Double Pulse Encoding

Evren Özarslan

Department of Physics, Boğaziçi University, İstanbul, Turkey

A biological tissue's structure is the most important determinant of its function. Alterations in the function of an organ, due to pathological perturbations, or processes such as development and aging, usually stem from changes that occur at microscopic level. Consequently, an investigative tool that provides information about the underlying microscopic and organizational structure has great utility in many areas of biological science. However, most techniques that provide detailed microstructural information are invasive, and as such, they cannot be used in routine clinical practice. MRI stands out as one of the few noninvasive methods that provide spatially dependent signal within a clinically acceptable timeframe. This capability and the sensitivity of MR signal to disease-related changes have turned MRI into an indispensable clinical tool.

Perhaps the most significant shortcoming of traditional MRI acquisitions is its poor spatial resolution, which prohibits direct visualization of tissue microstructure. Diffusive-attenuation of the MR signal, e.g., achieved by applying pulsed field gradients (PFGs) [1], can be exploited to obtain the desired sensitization to the microscopic environment. This technique, whose inception precedes the invention of MRI, can be used for microstructure elucidation because distances traversed by randomly moving molecules during the course of the MR signal acquisition are in the micrometer range. Assuming that the microstructure does not vary drastically within each voxel, diffusion in different parts of the voxel is expected to be similar. Thus, there is no need to 'localize' or 'isolate' the signal for one microscopic domain from the signal in another domain as necessitated by traditional microscopy. Instead, we can collect a series of diffusion-weighted signal values for the same macroscopic voxel by varying the parameters related to diffusion sensitization, and subsequently fit an appropriate model, descriptive of the microstructure, to the acquired signal profile. The end result yields the quantitative markers of tissue microstructure.

Clearly, extracting such quantitative measures involves two interdependent steps: (i) a diffusion-weighted acquisition scheme that could generate a series of signal values, and (ii) a biophysical model that relates the microstructure to the diffusion sensitized signal. Neither of these steps is rigid, and a particular choice has to be made based on the characteristics of the tissue being examined. Most common approach to generate a profile of signal values involves repeating measurements by varying the PFGs' strength and/or orientation, though variations in other parameters of the pulse sequence or employing sequences tailored to the measured characteristics could greatly strengthen the ability to obtain the desired information.

A perfect example to the above-mentioned experimental frameworks involves the multiple-PFG experiments, which employ two or more pairs of gradients [2]. Hence, such acquisitions can be envisioned to be natural extensions of the traditional Stejskal-Tanner (single-PFG) measurements that employ only one pair of diffusion gradients. For simplicity, unless otherwise stated, we shall focus on the double-PFG acquisitions. Two new independent experimental parameters, the delay between the two gradient pairs or blocks (i.e., the mixing time), and the angle between the two gradient vectors applied in each block have no analog in the conventional PFG MR sequence with a single pair of PFGs. These enhancements are exploited in the field of double-PFG MR to relate the signal to anisotropy at different length scales and to obtain new microstructural information and new types of contrast. The reader is referred to two recent reviews [3,4] of double-PFG MR for many details that are not discussed here.

Before we start discussing anisotropy in the context of double-PFG measurements, we shall visit another interesting question, which could be important in the future. Specifically, we shall keep the mixing time to be very short. This condition can be realized by using a three-pulse sequence wherein the second

gradient is the vector sum of the two gradients [5]. Further, we shall keep the orientations of the two vectors constant and vary their strengths simultaneously. In this case, the entire data set can be plotted against a single q-value. In the case of single-PFG acquisitions, the signal profile appears non-monotonic (oscillatory) at large q-values [6]. However, this oscillatory behavior is observed only for very homogeneous specimens. If there is some dispersion in the size or orientation of the compartments, the signal becomes monotonic, and no information regarding the restricted character of the diffusion process can be inferred. When we consider double-PFG measurements, however, an even more interesting effect was predicted: the signal crosses the horizontal axis and assumes negative values [7]. As an example of a heterogeneous medium, let's consider a medium comprising spherical pores with varying diameters. The smoothing effect in single-PFG acquisitions results from constructive interference of the diffusion patterns associated with pores of different diameters. However, around the zero-crossings of the double-PFG signal, the interference is destructive. In other words, signal contributions from larger pores cancel those of smaller pores, and the zero-crossing prevails. This explains the robustness of the zero-crossings to the heterogeneity of the specimen. Similarly, in asymmetric pore shapes, the double-PFG signal is complex-valued. These findings suggest phase disambiguation in the signal, which can be used to map the actual pore shape for symmetric [8] and general [9] pores. Unlike the case of propagator mapping, which can be related to the autocorrelation function of the pore shape, the phase information provided by double-PFG measurements enables the mapping of real pore shapes like in diffusion pore imaging [10].

Perhaps more important for investigations on nervous tissue is the anisotropy information (angular dependence) available in double-PFG acquisitions. First we shall start with the very short mixing time regime. Under a series of ideal experimental conditions, the signal, when plotted against the angle (ψ) between the two gradients, was predicted [11] to follow a bell-shaped curve characterized by the function $-(2+\cos\psi)$. The sharpness of the curve is related to the average radius of gyration of the pores, thus enabling the estimation of the compartment size at low q-values. This effect is referred to as microscopic anisotropy [5], restriction effect [3], or Mitra's paradox [12]. This result was generalized to accommodate all parameters of the double-PFG measurement for specific pore shapes [5]. Imaging sequences were developed in various platforms. Measurements on well-characterized glass capillary arrays [13] confirmed the theory. Further experiments on porcine spinal cord specimens yielded meaningful (size-dependent) contrast with good correlation with histology [14]. Adopting the technique in clinical environment is relatively challenging because of the small axonal diameters and limited gradient strength. Therefore, it is beneficial to employ more than one pair of gradients, which has been shown [15] to yield sharper angular profiles when compared to double-PFG scans. Therefore, Avram et al. [16] implemented a quadruple-PFG sequence to boost the angular dependence. Rather than measuring a single "apparent" pore size, double-PFG MR has also been used to characterize pore size distributions in heterogeneous media [17]. An alternative approach demonstrated that the quadratic term of the signal expression can be related to some displacement correlation tensor [18], which can be related to the diffusion tensor measured at different diffusion times [19].

Since its first inception [2], double-PFG acquisitions have received some attention due to its prospect to provide information about the shape of the compartments. Early experimental works have observed such shape anisotropy (also referred to as compartment shape, pore shape, microscopic diffusion and local anisotropy) in elongated yeast cell suspensions [20], and a gray-matter phantom [21]. Due to the importance of the problem, a comprehensive theory for shape anisotropy was developed [22]. This study established that when the double-PFG acquisition is performed at long mixing times, the second order term of the Taylor series expansion of the signal is flat. However, the fourth-order term leads to a W-shaped modulation of the signal characterized by the function $\cos(2\psi)$. The sharpness of the modulation could be used to quantify the shape anisotropy (eccentricity) of the pores. As the pores get less anisotropic, signal profile gets flatter; for spherical pores, the signal is always a constant. Note that this angular dependence is different than the one discussed in the preceding paragraph, demonstrating the specificity of double-PFG measurements. Several quantitative measures of shape anisotropy have been

proposed [23,19]. A significant challenge in the analysis of real data is the coexistence of ensemble (global) anisotropy, which is the anisotropy of the orientation distribution function—the kind of anisotropy that can be measured using single-PFG methods. To get rid of the influence of ensemble anisotropy, an averaging trick [22] was employed on real data [24] that isolates the two types of anisotropy, and yields a single angular profile that exhibits only shape anisotropy even in significantly anisotropic regions like the white-matter.

For analyzing real data, there appear to be three alternatives. One approach [25] involves the moment expansion, which is a Taylor series expansion of the signal. An alternative that significantly improves the range of applicability of the technique, is the cumulant expansion, which is a Taylor series expansion of the logarithm of the signal [18,19]. These two approaches express the signal in terms of higher order tensors, and given the complexity of the experiment, it is a formidable task to derive expressions that are valid beyond the fourth order terms. The third approach [26] assumes specific pore shapes, and is valid for arbitrary values of the experimental parameters. Rather than higher order tensors, the parameters that are estimated are microstructural quantities like the pore size and orientation distribution function.

Among other applications of double-PFG acquisitions, one can list the measurements of local anisotropy in liquid crystals [27], correlations associated with coherent motion (flow) [28], and exchange between different domains in a heterogeneous specimen [29]. Given the prevalence of the above mentioned phenomena and significance of characterizing them, one can expect continuing activity and many more important findings in the field of double-PFG MR. As such, structure elucidation using multiple-PFG MR techniques is expected to yield many novel quantitative markers of neural tissue microstructure, which could improve the diagnostic utility and specificity of diffusion-weighted MRI.

References:

[1] E. O. Stejskal and J. E. Tanner, J Chem Phys, 42, 288 (1965).
[2] D. G. Cory, et al., Polym Prepr (Am Chem Soc Div Polym Chem), 31, 149 (1990).
[3] J. Finsterbusch, in Annual Reports on NMR Spectroscopy (Ed: G. A. Webb), Academic Press, pp. 225–299 (2011).
[4] N. Shemesh, et al., NMR Biomed. 23, 757, (2010).
[5] E. Özarslan and P. J. Basser, J Chem Phys, 128, 154511 (2008).
[6] P. T. Callaghan et al., Nature, 351, 467 (1991).
[7] E. Özarslan and P. J. Basser, J. Magn Reson, 188, 285 (2007).
[8] N. Shemesh et al., Phys Rev Lett, 108, 069902 (2012).
[9] T. A. Kuder and F. B. Laun, Magn Reson Med, in press.
[10] F. B. Laun et al., Phys Rev Lett, 107, 048102 (2011).
[11] P. P. Mitra, Phys Rev B, 51, 15074, (1995).
[12] P. T. Callaghan, Oxford University Press, USA (2011).
[13] M. E. Komlosh, et al., J Magn Reson, 208, 128 (2011).
[14] M. E. Komlosh et al., Neuroimage, 78, 210 (2013).
[15] J. Finsterbusch, J Magn Reson, 198, 174 (2009).
[16] A. V. Avram et al., Neuroimage, 64, 229 (2013).
[17] D. Benjamini et al., J Chem Phys, 137, 224201 (2012).
[18] S. N. Jespersen and Buhl, J Magn Reson, 208, 34, (2011).
[19] S. N. Jespersen, NMR Biomed, 25, 813 (2012).
[20] Y. Cheng and D. G. Cory, J Am Chem Soc, 121, 7935 (1999).
[21] M. E. Komlosh et al., J Magn Reson, 189, 38 (2007).
[22] E. Özarslan, J Magn Reson 199, 56 (2009).
[23] M. Lawrenz et al., J Magn Reson, 202, 43 (2010).
[24] M. Lawrenz and J. Finsterbusch, Magn Reson Med, 69, 1072 (2013).

[25] J. Finsterbusch and M. A. Koch, J Magn Reson, 195, 23 (2008).
[26] E. Özarslan et al., J Chem Phys, 130, 104702 (2009).
[27] P. T. Callaghan and M. E. Komlosh, Magn Reson Chem, 40, S15 (2002).
[28] Stapf et al., Concepts Magn Reson A, 14, 172 (2002).
[29] Nilsson et al., Magn Reson Med, 69, 1573 (2013).