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Generalized mean apparent propagator (GMAP) MRI to measure and image advective and dispersive flows in medicine and biology

Dan Benjamini,

The Section on Quantitative Imaging and Tissue Sciences, NICHD, National Institutes of Health, Bethesda, MD 20892, USA.

Michal E. Komlosch,

The Section on Quantitative Imaging and Tissue Sciences, NICHD, National Institutes of Health, Bethesda, MD 20892, USA, the Center for Neuroscience and Regenerative Medicine, The Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD 20892, USA.

Nathan H. Williamson, and

The Section on Quantitative Imaging and Tissue Sciences, NICHD, National Institutes of Health, Bethesda, MD 20892, USA.

Peter J. Basser

The Section on Quantitative Imaging and Tissue Sciences, NICHD, National Institutes of Health, Bethesda, MD 20892, USA.

Abstract

Water transport in biological systems spans different regimes with distinct physical behaviors: diffusion, advection, and dispersion. Identifying these regimes is of paramount importance in many *in vivo* applications, among them, measuring microcirculation of blood in capillary networks and cerebrospinal fluid (CSF) transport in the glymphatic system. Diffusion magnetic resonance imaging (dMRI) can be used to encode water displacements, and a Fourier transform of the acquired signal furnishes a displacement probability density function, known as the propagator. This transformation normally requires the use of a fast Fourier transform (FFT), which presents major feasibility challenges when scanning *in vivo*, mainly because of dense signal sampling, resulting in long acquisition times. A second approach to reconstruct the propagator is by using analytical representation of the signal, overcoming many of the FFT's limitations. In all analytical implementations of dMRI to date, the translational motion of water has been assumed to be exclusively diffusive, which is the case only in the absence of flow. However, retaining the phase information from the diffusion signal provides the ability to measure both mean coherent velocity and random diffusion from a single experiment. We implement and extend an analytical framework, mean apparent propagator (MAP), which can account for non-zero flow conditions. We call this method generalized MAP, or GMAP. We describe a numerical optimization scheme and implement it on data from an MRI flow phantom constructed from a pack of 10 μm beads. The advantages of GMAP over the FFT-based method in the context of sampling density and low-flow detection were demonstrated, and analytically derived propagator moments were shown to agree with theoretical values even after data subsampling. GMAP would enable the detection of microflow *in vivo* that could help elucidate many important biological processes.

Keywords

Diffusion; Advection; Flow; MRI; q -space; Propagator; Velocimetry; DSI; MAP; Glymphatics; Convection; Dispersion

I. INTRODUCTION

WATER translational motion provides valuable information on the viability, structure, and function of biological tissue. Diffusion magnetic resonance imaging (dMRI) is the most commonly used method to noninvasively measure the microscopic displacements of diffusing water molecules interacting with their environment [1]. In conjunction with tissue models, dMRI experiments can be used to infer macroscopic (diffusion tensor imaging, DTI) [2], [3], [4] and microscopic structural features [5], [6], [7], [8], [9], [10], [11], [12], on the basis of the diffusive transport of water molecules in heterogeneous systems.

Diffusion-based approaches that do not assume a specific tissue model generally fall into two categories: Laplace and Fourier transform-based. In the former case, the underlying microstructure is captured by a distribution of effective diffusivities that is related to the diffusion signal data via a Laplace transform [13], [14]. This approach can be extended by combining it with other magnetic resonance (MR) observables, e.g., relaxation, to deliver multidimensional information with high sensitivity and specificity to different microenvironments within biological tissue [15].

The second model-free approach exploits the Fourier relation between the diffusion-weighted signal and an important quantity, referred to as the propagator [16]

$$P(r) = \int e^{i2\pi q \cdot r} E(q) dq, \quad (1)$$

where $P(r)$ denotes the propagator, indicating the likelihood for particles to undergo net displacement, r . The spin echo signal, $E(q)$, depends on the reciprocal space vector $q = (2\pi)^{-1}\gamma G\delta$, which is determined by the acquisition [17], [18], composed of a pair of magnetic pulsed gradients [19] of duration δ , separation τ , and amplitude and direction G , with γ being the gyromagnetic ratio. In general, the coherent phase shift between the real and imaginary channels and the attenuation of the signal intensity provide the ability to measure both mean coherent velocity and random diffusion from a single experiment. In this case, the signal describes the sum of the phase shifts associated with molecular displacements, which is shown in Eq. 1.

Practically, the propagator can be reconstructed using two approaches: fast Fourier transform (FFT) and analytical. The FFT-based method is usually referred to as q -space imaging (QSI) or diffusion spectrum imaging (DSI) [20], [21], [22], and it involves the direct inversion of the acquired signal, $E(q)$, using the discrete Fourier transform. Although Eq. 1 presents a simple relationship between the diffusion signal profile and the propagator, with a well-posed inversion procedure, a major disadvantage of DSI is that it requires dense sampling of

the diffusion signal on a Cartesian q -space lattice, resulting in long acquisition times compared with clinically acceptable methodologies [22], [23]. Conversely, the second approach involves analytical representations of the signal. Those methods are convenient because they are inherently less susceptible to noise, and they provide compact representations of the signal and the estimated quantities [24], [25], [26], [27].

To date, all of the analytical representations have assumed that the odd moments of the estimated propagator are zero (e.g., symmetric propagator with zero mean), which is the case only in the absence of flow. Nevertheless, FFT-based propagator estimation has been used to accurately measure flow in a range of plants physiology and industrial applications for over two decades [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38]. While these systems do not present crucial experimental limitations, biological systems, and specifically *in vivo* applications, suffer from low signal-to-noise ratio (SNR) and limited scan time. Likely for these reasons, as well as other confounds, velocity imaging (i.e., velocimetry) in *in vivo* systems has been limited to measuring fast flows [39], [40], [41], [42], [43], [44].

Water transport in biological systems may have different properties: diffusive, advective (i.e., bulk motion), dispersive (i.e., shear flow that increases the effective diffusivity), and the mixture of them. Despite growing interest in the medical and biological communities, microscopic flow and low-flow in *in vivo* systems were not the focus of these previous studies. Examples of important biological mechanisms associated with low-flow include the lymphatic system and blood microcirculation. The former is a recently discovered [45] cerebral spinal fluid (CSF)–mediated transport system that clears metabolic and cellular waste products in the brain, which currently cannot be detected noninvasively. Although MRI methods were developed to measure microcirculation of blood in the capillary network (e.g., intravoxel incoherent motion, IVIM [46], [47]), separation of advection from diffusion is prone to artifacts from other bulk flow phenomena [48], [49].

A clinically feasible propagator estimation framework that accounts for flow would characterize diffusive, advective, and dispersive transport processes in each voxel of brain parenchyma. Furthermore, with recently developed feasible MRI methods that measure water molecular exchange [50], [51], an array of complementary approaches would provide a promising step toward *in vivo* microflow detection.

We present here an implementation of the mean apparent propagator (MAP) MRI method [27] that accounts for flow, both macroscopic and microscopic, which we call generalized MAP, or GMAP. We describe a numerical optimization framework and demonstrate it by using data from an MRI flow phantom constructed from a pack of 10 μm beads. The advantages of GMAP over the FFT-based method are compared on the basis of their q -space sampling density, maximal q -value, and ability to detect low-flow.

II. THEORY

For the purpose of the current experimental design a 1D version of MAP, termed simple harmonic oscillator-based reconstruction and estimation (SHORE) [52] was used here. In this case, q has a fixed direction and therefore reduces to a scalar, q .

For completeness, we have briefly summarized the essential derivation of the SHORE framework. The q -space MR signal is expressed in terms of the eigenfunctions of the quantummechanical simple harmonic oscillator Hamiltonian (i.e., the Hermite functions), which form a complete orthogonal basis for the space of square integrable functions:

$$S(q) = \sum_{n=0}^{N-1} a'_n \phi_n(u, q), \quad (2)$$

With

$$\phi_n(u, q) = \frac{i^{-n}}{\sqrt{2^n n!}} e^{-2\pi^2 q^2 u^2} H_n(2\pi u q). \quad (3)$$

$H_n(x)$ is the n th order Hermite polynomial, and u is a characteristic length to be estimated. The parameter u is a tissue/data driven parameter that depends on tissue microstructure, orientation, anisotropy, and flow patterns, and should be interpreted similarly to the way in which the apparent diffusion coefficient is interpreted. The signal, $E(q) = S(q)/S(q=0)$, can be expressed in the same basis as

$$E(q) = \sum_{n=0}^{N-1} a_n \phi_n(u, q), \quad (4)$$

where

$$a_n = \frac{a'_n}{S(q=0)}, \quad (5)$$

and

$$S(q=0) = \sum_{n=0}^{N-1} a'_n \phi_n(u, 0) = \sum_{n=0,2,4,\dots}^{N-1} \frac{(n-1)!!}{\sqrt{n!}} a'_n. \quad (6)$$

Because Fourier transforms of the Hermite functions are Hermite functions themselves, the propagator can be expressed in the same set of basis functions as the signal,

$$P(x) = \sum_{n=0}^{N-1} a_n \psi_n(u, x), \quad (7)$$

With

$$\psi_n(u, x) = \frac{1}{\sqrt{2^{n+1} \pi n!} u} e^{x^2/(2u^2)} H_n(x/u). \quad (8)$$

Apart from estimation of the displacement probability density function, the MAP framework can be used to analytically and directly compute all moments of the propagator using the Hermite function representation of the $E(q)$ profile, regardless of the choice of x grid discretization. The explicit relationship between the m th moment of the propagator, μ_m , and the GMAP coefficients is given by [52]

$$\mu_m = u^m \sum_{k=0,2,\dots}^{N-1} \frac{(k+m-1)!!}{k!} \times \sum_{l=0,2,\dots}^{N-k-1} (-1)^{l/2} \frac{\sqrt{s^{k-l}(k+l)!}}{(l/2)!} a_{k+l}, \quad (9)$$

when m is even. Odd-ordered moments can be computed by using Eq. 9 where the index k takes odd values, i.e., $k = 1, 3, 5, \dots$

The above expressions can capture and describe any type of water translation. This approach was demonstrated by analyzing a simulated flowing fluid with the assumption that the molecules undergo a net coherent displacement [53]. The purpose of this work is to generalize the method to fit experimental data from porous media flow, and to use it on a biomimetic MRI phantom.

III METHODS

A. Optimization procedure

The implementation here follows the ideas outlined in the original SHORE publications [52], [53], with some modifications and additional steps to account for flow conditions. GMAP can be extended from 1D to 3D in a similar manner as SHORE [52] was generalized to MAP [53].

- 1) The first step involves finding the characteristic length u . The magnitude of the signal attenuation at the low- q regime was fitted to $E(q) = e^{-2\pi^2 q^2 u^2}$ with a trust-region-reflective nonlinear optimization procedure by using MATLAB's *lsqcurvefit* function (The Mathworks, Natick, MA).
- 2) Once u was determined, the search for the optimal a_n coefficient vectors, $\mathbf{a}$, begins. According to Eq. 4 the acquired signal $E(q)$ is a linear combination of the function $\phi_n(u, q)$ weighted by the appropriate a_n coefficients. This function can be written in a matrix form Φ , where one dimension accounts for different orders of Hermite functions (up to N) and the other dimension for the number of experimental q -values, N_q . Eq. 4 can then be written as

$$\mathbf{E}_N = \Phi_N \mathbf{a}_N, \quad (10)$$

where the subscript N indicates the chosen maximal order (and subsequent number of estimated coefficients). The procedure of choosing the optimal N is detailed in section III-B. Similarly, Eq. 7 can be turned into a matrix equation, with the propagator P defined over a grid with N_x samples in the displacement space, and spacing between adjacent points, δx .

- 3) Finding a_N is performed by minimization,

$$a_N = \arg \min(\| \Phi_N a_N - E \| ^2), \quad (11)$$

subject to two sets of constraints:

$$\Psi_N a_N \geq 0, \quad (12)$$

and

$$\delta x^T (\Psi_N a_N) = 1, \quad (13)$$

where δx^T is a $1 \times N_x$ vector containing δx . Eq. 12 enforces the nonnegativity condition that $P(x) \geq 0$ for any x . Eq. 13 ensures that the propagator is a proper probability density function, i.e., that $\int P(x) dx = 1$. To solve Eq. 11 subject to the above constraints we used CVX, a package for specifying and solving convex programs [54], [55].

- 4) For addressing cases with non-zero flow, the phase shift information from the signal must be retained and $E(q)$ is complex. Complex functions were optimized by separating their real and imaginary parts. The matrix Φ_N , which is $N_q \times N$, was split into two matrices: the even columns ($n = 0, 2, 4, \dots$), which contain exclusively real values, and the odd columns ($n = 1, 3, 5, \dots$), which contain exclusively imaginary values, were stored as Φ_N^e and Φ_N^o , respectively. We then defined $\Phi_N^{\mathbb{R}} = \text{Re}(\Phi_N^e)$ and $\Phi_N^{\mathbb{I}} = \text{Im}(\Phi_N^o)$ and solved

$$a_N = \arg \min(\| [\Phi_N^{\mathbb{R}} a_N^{\mathbb{R}} - \text{Re}(E)] \oplus [\Phi_N^{\mathbb{I}} a_N^{\mathbb{I}} - \text{Im}(E)] \|^2), \quad (14)$$

where $a_N^{\mathbb{R}}$ and $a_N^{\mathbb{I}}$ are the even and odd coefficients vectors, respectively, and the $\oplus$ operation indicates vector concatenation. The constraints in Eqs. 12 and 13 were separated into real and imaginary components in a similar fashion.

B Parsimonious order selection

The maximal order of the Hermite function directly affects the fitting quality. Higher order N would allow sharper oscillations in $E(q)$ to be captured, with the downside of additional

coefficients and the risk of overfitting or fitting the noise. We therefore present a scheme to select the optimal N : the optimization in section III-A was repeated iteratively with an increasing maximal value of N in each iteration, $\tilde{N}$. In each iteration the estimated real and imaginary parts of the signal, $E_N^{\mathbb{R}} = \Phi_N^{\mathbb{R}} a_N^{\mathbb{R}}$ and $E_N^{\mathbb{I}} = \Phi_N^{\mathbb{I}} a_N^{\mathbb{I}}$, were computed, and a distance measure from the complex signal is defined as

$$\xi = \frac{\xi^{\mathbb{R}} + \xi^{\mathbb{I}}}{2}, \quad (15)$$

where

$$\xi^{\mathbb{R}} = \sum_{i=0}^{N_q} D_M[\mathbf{E}_N^{\mathbb{R}}, \text{Re}(\mathbf{E})]_i \quad (16)$$

and

$$\xi^{\mathbb{I}} = \sum_{i=0}^{N_q} D_M[\mathbf{E}_N^{\mathbb{I}}, \text{Im}(\mathbf{E})]_i \quad (17)$$

The D_M operator indicates the Mahalanobis distance operation. The average distances sum in Eq. 15 was then combined with a Bayesian information criterion (BIC)[56], [57] to yield a parsimonious order selection

$$\epsilon_{\tilde{N}} = \log\left(\frac{\xi}{N_q}\right) + \tilde{N} \frac{\log(N_q)}{N_q}. \quad (18)$$

The resulting computed index, $\epsilon_{\tilde{N}}$, balances the choice of N by imposing penalties for models with a larger number of free parameters and a larger mean residual error. The index, $\epsilon_{\tilde{N}}$, was stored and compared with the one in the previous iteration. The selection process for N stops when $\epsilon_{\tilde{N}}$ stops decreasing.

IV EXPERIMENTS

A Phantom preparation

The MRI flow phantom was constructed from 10 μm monodisperse polystyrene beads (Duke standard) loosely packed under flow conditions in a 5 mm Tricorn column (GE Healthcare) into which water was pumped. This phantom had two regions: beads and bulk water. The bulk water compartment modeled the advective motion in the CSF-filled ventricles, while the packed beads represented dispersive flow in brain interstitial space. We chose this bead size since it roughly corresponds to the diameter of neurons in gray matter. A peristaltic

water pump (Pharmacia Biotech) pumped water at two constant flow rates of $Q = 0.876$ ml/min, and $Q = 0.041$ ml/min. The flow in the bulk water region of the column (with radius $R = 2.50$ mm) exhibits Poiseuille flow, in which the velocity profile is

$$v(r) = \frac{2Q}{\pi R^2} \left[1 - \left(\frac{r}{R} \right)^2 \right]. \quad (19)$$

Theoretical values can then be computed, resulting in average velocities of $\bar{v}_{bulk} = 743, 34.8 \mu\text{m/s}$ and peak velocities of $\max(v_{bulk}) = 1490, 69 \mu\text{m/s}$, for the high- and low-flow rates, respectively.

B. MRI data acquisition

MRI data were collected on a 7 T Bruker wide-bore vertical magnet with an AVANCE III MRI spectrometer equipped with a Micro2.5 microimaging probe and three GREAT60 gradient amplifiers, which have a nominal peak current of 60 A per channel. This configuration can produce a maximum nominal gradient strength of 24.65 mT/m/A along each of the three orthogonal directions.

Diffusion-weighted (DW) data were acquired with the diffusion-encoding direction set to the direction of flow, such that $|G|=G$, with 61 linear steps from 0 to 300 mT/m for high-flow, and with 41 linear steps from 0 to 400 mT/m for low-flow. In both cases $\delta = 3.15$ ms, resulting in a maximal q -value of 402 cm^{-1} and 536 cm^{-1} for the high- and low-flow cases, respectively. The high-flow acquisition was repeated with two diffusion periods, $\tau = 25, 75$ ms, and the low-flow data were acquired with a single $\tau = 50$.

The high-flow rate data were acquired using a spin-echo DW echo planar imaging (DWI-EPI) sequence with $TR = 7$ s, $TE = 90$ ms. Two 2 mm axial slices imaging CSF (bulk water) and interstitial (beads water) model phantoms, with a matrix size of 64×64 and an in-plane resolution of $187 \times 187 \mu\text{m}^2$, were acquired with two averages and two segments. The low-flow rate data were acquired using the same sequence with $TR = 3$ s, $TE = 59$ ms. Two 2 mm axial slices imaging CSF (bulk water) and interstitial (beads water) model phantoms, with a matrix size of 64×64 and an in-plane resolution of $125 \times 125 \mu\text{m}^2$, were acquired with four averages and eight segments.

In the case of the highest flow rate the spatial image in-plane resolution was $187 \times 187 \mu\text{m}^2$ while the third dimension of the voxel (i.e., direction of the flow) was much larger ($2000 \mu\text{m}$). These space-time scales ensured that the fluid elements moved several pore spacings during the measurement, but did not leave the voxel.

V RESULTS AND DISCUSSION

A. Effect of increased observation time

We first discuss the high-flow rate case, in which the effect of the observation time, τ , is most prominent. The propagators were obtained by finding the coefficients in Eq. 4 by using the procedure described in the Methods section. Once the coefficients have been estimated,

$E(q)$ can be evaluated analytically at any q -value on the lattice. An example of such a fit to the data acquired with a high-flow rate through the packed beads with $\Delta t = 25$ ms is shown in Fig. 1A. Both the real and imaginary components of the evaluated signal profile (solid lines) and the corresponding data (symbols) are presented, and the good agreement between them is evident. The residuals from the fit are presented in Fig. 1B, and mostly appear randomly scattered around zero (within two standard deviations) indicating that the model describes the data well.

Next we examine the GMAP-based propagators in Fig. 2, reconstructed at $\Delta t = 25$ ms and $\Delta t = 75$ ms, both in the bead pack and the bulk water regions. When considering bulk water, a characteristic Gaussian displacement distribution due to pure diffusion, is expected in the absence of flow (Fig. 2A, dashed lines). As Δt increases, the Gaussian curve gets broader, proportional to $\sqrt{2D\Delta t}$ (D is the diffusion coefficient). Bulk water flow under the current experimental conditions exhibits a laminar flow profile, in which the entire Gaussian distribution simply shifts with some gradual broadening. The bulk water flow propagators from a small region of interest (ROI) at the center of the tube are shown in Fig. 2A (solid lines). For reference, black lines are Gaussian or shifted Gaussian distributions, plotted using the apparent diffusivity found from fitting the low- q data and the theoretical mean velocity. All of the theoretical Gaussian curves fit nicely to the estimated propagators, with the exception of bulk flow at $\Delta t = 75$ ms where some unexpected asymmetry is evident, conceivably due to noise in the data.

When the GMAP framework is used, there are two possible ways to obtain moments of the propagator: (1) numerically integrating over the propagator with respect to the displacement axis, x , and (2) analytically compute the moment by using Eq. 9. The first moments, which are the average water displacements, $\bar{x}^{num}$ and $\bar{x}^{ana}$ were obtained by using numerical integration and analytical methods, respectively. Dividing those by the observation time, Δt , resulted in the average fluid velocity. The maximal bulk velocity (center of the tube) averaged from the $\Delta t = 25$ ms and $\Delta t = 75$ ms propagators can be computed and compared to the known Poiseuille flow theoretical velocity from Eq. 19. The GMAP-derived values were $\bar{v}^{num} = 1430 \pm 114$ and $\bar{v}^{ana} = 1470 \pm 122$ $\mu\text{m/s}$, compared with the theoretical value of 1490 $\mu\text{m/s}$, indicating high accuracy.

In the case of the bead pack (Fig. 2B), the reduced fluid volume leads to higher average and peak velocities compared with the bulk water flow. The velocity distribution within the bead pack puts stationary fluid and fast-moving fluid in close proximity, such that fluctuations and diffusion across streamlines are expected, causing the propagator to broaden. The propagators in Fig. 2B have distinct non-Gaussian characteristics, e.g., long tails and asymmetric shapes, which clearly indicate both diffusive and dispersive effects through the column.

Repeating the GMAP estimation in a voxelwise manner results in a water displacement distribution in each of the image voxels. Integrating with respect to the displacement variable results in quantitative images of average water displacement. Such images are shown in Fig. 3 for the bulk and beads regions, with different observation times (all at $Q = 0.876$ ml/min). The expected parabolic flow profile (Poiseuille) is evident in the bulk water

images (top row). The relatively uniform plug flow profile in the beads water images (bottom row) was also expected. Note the higher overall average displacement of the bead pack region compared with the bulk water.

B. q-space subsampling

One of the limiting factors of the FFT (and implementations such as DSI) is the dense sampling of the diffusion signal on a Cartesian q -space lattice. In biological applications, where the sample has three-dimensional heterogeneity, the q -space lattice is three-dimensional, leading to a time-intensive acquisition protocol. These data would be difficult to acquire when strong gradient coils, high SNR, and/or long acquisition times are unavailable, which is invariably the case in clinical settings.

A good indicator of the clinical feasibility of this approach is whether it is possible to reduce the amount of data while maintaining the reliability and stability of the reconstructed propagators. The q -space data sampling scheme has a direct impact on the FFT-based propagator. The reciprocal displacement vector, x , is computed directly from the q vector; thus, reducing the number of q samples leads to the same reduction in x . The resolution in x , δx , is determined by the maximal q -value; therefore, reduction in the q -space sampling density reduces the range of the reciprocal displacement space. In theory, optimal q -space sampling may not be uniform. Although the GMAP framework can evaluate the propagator regardless of the q -space sampling scheme, FFT-based reconstruction requires uniform sampling. Thus, we limited our analysis here to uniform subsampling to allow for comparison between the methods.

Even though the current work uses a 1D flow phantom with 1D acquisition, these results can be generalized to the 3D case. Focusing on the more challenging case of low-flow, the $Q = 0.041$ ml/min full data set contained 41 q -values, which in itself is not a large number of acquisitions. However, when considering a 3D generalization, sampling of a 3D grid at such density results in 41^3 images, which is infeasible. To test the robustness to data reduction, we tested a range of data subspaces, spanning from $N_q = 41$ (full) to $N_q = 6$ data points. Adhering to the uniform subsampling requirement (for FFT) resulted in 7 subspaces.

The full data and one instance of subsampled q -space ($N_q = 11$) propagators are shown, respectively, in Figs. 4A and B. No flow and $Q = 0.041$ ml/min flow at $\tau = 50$ ms were compared, along with FFT- and GMAP-based reconstruction (symbols and solid lines, respectively). Qualitatively, GMAP- based analysis is almost not affected by partial data reconstruction, despite significant reductions in the number of images. Aside from the inherent reduction in the displacement space range, the FFT-based analysis resulted in evident wiggles and nonphysical negative values of the displacement probability.

The odd moments of the propagator contain most of the coherent water motion information and, therefore, should be very useful for flow characterization. As shown above, average velocities can be computed from the first moment. In addition, the asymmetry of the propagator is another important feature that is captured by the third moment, μ_3 . It can be used to derive a dimensionless quantity, the skewness of the propagator, which is defined as $\gamma_1 = \mu_3/\mu^{3/2}$. For imaging purposes, $\bar{v}$ and γ_1 can be used to generate quantitative maps that

reflect information about water dynamics. It is therefore important that estimations of these quantities are robust to data reduction.

Computing the average velocity and skewness of the different propagators (i.e., fully sampled and subsampled) would result in a quantitative assessment of the impact of subsampling. Using the three methods that were described above, numerical integration on FFT- and GMAP-based propagators, and analytically using the GMAP coefficients, the “baseline” quantities were first computed (i.e., using full data set): $\bar{v}^{num} = 55.6 \pm 8.1 \mu\text{m/s}$, and $\gamma_1^{num} = 0.635 \pm 0.36$ from the FFT-based propagator, and $\bar{v}^{num}/\bar{v}^{ana} = 61.0 \pm 4.9/71.1 \pm 5.9 \mu\text{m/s}$, and $\gamma_1^{num}/\gamma_1^{ana} = 0.498 \pm 0.10/0.620 \pm 0.090$ from the GMAP-based propagator.

Figures 5 A and B show the percent error from the baseline values of the velocity and skewness estimations as a function of the number of q data points, respectively. The velocity estimates, which are based on the first moment of the propagator, all generate a relatively large error using the FFT-based method, with percent errors mostly larger than 20%, and in two instances larger than 40%. Conversely, both approaches to calculate the velocity using the GMAP framework resulted in quite robust velocity estimates, with all subspaces but one yielding percent errors lower or about 10%. Because the third moment is more susceptible to effects of noise than the first moment of the propagator, skewness estimation accuracy should be expected to be lower than that of velocity. And indeed, Fig. 5B shows a similar trend in the skewness parameter estimation compared to the velocity estimation, with the distinction of much higher percent error values in the case of the FFT-based method. While the percent error values of the FFT-based skewness estimation reached 600%, these values did not cross 40% and 30% using the numerical and analytical GMAP methods, respectively. These results point to the analytically derived moments having increased stability and robustness to reduced data, which is a unique feature of GMAP.

The fully sampled and subsampled q -value ranges in this experiment resulted in an FFT x lattice that ranges from $x \pm 377 \mu\text{m}$ for $N_q = 41$ to $x = 59.2 \mu\text{m}$ for $N_q = 6$, with $\delta x = 9.44 \mu\text{m}$. Integrating over the entire x range of the FFT-based propagators resulted in very poor estimates of the moments, and subsequent $\bar{v}$ and γ_1 . For example, when FFT analysis was used in the no-flow case, the estimates of the average velocities were 62.2 and $-9.39 \mu\text{m/s}$ for full and the $N_q = 11$ data, respectively, when they both should have been 0. To permit a fair comparison between the FFT- and GMAP- based results, we computed the moments by integrating over the same displacement range for all propagators at a given N_q , which was usually smaller than the full FFT reciprocal displacement range: $x = \pm 85.2 \mu\text{m}$ for $N_q > 9$, and the full FFT reciprocal space for $N_q \leq 9$. This partial-range integration, in fact, uses prior knowledge about the flow conditions and may not be possible to generalize, emphasizing another limitation to the FFT approach.

C. Low-flow sensitivity and detection

Sensitivity to low-flow conditions and the ability to measure and differentiate between microscopic and macroscopic flows are crucial in detecting features of lymphatic transport. Because GMAP provides an analytical closed-form expression for the displacement

probability density function, it is continuous and does not suffer from the resolution limit the FFT-based propagators have. The discrete nature of the FFT-based distributions is directly determined by the maximal q -value, which is inversely proportional to the spatial resolution, δx . Strong diffusion gradients, and subsequently high q -values, are unavailable on conventional clinical scanners, leading to a (relatively low) upper boundary on the maximal q -value. In some cases, this limitation can be circumvented by zero filling the signal profile and artificially increasing the maximal q -value and, with it, the spatial resolution [58]. This procedure requires that the acquired signal decays sufficiently into the noise before zero filling, which is rarely the case for biological tissue, in which the experimentally applied q -values usually do not attenuate the signal close to zero [59], [60], [15]. Because the context of the present work is biological, we avoid the use of the zero-filling technique. For the FFT, not sampling the data to a sufficiently high q -value is effectively the same as multiplying the true $E(q)$ decay by a hat filter, which results in the measured propagator being convolved with a sinc function. In that case, the propagator exhibits wiggles that are difficult to discern from true flow. GMAP is well behaved for subsampled data, thus eliminating this limitation.

The lowest flow rate in our experimental setup was that of bulk water pumped at $Q = 0.041$ ml/min, within close proximity to the tube wall. These data were analyzed by selecting an ROI at a distance of $r = 2.20$ mm from the center of the tube; then the theoretical velocity was calculated by using Eq. 19 and resulted in $\bar{v} = 15.7 \mu\text{m/s}$. Estimating the average velocities from the GMAP- and FFT-based propagators resulted in $\bar{v}^{num} = 17.9 \pm 0.13$ and $\bar{v}^{ana} = 16.47 \pm 0.11 \mu\text{m/s}$, and $\bar{v}^{ana} = 16.47 \pm 0.11 \mu\text{m/s}$, respectively (again here the integration range was set at $\pm 85.2 \mu\text{m}$; the FFT-based velocity estimation over the entire FFT x axis range was $-127 \mu\text{m/s}$). The velocity estimated by using GMAP was quite close to the theoretical value, with overestimations of 14% and 4.9% using the numerical integration and analytical methods to compute the moments, respectively. In contrast, the FFT-based velocity overestimated the theoretical value by 119.0%.

Both the current and the previous subsections demonstrated the unreliability in estimating the average displacement and velocity from the FFT-based propagators when integrating over the entire range of x . A frequently used alternative method for the determination of the mean molecular velocity is locating the peak of the displacement distribution and dividing it by the observation time [58]. This alternative method also presents a challenge for the FFT-based estimation because its discrete nature prevents it from being able to detect very small water displacements. To illustrate, a magnified range of -5 to $15 \mu\text{m}$ of both GMAP- and FFT-based low-flow propagators are shown in Fig. 6. The densely dashed vertical line indicates zero displacement, and the second vertical line indicates the theoretical displacement, $0.78 \mu\text{m}$. While the peak of the GMAP-based propagator ($0.89 \mu\text{m}$) is closely aligned with the theoretical displacement value, the peak of the FFT-based propagator is at 0, which would lead one to conclude zero flow.

VI. CONCLUSION

We presented a generalization of a previously suggested analytical propagator representation, MAP-MRI. In our implementation we account for fluid flow and adjust the numerical optimization accordingly. We tested the GMAP framework on a biomimetic MRI

flow phantom with different flow rates, different flow regimes, and under different experimental conditions. The presented framework provides a stable and robust means to analytically derive all moments of the water displacement probability density function, $P(r)$, and propagator-derived features such as the mean displacement and skewness. GMAP MRI resulted in accurate estimates of the expected theoretical flow rates and exhibited high sensitivity in detecting very low-flow rates. The advantages over the traditional FFT-based method in the context of limited data and low-flow detection were experimentally demonstrated. GMAP is expected to be especially useful with nonuniform q -space sampling, limited data and when the expected signal does not fully decay. The current imaging framework was developed to enable the characterization of *in vivo* diffusive, advective, and dispersive transport processes such as glymphatic transport-induced CSF flow and blood microcirculation. GMAP can be extended from 1D to 3D in a straightforward manner (as SHORE [52] was generalized to MAP [53]). Three-dimensional GMAP would provide a full description of the water displacement probability density function in the voxel, thus it would not require that the direction of the flow be known *a priori*.

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REFERENCES

- [1]. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, and Laval-Jeantet M, "MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders." *Radiology*, vol. 161, no. 2, pp. 401–7, 1986. [PubMed: 3763909]
- [2]. Basser PJ, Mattiello J, and Le Bihan D, "MR diffusion tensor spectroscopy and imaging," *Biophysical Journal*, vol. 66, no. 1, pp. 259–67, 1994. [PubMed: 8130344]
- [3]. Basser PJ, Pajevic S, Pierpaoli C, Duda J, and Aldroubi A, "In vivo fiber tractography using DT-MRI data." *Magnetic Resonance in Medicine*, vol. 44, no. 4, pp. 625–32, 2000. [PubMed: 11025519]
- [4]. Shepherd TM, Ozarslan E, King MA, Mareci TH, and Blackband SJ, "Structural insights from high-resolution diffusion tensor imaging and tractography of the isolated rat hippocampus." *NeuroImage*, vol. 32, no. 4, pp. 1499–509, 2006. [PubMed: 16806988]
- [5]. Frank LR, "Characterization of anisotropy in high angular resolution diffusion-weighted MRI." *Magnetic Resonance in Medicine*, vol. 47, no. 6, pp. 1083–99, 2002. [PubMed: 12111955]
- [6]. Tuch DS, "Q-ball imaging." *Magnetic Resonance in Medicine*, vol. 52, no. 6, pp. 1358–72, 2004. [PubMed: 15562495]
- [7]. Assaf Y and Basser PJ, "Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain." *NeuroImage*, vol. 27, no. 1, pp. 48–58, 2005. [PubMed: 15979342]
- [8]. Alexander DC, Hubbard PL, Hall MG, Moore EA, Ptito M, Parker GJM, and Dyrby TB, "Orientationally invariant indices of axon diameter and density from diffusion MRI." *NeuroImage*, vol. 52, no. 4, pp. 1374–89, 2010. [PubMed: 20580932]
- [9]. Benjamini D, Elsner JJ, Zilberman M, and Nevo U, "Pore size distribution of bioresorbable films using a 3-D diffusion NMR method," *Acta Biomaterialia*, vol. 10, no. 6, pp. 2762–2768, 2014. [PubMed: 24534719]
- [10]. Szczepankiewicz F, Lasi S, van Westen D, Sundgren PC, Englund E, Westin C-F, Sthlberg F, Latt J, Topgaard D, and Nilsson M, "Quantification of microscopic diffusion anisotropy

- disentangles effects of orientation dispersion from microstructure: Applications in healthy volunteers and in brain tumors,” *NeuroImage*, vol. 104, pp. 241–252, 2015. [PubMed: 25284306]
- [11]. Benjamini D, Komlosh ME, Holtzclaw LA, Nevo U, and Basser PJ, “White matter microstructure from nonparametric axon diameter distribution mapping,” *NeuroImage*, vol. 135, pp. 333–344, 2016. [PubMed: 27126002]
- [12]. Magin RL, “Models of diffusion signal decay in magnetic resonance imaging: Capturing complexity,” *Concepts in Magnetic Resonance Part A*, vol. 45A, no. 4, p. e21401, 2016.
- [13]. Pfeuffer J, Provencher SW, and Gruetter R, “Water diffusion in rat brain in vivo as detected at very large b values is multicompartmental,” *Magnetic Resonance Materials in Physics, Biology, and Medicine*, vol. 8, no. 2, pp. 98–108, 1999.
- [14]. Ronen I, Moeller S, Ugurbil K, and Kim D-S, “Analysis of the distribution of diffusion coefficients in cat brain at 9.4 T using the inverse Laplace transformation,” *Magnetic Resonance Imaging*, vol. 24, no. 1, pp. 61–68, 2006. [PubMed: 16410179]
- [15]. Benjamini D and Basser PJ, “Magnetic resonance microdynamic imaging reveals distinct tissue microenvironments,” *NeuroImage*, vol. 163, pp. 183–196, 2017. [PubMed: 28943412]
- [16]. Kärger J and Heink W, “The propagator representation of molecular transport in microporous crystallites,” *Journal of Magnetic Resonance*, vol. 51, no. 1, pp. 1–7, 1983.
- [17]. Callaghan PT, Eccles CD, and Xia Y, “NMR microscopy of dynamic displacements: k-space and q-space imaging,” *Journal of Physics E: Scientific Instruments*, vol. 21, no. 8, pp. 820–822, 1988.
- [18]. Callaghan P, *Principles of Nuclear Magnetic Resonance Microscopy* New York: Oxford University Press, 1991.
- [19]. Stejskal E and Tanner J, “Spin diffusion measurements: Spin echoes in the presence of a time-dependent field gradient,” *Journal of Chemical Physics*, vol. 42, no. 1, pp. 288–292, 1965.
- [20]. Callaghan PT, Eccles CD, and Xia Y, “NMR microscopy of dynamic displacements: k-space and q-space imaging,” *Journal of Physics E: Scientific Instruments*, vol. 21, no. 8, pp. 820–822, 1988.
- [21]. Callaghan P, MacGowan D, Packer K, and Zelaya F, “High-resolution q-space imaging in porous structures,” *Journal of Magnetic Resonance*, vol. 90, no. 1, pp. 177–182, 1990.
- [22]. Wedeen VJ, Hagmann P, Tseng W-YI, Reese TG, and Weisskoff RM, “Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging,” *Magnetic Resonance in Medicine*, vol. 54, no. 6, pp. 1377–86, 2005. [PubMed: 16247738]
- [23]. Canales-Rodríguez EJ, Melie-García L, and Iturria-Medina Y, “Mathematical description of q-space in spherical coordinates: exact q-ball imaging,” *Magnetic Resonance in Medicine*, vol. 61, no. 6, pp. 1350–67, 2009. [PubMed: 19319889]
- [24]. Cheng J, Ghosh A, Jiang T, and Deriche R, “Model-free and analytical EAP reconstruction via spherical polar Fourier diffusion MRI,” *Medical Image Computing and Computer-Assisted Intervention: MICCAI*, vol. 13, no. Pt 1, pp. 590–7, 2010. [PubMed: 20879279]
- [25]. Descoteaux M, Deriche R, Le Bihan D, Mangin J-F, and Poupon C, “Multiple q-shell diffusion propagator imaging,” *Medical Image Analysis*, vol. 15, no. 4, pp. 603–21, 2011. [PubMed: 20685153]
- [26]. Hosseinbor AP, Chung MK, Wu Y-C, and Alexander AL, “Bessel Fourier orientation reconstruction: an analytical EAP reconstruction using multiple shell acquisitions in diffusion MRI,” *Medical Image Computing and Computer-Assisted Intervention: MICCAI*, vol. 14, no. Pt 2, pp. 217–25, 2011. [PubMed: 21995032]
- [27]. Özarslan E, Koay CG, Shepherd TM, Komlosh ME, Irfano lu MO, Pierpaoli C, and Basser PJ, “Mean apparent propagator (MAP) MRI: A novel diffusion imaging method for mapping tissue microstructure,” *NeuroImage*, vol. 78, pp. 16–32, 2013. [PubMed: 23587694]
- [28]. Seymour JD and Callaghan PT, “Generalized approach to NMR analysis of flow and dispersion in porous media,” *AIChE Journal*, vol. 43, no. 8, pp. 2096–2111, 1997.
- [29]. Manz B, Gladden LF, and Warren PB, “Flow and dispersion in porous media: Lattice-Boltzmann and NMR studies,” *AIChE Journal*, vol. 45, no. 9, pp. 1845–1854, 1999.
- [30]. Scheenen TW, Vergeldt FJ, Windt CW, de Jager PA, and Van As H, “Microscopic imaging of slow flow and diffusion: a pulsed field gradient stimulated echo sequence combined with turbo spin echo imaging,” *Journal of Magnetic Resonance*, vol. 151, no. 1, pp. 94–100, 2001. [PubMed: 11444942]

- [31]. Gladden L, Lim M, Mantle M, Sederman A, and Stitt E, "MRI visualisation of two-phase flow in structured supports and trickle-bed reactors," *Catalysis Today*, vol. 79-80, pp. 203–210, 2003.
- [32]. Scheven UM, Seland JG, and Cory DG, "NMR propagator measurements on flow through a random pack of porous glass beads and how they are affected by dispersion, relaxation, and internal field inhomogeneities," *Physical Review E*, vol. 69, no. 2, p. 021201, 2004.
- [33]. Elkins CJ and Alley MT, "Magnetic resonance velocimetry: applications of magnetic resonance imaging in the measurement of fluid motion," *Experiments in Fluids*, vol. 43, no. 6, pp. 823–858, 2007.
- [34]. Zhang J and Balcom BJ, "Parallel-plate RF resonator imaging of chemical shift resolved capillary flow," *Magnetic Resonance Imaging*, vol. 28, no. 6, pp. 826–833, 2010. [PubMed: 20444567]
- [35]. Nagata A, Kose K, and Terada Y, "Development of an outdoor MRI system for measuring flow in a living tree," *Journal of Magnetic Resonance*, vol. 265, pp. 129–138, 2016. [PubMed: 26896868]
- [36]. Maier RS, Nybo E, Seymour JD, and Codd SL, "Electroosmotic Flow and Dispersion in Open and Closed Porous Media," *Transport in Porous Media*, vol. 113, no. 1, pp. 67–89, 2016.
- [37]. Sinha S, Bender AT, Danczyk M, Keepseagle K, Prather CA, Bray JM, Thrane LW, Seymour JD, Codd SL, and Hansen A, "Effective Rheology of Two-Phase Flow in Three-Dimensional Porous Media: Experiment and Simulation," *Transport in Porous Media*, vol. 119, no. 1, pp. 77–94, 2017. [PubMed: 28794576]
- [38]. Nybo E, Maneval JE, Codd SL, Ryder MA, James GA, Woodbury J, and Seymour JD, "Flow velocity maps measured by nuclear magnetic resonance in medical intravenous catheter needleless connectors," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 152, pp. 1–11, 2018. [PubMed: 29413999]
- [39]. Moran PR, "A flow velocity zeugmatographic interlace for NMR imaging in humans." *Magnetic Resonance Imaging*, vol. 1, no. 4, pp. 197–203, 1982. [PubMed: 6927206]
- [40]. O'Donnell M, "NMR blood flow imaging using multiecho, phase contrast sequences." *Medical Physics*, vol. 12, no. 1, pp. 59–64, 1985. [PubMed: 3974526]
- [41]. Dumoulin CL, Souza SP, Walker MF, and Wagle W, "Three- dimensional phase contrast angiography." *Magnetic Resonance in Medicine*, vol. 9, no. 1, pp. 139–49, 1989. [PubMed: 2709992]
- [42]. Pelc NJ, Herfkens RJ, Shimakawa A, and Enzmann DR, "Phase contrast cine magnetic resonance imaging." *Magnetic Resonance Quarterly*, vol. 7, no. 4, pp. 229–54, 1991. [PubMed: 1790111]
- [43]. Enzmann DR and Pelc NJ, "Cerebrospinal fluid flow measured by phase-contrast cine MR." *American Journal of Neuroradiology*, vol. 14, no. 6, pp. 1301–7, 1993. [PubMed: 8279323]
- [44]. Frydrychowicz A, Markl M, Hirtler D, Harloff A, Schlensak C, Geiger J, Stiller B, and Arnold R, "Aortic hemodynamics in patients with and without repair of aortic coarctation: in vivo analysis by 4D flow-sensitive magnetic resonance imaging." *Investigative Radiology*, vol. 46, no. 5, pp. 317–25, 2011. [PubMed: 21285892]
- [45]. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, and Nedergaard M, "A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid," *Science Translational Medicine*, vol. 4, no. 147, pp. 147ra111–147ra111, 2012.
- [46]. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, and Laval-Jeantet M, "MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders." *Radiology*, vol. 161, no. 2, pp. 401–7, 1986. [PubMed: 3763909]
- [47]. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, and Laval-Jeantet M, "Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging." *Radiology*, vol. 168, no. 2, pp. 497–505, 1988. [PubMed: 3393671]
- [48]. Notohamiprodjo M, Chandarana H, Mikheev A, Rusinek H, Grinstead J, Feiweier T, Raya JG, Lee VS, and Sigmund EE, "Combined intravoxel incoherent motion and diffusion tensor imaging of renal diffusion and flow anisotropy," *Magnetic Resonance in Medicine*, vol. 73, no. 4, pp. 1526–1532, 2015. [PubMed: 24752998]
- [49]. Iima M and Le Bihan D, "Clinical Intravoxel Incoherent Motion and Diffusion MR Imaging: Past, Present, and Future," *Radiology*, vol. 278, no. 1, pp. 13–32, 2016. [PubMed: 26690990]

- [50]. Benjamini D, Komlosh ME, and Basser PJ, "Imaging Local Diffusive Dynamics Using Diffusion Exchange Spectroscopy MRI," *Physical Review Letters*, vol. 118, no. 15, p. 158003, 2017. [PubMed: 28452522]
- [51]. Bai R, Benjamini D, Cheng J, and Basser PJ, "Fast, accurate 2D- MR relaxation exchange spectroscopy (REXSY): Beyond compressed sensing," *The Journal of Chemical Physics*, vol. 145, p. 154202, 2016. [PubMed: 27782473]
- [52]. Özarslan E, Koay CG, and Basser PJ, "Simple harmonic oscillator based estimation and reconstruction for one-dimensional q-space MR," in *Proc Intl Soc Mag Reson Med*, 2008, p. 35.
- [53]. Özarslan E, Koay CG, and Basser PJ, "Simple Harmonic Oscillator Based Reconstruction and Estimation for One-Dimensional q- Space Magnetic Resonance (1D-SHORE)," in *Excursions in Harmonic Analysis, Volume 2* Boston: Birkhäuser Boston, 2013, pp. 373–399.
- [54]. Grant MC and Boyd SP, "Graph Implementations for Nonsmooth Convex Programs," in *Recent Advances in Learning and Control* London: Springer London, 2008, pp. 95–110.
- [55]. CVX Research, "CVX: Matlab Software for Disciplined Convex Programming, version 2.0," 2012 [Online]. Available: <http://cvxr.com/cvx>
- [56]. Schwarz G, "Estimating the Dimension of a Model," *The Annals of Statistics*, vol. 6, no. 2, pp. 461–464, 1978.
- [57]. Freidlin RZ, Ozarslan E, Komlosh ME, Chang L-C, Koay CG, Jones DK, and Basser PJ, "Parsimonious model selection for tissue segmentation and classification applications: a study using simulated and experimental DTI data." *IEEE Transactions on Medical Imaging*, vol. 26, no. 11, pp. 1576–84, 2007. [PubMed: 18041272]
- [58]. Wassenius H and Callaghan PT, "Nanoscale NMR velocimetry by means of slowly diffusing tracer particles," *Journal of Magnetic Resonance*, vol. 169, no. 2, pp. 250–256, 2004. [PubMed: 15261620]
- [59]. Tirosh N and Nevo U, "Neuronal activity significantly reduces water displacement: DWI of a vital rat spinal cord with no hemodynamic effect," *NeuroImage*, vol. 76, pp. 98–107, 2013. [PubMed: 23507391]
- [60]. Komlosh M, Benjamini D, Barnett A, Schram V, Horkay F, Avram A, and Basser P, "Anisotropic phantom to calibrate high-q diffusion MRI methods," *Journal of Magnetic Resonance*, vol. 275, pp. 19–28, 2017. [PubMed: 27951427]

Fig. 1.

Complex signal from water pumped through the packed beads with $\Delta = 25$. (A) The data (symbols) are shown along with the analytical form of $E(q)$ estimated by using the GMAP framework (solid lines). Error bars indicate standard error from the voxels within the ROI. (B) The GMAP standardized residuals relative to the fit for the real and imaginary parts.

Fig. 2. Propagators reconstructed at different observation times and different flow regimes. (A) Bulk and (B) bead pack water propagators at $Q=0, 0.876$ ml/min (dashed and solid lines, respectively). Solid black lines are Gaussian or shifted Gaussian propagators.

Fig. 3. Average displacement images of the different flow regimes under different experimental conditions. Note the signature Poiseuille flow profile of the bulk water images and the overall higher displacement of water transported through the bead pack compared with bulk water.

Fig. 4. Bead pack propagators at $Q = 0$, 0.041 ml/min, reconstructed by using GMAP- and FFT-based methods, and the effect of limited data. (A) Full data set ($N_q = 41$). (B) Partial data set ($N_q = 11$). Error bars indicate standard error from the voxels within the ROI.

Fig. 5. The effect of reduced data on the (A) velocity and (B) skewness estimations, using GMAP- and FFT-based methods. Error bars indicate standard error from the voxels within the ROI.

Fig. 6. Bulk water propagators at $Q = 0, 0.041$ ml/min at 2.2 mm from the center of the tube. Vertical dashed lines indicate zero and theoretical displacements. GMAP- and FFT-based propagators are compared.