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A proposed 2D framework for estimation of pore size distribution by double pulsed field gradient NMR

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Reconstructing a pore size distribution of porous materials is valuable for applications in materials sciences, oil well logging, biology, and medicine. The major drawback of NMR based methods is an intrinsic limitation in the reconstruction which arises from the ill-conditioned nature of the pore size distribution problem. Consequently, while estimation of the average pore size was already demonstrated experimentally, reliable evaluation of pore size distribution remains a challenging task. In this paper we address this problem by analyzing the mathematical characteristics that create the difficulty and by proposing an NMR methodology and a numerical analysis. We demonstrate analytically that an accurate reconstruction of pore size distribution is problematic with the current known strategies for conducting a single or a double pulsed field gradient (s-PFG, d-PFG) experiment. We then present a method for choosing the experimental parameters that would significantly improve the estimation of the size distribution. We show that experimental variation of both \( \mathbf{q} \) (the amplitude of the diffusion gradient) and \( \varphi \) (the relative angle between the gradient pairs) is significantly favorable over single and double-PFG applied with variation of only one parameter. Finally, we suggest a unified methodology (termed Concentric d-PFG) that defines a multidimensional approach where each data point in the experiment is characterized by \( \varphi \) and \( \mathbf{q} \). The addition of the angle parameter makes the experiment sensitive to small compartment sizes without the need to use strong gradients, thus making it feasible for in-vivo biological applications. © 2012 American Institute of Physics. [http://dx.doi.org/10.1063/1.4769792]

I. INTRODUCTION

Noninvasive characterization of porous materials is a desirable task in many fields, among them is tissue characterization in biological and clinical applications, material sciences, food sciences, characterization of rocks and soils in geology, emulsions, porous polymers, and more. Materials in all of these fields are characterized by an \textit{a priori} unknown and usually wide distribution of pore sizes (in many cases with pores’ diameters distributed over multiple scales). Comprehensive characterization of such materials should include description of all compartment size scales rather than just an average size. Meeting this demand would be a quantification of the material’s pore size distribution.

Single pulsed field gradient\(^7\) (s-PFG) pulse sequence (Fig. 1(a)) based methodologies are widely used in order to obtain structural properties of porous materials. An insightful approach is the \( \mathbf{q} \)-space experiment\(^8\) in which multiple s-PFG experiments with ascending gradient strength are performed. The vector \( \mathbf{q} \equiv (2\pi)^{-1}\gamma\delta\mathbf{G} \) is defined where \( \mathbf{G} \) is the gradient wave vector and its duration \( \delta \), and \( \gamma \) is the gyromagnetic ratio. When the pores are monodisperse and hold the same orientation, the s-PFG \( \mathbf{q} \)-space attenuation spectrum resembles a diffraction pattern, from which it is directly possible to obtain their size.\(^9\) However, this methodology is sensitive to pore size distribution, and the diffraction pattern is lost when polydisperse porous systems are explored.\(^{10,11}\)

If a second PFG pair is added\(^{12}\) to the s-PFG pulse sequence, successive displacements of the same molecule may be correlated by orientation. The addition of a second PFG pair results in the double PFG (d-PFG) pulse sequence (Fig. 1(b)). In this sequence, two gradient vectors, \( \mathbf{G}_1 \) and \( \mathbf{G}_2 \), are applied successively, with durations of \( \delta_1 \) and \( \delta_2 \), and diffusion periods of \( \Delta_1 \) and \( \Delta_2 \). The time \( \Delta_0 \) is the interval between \( \mathbf{G}_1 \) and \( \mathbf{G}_2 \), and is called the mixing time. Similarly to the s-PFG case, the absolute value of the signal attenuation spectrum from water molecules confined in basic geometries resembles a diffraction pattern as predicted by Özarslan and Basser.\(^{13}\) This pattern was then shown in simulations and in experiments\(^{14}\) to provide average pore size of polydisperse porous systems.

Both single and double-PFG diffraction experiments are limited since a relatively high \( \mathbf{q} \)-value must be used in order to estimate the size of the restricting compartment.\(^{15}\) This limitation arises from the inverse relation between \( \mathbf{q} \) and the probed compartment’s size, and is especially important when applying these experiments on biological samples. Thus probing small compartments requires the use of strong gradients or long \( \delta_1 \). Increasing the length of the diffusion gradients will result in a violation of the short gradient pulse approximation, which assumes that the mean square displacement of the protons during the application of the gradients is negligible compared to their displacement during the diffusion.

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FIG. 1. Pulse sequences. (a) A Stejskal-Tanner single-PFG experiment. (b) A double-PFG sequence. The two diffusion gradient blocks, \( G_1 \) and \( G_2 \), with durations of \( \delta_1 \) and \( \delta_2 \), and diffusion periods of \( \Delta_1 \) and \( \Delta_2 \), respectively. The two blocks are distinguished by color, with a mixing time \( t_m \) between them. (c) The angular d-PFG methodology. For chosen gradient amplitude, \( \phi \), and \( \psi \), the angle between the gradients, \( \phi \), and \( \psi \), is varied.

period. Applying very strong gradients for short periods has two major restrictions: first, a hardware limitation of producing such short and strong pulses; second, the strong gradients may induce alternating electric fields that are not safe for clinical use.

Upon introducing the d-PFG pulse sequence, the relative directions in which the two pairs of gradient pulses are applied can influence the signal attenuation spectrum. This new addition, the relative angle between \( G_1 \) and \( G_2 \), is labeled here as \( \phi \). Varying this parameter while fixing the gradient amplitude results in the angular d-PFG methodology (Fig. 1(c)), which was first introduced by Mitra.\(^{16}\) This method allows to obtain the dimensions of a probed compartment without the need to apply strong gradients,\(^{17}\) thus can be easily used in clinical applications.

Several approaches to quantify pore size distribution by means of NMR were previously explored and implemented. The decay due to diffusion in internal field method\(^{18}\) and transverse relaxation (\( T_2 \)) distribution (which can be translated into a surface-to-volume ratio distribution\(^{19,20}\)) both involve the application of inverse Laplace transform on the governing equation, which its solution is ill-conditioned.\(^{21}\) Another approach was reviewed extensively by Hollingsworth and Johns\(^{22}\) where they used the s-PFG \( q \)-space experiment to reproduce the relative contribution of each pore size to the total signal obtained from an emulsion sample by solving a set of linear equations.

Normally, solving this set of equations is achieved by multiple linear regression (MLR) method. This method is used to model the linear relationship between a dependent variable (predictand) and one or more independent variables (predictors). A simple solution to an MLR problem is based on least squares: the model is fit such that the sum-of-squares of differences of observed and predicted values is minimized. For the specific problem which will be dealt here the predictors depend on different experimental parameters, and the predictors depend on different pore radii.

In the case of the reconstruction of size distribution, the matrix used to solve this set of equations is highly ill-conditioned (i.e., small noise in the data can cause large changes in the reconstructed pore size distribution) since some of the columns are nearly linearly dependent. The term multicollinearity can be used whenever two or more of the predictor variables (i.e., the different columns of the solving matrix, each representing a different radius) in a regression model are moderately or highly correlated,\(^{23}\) as in this case. The presence of multicollinearity has serious effects on the least squares estimation for variables that are highly related to one another. Since multicollinearity is inherent in the pore size distribution problem, we shall discuss its detection, consequence, and possible reduction.

Callaghan recently showed\(^{24}\) how angular d-PFG experiment had the theoretical potential of producing an orthogonal basis function from the signal associated with the distribution. The value of such an orthogonal basis is the direct analytical derivation of the pore size distribution. Although an analytical closed-form expression of the pore size distribution is desirable, the orthogonal basis analysis is very hard to experimentally implement since it requires the application of infinite \( q \)-values. Nevertheless, Callaghan’s important notion will be brought here for completeness, as the basis for the present study.

In this work we first suggest a different analytical derivation in which multiple angles are taken with a finite \( q \)-value. This method allows the reconstruction of the size distribution, although the gradient’s choice dictates specific pore diameters in the spectrum. To be able to reconstruct a full radii spectrum, we further suggest to apply more than one \( q \)-value, thus making it a 2D experiment. We term the combined methodology Concentric d-PFG (CDPFG), where both the amplitude of the applied gradients and their relative direction, \( \phi \), are varied from one repetition to another, thus creating virtual concentric circles. The addition of the angle variation potentially allows application on biological samples, since it does not require the use of strong gradients. Finally, we present a method of finding the favorable angles and gradient amplitudes such that the correlation between the columns of the associated matrix is minimized. We then compare the level of multicollinearity, expressed as pairwise correlation, of the CDPFG method to a regular s-PFG, d-PFG, and angular-PFG methods.
II. ANALYTICAL DERIVATION FOR SIZE DISTRIBUTION

A. Bessel function based signal attenuation calculation

In order to derive analytical solutions, we first need to consider the asymptotic signal attenuation expression for the N-PFG experiment (i.e., N diffusion gradient pairs). In this case the diffusion period is infinite, \( \Delta \to \infty \), and the time interval between the gradient pairs, \( t_m = 0 \).

\[
E_{\infty,0}(q, N) = \begin{cases} 
|\tilde{\rho}(q)|^2 \, \tilde{\rho}(2q)|^{N-1}, & N \text{ is odd} \\
\tilde{\rho}(q)^5 \, \tilde{\rho}(2q)^{N-5}, & N \text{ is even}, 
\end{cases} \quad (1)
\]

where

\[
\tilde{\rho}(q) = \int \rho(r) \exp(i2\pi q \cdot r) dr,
\]

and \( \rho(r) \) is the initial spin density. In the case of the following three simple geometries, the structure factors for uniform distribution, \( \tilde{\rho}(q) \), are

\[
\tilde{\rho}(q) = \begin{cases} 
sin[\pi q L] \, e^{-i\pi q L}, & \text{parallel plane} \\
\frac{1}{2} j_1(2\pi q L), & \text{cylindrical pore} \quad (3) \\
\frac{3}{2} j_2(2\pi q L), & \text{spherical pore}
\end{cases}
\]

\( L \) being the half-plane spacing, or the cylinder/sphere radius. \( J_n \) and \( J_m \) are the nth order Bessel function and Spherical Bessel function of the first kind, respectively. When a general case of the d-PFG (\( N = 2 \)) pulse sequence is considered, with \( G_1 = G_2 \) and a relative angle, \( \theta = \phi/2 \) (the angle between the superposed gradient vectors \( (G_1 + G_2) \) and \( G_1 \)), the asymptotic signal attenuation is

\[
E_{\infty,0}(q, x) = \tilde{\rho}(q)^2 \tilde{\rho}(2q x)^x, \quad (4)
\]

where \( x = \cos(\theta) \).

B. Analytical reconstruction of size distribution using an infinite gradient

We shall concentrate on a sample which is composed of pores of the same shape with different radii. The signal from the entire sample is a superposition of the signals from pores with different radii, each weighted by its probability density function. For a pore size distribution \( f(L) \) the signal is

\[
E(q, x) = \int_0^\infty f(L) E(q, x, L) dL. \quad (5)
\]

Callaghan\(^{24}\) suggested that obtaining the distribution \( f(L) \) would be much simpler when the signal associated with each parameter of the distribution (i.e., the pore size) belongs to an orthogonal basis. When considering Eqs. (1) and (3) this orthogonality cannot be achieved by performing a s-PFG experiment since the resulting signal attenuation is always positive, but rather with the addition of other diffusion gradient pairs (e.g., d-PGF), thus demonstrating the advantage of d-PFG over s-PFG pulse sequence. For completeness we shall show the way to do so for cylindrical pores. For cylindrical pores the obtained signal after applying the pulse sequence in Fig. 1(b), is

\[
E(q, x) = \int_0^\infty f(L) \left( \frac{J_2(2\pi q L)}{\pi q L} \right)^2 \frac{J_1(4\pi q x L)}{2\pi q x L} dL. \quad (6)
\]

We shall assume that \( q \) is constant and large enough to sufficiently attenuate the echo when \( x = 1 \). Since \( q \) is constant it is simpler to define a new parameter, \( \omega \equiv qx \). The continuous pore size distribution is then

\[
f(L) = \left( \frac{J_1(2\pi q L)}{\pi q L} \right)^2 2L^2 \int_0^\infty E(\omega)(4\pi \omega)^2 J_1(4\pi \omega L) d\omega, \quad (7)
\]

Although very elegant and inspiring, this method is not feasible in a real experiment due to the inherent demand of very high \( q \)-values. Note that in order to respect the upper integration boundary in Eq. (7) (i.e., \( \omega \to \infty \)), an infinite \( q \)-value must be used. These very high \( q \)-values are experimentally inapplicable. In addition, in the regime of very high \( q \)-values the acquisition is governed by noise.

C. Analytical reconstruction of size distribution using a finite gradient

Physically using an infinite \( q \)-value is not possible. We therefore derived an analytical solution when using a single finite \( q \)-value with many angles between the two equal gradients. When using a finite \( q \)-value we first need to assume that the sample has a discrete pore size distribution, Eq. (5) therefore transforms into

\[
E(q, x) = \int_0^\infty f(L) E(q, x, L) dL \approx \sum_{L=1}^{L_N} f(L) E(q, x, L), \quad (8)
\]

where \( N \) is the number of different radii in the sample, and \( f(L) \) is the pore size distribution that satisfies \( \sum_{L=1}^{L_N} f(L) = 1 \). In the case of a cylindrical geometry rewriting Eq. (6) yields

\[
E(q, x) = \sum_{L=1}^{L_N} f(L) \left( \frac{J_1(2\pi q L)}{\pi q L} \right)^2 \frac{J_1(4\pi q x L)}{2\pi q x L}. \quad (9)
\]

It follows for radii which satisfy the condition specified in Appendix A, that

\[
f(L) = \left( \frac{J_1(2\pi q L)}{\pi q L} \right)^2 \frac{\pi L}{\Omega^2 (J_2(4\pi \Omega L))^2} \times \int_0^\Omega E(\omega)(2\omega)^2 J_1(4\pi \omega L) d\omega, \quad (10)
\]

where in this case \( \Omega \equiv q \) (see Appendix A).

Using a similar derivation (detailed in Appendix B), the pore size distribution for an ensemble of spheres is

\[
f(L) = \frac{32}{27} \left( \frac{j_1(2\pi q L)}{\pi q L} \right)^2 \frac{\pi L}{\Omega^3 (j_2(4\pi \Omega L))^2} \times \int_0^\Omega E(\omega) \omega^5 j_1(4\pi \omega L) d\omega. \quad (11)
\]
This analytical framework allows us to accurately obtain, without the application of infinite gradients, the pore size distribution for cylindrical and spherical pores in samples which contain pores with a radius that satisfy the condition mentioned in Appendices A and B, i.e., \( L = b_n/4\pi \Omega \) (where \( b_n \) is the zero of \( J_1 \) and \( j_1 \), for cylinders and spheres, respectively). This method is still limited since a sample which contains radii that do not satisfy the condition above will result in a distorted reconstructed size distribution. The “allowed” possible sizes in a sample are dictated and predetermined by one factor—the chosen \( q \)-value (since \( \Omega = q \), and since \( q \) determines the argument of the Bessel function, thus setting \( b_n \)). A way to represent a broader spectrum of radii would be to repeat the angular experiment with different \( q \)-values. This notion gives insight regarding the importance of incorporating multiple angles and \( q \)-values in a single experiment. The above treatment provides the theoretical basis for the Concentric d-PFG method, and the value of adding a second dimension to the experiment.

III. NUMERICAL ANALYSIS

The importance of preforming the experiment with multiple \( q \)-values and angles is demonstrated in the analytical derivation. Under the current mathematical framework, generalizing Eq. (10) so that it would account for variation of \( q \)-values is not possible. However, it improves existing numerical methods that are based on the inversion of the data to obtain the pore size distribution, as will be shown here. In addition, this 2D approach will allow estimation of smaller pores without the use of strong gradients, thus making it feasible to use with biological materials.

A. Multiple correlation function (MCF) based signal attenuation calculation

In this section of the study the theoretical signal was obtained by the MCF method, which yields simple analytical expressions for the NMR echo intensity. The method was presented by Grebenkov,25,26 and further developed and integrated with the subsequent publications of Özarslan.27,28 These expressions are given by a product of temporal evolution operators, represented by matrix exponentials, where the elements of these matrices are detailed in Ref. 25 for simple geometries. A major advantage of the MCF approach is the ability to calculate the signal attenuation in a very accurate manner for the three simple geometries of parallel planes, cylinders, and spheres, and for arbitrary gradient waveforms (i.e., the algorithm can receive as input any pulse sequence with arbitrary timing parameters).

B. 2D generalization

The MLR based method for extracting pore size distribution22 is generalized here to include the relative angle, \( \varphi \), along with the gradient amplitude. Consider a porous sample which represents a heterogeneous system of pore sizes. The NMR signal (for each \( q \)-value and angular step in the experiment) is a superposition of the signals resulting from different pore sizes. The NMR signal \( E(q, \varphi, L_i) \) of water molecules restricted in pores of radius \( L_i \) (for each value of \( q, \varphi \)) is then calculated based on the MCF method. Assuming the sample is consisted of \( N \) different compartment sizes, \( L_i \), in the range \( \sqrt{2D\delta} < L_i < \sqrt{2D\Delta} \), the signal is the superposition

\[
E_{\text{data}}(q, \varphi) = \sum_{i=1}^{N} f(L_i) E(q, \varphi, L_i),
\]

where \( f(L_i) \) are the volumetric fractions that satisfy \( \sum_{i=1}^{N} f(L_i) = 1 \), and \( E_{\text{data}}(q, \varphi) \) is the superposed signal. By finding the coefficients \( f \), the relative volumetric fraction of each pore size is determined. Note that Eq. (12) is a discrete Fredholm equation of the first kind, and solving the inverse problem associated with it involves the inversion of an ill-conditioned matrix, which is obtained by varying both \( q \) and \( \varphi \). Thus this linear set of equations can be written as the matrix equation

\[
E = Ef,
\]

where \( E \) is the experimental data (i.e., the superposed NMR signal curves) and \( f \) is the vector of coefficients needed to produce the distribution. It is not possible to invert the matrix because normally it is not square, therefore a non-negative least-square algorithm is used in order to find \( f \). High intercorrelation of predictors (i.e., different columns) leads to high multicollinearity in \( E \) and to a more sensitive and unstable estimation. In the case that the columns are orthogonal, a unique solution to the set of equations is guaranteed. As the correlation between the predictors rises, the estimation draws away from being accurate and stable.

C. Optimizing the choice of experimental parameters

Obtaining a reliable multicollinearity index of a matrix is not a straightforward task, with several possible strategies. High correlation between pairs of predictor variables (i.e., the columns of \( E \)) can indicate multicollinearity.23 Another popular method is to calculate the variance inflation factor (VIF) for each of the columns in the matrix. The VIF method is based on the multiple coefficient of determination in regression (i.e., \( R^2 \)) of each predictor in multivariate linear regression on all the other predictors, such that \( VIF = 1/(1 - R^2) \). This criterion is attractive since multicollinearity depends not just on the bivariate correlations between pairs of predictors (as in the case of pairwise column correlation), but on the multivariate predictability of any one predictor from the other predictors. Unfortunately, in this case the matrix \( E \) has a very high degree of multicollinearity, such that \( R^2 \rightarrow 1 \). As a result the VIF values are extremely high, and therefore using them as a multicollinearity criterion is not feasible. Consequently, we chose in the present study the pairwise correlation (i.e., correlation between all pairs of predictor variables) as the multicollinearity criterion.

In order to optimize the choice of \( (q, \varphi) \), one must first establish the number of wanted acquired data points, \( M \), in the experiment. Given \( N \) different pore sizes, the signal

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attenuation is then calculated for each angle, $\varphi$, and $q$-value, in the experimentally allowed range. Denoting $q_{\text{max}} = q_0$ and $\varphi_{\text{max}} = \varphi_p$, the matrix $E_0$ will be

$$E_0 = \begin{bmatrix}
E(q_1, \varphi_1, L_1) & \cdots & E(q_1, \varphi_1, L_N) \\
E(q_1, \varphi_p, L_1) & \cdots & E(q_1, \varphi_p, L_N) \\
\vdots & \ddots & \vdots \\
E(q_0, \varphi_p, L_1) & \cdots & E(q_0, \varphi_p, L_N)
\end{bmatrix}.$$ 

$E_0$ contains all the possible data points, $E(q, \varphi, L)$, that are chosen to be considered in the model. When designing an experiment, one should wisely choose the amplitude of the gradient and its direction, in order to minimize the intercorrelation of the predictors that will lead to a more accurate least squares parameter estimation.

Choosing $M$ data points out of $(Q \cdot P)$ possible points is an NP-hard problem, therefore a heuristic approach is needed in order to find the optimal solution. We suggest an iterative algorithm that will find $M$ data points $(q, \varphi)$ such that the intercorrelation of the matrix is minimized by the following scheme ($E_i$ represents the $i$th iteration of the transfer matrix, where $i = 1 \ldots (Q \cdot P - M + 1)$):

1. $i = 1$.
2. Remove the $j$th ($j = 1 \ldots (Q \cdot P - i + 1)$) row from $E_i$ and save the averaged correlation of the matrix, $C_j$. Note that a row in the matrix represents a data point in the experiment. Repeat for $\forall j$.
3. Find $j_{\text{min}} = \arg\min_j C(j)$. Permanently remove row $j_{\text{min}}$ from $E_i$, thus eliminating the data point which its exclusion minimized the correlation.
4. $i = i + 1$, and return to (2). Repeat for $\forall i$.

The optimization is achieved by iteratively eliminating data points, and recording its effect on the multicollinearity of the columns. In order to do so, a correlation matrix is calculated in each iteration (i.e., after temporarily eliminating a data point) and the average correlation is saved. After this process is done for all data points, the point which its exclusion led to minimal correlation is permanently eliminated, and the process restarts for the remaining points, and so on, until we are left with a $M \times N$ matrix of the data points that will optimize the least squares parameter estimation. We shall denote this matrix $E$.

This algorithm is primarily important to help design a favorable experiment for pore size distribution estimation by choosing optimal experimental parameters, for any pore geometry. In addition, this method can establish whether the CDPFG method holds an advantage over the single and double PFG methods in solving the inverse problem depicted in Eq. (13). In case the $M$ optimal data points are found such that the angle $\varphi$ is constant (i.e., $M$ different $q$-value with a constant angle), it would imply that the addition of a second dimension, as proposed by the CDPFG method, is insignificant.

D. Implementation of the method

The theoretical signal attenuation from the pulse sequence described in Fig. 1(b) was numerically calculated according to the MCF method with different experimental parameters, $q$ and $\varphi$, for a cylindrical geometry. The ranges of the experimental parameters were taken to account for the most general case, under several realistic experimental conditions. First, a long diffusion period, $\Delta$, had to be taken in order to allow sensitivity to the widest pore size range. Too long diffusion period would result in a severe signal attenuation due to $T_2$ relaxation. Accordingly, the value was set on $\Delta_1 = \Delta_2 = 500 \text{ ms}$, the gradient duration was taken to be $\delta = 3 \text{ ms}$, and a stimulated echo variation of the pulse sequence in Fig. 1(b) was used in order to diminish the $T_2$ relaxation effect. The range of pore sizes is consequently $\sqrt{2D\delta} < L < \sqrt{2D\Delta}$, which results in $3.5 \mu \text{m} < L < 45 \mu \text{m}$. The mixing time, $t_m$, was set to 0 in order to allow maximal correlation of molecular positions at the end of the first and start of the second pulse pair. We assume a maximal gradient amplitude of $G_{\text{max}} = 800 \text{ mT/m}$ for the d-PFG experiment, and $G_{\text{max}} = 1600 \text{ mT/m}$ for the s-PFG experiment. Finally, the relative angle, $\varphi$, is taken over the range $[0^\circ, 180^\circ]$.

The spatial resolution of the reconstructed size distribution was chosen to be 0.85 $\mu \text{m}$, which led to $N = 50$ different pore sizes in the model (i.e., 50 columns in the matrix $E$). Considering the multicollinearity, a stable solution to Eq. (13) will require more equations than coefficients. Therefore $M = 100$ was set, which led to $2N$ rows in the matrix $E$. To avoid a bias of the result when finding the optimal subset of $M$ data points from $Q \cdot P$ possibilities, the initial condition $M = P = Q$ must be applied, therefore in this case $P = Q = 100$.

The $M = 100$ optimal acquisition data points which will minimize the pairwise correlation of predictor variables were found by the proposed algorithm, and are shown in Fig. 2. Each data point is characterized by the two experimental parameters, $q$ and $\varphi$. It is clear from Fig. 2 that performing the experiment with a single angle and $M$ different $q$-values is not favorable. On the contrary, the multicollinearity analysis leads to the conclusion that a wide range of angles and gradient amplitudes should be used, as the CDPFG methodology assumes.

E. CDPFG compared to single and double PFG

The biggest advantage of integrating multiple angles and $q$-values acquisitions is the potential use in biological applications, as discussed in the Introduction. In addition, quantifying the advantage of CDPFG over the existing methods (i.e., single or double PFG $q$-space, and angular-d-PFG) can be achieved by comparing the averaged Pearson pairwise correlation of the matrix $E$ that solves Eq. (13). The matrices $E_{sPFG}, E_{dPFG}, E_{angPFG}$ were constructed accordingly where the $i$th column contains the signal attenuation from a s-PFG, d-PFG, and angular-d-PFG experiment, respectively, for a radius $L_i$. In addition, the matrix $E_{CDPFG}$ contains in each column the data points chosen by the algorithm.

The resulting columnwise average correlations of the $E_{sPFG}, E_{dPFG}, E_{angPFG}$, and $E_{CDPFG}$ matrices are shown...
in Table I. This quantification suggests that using the CDPFG methodology with carefully chosen experimental parameters, \( q \) and \( \varphi \), will reduce the pairwise correlation of the design matrix \( \mathbf{E} \) used to solve Eq. (13) by 55.83\%, 55.81\%, and 49.49\%, compared to the 1D s-PFG, d-PFG, and angular-d-PFG methodologies, respectively.

IV. DISCUSSION AND CONCLUSION

In this paper we addressed the general problem of estimating pore size distribution by means of diffusion weighted NMR. We suggested here to use the multi-angular variant of the d-PFG incorporated with a \( q \)-space experiment. This will allow us to reconstruct a wide pore size spectrum while applying much lower \( q \)-values, making it feasible to use on biological samples.

The idea to change more than one experimental parameter at the same measurement was inspired by recent work of Callaghan.\(^{24}\) Our specification of his work showed that using a single and finite \( q \)-value with multiple angles results in an analytical expression of the size distribution, but is limited to certain sizes that are set according to the chosen \( q \)-value. Theoretically, in order to include all sizes one should use all \( q \)-values, thus the concept of the CDPFG method was conceived. Accordingly, we decided that a numerical approach using multiple \( q \)-values with multiple angles might assist us in finding the pore size distribution.

A general method for choosing wisely the experimental parameters in a d-PFG experiment (i.e., the relative angle between the gradients and their amplitude) was presented, so that the inversion of Eq. (13), and therefore the estimated pore size distribution, would be as accurate as possible. Our analysis takes into account the multicollinearity of predictor variables in the transfer matrix, and assumes reducing it is possible. Since calculation of the variance inflation factor is not feasible, it cannot be used to quantify the multicollinearity of the matrix. Consequently, we chose to use pairwise correlation (i.e., correlation between all pairs of predictor variables). Looking at correlations only among pairs of predictors, however, is limiting since it is possible that the pairwise correlations are small, and yet a linear dependence exists among three or even more variables.

In addition to allowing the use of low gradients, the 2D experiment presented in this study reduces the pairwise correlation within the columns of the matrix, which can reduce its multicollinearity, thus improving the parameter estimation. It should be noted that the \( M \) experimental parameters chosen by the algorithm improve the estimation in a purely mathematical way. The criterion used here does not take into account the physics of the diffusion weighted NMR experiment. Specifically, the \( q \)-value is inversely proportional to the investigated pore size. Therefore only a measurement with several different \( q \)-values will lead to a full representation of all pore sizes within the sample, with no regard to the algorithm’s choice of parameters. However, the physical importance of multiple \( q \)-values is reflected in the experimental parameters found by the algorithm, as more than one \( q \)-value is suggested.

Few fundamental limitations, which are shared by most diffusion weighted NMR and MRI methodologies, exist here as well: (1) The pores should be filled with an NMR visible fluid or gas. (2) Prior knowledge or assumption on the pore geometry is needed. (3) The technique is sensitive to a certain range of pores sizes (as determined by the diffusion period \( \Delta \) and the diffusion gradient length \( \delta \)).
The application of this technique to the case of tissues is not immediate. Cells are not ideal spherical or cylindrical pores, but have multiple non-symmetric shapes. Organelles such as the nucleus occupy a significant percentage of the cell volume. Moreover, the cell walls set different boundary conditions, since they are permeable and water is exchanged across these membranes. These differences imply that a first order model of a cell body would be more accurate if cells are viewed as composed of two concentric spheres with different diffusion coefficients, and with permeable walls. It should be noted that, however complex, such a geometry may be solvable, with the framework described above. Additional characteristics of tissues further complicate the problem: the contribution of extra-cellular fluid in between packed cells,\textsuperscript{32, 33} the problem of diffusion in a gel like medium, and the cytoplasm and intra-cellular micro-streaming.\textsuperscript{34} The experimental treatment of tissues sets specific restrictions. To characterize large cells ($R \approx 15–30 \mu m$) long diffusion times are needed. $T_2$ values in tissues (usually 50–100 ms) dictate that in order to reach sufficiently long diffusion times, stimulated echo experiments will have to be used. In the long diffusion times $T_1$ values (usually 0.6–2 s) will affect signal amplitude. Total scan times in imaging will restrict the use of multiple angles in diffusion tensor imaging experiments will aid in designing such experiments with multiple $(q, \phi)$, and in avoiding experimental artifacts.

When exploring porous materials one should take into account an additional internal field gradient. This magnetic field rises from a distribution of background gradients due to magnetic susceptibility differences within a heterogeneous sample. The microscopic magnetic field is a function of the compartment shape and of the packing arrangement of the structure. A bipolar variation of the pulse sequence was first proposed by Karlicek and Lowe\textsuperscript{35} (the details of which are out of the scope of the present study) in order to overcome most of the susceptibility artifacts. Its application in cases similar to this study should provide a significant improvement to the SNR.

NMR is not the only tool to estimate a pore size distribution with pores in the range discussed in this work. Mercury porosimetry is frequently used to analyze pore size distribution in porous media\textsuperscript{36} (while the gas adsorption isotherms method is suitable only for nano-scale pores). Mercury is injected into the sample and its volume/mass is measured as a function of the pressure applied.\textsuperscript{37} and pore size distribution is calculated according to the Washburn equation. For the case of characterization of live tissues, mercury porosimetry is obviously inapplicable, while CDPFG is well suited for such a task. Mercury porosimetry is limited also to the characterization of dry materials, and is thus inapplicable for fixed biological tissues and for other porous materials that are filled with fluid.

The nature of the proposed experimental setup allows the addition of other independent dimensions: the mixing time $t_m$, the diffusion time $\Delta$ or $q$ (it is possible to take $\Delta_1 \neq \Delta_2$, or $q_1 \neq q_2$ thus create more independent dimensions) and the echo time $T_E$. The increase of the dimensionality in the proposed framework is straightforward: for example, adding $T$ different echo times to the simulation would result in a $Q \cdot P \cdot T$ possible data points, and from them the optimal subset would perhaps further reduce the multicollinearity. Incorporation of more dimensions to the experiment could improve the estimation of the pore size distribution, and can be further investigated in the future.

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**APPENDIX A: ANALYTICAL ESTIMATION OF PORE SIZE DISTRIBUTION IN CYLINDRICAL PORES**

If a cylindrical geometry is considered, Eq. (6) becomes

$$E(q, x) = \sum_{L=L_1}^{L_N} f(L) \left( \frac{J_1(2\pi qL)}{\pi qL} \right)^2 \frac{J_1(4\pi qxL)}{2\pi qxL}. \quad (A1)$$

Similarly to the continuous case, multiplying both sides of the equation by $\omega^2 J_1(4\pi \omega L')$ and integrating $\omega$ over 0 and $\Omega$ yields

$$\int_0^{\Omega} E(\omega) \omega^2 J_1(4\pi \omega L')d\omega = \sum_{L=L_1}^{L_N} f(L) \left( \frac{J_1(2\pi qL)}{\pi qL} \right)^2 \frac{1}{2\pi L} \times \int_0^{\Omega} \omega J_1(4\pi \omega L)J_1(4\pi \omega L')d\omega.$$  

(A2)

When taking specific radii $L = b_p/4\pi \Omega$ and $L' = b_m/4\pi \Omega$ where $b_p$ and $b_m$ are zeros of first order Bessel function of the first kind, we can use the mathematical identity\textsuperscript{38}

$$\int_0^{\Omega} \omega J_1(4\pi \omega L)J_1(4\pi \omega L')d\omega = \frac{\Omega^2}{2} \left( J_2 (4\pi \Omega L) \right)^2 \delta_{L,L'}, \quad (A3)$$

where $\delta_{L,L'}$ is Kronecker delta function and $J_2(x)$ is second order Bessel function of the first kind. Thus, for specific pore radii which satisfy the condition $L = b_p/4\pi \Omega$, the Bessel function orthogonality allows an analytical calculation of the pore size distribution using the formula

$$f(L) = \left( \frac{J_1(2\pi qL)}{\pi qL} \right)^2 \frac{\pi L}{\Omega^2 (J_2 (4\pi \Omega L))^2} \times \int_0^{\Omega} E(\omega)(2\omega)^2 J_1(4\pi \omega L)d\omega. \quad (A4)$$

Using angles, $\phi$, in the range $[0^\circ, 180^\circ]$ will allow to achieve the maximal spatial resolution for a constant $q$-value. Using these angles yields $x (x = \cos(\phi/2))$ values between 0 to 1 and results in $\Omega = q$. The spatial resolution of the reconstructed size distribution is also determined by the position...
of the zeros of first order Bessel function of the first kind, which is denoted as $\Delta b$. Since $\Delta b$ is not constant, the spatial resolution, $\Delta L = \frac{\Delta b}{4\pi}$, is not constant either. When the argument of the Bessel function is large enough it behaves as a cosine, therefore the spacing between the zeros, $\Delta b$, becomes constant and equals to $\pi$. In that case the maximal spatial resolution is $\Delta L = \frac{1}{4q}$.

**APPENDIX B: ANALYTICAL ESTIMATION OF PORE SIZE DISTRIBUTION IN SPHERICAL PORES**

A similar solution can be used for spherical pores, in which the signal is

$$E(q, x) = \sum_{L=L_1}^{L_x} f(L) \left( \frac{3j_1(2\pi q L)}{2\pi q L} \right)^2 \frac{3j_1(4\pi q x L)}{4\pi q x L}, \quad (B1)$$

where $j_1(x)$ is the first order spherical Bessel function of the first kind.

We can use the same parameter $\omega$, multiply both sides of the equation by $\omega^2 j_1(4\pi \omega L')$ and integrate $\omega$ over $0$ and $\Omega$. Similarly, if the radii are chosen according to $L = a_n/4\pi \Omega$ and $L' = a_m/4\pi \Omega$ where $a_n$ and $a_m$ are zeros of first order spherical Bessel function of the first kind, we can use the similar mathematical identity:

$$\int_0^\Omega \omega^2 j_1(4\pi \omega L) j_1(4\pi \omega L') d\omega = \frac{\Omega^2}{2} \left( j_2(4\pi \Omega L) \right)^2 \delta_{L,L'}. \quad (B2)$$

This allows the analytical calculation of the pore size distribution for spherical pores using

$$f(L) = \frac{32}{27} \left( \frac{j_1(2\pi q L)}{\pi q L} \right)^{-2} \frac{\pi L}{\Omega^3} \left( j_2(4\pi \Omega L) \right)^2 \times \int_0^\Omega E(\omega) \omega^3 j_1(4\pi \omega L) d\omega. \quad (B3)$$


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