Estimation of pore size distributions with diffusion MRI: feasibility for clinical scanners

Gaetan Duchene[1], Frank Peeters[1], and Thierry Duprez[1]
[1]*Medical Imaging, Université Catholique de Louvain, Brussels, Brussels, Belgium*

TARGET AUDIENCE: This study should be of interest for people interested in the quantification of pore size distributions using diffusion MRI.

PURPOSE: Pore size distribution (PSD) estimation has been proposed[1] through the application of a d-PFG (double pulsed field gradients) sequence (double wavevector encoding) with zero mixing time and infinite diffusion time Δ under the short gradient pulse approximation. Such an idealization is not valid for clinical scanners. In this work, we investigate the effect of finite gradient durations δ on PSD's estimation and assess the feasibility of the technique on clinical scanners on the basis of simulations. We also discuss the choice of experimental parameters and the influence of noise.

METHODS: Application of a d-PFG-sequence with varying gradient strengths G and relative angles Φ between the two pairs of gradient pulses leads to an integral equation for the PSD. In discrete form it can be written as a matrix equation[2]: $\boldsymbol{E} = K\,.\boldsymbol{P}$. Here the PSD is a vector $\boldsymbol{P}$ with components $P_i = P(a_i)$ (a_i is the i-th pore size), $\boldsymbol{E}$ is a vector with the measured signal attenuations $S(q)/S(0)$ for different pairs (q, Φ) ($q = \gamma G\delta/2\pi$) and the kernel matrix K depends on the pore's geometry as well as the gradient waveform and can be calculated numerically with the Multiple Correlation Function (MCF) method[3]. Inverting this equation to get $\boldsymbol{P}$ constitutes an ill-posed problem: the least-squares method will yield unstable solutions. We solved the problem using Tikhonov regularization[4] .
As our 'ground-truth' distribution, we used a Gaussian PSD (mean $25\mu m$ and standard deviation $6.25\mu m$) of cylinders with radii a ranging from 0 to $50\mu m$. In each simulation, $\boldsymbol{E}$ was generated with a 100 points distribution (with resolution 0.5 μm to mimic a continuum of pores) for q and ϕ ranging equidistant as $0 \rightarrow q_{Max} = \gamma G_{Max}\delta/2\pi$ and $0 \rightarrow 180°$ respectively and taking the exact gradient waveform into account. The estimation was then performed to obtain a 20 points $\boldsymbol{P}$ from which the estimation's error (EE) was assessed through the sum of squared differences with the ground-truth PSD. The influence of δ on EE was investigated for conditions corresponding to two clinical and one pre-clinical MR-scanners with maximum gradient strengths of 40, 80 and 400 mT/m and with $\Delta = 200ms$. We also evaluated the consequences of changing the number of (q, ϕ) values and the effect of adding noise.

RESULTS: Figure (**A**) represents 4 estimated PSD's for data $\boldsymbol{E}$ generated using increasing gradient durations δ while the estimation of $\boldsymbol{P}$ used an ideal gradient ($\delta = 0$) kernel K . The influence of δ on the EE for 3 gradient strengths (16 q-values , 10 Φ-values) is shown on Fig (**B**). The effect of decreasing the number of q values is shown on Fig (**C**). Finally, Fig (**D**) displays systematic and random errors on the PSD when using a 3% noise corrupted signal. Note that, unlike in Fig (**A**), in Figs (**B**), (**C**) and (**D**) the estimation kernel K was calculated using the exact gradient waveform ($\delta \neq 0$).

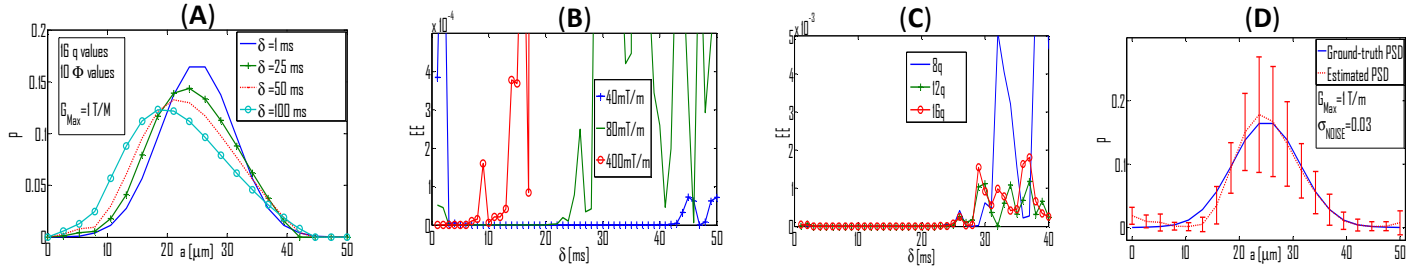

FIGURE: (**A**) Four estimated PSD's for increasing δ ($\Delta \rightarrow \infty$). (**B**) EE versus δ for 3 G_{Max} values (16 q and 10 Φ values, $\Delta = 200ms$). Note the cut-off of EE axis at 5.10^{-4}. (**C**) EE versus δ for varying number of q values ($G_{Max} = 80mT/m$,10 Φ values, $\Delta = 200ms$). (**D**) Influence of noise (a bar represents 1 standard deviation, $\Delta \rightarrow \infty$) .

DISCUSSION: The shift to smaller pore sizes that affects PSD's when δ increases (Fig. (**A**)) is consistent with the 'pore shrinkage effect' of finite gradient-pulse widths described in reference[5]. Although this artefact could suggest a increasing EE with δ, the curves in Fig (**B**) exibhit rather a plateau at minimum EE, surrounded by two areas of inaccurate estimation. The plateau can be explained by the fact that (unlike in Fig(**A**)) the estimation has been done with a kernel K that accounts for the actual temporal profile of the gradient ($\delta \neq 0$). However, as δ is increased, so is q_{Max} (with G_{Max}fixed) and so the attenuations E become to smal for any Φ, leading to inaccurate estimations (i.e. to many data are measured in the noise in practice). On the other hand, at to short δ (too small q_{Max}), the undersampled signals cannot detect pore-induced signal variations leading again to inaccurate estimations. Figure (**C**) shows that decreasing the number of q-values has no significant effect except in the inaccuate region. Varying the number of Φ values (not shown here) leads to similar conclusions. Figure (**D**) shows that noise induced systematic errors occur when estimating PSD for small sizes. This can be understood by noting that smaller pores are those for which higher q-values are needed and thus noisier signal attenuations are used. Large fluctuations can arise due to the noise (see bars standard deviation) and when designing an experiment, one should keep in mind that selecting δ, and thus q_{Max}, requires a trade-off between completely sampling $\boldsymbol{E}$ and avoiding noisy data. Finally, as we used $\Delta = 200ms$ in (**B**) and (**C**) the free mean displacement during the diffusion period may be approximated by $\sqrt{2D\Delta} = 30\mu m$ (D the water diffusion coefficient). Nevertheless, we correctly estimated PSD's up to $50\mu m$, which is larger than the mean displacement encountered in about 15% of our pores. This was also recently observed in reference[6].

CONCLUSION: Accurate quantification of pore size distributions seems possible on clinical MR-scanners as long as the exact gradient waveform and the pores geometry are taken into account in the estimation procedure and if the data are not too noisy. Extension of the method to more complex pore geometries and with intra- and extracellular compartments is in progress.

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