Protocol optimization of the double pulsed field gradient (d-PFG) based filter-exchange imaging (FEXI) sequence enables comparative studies of the diffusional apparent exchange rate (AXR) at reduced scan times and smaller group sizes.

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Introduction: Alteration in the rate of water exchange across cellular membranes is commonly present in brain pathologies involving edema, as for example stroke, tumor and infection [1]. Diagnosis, characterization and follow-up of treatment in these conditions may be improved by a method for fast quantification of water exchange. Filter-exchange imaging (FEXI) provides a non-invasive means for mapping the diffusional water exchange by measurement of the apparent exchange rate (AXR) [2]. The aim of this study was to optimize the FEXI protocol in order to maximize the precision of the AXR estimate, by using the Active Imaging approach described by Alexander [3]. Here, we present a new protocol offering a 30% reduction in the coefficient of variation (CV) of the AXR estimate, compared to previously presented protocols [2]. The group size required, given some effect sizes, to achieve a predetermined statistical power is compared for varying ROI sizes.

Theory: FEXI is based on a double pulsed field gradient (d-PFG) sequence, and uses two pairs of diffusion-weighting gradients that are separated by a variable mixing time (t_m) [4]. The first encoding block, which has a constant b-value (b_f), acts as a low-pass filter and shifts the contribution of signal towards water exhibiting a lower apparent diffusion coefficient (ADC). The reduced diffusion coefficient (ADC′) restores to equilibrium (ADC_{eq}) during the mixing time to a degree that is given by $ADC'(t_m) = ADC_{eq}[1 - \sigma \exp(-AXR \cdot t_m)]$, where $\sigma = 1 - ADC'(0)/ADC_{eq}$. In practice, the signal is sampled for a range of mixing times and b-values, and the total signal expression for mixing time (k) and b-value (l) is given by $S_{kl} = S_0\exp(-(TE + TE_f)/T_2)\exp(-t_{mk}/T_1)\exp(-b_l ADC'(t_{mk}))$, where S_0 is the non attenuated signal and TE_f is the echo time for the filter block. Assuming that the signal noise is normally distributed and building on the Active Imaging approach [3], we derived an expression for the Cramer-Rao Lower Bound (CRLB). Thereby, a lower bound of the variance in the estimated AXR can be computed for any protocol and set of model parameters, contributing to a suitable objective function for protocol optimization.

Method: The variables considered in the optimization of the FEXI protocol were the composition of mixing times and b-values, the filter strength (b_f), the number of acquisitions with the filter turned off and the readout time (τ_{EPI}). Previous work shows that the ADC is optimally estimated using only two b-values, a low (b^0) and a high (b^{Max}) [5]. We extended this to the mixing times, assuming that only a low (t_m^0),and a high (t_m^{Max}) mixing time would be optimal, since the AXR model can be seen as a two-step exponential fit. The set of possible protocols was defined by the current FEXI implementation, which requires all combinations of b-values, mixing times and diffusion encoding directions to be acquired. Protocol variables, presented along with the ranges over which the optimization took place, were $t_m^{Max} \in [0.25, 0.6]$ s, b^{Max} and $b_f \in [200, 1300]$ s/mm^2, $f(t_m^0)$, $f(b_f^0)$ and $f(b^0) \in [0.1, 0.8]$, $\#t_m \in [3, 10]$, and $\tau_{EPI} \in [30, 100]$ ms, where the $f(\cdot)$ are the fractions of acquisitions with the lower mixing time, lower b-value and with the filter turned off. These were optimized using the stochastic Self Organizing Migrating Algorithm (SOMA, http://www.ft.utb.cz/people/zelinka/soma/). The objective function was defined as the CV of the AXR, averaged over model parameter intervals and with the standard deviation in the CV definition replaced with $CRLB^{½}$. In order to optimize for biophysically plausible tissue compositions, the intervals were generated using the two-component exchange model [6], and defined as: $f_f \in [0.4, 0.7]$ μm^2/ms, $D_f \in [0.9, 1.3]$, $D_s \in [0.1, 0.3]$ μm^2/ms, $\tau \in [1.0, 4.0]$ s. Here, f_f is the fraction of fast diffusing water, D_f/D_s is the diffusivity of the fast/slow fraction and τ is the intracellular exchange time. Protocol optimization involved three constraints: maximum scan time of 15 minutes for acquiring seven slices at spatial resolution 3×3×5 mm^3, acquisition of six diffusion-encoding directions, and b-value below 1300 s/mm^2 (required for the assumption that the signal was normally distributed). The optimized protocol was used to determine group sizes in a comparative study given varying effect and ROI sizes, where a statistical power of 0.8 at a significance level of 0.05 was required. The effect size was defined as the difference in population means ($\Delta\mu$) divided by the inter-subject standard deviation (σ_i) (approximated to 0.14 s^{-1} in a previous study [2]). Finally, the efficacy of the protocol to produce AXR maps was tested in one volunteer at a Philips Achieva 3T system. Total scan time was 13 min with $TE/TE_f/TR$ = 68/38/2500 ms.

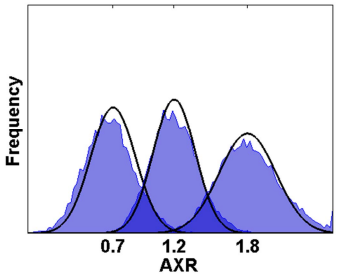

Fig. 1 (left) – Distribution of measured AXR around the true value as predicted by the CRLB (black lines) compared to posterior distributions (blue fields) generated by bootstrapping.

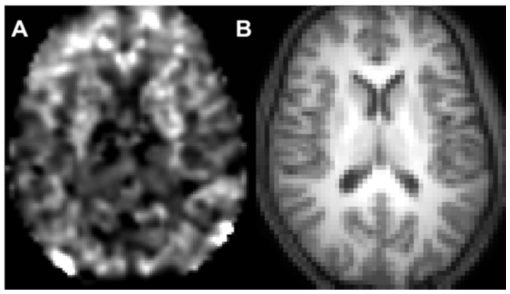

Fig. 2 (right) – In vivo AXR map (A) and reference T1-weighted image (B) obtained on a healthy volunteer using the optimized protocol. High AXR-values were observed frontally, but also in the putamen.

Results: Comparison to bootstrapped data first verified the accuracy of the CRLB based objective function at determining variability (Fig. 1). The assumption that using only two different mixing times is optimal was verified by observing that the CRLB increased monotonically when the signal was sampled at a third intermediary mixing time. An optimized protocol is presented in Table 1, which has a 30% reduction in CV compared to the protocol used in a previous study [2]. The AXR map obtained using the protocol is shown in Fig. 2A, which reproduce the previously observed high AXR in anterior regions of the brain [2]. Table 2 lists the group sizes required in a study searching for potential AXR differences between two groups when using the optimized protocol for the average CV value.

t_m^{Max} (ms)	b^{Max} (s/mm^2)	b_f (s/mm^2)	$f(t_m^0)$
442	1300	830	2/4
$f(b^0)$	$f(b_f^0)$	$\#t_m$	τ_{EPI} (ms)
3/9	1/4	4	63

Table 1 (left) – Optimized protocol for human white matter prior distribution.

Table 2 (right) – Group sizes (n) required for a statistical power of 0.8 at a significance level of 0.05, assuming different effect sizes and varying ROI size.

		n		
Effect size ($\Delta\mu/\sigma_i$)		1	2	3
ROI size	1	60	16	8
(#voxels)	3	31	9	5
	10	21	7	4

Discussion and conclusions: Using the new protocol with a scan time below 15 minutes, the issue whether any patient group, in a given brain region, has alterations in AXR three times larger than the inter-subject standard deviation can be addressed using as few as four individuals per group, on average. However, the group size also depends on the specific properties of the investigated tissue. Limitations of the method and protocol presented here include model assumptions, imprecise knowledge of model priors, the Gaussian approximation of the noise distribution, and a slight protocol dependence on the number of slices. The two primary hardware factors that could be improved to reduce the CV of the AXR are the maximal gradient amplitude and the duty cycle of the gradients. Future work will investigate the potential gain of optimizing the protocol for a narrower range of priors, specific for the tissue under investigation.

References: [1] Huber *et al.* Molecular Aspects of Medicine 2012;33:691-703 [2] Nilsson, *et al.* MRM 2012;doi:10.1002/mrm.24395 [3] Alexander MRM 2008;60:439–448 [4] Lasiĉ *et al.*MRM 2011;66:356-365 [5] Eis and Hoehn-Berlage JMR 1994;107:222-234 [6] Nilsson *et al.* JMR 2010;206:59-67