Spectral lineshape reflects microscopic structure and ordering

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Introduction: The cellular structure of living tissues is much finer than the achievable resolution of MRI images. Water molecules diffusing through the tissue explore its microstructure, but the observed signal, the sum of all spin contributions, is effectively averaged over macroscopic voxels, so that most of the subvoxel information is lost. The relevant question is which of the structural parameters survive this averaging and can be quantified from the NMR signal. In this work we show for the first time that the NMR spectral lineshape is sensitive to the degree of *structural order* in tissues. That is, the lineshape distinguishes between an ordered and a disordered arrangement of cells with otherwise identical NMR parameters (Fig. A). Our analytical results agree well with Monte Carlo simulations of transverse relaxation in synthetic three-dimensional media.

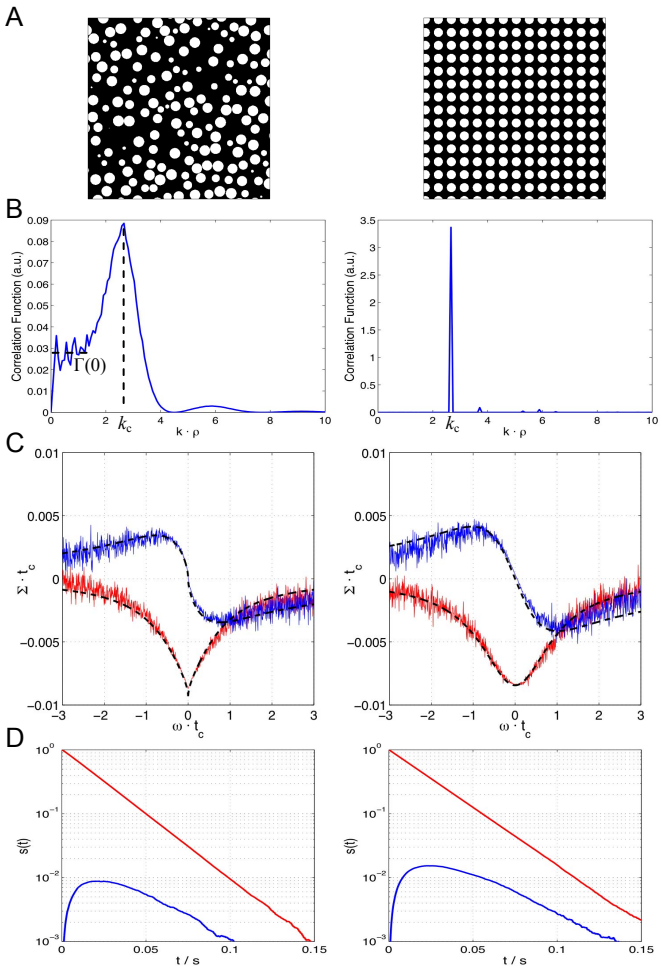
Background: We begin with the Bloch-Torrey equation for the transverse magnetization in the presence of a varying component $\Omega(\mathbf{r})$ of the local Larmor frequency. To obtain the signal $s(t)$ from a macroscopic sample we utilize the recently developed effective medium approach [1,2], which treats the medium statistically, via the correlation functions of the structural parameters. The resulting spectral lineshape $s(\omega)$ is given by equation (1), where $\Sigma(\omega)$ is the so-called *self-energy part* [1,2]. Its dispersion quantifies the complexity of a medium as compared to a uniform liquid.

$$s(\omega) \equiv \int_0^\infty dt\; s(t)\, e^{i\omega t} = \frac{1}{-i\,\omega - \Sigma(\omega)} \quad (1) \qquad \Sigma^{pert}(\omega) = -\int \frac{d^3k}{(2\pi)^3}\, \frac{\Gamma_2(k)}{-i\,\omega + D\,k^2} \quad (2)$$

For media with small Larmor frequency dispersion $\delta\Omega \equiv \sqrt{\langle\Omega^2\rangle}$ we use perturbation theory. The self-energy part up to the second order in field is given by equation (2), where $\Gamma(k) = \langle\Omega(\mathbf{k})\,\Omega(-\mathbf{k})\rangle_{\hat{\mathbf{k}}}$ is the angular-averaged Fourier transform of the two-point correlation function of the Larmor frequency. This correlator is proportional to that of the local susceptibility profile, which embodies the structural architecture [1]. Hence, the effective medium theory relates the spectral lineshape (1) to the tissue structure reflected in the shape of the correlator $\Gamma(k)$.

Results: First, we focus on the qualitative features of the Larmor frequency correlator $\Gamma(k)$, which is shown for the two simulated media (Fig. A) in Fig. B. In both cases, $\Gamma(k)$ exhibits a pronounced peak at $k = k_c$, with k_c inversely proportional to the correlation length of the local Larmor frequency. This peak signifies the *short-ranged order* due to tight packing. The behavior of $\Gamma(k)$ at small k reflects the *long-range structural fluctuations*. For the random medium (left column), there indeed exists a non-zero value (a plateau) $\Gamma(0)$ for small k, in contrast to $\Gamma(0) = 0$ for the ordered (periodic) medium (right column) where the long-range structural fluctuations are absent.

We now argue that the qualitatively different correlator shapes (Fig. B) result in the qualitatively different frequency dependencies of the self-energy part (2). In Fig. C, we show the real part (red) and imaginary part (blue) of $\Sigma(\omega)$ obtained from the Monte Carlo simulated $s(t)$ using equation (1). They agree very well with the corresponding theoretical predictions (black dashed lines) evaluated using the correlators from Fig. B in equation (2), confirming the accuracy of our perturbative treatment. The qualitative difference between the relaxation in these two kinds of media manifests itself at small ω, corresponding to exploring the structural fluctuations over times exceeding the correlation time $t_c = 1/Dk_c^2$ to diffuse across the correlation length. In particular, the dominant contribution to (2) for $\omega \cdot t_c << 1$ originates from small k values, yielding $\Sigma(\omega) - \Sigma(0) \sim \Gamma(0)\cdot(i\omega)^{1/2}$. *The square root singularity in $\Sigma(\omega)$ is a landmark of the structural fluctuations.* This singularity is indeed present in both Re $\Sigma(\omega)$ and Im $\Sigma(\omega)$ (Fig. C, left panel), with the fitted power law exponent 0.52. Conversely, for the periodic case, Re $\Sigma(\omega) \sim \Sigma(0) + C\cdot\omega^2$ is regular, and the curve looks rounded at $\omega = 0$ (Fig. C, right panel). The scale for both $\Sigma(\omega)$ and ω is set by the inverse correlation time $t_c^{-1} = Dk_c^2$ in both random and ordered media.



Simulations: Two three-dimensional media of non-overlapping spheres with radius ρ and the same volume fraction of about 30% were created. In the disordered one, spheres were randomly added ensuring no overlap, while in the ordered one they form a cubic lattice. The cutouts (1/2 of the total length in each direction) are shown in Fig. A. The local Larmor frequency $\Omega(\mathbf{r})$ was computed through a convolution of the local susceptibility profile $\chi(\mathbf{r})$ with an elementary dipole field [3,4]. The NMR signal was obtained from Monte Carlo simulations of $2\cdot10^7$ spins randomly diffusing on a cubic lattice (1024^3 sites) with the dephasing strength $\alpha = \delta\Omega \cdot t_c \approx 0.1$, where $(\delta\Omega)^2$ is the Larmor frequency variance.

Conclusions: The dispersive self-energy part of a spectral lineshape is a qualitative and quantitative measure for tissue heterogeneity. It distinguishes between the different ordering types, not immediately obvious in the simulated signals $s(t)$ (Fig. D: real part in red, imaginary part in blue). Hence, the effective medium approach [1,2] provides a novel way to quantify structural composition of complex samples.

References: [1] D.S. Novikov, V.G. Kiselev, J Magn Reson 195 (2008) 33; [2] D.S. Novikov, V.G. Kiselev, NMR Biomed 23 (2010) 682; [3] V.G. Kiselev, D.S. Novikov, Phys Rev Lett 89 (2002) 278101; [4] J.P. Marques, R. Bowtell, Concepts Magn Reson 25B (2005) 65