Unifying Transverse Relaxation and Diffusion: An Effective Medium Approach

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Introduction: Quantifying tissue properties is a challenging inverse problem: While the MR signal is acquired over a millimeter-size voxel, the relevant physiological information is found on the cell scale of a few μm. The transverse nuclear magnetization $\psi(t,\mathbf{r})$ evolves according to Bloch-Torrey equation

$$\partial\psi(t,\mathbf{r})/\partial t = \left[\nabla D(\mathbf{r})\nabla - R_2(\mathbf{r}) - i\Omega(\mathbf{r})\right]\cdot\psi. \qquad (1)$$

The tissue complexity is embodied in the spatially varying local diffusivity $D(\mathbf{r})$, local relaxation rate $R_2(\mathbf{r})$, and susceptibility-induced local Larmor frequency offset $\Omega(\mathbf{r})$, which follow the intricate geometric structure of cells, intracellular organelles and cell clusters.

Solving the Bloch-Torrey equation (1) is impractical, as its solution depends on an enormous number of parameters describing the tissue structure at a cellular level. Besides, the MR signal from a voxel is effectively averaged over all possible local environments characterized by spatially varying $D(\mathbf{r})$, $R_2(\mathbf{r})$ and $\Omega(\mathbf{r})$. The practical question is, therefore, *What are the geometric tissue features that survive the voxel averaging and, hence, can be quantified by MR measurements?*

Results: To address this question, we develop an effective-medium (EM) framework which yields the voxel-averaged analog of Eq. (1),

$$-i\omega\psi(\omega,\mathbf{q}) = \left[-\overline{D}q^2 - \overline{R_2} - i\overline{\Omega} + \Sigma(\omega,\mathbf{q})\right]\cdot\psi. \qquad (2)$$

The EM approach provides a unified description of the MR signal accounting for both the heterogeneous diffusion and the transverse relaxation, bridging the gap between the diffusion and relaxation measurements and methods.

The voxel-averaged Bloch-Torrey equation (2) is conveniently written in the frequency and wave number representation $\psi(\omega,\mathbf{q}) = \int \mathrm{d}t\mathrm{d}\mathbf{r}\, e^{i\omega t - i\mathbf{q}\mathbf{r}}\psi(t,\mathbf{r})$. Working in the frequency domain is natural since the geometric structure is time-independent, while transforming to the **q**-space is justified since, after voxel-averaging, only the relative molecular displacements remain relevant (translation-invariance implied in DWI).

The voxel-averaged diffusivity $\overline{D} = <D(\mathbf{r})>$, relaxation rate $\overline{R_2} = <R_2(\mathbf{r})>$, and Larmor frequency offset $\overline{\Omega} = <\Omega(\mathbf{r})>$ enter Eq. (2) in an expected way. Keeping only these terms would correspond to the Bloch-Torrey equation in a uniform system.

All the measurable information about tissue heterogeneity is contained in the so-called *self-energy part* $\Sigma(\omega,\mathbf{q})$ (the name historically comes from high-energy and condensed-matter physics, as this quantity modifies the energy-momentum relation $\omega(\mathbf{q})$ due to interaction with environment). This is the main object of the EM approach. This quantity is related to the *correlation functions* of the locally varying characteristics $D(\mathbf{r})$, $R_2(\mathbf{r})$ and $\Omega(\mathbf{r})$. For small deviations $\delta D(\mathbf{r})$, $\delta R_2(\mathbf{r})$ and $\delta\Omega(\mathbf{r})$ from their mean values, the respective contributions to the self-energy part in d spatial dimensions

$$\Sigma(\omega,\mathbf{q}) = \int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\frac{[\mathbf{q}(\mathbf{q}+\mathbf{k})]^2 <\delta D(-\mathbf{k})\delta D(\mathbf{k})>}{-i\omega+\overline{D}(\mathbf{k}+\mathbf{q})^2} + \int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\frac{<\delta R_2(-\mathbf{k})\delta R_2(\mathbf{k})>}{-i\omega+\overline{D}(\mathbf{k}+\mathbf{q})^2} - \int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\frac{<\delta\Omega(-\mathbf{k})\delta\Omega(\mathbf{k})>}{-i\omega+\overline{D}(\mathbf{k}+\mathbf{q})^2}. \qquad (3)$$

Here the respective two-point correlators are $<\delta D(-\mathbf{k})\delta D(\mathbf{k})> \equiv \int \mathrm{d}\mathbf{r}\, e^{i\mathbf{k}\mathbf{r}} <\delta D(\mathbf{r})\delta D(0)>$, where <…> stands for voxel-average, and similarly for $\delta R_2$and $\delta\Omega$. The similarity of the above contributions is due to their common origin, the Bloch-Torrey equation (1). Further contributions to (3) involve multiple-point correlation functions, as well as their cross-correlators. They describe the interference between different types of diffusion and relaxation measurements.

Expansion of $\Sigma(\omega,\mathbf{q})$ in ω and **q** is equivalent to higher-order termporal and spatial derivatives in the voxel-averaged Bloch-Torrey equation (2) arising after averaging over tissue inhomogeneities. Practically, diffusion and relaxation measurements access different terms in the Taylor expansion

$$\Sigma(\omega,\mathbf{q}) = \Sigma(\omega,0) + \Sigma_2(\omega)q^2 + \Sigma_4(\omega)q^4 + \ldots . \qquad (4)$$

In particular, without diffusion weighting, q=0, Eq. (2) describes the non-Lorentzian spectral line shape with a dispersive relaxation rate $-\Sigma(\omega,0)$ [1]. The $O(q^2)$ term yields the dispersive diffusion coefficient [2,3], $D(\omega) = \overline{D} - \Sigma_2(\omega)$. For $\delta R_2 \equiv \delta\Omega \equiv 0$, the quantity $D(\omega)$ is the correlation function of molecular velocity [4], accessible via the oscillating gradients [4,5]. Both the term $\Sigma_4(\omega)$ and the dispersive part of $\Sigma_2(\omega)$ contribute to the time-dependent diffusional kurtosis [2,3]. Higher-order diffusion cumulants originate from subsequent terms in the expansion (4).

Discussion: From Eq. (3) it is evident that tissues are distinguishable by MR measurements as much as their correlation functions differ on the diffusion length scale. The tissue features that stand out after voxel-averaging are the distinct *length scales* on which $D(\mathbf{r})$, $R_2(\mathbf{r})$ and $\Omega(\mathbf{r})$ vary. The length scales correspond to pronounced peaks in the **k**-dependence of the correlators entering integrals in Eq. (3); these peaks determine the ω-dependence of $\Sigma(\omega,\mathbf{q})$ and, hence, can be quantified via time-resolved MR measurements. The effect of relaxation on the DWI is manifest in the expansion in q^2 of the two last terms in (3): they modify $\Sigma_2(\omega)$ and thereby cause the local field-induced deviation of the ADC from its intrinsic value given by the velocity autocorrelation function. Finite $\Sigma(\omega,\mathbf{q})$ is a *quantitative measure of the complexity* at the scale of the diffusion length. Different MR relaxation and diffusion measurements are simply the different means to access $\Sigma(\omega,\mathbf{q})$ or the particular terms in its Taylor expansion (4). Hence, we suggest to analyze the MR measurement results in terms of $\Sigma(\omega,\mathbf{q})$, as it quantifies all measurable differences of a tissue from a uniform medium.

References: [1] D.S. Novikov and V.G. Kiselev, JMR 195(2008)33; [2] D.S. Novikov et al, proc. ISMRM 2009, No. 450; [3] D.S. Novikov and V.G. Kiselev, abstract submitted to ISMRM 2010. [4] J. Stepisnik, Physica 104B(1981)350. [5] M.D. Does et al, MRM 49(2003)206.