

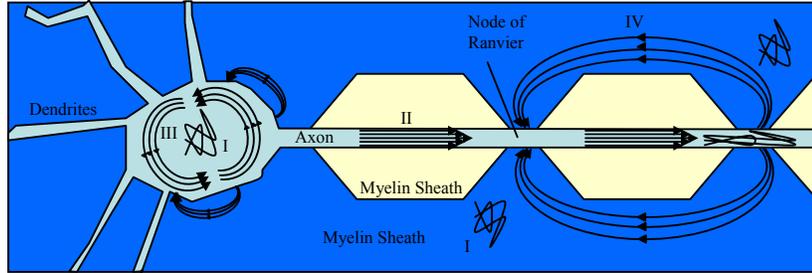
## Modeling the effect of micro-streaming on DWI data

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### Introduction

The displacement that is measured in diffusion weighted MRI is usually attributed to random Brownian motion that is restricted by various barriers and is hindered in some cellular compartments. This assumption is at the basis of most models of water displacement, and is used in the analysis of experimental DWI data. However, any (even non-random) incoherent displacements, such as shear flow or shearing motion, may cause dephasing of the magnetization and attenuation of the DW-MRI signal. Such displacements could originate from any mechanism that creates velocity gradients across the tissue, including (a) thermal or electrical gradients within the tissue, (b) cell streaming, (c) molecular transport, (d) ionic and electric driven currents, with/without relation to cellular activity, etc. It is suggested that most of these flow patterns can be described as combinations of symmetrical and mathematically-solvable patterns of flow (Fig. 1). In this work we study, analytically and experimentally, the effect of shear flow on conventional diffusion MRI measurements. We calculate the contributions due to shear motion to signal attenuation, and validate it experimentally using a Rheo-NMR instrument (Fig. 2a). We demonstrate how non-Brownian displacements can be erroneously interpreted as arising from molecular diffusion, and suggest means to avoid such misinterpretations.

**Figure 1:** Illustration of possible types of incoherent molecular displacements in the vicinity of a neuron. These include intra- and extra-cellular Brownian motion (I), linear shear flow (II) inside axons, circular shear flow (III), and dipolar flow (IV).



### Symmetrical patterns of shear flow in DW-MRI

**Linear shear flow** - Consider the geometry shown in Figure 2b, where the molecules undergo flow along the x-direction with linear shear,  $\beta$  (Fig. 2b). We assume that the stochastic nature of the displacement is fully described by diffusion and dispersion along the x-direction caused by the shear flow (Taylor dispersion [1]). We can thus describe the average propagator to be composed of three contributions: (a) diffusion, (b) modified diffusion parallel to the direction of flow (Taylor-dispersion), and (c) shear flow:

$$\bar{P}_s(\mathbf{R}, t) = (\bar{P}_{x, flow}(x, t) \otimes \bar{P}_{x, Taylor-diff}(x, t)) \cdot \bar{P}_{y, diff}(y, t) \cdot \bar{P}_{z, diff}(z, t)$$

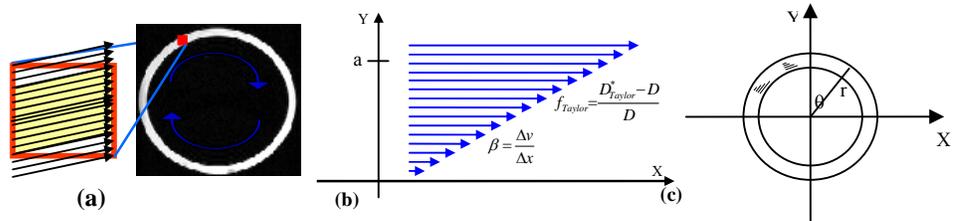
The attenuation in a PGSE experiment with diffusion time,  $t$ , over a square voxel of area  $a^2$ , in such a sample will be:

$$E(\mathbf{q}, t) = E_{flow}(q_x, t) \cdot E_{diff}(\bar{q}, t)$$

where  $E_{flow}(q_x, t) = e^{-2\pi i q_x v_{av} t} \cdot \text{sinc}(\pi q_x \beta a t)$  and  $E_{diff}(\bar{q}, t) = e^{-(q_x^2 (1 + f_{Taylor}) + q_y^2 + q_z^2) D t}$

Taylor dispersion enhances the apparent diffusion coefficient along the x-axis by a factor  $f_{Taylor}$ , relative to the actual diffusion coefficient (in the absence of flow)  $D$ .

**Figure 2:** (a) An axial cross section of the Rheo-NMR with 'zoom' on a Cartesian voxel. Linear (b) and circular (c) shear flow.



**Microcirculation** – In the case of viscous circular motion (Fig. 2c), it can be shown that when the shear dominates, the attenuation for an infinitesimal ring is:

$$E_{ring}(\omega, \Delta) = \frac{1}{2\pi} \int_0^{2\pi} e^{2\pi i q_x r (\cos(\theta + \omega \cdot \Delta) - r \cos \theta)} d\theta = \frac{1}{2\pi} \int_0^{2\pi} e^{i\kappa r \sin \alpha} d\alpha = J_0(\kappa) \quad \text{where} \quad \kappa(r) = 4\pi q_x r \sin \frac{\omega(r) \cdot t}{2}$$

and  $J_0$  is the zeroth order Bessel function of the first kind. The attenuation of a circulating band of fluid of area,  $A=\pi\cdot(r_{\text{ext}}^2 - r_{\text{int}}^2)$  is obtained by integrating over all rings from  $r_{\text{int}}$  to  $r_{\text{ext}}$ :

$$E_{\text{shear}}(\omega(r),t) = \frac{1}{A} \int_{r_{\text{int}}}^{r_{\text{ext}}} J_0(k(\omega(r))) \cdot r dr$$

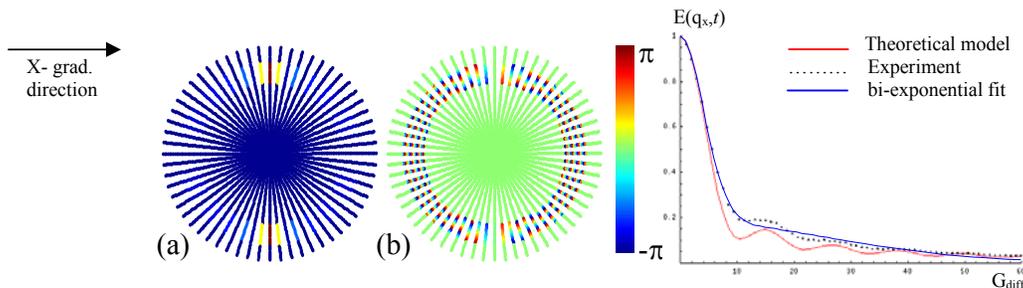
These symmetrical cases of shear flow can serve as ‘building blocks’ to describe more complicated flow patterns found in tissues and cells..

## Methods

To mimic a micro-circular flow within a voxel, we performed a DW-NMR measurement using a rotating Couette cell, with the RheoNMR system [2], inside a 7-T vertical scanner (Bruker). The inner cylinder of the Couette cell (1.7cm ID, 1.9cm OD) is rotated by a stepper motor at a frequency of 0.96 rpm, creating a shear flow in the fluid within the cell (PDMS, 1000cst). PGSE experiments were performed with TR/TE= 6000/300 msec,  $\Delta/\delta=200/12$  msec,  $G_d=0-60$  mT/m (65 values). Data-analysis and simulations were performed using Matlab™ and Mathematica™.

## Results and Discussion

Simulations of the voxel-wise attenuations (Fig. 3a & b), demonstrate how shear flow leads to signal attenuation in a PGSE experiment. Notice the dependence of the attenuation on the relative direction of the shear and the gradients. Experimentally, the diffusion coefficient of PDMS in the absence of flow was found to be  $3.75 \times 10^{-6}$  mm<sup>2</sup>/sec. Figure 3 shows the measured DW attenuation in an experiment with a rotating Couette cell. Experimental data fits the predictions of our analytical model. Disparities are probably due to inhomogeneities in the magnetic field and the field gradients (our sample which is much larger than the focal center of our scanner). The oscillating pattern of the Bessel function is apparent in the data. In addition, the attenuation versus gradient strength is characterized by a sharp drop followed by a moderate drop. Such an attenuation profile could be modeled by a bi-exponential function. In this case, a biexponential fit to data yielded diffusion coefficient values of  $D_{\text{fast}} = 0.0148$  and  $D_{\text{slow}} = 0.00037$  mm<sup>2</sup>/sec. However, this bi-exponential model would inappropriately assume that the attenuation profile is composed of a “fast” and “slow” component. Note that in tissues, the velocity distribution will be wider and more heterogeneous, than in the Couette cell. Consequently, the oscillations in the attenuation curve are not predicted to appear in DWI data, and the simplest model describing the attenuation curve will likely be a multi-exponential one.



**Figure 3:** Simulation-based and experimental results from a rotating Rheo NMR system. (a) The simulated effect of a PGSE experiment when the gradients are applied along the x direction on the voxel-wise magnetization (in polar coordinates). (b) The resulting effect of the average bulk flow within a voxel, on the phase of the magnetization. (c) Experimental and theoretical curves of a NMR-PGSE experiment with a rotating Couette cell, mimicking the case of micro-circulation within a voxel.

## Conclusions

This work calculates the effect of simple shear flow profiles on the signal attenuation in a DW-NMR experiment. The induced attenuation patterns are shown to be similar to those usually observed in DW-MRI of biological tissues (pseudo multi-exponential behavior). Such displacement mechanisms may explain some of the observed discrepancies between experiment and theory in biological DW-MRI [3]. The directional dependence (direction of shear relative to direction of gradients) implies that in structures with directional shear (e.g. flow in aligned tubes), the effect of the shear flow may be erroneously interpreted as anisotropic diffusion (with  $\lambda_1$  in the direction of flow). The suggested mechanism of shear induced signal loss applies to the cellular level, and could improve our understanding of the origins of the DW-MR signal.

## References

- [1] Brenner H. & Edwards D.A. Macrotransport processes, Butterworth-Heinmann 1993. [2] Britton M.M. *et al.* Applied Magnetic Resonance, 1998. [3] Assaf Y. & Cohen Y., NMR Biomed. 2002.