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Diffusion MRI/NMR at high gradients: Challenges and perspectives

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ABSTRACT

We discuss some challenges and recent advances in understanding the macroscopic signal formation at high non-narrow magnetic field gradients at which both the narrow pulse and the Gaussian phase approximations fail. The transverse magnetization and the resulting signal are fully determined by the spectral properties of the non-selfadjoint Bloch-Torrey operator which incorporates the microstructure of a sample through boundary conditions. Since the spectrum of this operator is known to be discrete for isolated pores, the signal can be decomposed onto the eigenmodes of the operator that yields the stretched-exponential decay at high gradients and long times. Moreover, the eigenmodes are localized near specific boundary points that makes the signal more sensitive to the boundaries and thus opens new ways of probing the microstructure. We argue that this behavior is much more general than earlier believed, and should also be valid for unbounded and multi-compartmental domains. In particular, the signal from the extracellular space is not Gaussian at high gradients, in contrast to the common assumption of standard fitting models.

Sixty years ago, Torrey has formulated the so-called Bloch-Torrey equation that describes the evolution of the transverse magnetization $m(\mathbf{r},t)$ from an initial uniform state after an exciting 90° rf pulse [1]:

$$\frac{\partial}{\partial t}m(\mathbf{r},t) = \left[D\nabla^2 - i\gamma\left(\vec{G}(t)\cdot\vec{r}\right)\right]m(\mathbf{r},t), \quad (1)$$

where D is the diffusion coefficient, ∇^2 the Laplace operator, i the imaginary unit, γ the gyromagnetic ratio, and $\vec{G}(t)$ the time-dependent gradient (that also includes the effect of refocusing rf pulses). The MR signal S at time t is obtained by integrating $m(\mathbf{r},t)$ over a voxel or the whole sample. The microstructure is incorporated *implicitly* through appropriate boundary conditions that describe the behavior of the nuclei at the boundaries (e.g., impenetrable walls, surface relaxation or diffusive exchange between adjacent compartments). From the mathematical point of view, the two major challenges of this linear diffusion equation are the imaginary character of the encoding term (yielding a non-self-adjoint governing operator) and boundary conditions. As a consequence, this equation does not admit simple explicit solutions except for free diffusion (i.e., without microstructure), for which

$$S = S_0\exp(-bD), \quad (2)$$

where S_0 is the reference signal without gradient (that also incorporates T_1 and T_2 relaxation that we excluded from Eq. (1)), and b is related to the gradient $\vec{G}(t)$ [2].

Since the seminal paper by Torrey, numerous theoretical approaches have been developed to relate the microstructure of a studied sample (e.g., a tissue or an oil-bearing rock) to the macroscopic signal and then to infer some structural information about the sample from the measured signal (see Refs. [3,4] and references therein). For instance, in the narrow pulse approximation, the assumption of infinitely narrow gradient pulses allows one to effectively remove the encoding term in Eq. (1) and thus to reduce the problem to pure diffusion. In turn, the Gaussian phase approximation treats the encoding term perturbatively that leads to an appropriate modification of the free diffusion signal in Eq. (2) at weak gradients. While both approximations are successfully used to interpret measured signals in various applications, they remain limited by the underlying assumptions. In particular, there are many experimental evidences of the non-Gaussian signal decay [5–7] that are typically attributed to (i) pore size distribution resulting in a superposition of Gaussian signals, the most famous example being the bi-exponential model for the MR signal from intracellular and extracellular regions; or (ii) exchange between compartments [8]. Overall, most of theoretical works aimed at

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keeping the Gaussian hypothesis at any cost, sometimes in a disguised form [9].

At the same time, the theoretical foundation of the Gaussian hypothesis has been broken 25 years ago by Stoller, Happer and Dyson [10] who provided an exact solution of the Bloch-Torrey equation for two simple one-dimensional configurations: the semi-axis $(0,\infty)$ and an interval $(0,L)$, both with reflecting endpoints. They showed that the macroscopic signal exhibits nontrivial stretched-exponential decay at high non-narrow gradients:

$$\ln(S/S_0) \propto G^{\frac{2}{3}} \propto b^{\frac{1}{3}}. \tag{3}$$

This behavior drastically differs from the conventional Gaussian decay in Eq. (2). Three years later, de Swiet and Sen derived the same asymptotic behavior for impermeable disk and sphere and argued that it should be generic for restricted diffusion in isolated bounded domains [11]. Hürlimann et al. confirmed these theoretical predictions in a pulsed-gradient spin-echo (PGSE) experiment for water diffusion between two parallel plates [12]. The measured signal was shown to decay as Gaussian at small gradients and then to switch to the above stretched-exponential decay at higher gradients. Remarkably, the transition between two regimes occurred at a moderate gradient of 15 mT/m, available at any modern clinical MR scanner. Since these pioneering works, no significant progress has been achieved in understanding the signal formation at high gradients, in spite the fact that very high gradients, up to few T/m, are available nowadays and become more and more often used in experiments to achieve higher sensitivity and selectivity (e.g., b-values up to 40 ms/μm^2, or 40 000 s/mm^2, were used for brain imaging [13]). Such an ignorance to this field from the theoretical MR community can partly be explained by: (i) rather involved, complicated mathematics needed to analyze the Bloch-Torrey equation at high gradients; and (ii) too small signals, often at the noise level, that makes challenging their practical use. Even if the purposeful application of high gradients may still be problematic nowadays (partly because of the lack of an appropriate theory to interpret such measurements), the outcomes of current experiments can be significantly affected by unnoticed, unexplained or misleadingly interpreted deviations from the Gaussian behavior. In this paper, we show that the stretched-exponential decay of the signal is a generic, universal feature of diffusion NMR that can be the origin of the non-Gaussian behavior in many experiments.

For the sake of clarity, we start with the time-independent gradient profile, $\vec{G}(t) = \vec{G}$, whereas the results for spin echoes after rectangular gradient pulses are obtained by combining solutions of the above equation in a standard way (see Ref. [4] for details). In this case, the solution of the Bloch-Torrey Eq. (1) can be formally written as

$$m(\mathbf{r},t) = \exp\left(- \underbrace{\left[-\nabla^2 + igx \right]}_{\text{BT}-\text{operator}} Dt \right) m_0, \tag{4}$$

where $g = \gamma G/D$, m_0 is the initial magnetization, and x is the coordinate along which the gradient is applied. We call the expression in square parentheses the Bloch-Torrey (or BT) operator which englobes the whole complexity of the problem (in particular, the microstructure). The transverse magnetization and the resulting MR signal are thus fully determined by the spectral properties of this non-selfadjoint operator.

For any bounded domain (e.g., an isolated pore), the spectrum of the BT-operator is discrete and bounded from below (it follows from the discrete spectrum of the Laplace operator and boundness of the term igx). As a consequence, the MR signal can be written as a spectral decomposition over eigenmodes of the BT-operator:

$$S = \sum_n A_n(g) \exp(- \lambda_n(g)\, Dt), \tag{5}$$

where $\lambda_n(g)$ are the eigenvalues and $A_n(g)$ are the squared projections of the corresponding eigenfunctions of the BT-operator onto a constant function. This representation, which is similar to the famous Brownstein-Tarr expansion derived for a simpler diffusion problem without gradients [14], is general and valid for any bounded domain, gradient amplitude and time. In particular, the eigenvalue with the smallest real part determines the signal decay at long times. The asymptotic behavior of the eigenvalues $\lambda_n(g)$ at high gradients ($g\to\infty$) was first analyzed for an interval [10] and then for a disk and a sphere [11], all with reflecting boundaries. The obtained leading behavior $\lambda_n(g) \propto g^{\frac{2}{3}}$ implied the stretched-exponential decay in Eq. (3).

More recently, the analysis was extended to multiple intervals with semi-permeable boundaries [15,16] and to arbitrary planar domains [17]. In the former papers, the effect of diffusive exchange between compartments onto the MR signal was investigated (see also [18] for a recent overview and references on this topic). In turn, a general asymptotic construction presented in Ref. [17] extends and improves the earlier result by de Swiet and Sen for bounded domains. It was shown that, for large enough g, the eigenfunctions of the BT-operator are localized near the boundary points $\mathbf{r}_j$ at which the normal vector to the boundary is parallel to the gradient direction. The four-term asymptotic behavior of the corresponding eigenvalues in powers of $g^{\frac{1}{6}}$ was obtained, the leading term $g^{\frac{2}{3}}$ being universal. In turn, boundary curvature, surface relaxation and membrane permeability were shown to affect the sub-leading terms of order $g^{\frac{1}{2}}$ and $g^{\frac{1}{3}}$. The representation (5) can be adapted for a PGSE experiment with rectangular gradient pulses [15,17].

Most importantly, the above asymptotic analysis is local and therefore independent of whether the domain is bounded or not. As a consequence, the localization of eigenfunctions and the asymptotics of eigenvalues as $g\to\infty$ are conjectured to hold for unbounded domains as well. For instance, we conjecture that the Bloch-Torrey operator for the exterior of a disk or a sphere has a discrete spectrum. Although its mathematical proof is still missing, it is strongly supported by numerical results [17]. This is an important statement that may drastically change the current view onto diffusion NMR. In fact, the gradient encoding term, igx, was always considered as a perturbation of the Laplace operator ∇^2, yielding the conventional Gaussian paradigm. This was mathematically justified for isolated pores. In turn, while the Laplace operator has a continuous spectrum for unbounded domains, the inclusion of the term igx, even with arbitrarily small g, is expected to make the spectrum of the BT-operator discrete so that igx cannot be considered as a perturbation anymore. Moreover, the limit $g\to 0$, in which the discrete spectrum should become continuous, turns out to be singular. If former theories relied on the Gaussian signal (2) and considered the stretched-exponential decay (3) as "pathologic", a new theory has to rely on the spectral decomposition (5) as the starting point and then explain how the Gaussian decay is recovered at weak gradients. Such an analysis was already performed for the case of an interval in Ref. [15] but further investigations are necessary for more realistic bounded and unbounded domains.

What does this mathematical discussion change in practice? For instance, all standard models of diffusion NMR signal in brain tissue assumed the extracellular (or extraneuronal) signal to be Gaussian (e.g., see Ref. [19]). To check this assumption, we study hindered diffusion of water molecules in the exterior space of an infinite

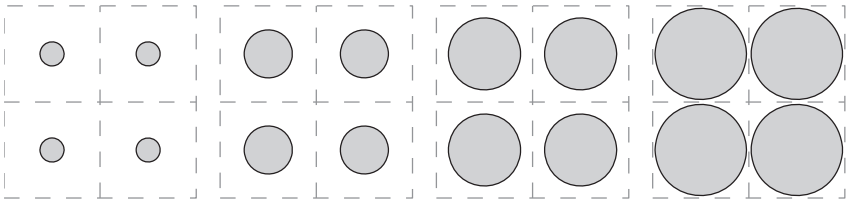

Fig. 1. Hindered diffusion in the exterior (white) space of a periodic arrangment of shadowed circular obstacles (cylinders) of radius R separated by distance $2L$. Four configurations are shown for $L = 20$ μm and $R = 5$ μm, 10 μm, 15 μm, 19 μm. Dashed lines indicate one computational domain which is repeated periodically in both directions. The volume fraction of fluid phase (white region), $1 - \pi R^2/(2L)^2$, is respectively 0.95, 0.80, 0.56 and 0.29.

periodic configuration of impermeable circular obstacles (cylinders) of radius R whose centers form a square lattice with spacing $2L$ (Fig. 1). We solve the Bloch-Torrey equation by a finite elements method [20] and then compute the macroscopic signal for a PGSE experiment with the gradient pulse duration δ and the interpulse time Δ, by setting $\delta = \Delta = 10$ ms, $D = 3$ μm^2/ms, and $\gamma = 2.675 \cdot 10^8$ rad/T/s. Here we vary the gradient G to get a broad range of b-values up to 30 ms/μm^2, with $b = (\gamma G)^2 \delta^2 (\Delta - \delta/3)$. The gradient is applied along the diagonal direction $(1, 1)$.

Figure 2 shows the signal S versus b-value for four choices of the obstacle size R ranging from 5 μm to 19 μm. One can clearly see the non-Gaussian features already at moderate b-values used in brain dMRI. For instance, in the case of large obstacles, deviations from the Gaussian behavior start at b-values of the order of 1 ms/μm^2, while the signal remains measurable (say, above 0.01) even at very large b-values. If these signals were conventionally fitted by a bi-exponential model, the apparent good agreement would lead to false interpretations of the signal behavior and meaningless fitting parameters.

While the simple microstructure of periodic circular obstacles was chosen to facilitate numerical computation, the observed stretched-exponential decay is expected to emerge for *any* nontrivial microstructure which can be two- or three-dimensional, bounded or unbounded, periodic or random, mono- or polydisperse, with obstacles of any shape, and even for multi-compartmental domains with semi-permeable interfaces. The observed localization phenomenon is thus generic and may be relevant for most physical and biomedical diffusion MRI/NMR applications. In particular, the Gaussian assumption of the extracellular signal may not be valid in many practical situations.

Although we presented the signal as a function of b-value for convenience of a broad MRI community, it is important to emphasize that the signal in (5) exhibits different dependences on the gradient parameters: G enters intrinsicly into spectral properties of the BT-operator, δ $(= t)$ stands only in the exponential function, whereas Δ is included through the coefficients A_n. While the universal form of the single b-value incorporating the experimental setup was helpful for the analysis at low b-values, the use of this parameter as a single descriptor of a diffusion NMR experiment is in general misleading. The parameters G, δ and Δ play different roles and affect the signal in distinct ways. While such non-universal dependences are more difficult to analyze and to control, they make the diffusion NMR richer, more sensitive and selective.

We conclude that the stretched-exponential decay of the MR signal at high gradients is not, as commonly believed, a pathological exception from the Gaussian realm but the intrinsic feature of the BT-operator for almost any microstructure. This finding can become a first step towards a new theory of signal formation at high gradients that should replace unconsolidated and sometimes

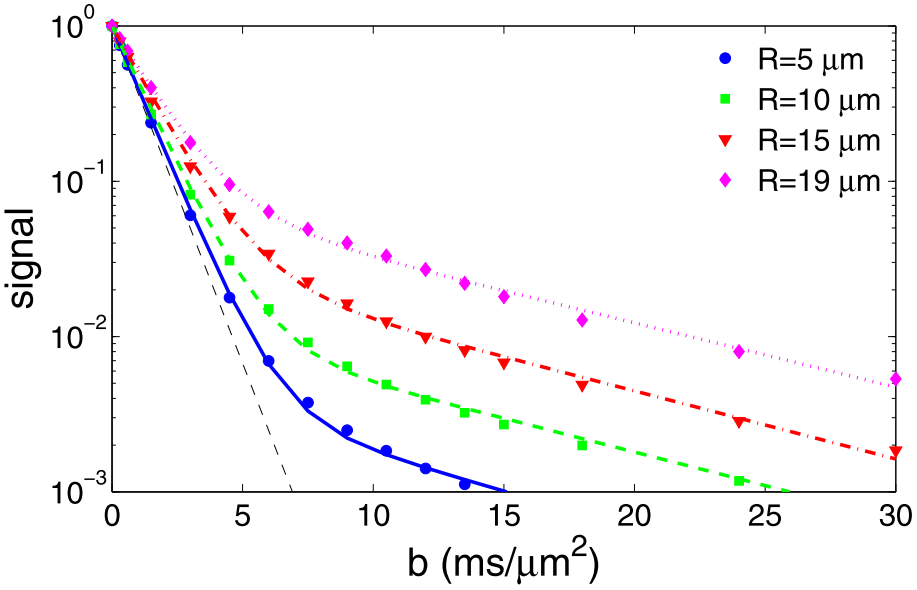

Fig. 2. PGSE signal as a function of b-value for the exterior space of a periodic arrangment of 2D disks of radius R separated by distance $2L = 40$ μm, with $D = 3$ μm^2/ms, $\delta = \Delta = 10$ ms and impermeable boundary. Different symbols correspond to $R = 5$ μm, 10 μm, 15 μm, 19 μm. Lines present bi-exponential fits of simulated signals over the range of b-values up to 10 ms/μm^2. Thin dashed line shows the signal (2) for free diffusion. The accuracy of simulations was validated by doubling the mesh size and checking the smallness of deviations between two cases (not shown).

misleading phenomenological fitting models used to interpret diffusion NMR measurements.

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