Assessment of a Continuous Multi-Compartmental Intra-Voxel Incoherent Motion (IVIM) Model for the Human Brain

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Introduction: Diffusion-weighted MRI (DWI) is a non-invasive imaging technique that detects thermally driven, random motion of water molecules in living tissue and is able to characterize its interaction with cell membranes, macromolecules and potential diffusion barriers in terms of an apparent diffusion coefficient ADC with or without restriction. Le-Bihan proposed a bi-exponential model to separate intra- and extracellular diffusion from incoherent motion of water molecules within randomly oriented capillaries – IVIM [1-3]. Several studies have utilized IVIM for various clinical applications in the abdomen (tumors, liver cirrhosis) and animal experiments [4]. However, studies evaluating this technique in the human brain are rare so far and without further consensus about its clinical value, application and comparison to currently conventional perfusion techniques [5].

The presence of noise and patient motion in DWI, which cannot be sufficiently eliminated through post-processing or special acquisition techniques, may substantially affect IVIM parameter estimation reliability [6]. Especially low number b-value DWI suffers from the intrinsic inability to differentiate bulk or peripheral motion (whole body movement, bowel motion, breathing, pulsation due to cardiac cycle) from the incoherent molecular motion (diffusion and perfusion). Additionally, the quantitative assessment of parameters in the IVIM-context is more complicated in the brain due to the fact of anisotropic diffusion properties of several brain structures, primarily the white matter but also translational interface structures between cortical, subcortical and deep white matter. The deconvolution of multi-exponential processes like water diffusion in living tissue is a strongly ill-posed problem and the necessity for a large number of signal points and high SNR are imminent for a reliable separation of more than one exponential time constant [7-10]. We are hereby proposing a semi-continuous multi-exponential approach to better characterize diffusion properties in the IVIM-context for the human brain.

Methods: Eight volunteers were examined on a 3T whole body MR-system (Philips Achieva, Best, The Netherlands) and Dual Nova gradients (80mT/m, 200 T/(m·s) with a whole brain single shot diffusion weighted sequence: voxel size 2x2x2mm^3, 36 slices, TR=4.1s, TE=66ms, matrix 116x112, 32 b-values from 0 to 2000 s/mm^2 with a higher sampling density in the range of low b-values, three orthogonal gradient directions (x,y,z) – total scan time 6.3min. The data were analyzed voxel as well as ROI-based with a regularized non-negative least squares (NNLS) and the corresponding diffusion signal kernel for 121 log-spaced diffusion coefficients between 0.1 and 1000 μm^2/ms (Fig.1, top). Each analyzed signal decay curve results in a diffusion distribution (spectrum) displaying the diffusion fraction for each apparent diffusion coefficient ADC (in the following denoted as D) (Fig.1, bottom). Taking into account that brain tissue exhibits highly anisotropic diffusion behaviour, the signal decay was analyzed for each orthogonal diffusion gradient encoding and for an overall "isotropic" b-value weighting from all three gradient directions. All individual DW-images were eddy current corrected and registered to the b=0 image. The novelty of this hereby introduced approach lies in its semi-continuous nature and therefore its ability to derive quantitative diffusion fraction maps from any arbitrary D or range of D-values. For example, the vascular perfusion fraction vPF can be determined from the inverse solution of the signal decay function (fig.1, top right) by taking the ratio of the integral D between 10-100μm^2/ms and the total integral.

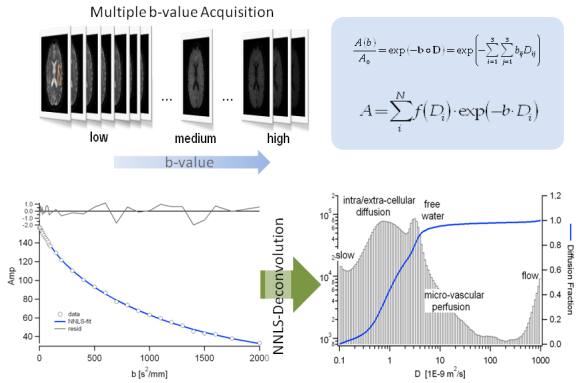

Fig.1: Data acq.scheme, mathematical diffusion kernel for NNLS de-convolution (top), signal decay curve and diffusion spectrum (bottom)

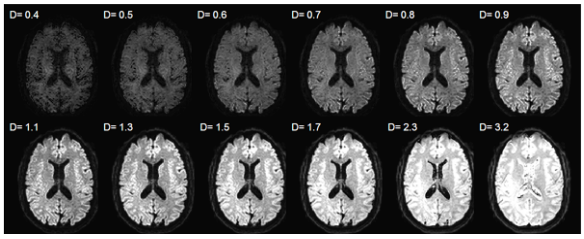

Fig.2: Quantitative diffusion fraction (DF) maps for any arbitrary apparent diffusion coefficient or range of D (normalized 0-1.0)

Results: 32 b-values from 0 to 2000 s/mm^2 allows for a wide range of incoherent motion detection of water protons in the human brain. Pixel-wise SNR evaluations (amplitude at b=0 divided by the standard deviation of the NNLS-fit residual) exhibit values from 50 up to 500 across the brain, depending on brain area, subject cooperation (head movements) and T_2 or susceptibility signal losses. SNR>150 proved to be sufficient for the separation of three incoherent motion regimes: **slow: D<0.5**, **intermediate: 0.5<D<3.0**, **fast: D>10.**. SNR>250 could even distinguish CSF diffusion (D=3.0) from vascular perfusion (D>10.0) and flow (D>500) as well as normal tissue diffusion from very slow (D<0.2) modes (units in μm^2/ms) (cf. Fig.1 bottom right, overall D-distribution from one entire axial slice through the brain).

Discussion: Since our numerical approach is quantitative and semi-continuous (121 points), individual motion specific diffusion fractions (DF) can be calculated for each arbitrarily desired D and displayed as quantitative DF-maps ranging from 0 to 1.0 (fig.2). The classical IVIM-model requires only one mono-exponential fit for the medium-to-large b-value range and estimates the perfusion fraction from its interception with the y-axis and the difference to the b0-amplitude. This approach is prone to fail in the brain for multiple reasons: i) low SNR at high b-values with contributions from Rician noise that will even make a classical mono-exponential decay look like bi- or multi-exponential, ii) brain exhibits more than only two distinct modes of diffusion, iii) the anisotropic diffusion properties in brain require a different approach compared to isotropic organs like liver.

With regularized NNLS and genetic algorithm we were able to achieve robust DF-maps from human brain in clinically feasible scan times (6 min) with robust parameter estimates.

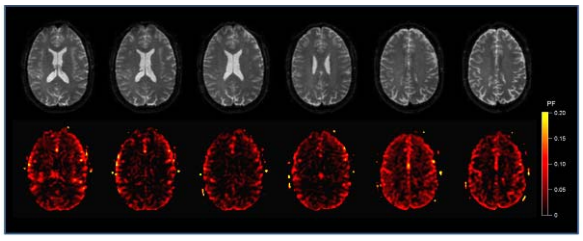

Fig.3: b0-DWI (top row) and corresponding perfusion fraction (PF) images calculated from the NNLS diffusion distribution. The PF was calculated with a range of D between 5-500 μm^2/ms.

Conclusion: Our aim of interest was to test performance and validity of a novel semi-continuous multi-exponential pulsed field gradient (PFG) diffusion signal analysis for the detection and possibly quantification of vascular perfusion in the brain previously described primarily for highly perfused organs like liver and kidney. Attempts to use the IVIM-model also in brain have been sporadic and remained so far inferior to the standard procedures of Gd-based perfusion or ASL-techniques possibly due to the complex diffusion properties in the nervous system and the inherently low SNR. Classical minimum chi-square (LS) multi-exponential fitting algorithms are susceptible to fail without sufficient SNR. We show that regularized NNLS-techniques show better performance on the estimation of IVIM parameters from noisy data and might revive the attempts of using IVIM-based methods in the brain.

References: [1] Le Bihan D, Radiology 161 (1986):401; [2] Le Bihan D, J Comput Assist Tomogr. 15 (1991),19; [3] Le Bihan, D. et al. *Radiology,* 168 (1988),497; [4] Henkelman, R.M. et al., MRM 32 (1994), 464; [5] Henkelman, R.M., MRM 16 (1991), 470; [6] ; Schneider, M. et al. ISMRM 2012, #2029; [7] Whittall, K. et al. MRM 41 (1999), 1255; [8] Whittall, K., MacKay, A., JMR 84 (1989), 134; Whittall, K. in "Signal treatment and signal analysis in NMR", p. 44, Elsevier, Amsterdam, 1996; Bennett, KM et al. MRM 50 (2003), 727