# IVIM-MRI Reproducibility for Functional Parametric Mapping of Treatment Response in High-Grade Glioma

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**TARGET AUDIENCE**: Researchers interested in diffusion MRI methods for quantifying perfusion-based changes in brain tumors.

**PURPOSE**: Perfusion MRI is often used in the evaluation of brain tumors, specifically in studies focusing on tumor treatment. Traditional methods for measuring perfusion rely on the injection of a contrast agent (CA) followed by fast $T_2^*$- (DSC-MRI) or $T_1$-weighted (DCE-MRI) measurements. Non-CA based methods, such as intravoxel incoherent motion (IVIM)-MRI [1], have also been shown to be sensitive to perfusion. Recently, IVIM-MRI was implemented in brain tumor patients, demonstrating use for deciphering tumor grade [2] and distinguishing recurrent tumor from chemo-radiotherapy treatment effect [3]. The effect of longitudinal treatment (e.g. bevacizumab) on IVIM model parameters in glioma is unknown. One tool that may help elucidate these effects is functional parametric mapping. Building on the framework of functional diffusion mapping (fDM) [4], a similar technique may be applied to longitudinal IVIM measurements to identify significant perfusion-based changes in tumor tissue. The application of this technique, however, requires knowledge of the expected change in IVIM parameters in healthy tissue over time. Therefore, the goal of this work is to establish IVIM reproducibility in healthy subjects for use in functional IVIM mapping of treatment response in brain tumor patients.

**METHODS**: Healthy subjects (n = 6) were scanned on two separate occasions, a week apart, at 3T (Achieva, Philips Healthcare) using a 32 channel head coil. As part of the scan protocol, an IVIM-MRI acquisition [5] (DW-SE ssEPI, TR = 6 s, TE = 48 ms, voxel size = 2.5 x 2.5 x 5.0 $mm^3$, NEX = 2, 3 directions, $b$ = 0, 25, 50, 75, 100, 200, 500, 1000 $s{\cdot}mm^{-2}$) was implemented. The multiple $b$-value data were fit in a least squares manner to a bi-exponential model, using a two-step process [2,5], to extract the perfusion fraction ($f$), pseudo-diffusion coefficient ($D^*$), and tissue diffusion coefficient ($D$). Measures of $ADC$ were also computed ($b$ = 0, 1000 $s{\cdot}mm^{-2}$). To avoid contributions from CSF and large vessels, voxels included in the analysis exhibited $f < 0.3$, $D < D^* < 100\ 10^{-3}mm^2{\cdot}s^{-1}$, and $D < 2.0\ 10^{-3}mm^2{\cdot}s^{-1}$. Changes in white matter over the two imaging sessions were used to establish reproducibility of each model parameter using previously established techniques [6]. Following fDM methodology [4], IVIM difference maps were created from longitudinal measurements (baseline, 2 weeks post-Tx) in high-grade glioma patients (n = 6) undergoing bevacizumab therapy and thresholds were set using the 95% CI from the reproducibility data.

Table 1. Reproducibility analysis for IVIM parameters in healthy brain

| Parameter | Mean | Mean Diff. | 95% CI for Mean Diff. | wSD | wCV(%) | r |
|---|---|---|---|---|---|---|
| f | 0.0616 | 0.0037 | ±0.0036(5.8%) | 0.0035 | 5.7% | 0.0098 |
| D* | 9.0504 | 0.1923 | ±2.1995(24.3%) | 1.4277 | 15.8% | 3.9547 |
| D | 0.6804 | 0.0045 | ±0.0285(4.2%) | 0.0187 | 2.7% | 0.0517 |
| ADC | 0.7372 | 0.0059 | ±0.0267(3.6%) | 0.0178 | 2.4% | 0.0492 |

*Values for D*, D, and ADC are x $10^{-3}$; repeatability (r) = 2.77 x wSD

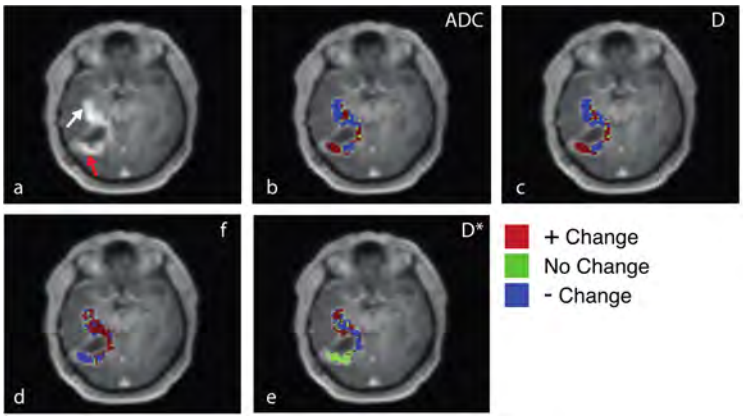


Figure 1. Functional IVIM maps in recurrent glioma. a) Post-Gd $T_1$w image. b) Δ$ADC$, c) Δ$D$, d) Δ$f$, and e) Δ$D^*$ maps.

**RESULTS AND DISCUSSION**: The IVIM parameters $f$ and $D$ were found to be reproducible (Table 1) with a 95% CI (for the mean difference) and a wCV less than 10%. $ADC$ was also found to be reproducible with metrics similar to $D$. $D^*$ was less reproducible with wCV≈16%. Example functional IVIM maps (Fig. 1) show an increase in perfusion ($f$, $D^*$) and decrease in diffusion ($D$, $ADC$) in an anterior enhancing tumor region (white arrow), later confirmed as disease progression. In comparison, increased diffusion ($D$, $ADC$), decreased $f$, and no change in $D^*$ were observed in the posterior enhancing region (red arrow) suspected to be chemo-radiotherapy treatment effect. Across all patients (Table 2), $f$ was found to predominately increase with treatment. Additionally, a robust decrease in $D$ was observed with treatment, however $ADC$ remained relatively unchanged, with a mean decrease of only 3.9%. This observation further emphasizes the need for perfusion-insensitive diffusion measures when monitoring treatment response.

**CONCLUSION**: IVIM model parameters reflecting both perfusion ($f$) and diffusion ($D$) were shown to be reproducible in healthy brain. IVIM-MRI, therefore, may potentially be used in monitoring brain tumor treatment response. In this regard, functional mapping of IVIM parameters may help identify local regions of tumor progression and/or treatment effect. Further investigation into this technique may elucidate its use as a tool for predicting tumor treatment response.

Table 2. Changes in IVIM parameter estimates 2 weeks post-Tx

| Patient | TTP (mo) | Δf (%) | ΔD* (%) | ΔD (%) | ΔADC (%) | % Δ Vox |
|---|---|---|---|---|---|---|
| 1 | 8.1 | 0.016 (37.0) | -0.723 (-2.9) | -0.263 (-25.0) | -0.011 (-1.0) | -2.9 |
| 2 | 13.8 | 0.036 (32.8) | 1.122 (6.6) | -0.140 (-11.0) | -0.054 (-4.0) | -13.5 |
| 3 | 13.7 | 0.026 (30.9) | -2.534 (-23.5) | -0.160 (-12.9) | -0.152 (-11.8) | -6.2 |
| 4 | 2.6 | 0.051 (37.2) | -9.015 (-43.7) | -0.087 (-7.7) | 0.022 (1.7) | -7.5 |
| 5 | 2.7 | 0.028 (45.3) | 9.034 (99.4) | -0.260 (-23.0) | 0.023 (1.9) | -9.8 |
| 6 | N/A | -0.005 (-6.3) | 0.743 (12.5) | -0.115 (-11.3) | -0.107 (-10.1) | 7.7 |

*Values for ΔD*, ΔD, and ΔADC are x $10^{-3}$; Δ Vox = Change in number of voxels analyzed

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