Purpose: Measuring sub-voxel structural dimensions such as cell size and vascular spacing can provide quantitative characterization of biological tissues. Here we describe a new type of measurement of tissue microstructure using spin-lattice relaxation in the rotating frame ($R_{1\rho}=1/T_{1\rho}$). $R_{1\rho}$ describes the rate that transverse bulk magnetization decays while under the influence of a spin-lock pulse, and it is well established that the locking field amplitude influences the relaxation rate by changing the effective field experienced by the magnetization, causing the rate to decrease from $\approx R_2$ at zero locking amplitude to $\approx R_1$ in the high locking field limit. We have exploited this behavior to estimate microvessel distributions within intact tissues. The relaxation rate changes because the effective field governs the time scale of the processes that give rise to relaxation. Spin-locking measurements have been used extensively to investigate slow molecular motions and chemical exchange processes[1], but more recently we have quantified how diffusion through internal susceptibility gradients may be used to derive structural information[2]. The diffusion and chemical exchange processes are independent and the time scales in practice tend to be very different, so they result in separate, independent $R_{1\rho}$ dispersions. The double dispersion phenomenon can be quantified by linearly combining the equations for the diffusion and exchange contributions described previously, $R_{1\rho}=R_{1\rho}^{\mathrm{Diff}}+R_{1\rho}^{\mathrm{Exch}}=\left[\frac{\gamma^2 g^2 D}{(q^2D)^2+\omega_1^2}\right]+\left[\frac{R_2+R_{1\rho}^{\infty}\omega_1^2/S_\rho^2}{1+\omega_1^2/S_\rho^2}\right]$. Here γ is the gyromagnetic ratio, g^2 is the mean squared intrinsic gradient, D is the self-diffusion coefficient, q represents the effective spatial frequency of the susceptibility gradients, ω_1 is the strength of the applied locking field, R_2 is the low locking field limit due to chemical exchange, $R_{1\rho}^{\infty}$ is the high locking field limit due to chemical exchange, and S_ρ^2 is a fitting parameter that is a function of the exchange rate. Appropriate analysis of the $R_{1\rho}$ dispersions thus allows derivation of q, which represents the spatial scale of susceptibility variations. Here we show the feasibility of measuring such intrinsic properties in rat liver. Liver was chosen because there will be a definite fast hydroxyl exchange contribution from glycogen that can be accounted for and, more importantly, a diffusion based dispersion caused by the diffusion of water around the microvasculature in an otherwise relatively homogeneous medium. Each contribution should be quantifiable from a double dispersion fit to the previous equation and the correlation time ($\tau_c = 1/q^2D$) will reflect the mean spatial distribution of the major susceptibility variations inside the region of interest. Tissues with and without a Gd-DTPA injection provide evidence of the effects of selectively altering the extracellular susceptibility.

Methods: Livers were removed from freshly euthanized healthy Sprague Dawley rats, and two other animals were injected with 0.5 mmol/kg Gd-DTPA through a tail vein injection before their livers were removed. The rats that received an injection were kept alive under isoflurane sedation for 10 minutes before being sacrificed to allow the gadolinium to distribute within the liver naturally. All livers were immediately imaged *ex vivo* at 7T using a spin-locking pulse sequence with six locking times from 10-80 ms for each of the 15 logarithmically spaced locking amplitudes ranging from 1-2,000 Hz. The images were analyzed by fitting for the $R_{1\rho}$ value at every voxel assuming a mono-exponential decay and subsequently fitting the $R_{1\rho}$ dispersion profile to the equation above to estimate the correlation times.

Results: The mean rat liver T_1 without GD-DTPA was 1.00 sec while the mean liver T_1 with GD-DTPA was 0.42 sec, confirming the successful injection. The mean correlation time of the low frequency dispersion without Gd-DTPA was τ_c = 14.27 ms compared to τ_c = 14.01 ms with Gd-DTPA, indicating the same size estimation for both conditions. No significant enhancement to the lower frequency dispersion was seen in the dispersion curves in figure 1 since the parameter g^2D did not change significantly, but the curves were instead just shifted by a constant due to the Gd-DTPA injection.

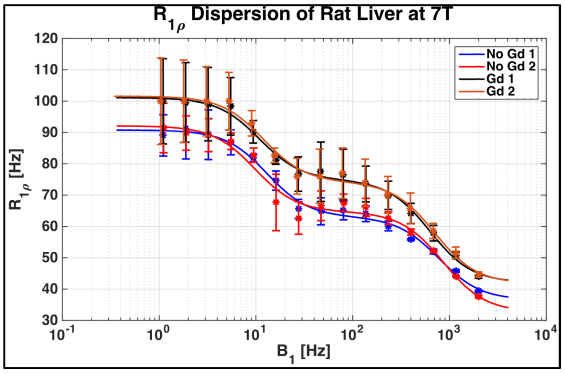

Figure 1: $R_{1\rho}$ dispersion curves for each liver with the corresponding double dispersion fits. The low frequency dispersion is due to diffusion around microvessels.

Discussion: The major source of susceptibility variations in tissue is expected to be hemoglobin in capillaries, and the finding that the Gd-DTPA does not change the low frequency dispersion provides evidence that there is little effect from differences between intra- and extracellular susceptibilities. Assuming D = 2x10^{-5} cm^2/s, a correlation time of 14 ms corresponds to a spacing of 16.6 microns. Our derived value of $g^2D \approx$ 2x10^{-4} G^2/s corresponds to $g \approx$ 3.16 G/cm. Such a gradient across 16.6 microns would be produced by a susceptibility variation of 0.075 ppm at 7T, close to the value (0.08 ppm for a hematocrit of 0.4) of deoxyhemoglobin[3]. Spin-lock methods have the ability to estimate structural dimensions, and the use of low frequency dispersion effects caused by diffusion provides a novel approach for estimating the scales of intrinsic inhomogeneities.

Conclusion: Our preliminary results suggest the low frequency dispersion is caused by susceptibility variations within the microvasculature but further validation is required. Future studies will include measurements on tissues without blood and subject to other manipulations. Tissue vessel density may thus be quantified by using $R_{1\rho}$ dispersions measured with spin-locking sequences, while the use of certain extracellular susceptibility agents may also allow the estimation of cell sizes.

References:

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