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CPMG relaxation rate dispersion in dipole fields around capillaries

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ABSTRACT

Transverse relaxation rates for Carr-Purcell-Meiboom-Gill (CPMG) sequences increase with inter-echo time in presence of microscopic magnetic field inhomogeneities due to nuclear spin diffusion. For a weak field approximation that includes diffusion effects, the CPMG relaxation rate shift for proton diffusion around capillaries in muscle tissue can be expressed in terms of a frequency correlation function and the inter-echo time. The present work provides an analytical expression for the local relaxation rate shift that is dependent on local blood volume fraction, diffusion coefficient, capillary radius, susceptibility difference and inter-echo time. Asymptotic regions of the model are in agreement with previous modeling results of Brooks et al., Luz et al. and Ziener et al. In comparison with simulation data, the model shows an equal or better accuracy than established approximations. Also, model behavior coincides with experimental data for rat heart and skeletal muscle. The present work provides analytical tools to extract sub-voxel information about uniform capillary networks that can be used to study capillary organization or micro-circulatory remodeling.

1. Introduction

Information on density, structure and supply properties of small vessels is useful to study the effects of disease, disease management or aging on myocardial and skeletal muscle tissue. These muscles consist of muscle fiber bundles that are usually arranged in parallel in a highly regular fashion and dense capillarization to facilitate blood oxygen transport during increased muscle activity or adaptation to different environmental demands [1]. Micro-vascular remodeling with a resulting decline in capillary supply has been observed in muscle denervation injury or aging as well as physical inactivity, and serves as an indicator of muscle functionality [2,3]. Likewise, in heart muscle tissue, tracking and evaluating changes in muscle microcirculation that are due to reperfusion injury or (non-)invasive therapeutical procedures are important to assess myocardial viability [4].

Capillaries can be considered as cylindriform vessels that generate a susceptibility difference to the surrounding tissue and, thus, the precession of nuclear spins in these magnetic field inhomogeneities is affected. In magnetic resonance imaging, such micro-structures are usually not possible to spatially resolve due to technical limitations. Uniform ensembles of capillaries, as found in skeletal or cardiac muscle tissue, consist of muscle fiber bundles that are usually arranged in parallel in a regular fashion [1,5,6]. Such micro-vascular networks have already been well-analyzed in theory and experiment for single spin-echo signals [7–9].

Both externally applied and locally generated gradients play an important role when analyzing MR signal formation in biological tissue; for instance, in diffusion-weighted imaging, a linear gradient is applied to whole tissue samples while non-linear gradients are generated by local tissue-inherent susceptibility differences. Dephasing of transverse magnetization based on the corresponding local magnetic field inhomogeneities can be refocused through spin echoes, but refocusing is only partially possible if diffusion effects are not negligible which gave the incentive to develop Carr-Purcell-Meiboom-Gill (CPMG) sequences [10,11]. Yet, local gradients around capillaries for CPMG signals have rarely been investigated: experimental evidence for a dependence of the transverse relaxation rate in CPMG signals on inter-echo time variation in muscle tissue has been provided by Rozenman et al. and Damon et al. for rat cardiac and leg muscle tissue, respectively [12,13]. While Rozenman et al. suggestively stated that transverse relaxation time "[...] T2 might be profoundly dependent on [inter-echo time] τ [...]" [12], relaxation rate dispersion has found multiple applications in NMR spectroscopy, lung imaging and the study of fluids in porous rocks [14–17]. Typically, CPMG relaxation rates follow a sigmoidally shaped curve for exponentially increasing inter-echo times. In muscle tissue, this effect is due to

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proton spin diffusion around capillaries which contain erythrocytes with paramagnetic deoxyhemoglobin and therefore possess a characteristic susceptibility difference to the surrounding tissue [18].

A theoretical description of spin dephasing based on the local susceptibility difference between a (cylindriform) capillary and its surrounding tissue has already been provided for different motion regimes, most notably for the static dephasing regime, i.e. a negligible influence of diffusion effects [19]. The inclusion of diffusion effects for spin dephasing around local field variations was then considered for fast and slow diffusion, respectively (see e.g. [20] for linear local field variations and [21] for the Gaussian phase approximation where the phases of spins for fast diffusion are considered to follow a Gaussian distribution). Thereby, it is possible to link changes of the transverse relaxation rate to changes of the mean radius of the capillaries. Of the currently employed approximations, however, only the strong collision approximation (where the diffusion operator in the problem-defining Bloch-Torrey equation is replaced by a simpler stochastic process) provides an adequate description of the whole dynamic range [22,23]. This has already been shown by Dickson et al., who considered the association of diffusion-dependent relaxation rate and mean radius of the local field inhomogeneity for different approximations in comparison to simulation data (Fig. 6 in [24]): while it should be acknowledged that small radii ($<5\,\mu$m) are arguably best covered by the Gaussian phase approximation, coverage of the whole range of radii is best for the strong collision approximation. This is especially important when dealing with pathological capillary distributions that involve larger vessel calibers.

Another approximation to describe the influence of microscopic magnetic field inhomogeneities on transverse NMR relaxation rate is the weak field approximation proposed by Jensen and Chandra that is valid for weak local susceptibility gradients [25]. This approximation can be used to study capillary arrangements since local resonance frequencies in the perivascular fields are weak compared to those caused by diffusion-mediated translational motion of nuclear spins. These diffusion effects are accounted for by a correlation function whose time evolution is more directly linked to the local magnetic field inhomogeneity than a simple relaxation rate [26,27]. Within the weak field approximation, knowledge of the correlation function allows examining the influence of differences in microstructural parameters, that characterize ensembles of capillaries, on MR signal decay (e.g. regional blood volume, capillary radius and diffusion coefficient).

While a similar study on CPMG signal formation was recently accomplished for spherical objects [28], the present analysis furthers and extends this previous study by using novel analytical expressions [29] in the context of cylindriform vessels that are arranged in parallel, which is generally the case in cardiac and skeletal muscle tissue. Analytical expressions will be provided that determine CPMG relaxation rates through parameters that characterize the capillaries within an MRI voxel. Model results will be compared with the Gaussian phase approximation [30] and the strong collision approximation [7] of single spin-echo signal formation as well as simulation data by Kennan et al. [31]. Furthermore, a generalization of the results to randomly oriented cylinders is compared with established approximations (Gaussian phase approximation, local linear field approximation and strong collision approximation) and simulation data from Dickson et al. [24]. In addition, the model's applicability to experimental data of CPMG relaxation in rat cardiac and skeletal muscle is evaluated.

2. Methods

2.1. Capillary model geometry

Magnetic field inhomogeneities in capillary networks are considered in Krogh's capillary supply model [32]: around each capillary with radius R_C a cylinder with radius R_D is chosen such that the regional blood volume fraction $\eta = R_C^2/R_D^2$ remains constant, see Fig. 1a–c. The rationale of such a "dephasing cylinder" with radius R_D is that diffusion processes with diffusion coefficient D occur in the "dephasing volume" $V = \pi R_C^2 l[\eta^{-1} - 1]$ (see Fig. 1c; l represents the capillary length) between the capillary and the outer cylinder wall. While the capillary wall can be considered to be impermeable for protons that diffuse around them [33], the Krogh model or "single capillary approximation" acknowledges that spin-carrying particles that cross the outer wall (green-dashed trajectory in Fig. 1c) can be thought of as being reflected back into the dephasing cylinder (green solid line in Fig. 1c), see also [34]. Next to MR signal formation in tissues with regular arrangements of capillaries, the Krogh model is extensively used to study capillary oxygen transport, water exchange, drug diffusion, and tumor and lung imaging, see e.g. [35–39] and references therein. Though based on a simplified geometry, most studies involving the Krogh model yield sufficient results to describe experimental data, however, it should be noted that other studies account for limitations of the Krogh cylinder model (e.g. effects of vessel tortuosity, geometrical distortions or permeability variations [40,41]). Application of the Krogh cylinder model is valid for a uniform arrangement of capillaries in a low density approximation $\eta \ll 1$ [42], which is appropriate for capillaries in muscle tissue [7,19].

The susceptibility difference $\Delta\chi$ of a capillary containing deoxygenated blood cells to the surrounding tissue generates a local field inhomogeneity in an external magnetic field B_0. Consequently, the diffusing spins experience a variation in the local Larmor frequency $\omega(\mathbf{r}) = \omega(r,\phi)$, where (r,ϕ) represent polar coordinates, given as

$$\omega(r,\phi) = \delta\omega \frac{R_C^2}{r^2} \cos(2\phi), \tag{1}$$

provided there is no possible restriction of diffusion through, for example, membranes [7]. These assumptions have been shown to coincide with the case of unrestricted diffusion in the same model geometry for small blood volume fractions [26,30]. Furthermore, for the sake of simplicity, the model only considers isotropic diffusion in a plane perpendicular to the capillary axis whereas, naturally, diffusion in muscle tissue is anisotropic [43,44]. The frequency shift on the capillary surface $\delta\omega = \gamma B_0 \Delta\chi \sin^2(\theta)/2$ is linearly related to susceptibility difference $\Delta\chi$ (with tilt angle θ between external magnetic field and capillary axis and gyromagnetic ratio $\gamma = 2.675 \times 10^8\ \mathrm{s^{-1}T^{-1}}$). In principle, by looking at a cross-section perpendicular to the axis direction of the arrangement of parallel capillaries (see Fig. 1 in [8] and Fig. 1b), dephasing volumes around capillaries, that cover the whole space, are given as hexagonal prisms that are aligned as in the cross-section of a face-centered cubic Bravais lattice known from solid state physics. Therefore, there is no residual space in-between dephasing volumina. The hexagonal prisms can then be replaced with cylinders of equal volume; thus, dephasing cylinders of neighboring capillaries slightly overlap and should be considered as mathematical entities rather than actual physiological boundaries. This approach is explained and justified in detail in Refs. [7,34,45] (though, we will also illustrate the influence of general (Fourier) boundary conditions on the relaxation rate in Section 2.3 and the Results section). The contribution of the remaining capillaries has also to be considered as shown in [46], however, for small volume fractions $\eta \lesssim 0.1$, reflecting boundary conditions at the surface of the dephasing cylinder justify their neglection [7].

2.2. Correlation function for restricted diffusion

Diffusion in such a setting can be examined with the help of a frequency auto-correlation function [26]

$$K(t) = \frac{1}{V} \int \mathrm{d}^3\mathbf{r} \int \mathrm{d}^3\mathbf{r}_0 \omega(\mathbf{r}) p(\mathbf{r}, \mathbf{r}_0, t) \omega(\mathbf{r}_0) \tag{2}$$