Optimal sampling settings for reliable Blood Brain Barrier permeability quantification using DCE-MRI, a Monte Carlo approach

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Target Audience: MRI physicists, Neuroscientists

Introduction A dysfunctional Blood Brain Barrier (BBB) may play a pivotal role in the etiology of cerebral small vessel disease [1]. To study its role, we aim to quantify the BBB permeability using DCE-MRI analysed by pharmocokinetic modelling. The parameter in the Patlak model that links to the BBB permeability is K_i, which is very low even in a dysfunctional BBB, i.e. range 0.001-0.01 min^{-1} [2,3]. Due to the slow leakage, it is expected that a prolonged scan duration is required for a reliable analysis. However, this leads to a reduced patient cooperation and comfort, and diminishes clinical applicability. Furthermore, on one hand, in the late phase contrast changes are graduate allowing a low temporal resolution in favour of spatial coverage, spatial resolution or signal-to-noise-ratio. On the other hand, it is expected that a high temporal resolution is required in the first phase to accurately sample the (rapid) blood phase which is required for the pharmocokinetic modelling [3].

Purpose Using Monte Carlo simulations, we aim to determine the optimal sampling settings for reliable permeability (K_i) and plasma volume (v_p) determination: 1) a single temporal resolution, i.e a single sample frequency (Δt), versus dual temporal resolution, i.e. a high initial sample frequency ($\Delta t1$=2.5s for 1:30 min) followed by a lower sample frequency ($\Delta t2$=10s—3min), and 2) scan duration.

Method In our Monte Carlo simulations we generated first a model tissue enhancement curve using a simulated biexponential AIF and the pharmacokinetic (Patlak) model [4]. Next, sample frequency dependent noise is added as well as jitter on the time axis (Fig 1). This curve is fitted using Patlak plots [4] yielding values for K_i and v_p which are compared to the input parameters (Bias = (output – input)/input parameter [%]). Every run (n=1000) results in an accuracy (median bias) and precision (5%/95% confidence intervals). This is repeated for combinations of K_i, (0.0005 – 0.01 min^{-1}), v_p, (0.01—0.1), scan duration (5-30 min) and sample frequency (2.5s-3min) for both single and dual temporal time resolution.

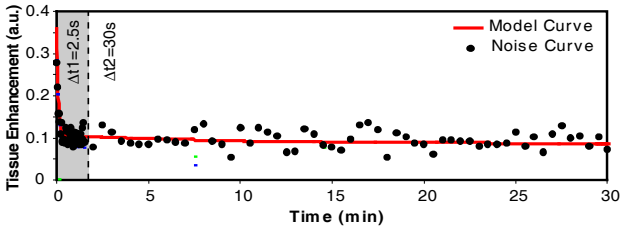

Fig 1: Dual temporal model tissue curve (red line) to which noise is added (black dots). Parameters: $\Delta t1$=2.5s; $\Delta t2$=30s, v_p = 0.02, K_i = 0.002 min^{-1}.

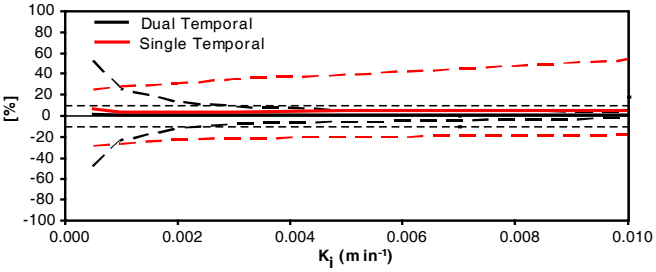

Fig 2: Relative accuracy (solid lines) and precision (dotted lines) of K_i as a function of K_i for a single (red) and dual (black) temporal resolution. Parameters: single temporal: Δt=30s, dual temporal: $\Delta t1$=2.5s; $\Delta t2$=30s, v_p = 0.02, Scan duration = 20 min.

Results and Discussion A dual temporal resolution shows an improved accuracy and precision of K_i (Fig 2) and v_p (data not shown) over the single temporal resolution. This means that accurate sampling of the blood phase tissue curve and arterial input function is required, while in the late phase a lower time resolution is sufficent. For dual temporal resolution, we find in all our simulations that typically the accuracy of K_i and v_p is high, but the precision is the critical factor. Favourable for precise K_i are lower v_p, higher K_i, or longer scan duration. Favourable for precise v_p determination are higher v_p, lower K_i, short scan duration, or longer $\Delta t2$. Prolonged sampling of the late phase, i.e. a longer scan duration, improves the precision of K_i, in particular for small K_i-values (0.0005-0.003 min^{-1}) (Fig 3). However, there is a degree of saturation: scanning beyond 15-20 minutes (for $\Delta t2$ =30s) has limited additional value for K_i, while for v_p it is disadvantageous (data not shown).

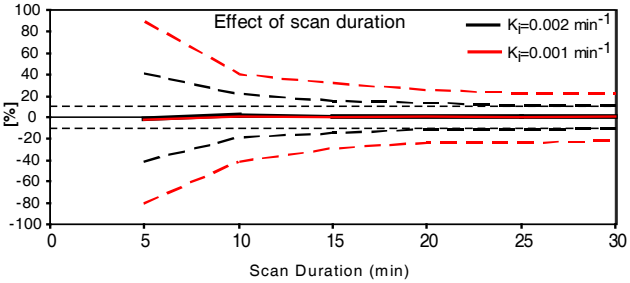

Fig 3: Relative accuracy (solid lines) and precision (dotted lines) of K_i as a function of scan duration for K_i = 0.001 min^{-1} (red) and 0.002 min^{-1} (black) and dual temporal resolution. Parameters: $\Delta t1$=2.5s; $\Delta t2$=30s, v_p = 0.02

Conclusion Using a dual temporal resolution protocol improves the reliability of K_i and v_p. A scan duration of 15-20 minutes allows a reliable K_i and v_p determination (5%/95% CI ≤ -/+ 10%) for K_i and v_p values down to K_i=0.002 min^{-1} and v_p = 0.01. Our next step is to validate these results in vivo.

References [1] Persidsky Y. et al. J Neuroimm Pharmac 1: 223 (2006); [2] Taheri S, et al. MRM 65: 1035 (2011); [3] Jelescu I.O., et al. JMRI 33:1291 (2011); [4] Patlak CS, et al. J Cereb Blood Flow Metab 3:1 (1983)