Model-free approach to the interpretation of restricted and anisotropic self-diffusion in magnetic resonance of biological tissues

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Magnetic resonance imaging (MRI) is the method of choice for noninvasive studies of micrometer-scale structures in biological tissues via their effects on the time/frequency-dependent ("restricted") and anisotropic self-diffusion of water. Traditional MRI relies on pulsed magnetic field gradients to encode the signal with information about translational motion in the direction of the gradient, which convolves fundamentally different aspects—such as bulk diffusivity, restriction, anisotropy, and flow—into a single effective observable lacking specificity to distinguish between biologically plausible microstructural scenarios. To overcome this limitation, we introduce a formal analogy between measuring rotational correlation functions and interaction tensor anisotropies in nuclear magnetic resonance (NMR) spectroscopy and investigating translational motion in MRI, which we utilize to convert data acquisition and analysis strategies from NMR of rotational dynamics in macromolecules to MRI of diffusion in biological tissues, yielding model-independent quantitative metrics reporting on relevant microstructural properties with unprecedented specificity. Our model-free approach advances the state-of-the-art in microstructural MRI, thereby enabling new applications to complex multi-component tissues prevalent in both tumors and healthy brain.

Subject Areas: Chemical Physics, Medical Physics, Physical Chemistry

I. INTRODUCTION

Nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) offer noninvasive characterization of cellular-level structures in intact biological tissues by employing time-varying magnetic field gradients to monitor the micrometer-scale translational motion of water molecules [1,2] and, by inference, their interactions with cell membranes and macromolecules [3]. While the use of diffusion MRI is in current clinical practice limited to rather basic measurements of diffusion-weighted images and apparent diffusion coefficients [4] to detect and grade ischemic stroke [5] and tumors [6], there is a recent trend of applying increasingly advanced motion-encoding gradients to isolate specific aspects such as diffusion anisotropy [7] and time/frequency-dependence [8], the latter traditionally known as “restricted diffusion” [9,10]. Despite the developments of specific encoding strategies and numerous examples of promising applications in clinical research [11], data analysis and interpretation remain a challenge—in particular for heterogeneous tissues where each imaging voxel contains multiple water populations, or “pools”, with distinct anisotropy and restriction properties [12,13].

The details of translational motion are described with the velocity autocorrelation function [14] and its Fourier transform, the tensor-valued diffusion spectrum $D(\omega)$ [15], which may be interrogated by applying modulated gradients with encoding spectra $h(\omega)$ having peaks at selected frequencies $\omega$ [16]. The $\omega$-dependence of $D(\omega)$ has been derived for simple pore shapes such as parallel planes, cylinders, and spheres [17], as well as for more elaborate geometries including the random permeable membranes model [18]. The experimentally accessible range of $\omega$ is determined by the performance of the gradient hardware and is in practice often limited to the rather narrow ranges 10-50 Hz for clinical and 1-1000 Hz for pre-clinical MRI systems, thus making it difficult to distinguish between different candidate models from the observed $\omega$-dependence alone [19]. The problem becomes even more severe when studying heterogeneous tissues with separate water pools potentially having different $\omega$-dependence.

Related ambiguities occur in NMR relaxation studies of molecular reorientation where multiple, equally plausible, models may be consistent with the experimental observations. In this area, dynamics is quantified with orientation autocorrelation functions, often assumed to be multieponential, and the corresponding spectral densities $J(\omega)$, which are probed by measuring relaxation rate constants determined by the values of $J(\omega)$ at sets of discrete frequencies given by the applied static and radiofrequency magnetic fields and the gyromagnetic ratios of the involved atomic nuclei [20]. In a highly influential paper, Lipari and Szabo introduced a “model-free approach” to convert relaxation rates measured for macromolecules in solution into a few unique dynamics parameters consistent with
more sophisticated models [21]. These ideas were recently
generalized by the concept of dynamics detectors [22–24]
where an approximation of $J(\omega)$ as a nonparametric
distribution of Lorentzians enables conversion of a discrete set
of relaxation observables to the average amplitudes of motion
within specific ranges of rotational diffusion times without
having to invoke an explicit motional model. Independently
of the information about dynamics, resolution of different
atomic sites is in NMR spectroscopy achieved by
multidimensional separation and correlation of chemical
shifts [25], including isotropic-anisotropic correlations in
solid-state NMR [26].

Building on these insights and after identification of
some key formal analogies revealing that both the $\omega$-de-
pendence in relaxation NMR and tensorial aspect in solid-
state NMR are captured in the composite acquisition variable
$b(\omega)$ of diffusion MRI (see methods for details), we
introduce a model-free approach to quantify restricted and
anisotropic diffusion of water in heterogeneous biological
tissues in terms of nonparametric distributions of tensor-
valued Lorentzians. In the limit of low frequencies, these
novel “$D(\omega)$-distributions” are equivalent to the ($\omega$-inde-
pendent) discrete [27] or continuous [28,29] diffusion
tensor distributions that are ubiquitous for analysis of diffusion
anisotropy in heterogeneous brain tissues. Signal encoding
using the principles of isotropic-anisotropic shift corre-
lation in solid-state NMR [30] and data inversion with Monte
Carlo methods from Laplace NMR [31] have recently ena-
bled estimation of nonparametric tensor distributions in
which distinct water pools may be identified as clusters of
components in an analysis space spanned by the isotropic,
anisotropic, and orientation dimensions [32,33]. Here we
augment the previous data acquisition scheme with explo-
ration of the $\omega$-dimension of $b(\omega)$ to allow estimation of
the restriction properties for each of the water pools resolved
in other dimensions.

The potential of the new method is demonstrated on
MRI phantoms with multiple well-defined water pools, ex
vivo rat brain, and excised tissue from a xenograft model of
neuroblastoma [34]. Encouraged by the recent profusion of
in vivo human studies using nearly identical MRI pulse se-
quences to explore either the spectral [35–41] or tensorial
[42–47] aspects of the encoding, we envision that the uni-
fication of the traditionally separate encoding strategies into
a common framework, enabled by our model-free approach
to data analysis, will catalyze the design of more informa-
tive and time-efficient data acquisition protocols for clini-
ical research studies of tissue microstructure in health and
disease.

II. RESULTS

The principles for using time-varying magnetic field
generators $g(t)$ to investigate tensor-valued diffusion spectra
$D(\omega)$ are illustrated in Fig. 1. For a closed compartment, the
$\omega$-dependence of each of the eigenvalues of $D(\omega)$ can be
written as a sum of Lorentzians with varying widths and
amplitudes [17] (see methods for details). The gradients de-
fine an encoding spectrum $b(\omega)$ which determines the sig-
nal attenuation via the integral of the generalized scalar
product $b(\omega)\cdot D(\omega)$ over $\omega$, implying that $D(\omega)$ can be re-
constructed from a series of measurement in which the fre-
quency content of $b(\omega)$ is varied [48]. Resolution of water
populations with distinct $D(\omega)$ requires measurements with
varying anisotropy of $b(\omega)$ [7,32]—preferably at each value of
$\omega$. Ideal measurements would be performed with
$b(\omega)$ having varying anisotropy and being finite at only a
single frequency, thus allowing $D(\omega)$ to mapped out fre-
quency by frequency. In practice, $b(\omega)$ invariably com-
prises a range of frequencies as illustrated in Fig. 1. Grad-
ient waveforms derived from the analogy between sample
spinning in solid-state NMR and $q$-vector trajectories in
diffusion NMR [49], in this specific case the double rota-
tion technique [50,51], allow generation of encoding spec-
tra $b(\omega)$ with reasonably narrow spectral content in multi-
ple dimensions. Similarly to the widely used cos-modulated
oscillating gradients [52], the characteristic frequencies are
adjustable by the number of gradient amplitude periods
within the duration of the waveform. Despite having more
well-defined spectral content than earlier incarnations of
tensor-valued encoding [53], the spread over frequencies

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**Fig. 1.** Principles for $b(\omega)$-encoding of the magnetic resonance
signal with information about restricted and anisotropic diffusion.
(a) Tensor-valued diffusion spectrum $D(\omega)$ for a liquid with bulk
diffusivity $D_b = 2 \times 10^{-9}$ m$^2$s$^{-1}$ confined in a cylindrical
compartment with radius $r = 3$ $\mu$m and orientation in the lab frame
given by the polar and azimuthal angles $\theta = –30^\circ$ and $\phi = 20^\circ$
(see Eqs. (20)-(25) in methods). Color coding of the elements $D_{ijkl}(\omega)$
is given in the legend to the right. (b) Tensor-valued encoding spec-
trum $b(\omega)$ corresponding to the time-dependent gradient vector
g(t) shown in the inset to the left. The relations between the Car-
tesian components $g(i\ell)$ and elements $b_{ijkl}(\omega)$ are given in the
equations to the right, where $\gamma$ is the gyromagnetic ratio, $q(\omega)$ is
the time-dependent dephasing vector, and $\text{FT}[*]$ denotes a Fourier
transformation. (c) Generalized scalar product $b(\omega)\cdot D(\omega)$, which
upon integration over frequencies $\omega$ gives the attenuation factor $\beta$
and signal according to the equations to the right.
Fig. 2. Comprehensive acquisition scheme and experimental results for b(ω)-encoded diffusion MRI. (a) Magnitude b, centroid frequency ω₀cent, normalized anisotropy bₙ, and orientation (Θ,Φ) of the tensor-valued encoding spectrum b(ω) vs. the acquisition number n_{acq} with maximum value 2880. Diffusion encoding was performed with pairs of gradient waveforms of the type shown in Fig. 1 with 25 ms duration and 3 Tm⁻¹ maximum amplitude. (b) Experimental data (circles: measured, points: back-calculated from the D(ω)-distributions) obtained at 11.7 T on a yeast cell sediment and a composite phantom comprising an assembly of glass tubes with pure water, an aqueous solution saturated with magnesium nitrate (brine), and a lamellar liquid crystal of water, sodium decanoate, and decanol. Monte Carlo inversions of the b(ω)-encoded signals yield D(ω)-distributions shown in the panels to the right as projections onto the 2D plane and 1D axes of the isotropic diffusivity D_{iso} and squared normalized anisotropy D_{b} for five values of ω (indicated with linear gray scale of contour lines). The intracellular water in the yeast is restricted (ω-dependent) while the four other water pools are Gaussian (ω-independent) within the investigated range of ω2π from 20 to 260 Hz.

means that each individual measurement contains entangled information on restriction and anisotropy.

As a solution to this problem, we here propose to estimate nonparametric D(ω)-distributions by global inversion of data acquired as a function b(ω) with varying magnitude b, spectral content summarized by the centroid frequency ω₀cent [36], normalized anisotropy bₙ [54], and orientation (Θ,Φ) (see Eqs. (4)-(8) in methods). The requirement of acquiring data at unique values of ω may be relaxed by sampling a range of spectral contents and invoking physically reasonable constraints on the components of the D(ω)-distributions—here by assuming that the ω-dependence of tensor eigenvalues is Lorentzian and the tensor shapes are axisymmetric [54] (see methods for justification of the assumptions). Under these constraints, each component of the distribution is described by its weight A, low-ω axial and radial diffusivities Dₐ and Dₙ, polar and azimuthal angles θ and φ, high-ω isotropic diffusivity D_{iso} and axial and radial transition rates Γₐ and Γₙ. The b(ω)-encoded signal for a...
The new approach may be recognized as an exponential velocity autocorrelation function corresponding to exponential velocity autocorrelation function.

\[ \text{The measured data. For } b \text{-values up to } 3.6 \times 10^3 \text{ sm}^{-2} \text{ and } \Delta t_{\text{m}} = 2\pi \text{ from 53 to 160 Hz. The results for the individual voxels at } \omega 2\pi = 53 \text{ Hz guide the division of the 2D } D_{\text{iso}}-D_{\text{an}}^2 \text{ projection into three bins—nominally specific for white matter, gray matter, and phosphate buffered saline—for the purpose of image segmentation by coding the per-bin signal fractions } f_{\text{bin1}}, f_{\text{bin2}}, \text{ and } f_{\text{bin3}} \text{ into RGB color and extraction of bin-specific diffusion metrics.} \]

\[ \text{The voxels from the granule cell layer in the dentate gyrus and white matter show the hallmarks of restriction ( } \omega \text{-dependence} \text{ and anisotropy } (D_{\text{an}}^2 \equiv 1) \text{, respectively.} \]

\[ \text{Fig. 3. } D(\omega) \text{-distributions for selected voxels in } ex \text{ vivo rat brain. The figures show } b(\omega) \text{-encoded signals and corresponding } D(\omega) \text{-distributions for the four voxels indicated with crosses in the } T_2 \text{-weighted image } S_0. \text{ The acquisition scheme is a 312-point abbreviated version of the 2880-point comprehensive one in Fig. 2 and limited to the range of } b \text{-values up to } 3.6 \times 10^3 \text{ sm}^{-2} \text{ and } \Delta t_{\text{m}} = 2\pi \text{ from 53 to 160 Hz.} \]

\[ \text{Through exponential velocity autocorrelation functions [48] with decay rate } \Gamma, \text{ Following earlier works [55], Monte Carlo inversion [31] is used to estimate ensembles of distributions consistent with the measured data. For visualization, the } D(\omega) \text{-distributions in the primary analysis space } [D_\alpha, D_B, \theta, \phi, D, \rho, \Gamma, \Gamma_B] \text{ are evaluated at selected values of } \omega, \text{ giving } [D_\alpha(\omega), D_B(\omega), \theta, \phi], \text{ and projected onto the dimensions of isotropic diffusivity } D_{\text{iso}}(\omega) \text{ and squared normalized anisotropy } D_\alpha(\omega)^2 \text{ [56], as well as the lab-frame diagonal values } D_\alpha(\omega), D_B(\omega), \text{ and } D_B(\omega). \text{ Although the } D(\omega) \text{-distributions are defined for all values of } \omega, \text{ only the rather modest range between the minimum and maximum values of } \omega_{\text{meas}} \text{ have been properly investigated in the encoding process and are meaningful to interpret.} \]

\[ \text{For generating parameter maps, the rich information in the } D(\omega) \text{-distributions is condensed into means } E[x], \text{ variances } V[x], \text{ and covariances } C[x,y] \text{ over relevant dimensions and subdivisions (“bins”) of the distribution space [33].} \]
The dependence on value of pure water yeast cell sediment investigated Fig.

Experimental demonstration of the approach is given in Fig. 4, the signal parameters derived from the per-bin fractions of bins in the 2D distribution. The yeast sample comprises three isotropic ($D_x^2 = 0$) pools, one Gaussian ($\omega$-independent) and one restricted ($\omega$-dependent) originating from, respectively, the extra- and intracellular spaces separated by the virtually impermeable plasma membranes [61]. The composite phantom yields three Gaussian pools, one of which being anisotropic with a value $D_x^2 = 0.25$ consistent with the essentially two-dimensional diffusion of water confined to the nanometer-scale.
gaps between the planar detergent bilayers in a lamellar liquid crystal [62]. With values of $\omega_{\text{rad}}/2\pi$ on the scale of $10^9$ Hz, it would be possible to observe effects of restricted diffusion across these gaps. Correspondingly, values of $\omega_{\text{rad}}/2\pi$ approaching $10^{12}$ Hz would allow investigating the regime of ballistic motion of the individual water molecules [63]. These high-$\omega$ regimes are however far beyond the range accessible with MRI methods based on magnetic field gradients.

Fig. 3 shows data for a few representative voxels in an ex vivo rat brain. The $\mathbf{D}(\omega)$-distributions for voxels in pure white matter (WM), gray matter (GM), and phosphate buffered saline (PBS) in the ventricles are qualitatively consistent with earlier in vivo mouse results [64] (WM: low $D_{\text{iso}}$ and high $D_{\text{iso}}$, GM: low $D_{\text{iso}}$ and low $D_{\text{iso}}$, and PBS: high $D_{\text{iso}}$ and low $D_{\text{iso}}$) with only barely detectable $\omega$-dependence in the investigated range from 53 to 160 Hz. The voxel in the granule cell layer in the dentate gyrus gives a $\mathbf{D}(\omega)$-distribution resembling the one from GM, but with more pronounced $\omega$-dependence in agreement with earlier observations using oscillating gradient encoding [65]. The $\omega$-dependence is consistent with granule cell dimensions on the 10 $\mu$m scale as seen in histology [66]. The $\mathbf{D}(\omega)$-distributions for WM, GM, and PBS guide the definition of three bins in the 2D $D_{\text{iso}}$-$D_{\text{iso}}$ projection to generate maps of nominally tissue type-specific per-bin signal fractions and diffusion metrics. Fig. 4 compiles maps of per-voxel and bin-resolved statistical descriptors $E[D_{\text{iso}}]$, $E[D_{\text{iso}}]$, $V[D_{\text{iso}}]$, $V[D_{\text{iso}}]$, and $C[D_{\text{iso}}, D_{\text{iso}}]$, typically associated with tensor-valued encoding [11,33], and rates of change of the diffusion metrics with frequency, for instance $\Delta_{\omega_{\text{rad}}} E[D_{\text{iso}}]$ often used to display results from oscillating gradient encoding.

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Fig. 5 Parameter maps for part of an excised tumor immersed in aqueous formaldehyde solution. See caption of Fig. 4 for detailed explanation of the panels. The acquisition scheme is a 480-point abbreviated version of the 2880-point comprehensive one in Fig. 2 and limited to the range $\omega_{\text{rad}}/2\pi$ from 44 to 140 Hz using $b$-values up to $11 \cdot 10^5$ $\text{sm}^{-2}$. The arrows in panels (c) and (e) show tumor areas with pronounced effects of restricted diffusion.
as well as novel metrics correlating information about restriction and anisotropy. Of special note in this latter category is the separation of high- and low-D_2 values, each being approximated as a sum of exponentials that, via Fourier transformation, gives spectral densities as a sum of Lorentzians. The mathematical convenience of this latter functional form, combined with its excellent ability to fit experimental data, has made it the point of departure in most contemporary works on rotational dynamics and NMR relaxation.

While many studies still discuss whether two, three, or a continuous distribution of Lorentzian components are required to fit the experimental data, the latest key development is the dynamics detectors [22-24] that have enabled extraction of information about the total amplitudes of motion within a few broad and partially overlapping ranges of correlation times. Despite yielding information on a coarser scale than traditional approaches, the responses of the dynamics detectors are independent of the exact details of the underlying distributions and are, consequently, less conducive to overinterpretation. These lessons from NMR relaxation are closely mirrored in our proposed approach with tensor-valued Lorentzian D(\omega)-components, ensembles of nonparametric D(\omega)-distribution estimated from the signal data via Monte Carlo inversion, and, finally, extraction of coarser-level projections and quantitative metrics that report on the relevant properties without providing ambiguous details that are not necessarily required by the input data.

With the comprehensive 2880-point acquisition scheme in Fig. 2, the presence of restriction and anisotropy can be deduced by simple visual inspection of the signal intensities as a function of the acquisition variables — especially D_2 and b, for a given value of b — and quantified from the 2D D_2-D_2 projections of the obtained D(\omega)-distributions. Ad-
mindedly, the data in Fig. 2 were acquired under exceptionally favorable circumstances, using 3 Tm⁻¹ gradient hardware and samples with sufficiently large values of the transverse relaxation time $T_2$ to allow for in total 0.050 s of diffusion-encoding gradients and the broad range 20-260 Hz of $\omega_{\text{enc}}/2\pi$ even at the highest $b$-value 6.4·10⁶ sm⁻². Conversely, the data in Fig. 3 to Fig. 5 represent more realistic conditions with short-$T_2$ fixed tissues and abbreviated acquisition schemes comprising only 312 or 480 data points over the limited ranges 53-160 or 44-140 Hz. Despite these limitations, the data in Fig. 4 reproduce earlier findings on both restrictions [65] and anisotropy [64] in rodent brain, as well as bring novel information on the correlations between the properties. The number of acquisitions is comparable to the 10-min and 300-point schemes used in early clinical implementations of tensor-valued encoding for studies of brain tumors [70], later to be truncated and optimized for 3-min measurements consistent with applications in clinical practice [44], thus indicating the potential for implementation of our proposed method for both clinical and pre-clinical research studies—initially maybe by simply interleaving the very latest protocols for oscillating gradient [36] and tensor-valued encoding [47] using identical pulse sequences and imaging settings.

### IV. CONCLUSION

In this work, we have taken a crucial step towards model-free investigations of restriction and anisotropy in heterogeneous biological tissues, having potentially far-reaching implications for our understanding of microstructural changes associated with pathology or normal brain development. Importantly, our identification of formal analogies between relaxation and solid-state NMR of rotational dynamics in macromolecules and diffusion MRI of translational motion in biological tissues enabled adaption of existing NMR data acquisition and analysis strategies to the context of microstructural MRI. Through measurements on phantoms, ex vivo rat brain, and excised tissue from a mouse model of human neuroblastoma, we demonstrated that our proposed model-free approach is sufficiently flexible to capture the signal modulations for extreme cases of restriction and anisotropy over exhaustive ranges of acquisition variables, while still being robust enough to give quantitative parameter maps reporting on relevant microstructural properties using abbreviated measurement protocols compatible with clinical research studies.

### V. METHODS

#### A. Experimental

MRI phantoms with well-defined diffusion properties were assembled from NMR tubes with yeast cell sediment, salt solution, lamellar liquid crystal, and water. Magnesium nitrate hexahydrate, cobalt nitrate hexahydrate, and 1-decanol were purchased from Sigma-Aldrich Sweden AB, sodium octanoate from J&K Scientific via Th. Geyer in Sweden, and fresh baker’s yeast (trade name: Kronjäst) at a local supermarket. Unless otherwise stated, water was purified with a Millipore-Q system. The yeast sample was prepared by dispersing a block of yeast in an equal amount of tap water, transferring 1 mL of the cell suspension to a 5 mm NMR tube, and allowing the cells to sediment under the action of gravity at 4 °C overnight [57]. To remove water-soluble nutrients and metabolites contributing to water $T_2$-relaxation via proton chemical exchange, the cells in the tube were washed by three cycles of removing the supernatant with a syringe, adding 2 mL tap water, resuspending by vigorous shaking, and renewed sedimentation at 4 °C. The aqueous salt solution comprised saturated magnesium nitrate [59] doped with cobalt(II) nitrate to reach $T_2$ of about 100 ms. The lamellar liquid crystal was prepared from 85.79 wt% water, 9.17 wt% 1-decanol, and 5.04 wt% sodium octanoate [60]. A composite phantom was assembled by inserting 4 mm NMR tubes with salt solution and liquid crystal into a 10 mm NMR tube with water.

Experiment on ex vivo rat brain were approved by the Animal Committee of the Provincial Government of Southern Finland in accordance with the European Union Directives 2010/63/EU. A healthy adult rat Sprague-Dawley was transcardially perfused with 0.9% saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH = 7.4). After extraction, the brain was sagittally sectioned along the brain midline and placed in a solution of phosphate buffered saline 0.1 M and gadoteric acid 50 µl/10 mL (Dotarem 279.3 mg/mL; Guerbet, France) for 24 h. During
MRI measurements, the brain was immersed in perfluoropolyether (Galden; TMC Industries, USA) within a 10 mm NMR tube.

Human neuroblastoma cells were cultured at 37º C and 5% CO₂ in complete medium (RPMI 1640 supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin). A female BALB/c mouse (Janvier Labs, France) was s.c. inoculated with 2 × 10⁶ tumor cells [34]. After ca. 5 weeks the mouse was sacrificed, the tumor was removed and immediately transferred to a 10 mm NMR tube containing 4% formaldehyde in phosphate buffer solution (Histolab, Sweden). The sample was stored at room temperature for 1 day before being investigated with MRI.

MRI measurements were performed on three different Bruker spectrometers (Karlsruhe, Germany) equipped with MIC-5 probes giving up to 3 Tm⁻¹ gradients on-axis. Diffusion encoding employed pairs of variable-angle spinning [30,62] or double rotation [50,51] gradient waveforms bracketing the 180° pulse in a spin echo sequence [71]. Numerical calculation of b(ω) included all diffusion and imaging gradients between the centers of the excitation pulse and the spin echo. Additional acquisition and processing parameters are compiled in Table 1. Reconstructed images were exported to NITTI format for further analysis with the md-dmri toolbox [72] in Matlab using custom code based on the novel theory explained in detail below.

B. Theoretical background

1. Tensor-valued encoding spectrum b(ω)

Within the Gaussian approximation in the cumulant expansion [15,17,48], the diffusion encoding properties are summarized by the tensor-valued encoding spectrum b(ω), which is given by the time-dependent magnetic field gradient vector g(t) via

\[ q(t) = \gamma \int_0^t g(t') dt'. \]  

(1)

\[ q(\omega) = \int_0^\tau q(t) \exp(i\omega t) dt, \]  

(2)

and

\[ b(\omega) = \frac{1}{2\pi} q(\omega) q(-\omega)^T. \]  

(3)

In the equations above, γ is the gyromagnetic ratio of the studied atomic nucleus, τ is the overall duration of the motion-encoding gradients, q(t) is the time-dependent dephasing vector subject to the echo condition q(t) \| 0, q(0) is the frequency-domain spectrum of the dephasing vector, and T denotes a matrix transpose. While the full ω-dependent and tensorial representation of b(ω) is used in our data processing, we find it instructive to summarize its most important aspects using the magnitude b [68,69], centroid frequency \( \omega_{\text{cent}} \) [36], and normalized anisotropy bₐ [54]. These variables are defined through the equations

\[ b(\omega) = \text{trace}(b(\omega)), \]  

(4)

\[ \omega_{\text{cent}} = \frac{\int_{-\infty}^{\infty} |b(\omega)| d\omega}{\int_{-\infty}^{\infty} b(\omega) d\omega}. \]  

(5)

\[ b = \int_{-\infty}^{\infty} b(\omega) d\omega, \]  

(6)

\[ b = \text{trace}(b) = \int_{-\infty}^{\infty} b(\omega) d\omega, \]  

(7)

and

\[ b_\Delta = \frac{b_A - b_R}{b_A + 2b_R}. \]  

(8)

In Eq. (6), b is the conventional (ω-independent) b-matrix [68] with axial and radial eigenvalues bₐ and b₉ and main symmetry axis orientation given by the angles Θ and Φ [54].

For a sub-ensemble of spins where the effects of restriction and anisotropy are described with the velocity autocorrelation function \( \langle v(t)v(t')^\top \rangle \) and its Fourier transform, the diffusion spectrum D(ω), the signal S at the time t = τ is given by

\[ S = S_0 \exp(-\beta), \]  

(9)

where \( S_0 \) is the signal at vanishing gradient amplitude and \( \beta \) is the attenuation factor. To prepare for comparisons with the corresponding equations in relaxation and solid-state NMR, the factor \( \beta \) is expressed in several equivalent ways that are all familiar from the literature [1,2,48]:

\[ \beta = \int_0^\tau \int_0^\tau q(t')^\top \cdot \langle v(t)v(t')^\top \rangle \cdot q(t') dt' dt', \]  

(10)

\[ \beta = \frac{1}{2\pi} \int_{-\infty}^{\infty} q(\omega)^\top \cdot D(\omega) \cdot q(-\omega) d\omega, \]  

(11)

and

\[ \beta = \int_{-\infty}^{\infty} b(\omega) \cdot D(\omega) d\omega, \]  

(12)

where the colon denotes a generalized scalar product [69]

\[ b(\omega) \cdot D(\omega) = \sum_{ij} \sum_{ij} b_{ij}(\omega) D_{ij}(\omega). \]  

(13)

At each time t or frequency ω, all of \( \langle v(t)v(t')^\top \rangle \), b(ω), and D(ω) are 3 × 3 symmetric positive-definite matrices with elements \( ij \in x,y,z \), while g(t), q(t), q(ω), and v(t) are 3 × 1 column vectors with elements \( i \in x,y,z \).

2. Formal analogies between relaxation and solid-state NMR and diffusion MRI

The formal analogies with relaxation and solid-state NMR become more apparent when focusing on the special
cases of either isotropic restricted (\(\omega\)-dependent) or anisotropic Gaussian (\(\omega\)-independent) motion. In the first case, Eqs. (10) and (12) may be written as

\[
\beta = \int_0^\tau \int_0^\tau q(t)\langle v(t)v(t')\rangle q(t')dt
dt' \quad (14)
\]

and

\[
\beta = \int_{-\infty}^{\infty} b(\omega)D(\omega)d\omega, \quad (15)
\]

respectively, where \(q(t)\) is the magnitude of \(q(t)\) and \(D(\omega)\) is 1/3 of the trace of \(D(\omega)\). Eq. (14) can be recognized as the spin-echo version of the famous Anderson-Weiss model [73] which has been valuable for predicting signal attenuation resulting from molecular reorientation on the time-scales of magic-angle spinning and dipolar recoupling [74]. Here, \(\langle v(t)v(t')\rangle\) corresponds to the Anderson-Weiss memory function, closely related to the rotational correlation function in the Lipari-Szabo model-free approach [21], and \(q(t)\) is analogous to the function describing the measurement conditions in terms of the timings of radiofrequency pulses and sample spinning. In Eq. (15), \(D(\omega)\) takes the role of the spectral density \(J(\omega)\), being the Fourier transform of the rotational correlation function, and \(b(\omega)\) resembles the set of delta-functions at the frequencies relevant for longitudinal, transverse, or rotating frame relaxation [20].

While relaxation NMR explores the time/frequency-dependence of the rotational correlation function and spectral density by varying the main and radiofrequency magnetic fields, as well as the sample spinning and radiofrequency pulse repetition rates, diffusion MRI relies on spectrally modulated magnetic field gradients [16].

For the anisotropic Gaussian case, Eq. (10) yields [49]

\[
\beta = \int_0^\tau q(t)^2\left( n(t)^T \cdot D \cdot n(t) \right) dt, \quad (16)
\]

where \(n(t)\) is the unit vector of \(q(t)\) and \(D\) is the plateau value of \(D(\omega)\) at frequencies much lower than any of the characteristic decay rates in \(\langle v(t)v(t')\rangle\). Comparison with the solid-state NMR equation for the signal evolution during sample reorientation [26] reveals that \(q(t)^2\) and \(n(t)\) correspond to the magnitude and direction of the main magnetic field \(B_0\) in the sample-fixed frame, while \(D\) is analogous to the second order tensors describing, for instance, chemical shielding or dipolar couplings. The separation and correlation of the isotropic and anisotropic tensor properties achieved by sample reorientation and radiofrequency pulse sequences in multidimensional solid-state NMR can in diffusion MRI be mimicked by the trajectory of the vector \(q(t)\) [32].

We emphasize that all of the cases in Eqs. (14)-(16) are just different manifestations of the more general expression in Eq. (12). Consequently, although Eqs. (10) and (11) are by far more common in the diffusion literature [1,2], we here favor Eq. (12) for its remarkable versatility, covering both frequency-dependence, corresponding to relaxation NMR, and tensorial aspects, analogous to solid-state NMR, in a surprisingly compact equation that is easily discretized and implemented in data processing code.

3. \(D(\omega)\)-distributions and the Lorentzian approximation

For a heterogeneous system comprising multiple subensembles with probability given by the distribution \(P[D(\omega)]\), Eq. (9) is here generalized to

\[
S[b(\omega)] = S_0 \int P[D(\omega)]\exp(-\beta)dD(\omega) \quad (17)
\]

where \(\beta\) is given by the integral of \(b(\omega);D(\omega)\) over \(\omega\) according to Eq. (12). For the case of Gaussian (\(\omega\)-independent) diffusion, Eq. (17) reduces to

\[
S(b) = S_0 \int P(D)\exp(-b;D)dD, \quad (18)
\]

where \(P(D)\) the diffusion tensor distribution that is ubiquitous in diffusion MRI in discrete [27] or continuous [28,29] forms. Here, we set out to characterize restricted and anisotropic diffusion in heterogeneous materials through the function \(P[D(\omega)]\)—the “distribution of tensor-valued diffusion spectra” or, for short, the “\(D(\omega)\)-distribution”—by acquiring signals as a function of \(b(\omega)\) and inverting the integral transform in Eq. (17).

To make the data inversion tractable, we make the ansatz that, for each sub-ensemble, \(D(\omega)\) is axially symmetric with frequency-dependent axial and radial eigenvalues, \(D_a(\omega)\) and \(D_r(\omega)\), described with Lorentzian transitions between the zero-frequency values, \(D_a\) and \(D_r\), and the common high-frequency plateau, \(D_a\), according to

\[
D_{AR}(\omega) = D_a - \frac{D_0 - D_{AR}}{1 + \omega^2/\Gamma_{AR}^2}, \quad (19)
\]

where \(\Gamma_a\) and \(\Gamma_r\) are the frequencies at the centers of the transitions. In the lab frame, \(D(\omega)\) is given by

\[
D(\omega) = R(\theta,\phi) \cdot D_{PAS}(\omega) \cdot R^{-1}(\theta,\phi), \quad (20)
\]

where \(\theta\) and \(\phi\) are polar and azimuthal angles, \(R(\theta,\phi)\) is a rotation matrix, and

\[
D_{PAS}(\omega) = \begin{pmatrix} D_a(\omega) & 0 & 0 \\ 0 & D_0(\omega) & 0 \\ 0 & 0 & D_r(\omega) \end{pmatrix}, \quad (21)
\]

is the diffusion spectrum in its principal axis system (PAS). With this approximation, each discrete component in the \(D(\omega)\)-distribution can be described with its statistical weight \(w\) and the parameter set \([D_a, D_r, \theta, \phi, D_0, \Gamma_a, \Gamma_r]\).

The functional form of Eq. (19) can be justified by comparison with the corresponding multi-Lorentzian expression for a liquid undergoing restricted diffusion along the principal axes of planar, cylindrical, and spherical compartments [17,48]:

\[
D(\omega) = \frac{D_0}{1 + \omega^2/\Gamma_a^2} - \sum_k \omega^2 \frac{D_0 - D_{\omega_k}}{1 + \omega^2/\Gamma_k^2}, \quad (22)
\]

This version of the well-known equation includes effects of the molecular-level transition from ballistic to diffusive motion via the decay rate \(\Gamma\) of the assumedly exponential velocity autocorrelation function [14], as well as the compartment-level transition between the bulk and long-range
diffusivities $D_0$ and $D_*$, the latter taking the finite permeability of the compartment walls into account [75]. The transition is determined by the weights $w_i$ and Lorentzian widths $\Gamma_i$ given by

$$w_k = \frac{2}{\zeta_k^2 + 1 - d}$$

and

$$\Gamma_k = \frac{\zeta_k^2 D_0}{r^2},$$

where $d = 1, 2, \text{and } 3$ for, respectively, the planar, cylindrical, and spherical cases, $r$ is the compartment radius, $\zeta_i$ is the $k$th solution of

$$\zeta J_{d/2-1}(\zeta) - (d - 1) J_{d/2}(\zeta) = 0,$$

and $J_r$ is the $r$th order Bessel function of the first kind. The sum in Eq. (22) is dominated by the first term and the sum of all $w_i$ equals unity, indicating that the multi-Lorentzian expression can be approximated with a single Lorentzian as in Eq. (19). Computer simulations of water at 298 K show that simple exponential autocorrelation is a rather crude approximation [63], but for the purpose of this paper it is sufficient to note that $\Gamma_0$ is on the order of $10^{13} \text{s}^{-1}$ and, within the regime accessible with NMR methods based on magnetic field gradients, the first term of Eq. (22) can be approximated with $D_0$ as in Eq. (19).

C. Monte Carlo inversion and extraction of relevant metrics

For each set of $b(\omega)$-encoded signals, ensembles of discrete $D(\omega)$-distributions are estimated by Monte Carlo inversion [31] that has previously been applied and described in detail for various diffusion and relaxation correlation measurements including $[D_A]_2$, $[D_A D_A \theta \phi]$, and $[D_A D_A \theta \phi R \Gamma_1]$ [55]. In terms of data inversion, the extension to the $[D_A D_A \theta \phi D_0 \Gamma_1 \Gamma_2]$-space is straightforward, and for information on the algorithm we refer the reader to the previous literature [55] and the corresponding Matlab code available at https://github.com/daniel-topgaard/md-dmr. Following the terminology in previous papers, the inversion was here performed with the limits $5 \times 10^{-12} \text{m}^2 \text{s}^{-1} < D_{\text{DAR}} < 5 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ and $0.1 \text{s}^{-1} < \Gamma_{\text{AR}} < 10^5 \text{s}^{-1}$, 20 steps of proliferation, 20 steps of mutation/extinction, 200 input components per steps of proliferation and mutation/extinction, 10 output components, and bootstrapping by 100 repetitions using random sampling with replacement.

While the individual realizations of the ensemble of solutions are “overfits”—containing spurious details consistent with, but not necessarily required by, the acquired data—it is possible to derive coarse-grained metrics, such as means and (co)variances over relevant dimensions, that are determined with higher precision quantifiable via bootstrapping [33]. Parameters values shown as projections and maps in the figures are obtained by taking the medians of the individual values for the ensemble of solutions. In the current context, the characteristic frequencies $\Gamma_{\text{AR}}$ require special attention as they assume a role equivalent to the rotational correlation times in the interpretation of NMR relaxation dispersion data [20]. Acknowledging that the allowed values of $\Gamma_{\text{AR}}$ extend beyond the range of $\omega$ actually encoded in the data, we use insights from the recent concept of dynamics detectors in relaxation NMR [22–24] to convert the noisy ensembles of $D(\omega)$-distributions in the primary analysis space $[D_A D_B \theta \phi D_0 \Gamma_1 \Gamma_2]$ into quantities better supported by the data. In practice, this means evaluating the $D(\omega)$-distributions at selected values of $\omega$ within the narrow range probed by the gradient waveforms, giving $[D_A(D(\omega), \theta, \phi)]$ via Eq. (19), projecting onto the dimensions of isotropic diffusivity $D_{\text{iso}}(\omega)$ and squared normalized anisotropy $D_\Delta(\omega)^2$ [56] through

$$D_{\text{iso}}(\omega) = \frac{D_A(\omega) + 2 D_R(\omega)}{3}$$

and

$$D_\Delta(\omega)^2 = \frac{[D_A(\omega) - D_R(\omega)]^2}{[D_A(\omega) + 2 D_R(\omega)]^2},$$

and calculating per-voxel and bin-resolved means $E[x]$, variances $V[x]$, and covariances $C[x,y]$ over the diffusion dimensions [33]. Following previous works using oscillating gradient encoding [36,65,67], the effects of restriction are quantified as a finite difference approximation of the rates of change of these metrics within the investigated frequency window, for instance

$$\Delta \omega/2\pi E[D_{\text{iso}}] = E\left[\frac{D_{\text{iso}}(\omega_{\text{max}}) - D_{\text{iso}}(\omega_{\text{min}})}{(\omega_{\text{max}} - \omega_{\text{min}})/2\pi}\right].$$

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COMPETING INTERESTS

D.T. owns shares in Random Walk Imaging AB (Lund, Sweden, http://www.rwi.se/), holding patents related to the described methods.

DATA AND CODE AVAILABILITY

Upon manuscript acceptance, data and code will be made available at https://github.com/daniel-topgaard/.

AUTHOR CONTRIBUTIONS

O.N and A.S: preparation of rat brain; acquisition, processing, and interpretation of MRI data. M.Y.: development of ParaVision data acquisition code and Matlab conversion code; acquisition of MRI data. H.J.: development and preparation of phantoms; acquisition and processing of MRI data. E.F.-A.: development of tumor model, interpretation of tumor data. D.B.: preparation of tumor samples.
and acquisition of MRI data. D.T.: development of theory, TopSpin data acquisition code, and Matlab data inversion code; drafting and revising the manuscript. All authors contributed to the final version of the manuscript.

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