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Assessing Parameter Identifiability for Tissue Microstructure Characterization with Optimized IMPULSED Diffusion MRI Acquisition Protocol

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ABSTRACT

Purpose: IMPULSED diffusion MRI estimates microstructural parameters (cell size, intracellular volume fraction) promising for monitoring radiation treatment response, but parameter identifiability limits reliable model fitting since multiple parameter combinations can produce similar signal curves. This study determines which IMPULSED parameters can be reliably estimated under an optimized acquisition.

Methods: Synthetic signals from 10,000 uniformly sampled parameter sets (r, v_{in}, D_{in}, D_{ex}, β_{ex}) were generated using a Bayesian-optimized protocol at SNR=20 across three pulse types (PGSE, OGSEn1, OGSEn2). Independent per-pulse linear regressions yielded a 3×5 sensitivity matrix; SVD identified resolvable parameter combinations against a noise threshold of 0.04.

Results: Regressions fit well (R^2 = 0.91/0.84/0.82). Two principal directions exceeded the noise floor: the first (93.2% variance) was dominated by D_{ex} (−0.71), v_{in} (+0.54), and r (−0.44); the second (6.2%) by r (+0.63), v_{in} (+0.59), and D_{in} (+0.50).

Conclusions: Only the combination {r, v_{in}, D_{ex}} is strongly identifiable at clinical SNR. We recommend fitting these three with informative priors while fixing D_{in} and β_{ex}.

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INTRODUCTION

Diffusion magnetic resonance imaging (dMRI) characterizes tissue **microstructure** by measuring water displacement under diffusion-weighted gradients. **Imaging Microstructural Parameters Using Limited Spectrally Edited Diffusion (IMPULSED)**[1] combines pulsed (PGSE) and oscillating gradient spin echo (OGSE) waveforms to probe multiple effective diffusion times, enabling estimation of cellular-scale parameters: cell radius (r), intracellular volume fraction (v_{in}), intracellular diffusivity (D_{in}), and extracellular diffusion parameters (D_{ex}, β_{ex}). These quantifications have shown promise as biomarkers for monitoring radiation-induced microstructural changes in tumors.

However, IMPULSED parameter fitting is intrinsically **ill-conditioned**, where different parameter combinations can produce nearly indistinguishable signal decays, particularly under the limited SNR of clinical **1.5T scanners**. Our recent work showed that a Bayesian-optimized acquisition protocol at SNR=20 substantially improves estimation accuracy[3], but the identifiability of individual parameters under that protocol remains uncharacterized. Conventional R^2-based evaluations can appear high even when parameters are strongly collinear and individually unreliable.

In this work, we apply singular value decomposition (SVD) to the parameter–signal sensitivity matrix derived from the **optimized IMPULSED protocol** to identify orthogonal, rank-ordered parameter combinations detectable above the noise floor at clinical SNR, providing actionable guidance on which parameters can be reliably fitted versus constrained by informative priors.

METHODS AND MATERIALS

Data generation: Synthetic IMPULSED signals were generated for 10,000 microstructural parameter sets drawn uniformly from physiologically plausible ranges[2]: $r \in [2, 12]$ μm, $v_{in} \in [0.2, 0.8]$, $D_{in}, D_{ex} \in [0.2, 2.0]$ μm²/ms, and $\beta_{ex} \in [0, 6]$ μm². Signals were simulated across three pulse types using an acquisition protocol previously optimized via Bayesian experimental design at SNR = 20: PGSE ($t_{diff} = 50$ ms, $b = 1000$ s/mm², 7 averages), OGSEn1 ($t_{diff} = 15$ ms, $b = 1000$ s/mm², 7 averages), and OGSEn2 ($t_{diff} = 7.5$ ms, $b = 350$ s/mm², 4 averages).

Sensitivity Analysis: All parameters were z-score normalized to ensure comparable coefficient magnitudes. Independent linear regressions were fitted for each pulse type:

$$y_i = c_0 + c_1 \cdot r + c_2 \cdot v_{in} + c_3 \cdot D_{in} + c_4 \cdot D_{ex} + c_5 \cdot \beta_{ex}, \text{ where } y_i \in \{\text{PGSE, OGSEn1, OGSEn2}\}$$

yielding a 3×5 coefficient matrix $\boldsymbol{C}$ that summarizes per-parameter measurement sensitivity.

SVD identifiability analysis was then applied to the coefficient matrix: $\boldsymbol{C} = \boldsymbol{U\Sigma V^T}$, where $\boldsymbol{U}$ spans the measurement space, $\boldsymbol{\Sigma}$ contains singular values σ_i indicating direction strength, and $\boldsymbol{V^T}$ contains singular vectors representing identifiable parameter combinations. The variance explained by each principal direction was computed as $pVar_i = \sigma_i^2 / \Sigma_j \sigma_j^2 \times 100\%$.

With single-acquisition noise $\sigma = 0.05$ ($SNR = 20$, $S_0 = 1$), signal averaging produced effective noise levels of $\sigma_{PGSE} = \sigma_{OGSEn1} = 0.05/\sqrt{7} \approx 0.019$ and $\sigma_{OGSEn2} = 0.05/\sqrt{4} = 0.025$. The combined 3D-observation noise was $\sigma_{total} \approx 0.04$ (root-sum-of-squares). Principal directions with $\sigma_i > 0.04$ were considered detectable above the noise floor and used to assess parameter identifiability.

RESULTS

Linear regression models demonstrated excellent goodness of fit ($R^2 = 0.910/0.837/0.823$ for PGSE/OGSEn1/OGSEn2, with $RMSE = 0.043/0.060/0.037$, respectively) (**Table 1**), indicating that linear approximation adequately captures parameter sensitivity within the sampled prior ranges. Three principal directions explained 93.2%, 6.2%, and 0.6% of the total measurement variance, with σ_i being 0.20, 0.05 and 0.02 (**Table 2**). Based on the effective noise threshold of 0.04, only the **first two principal directions** were **detectable** while the third direction fell below the noise floor. For the first principal direction, top components of D_{ex}, v_{in} and r contributes $0.7084^2 \approx 50\%$, $0.5393^2 \approx 29\%$ and $0.4397^2 \approx 19\%$ of the variance; for the second principal direction, r, v_{in} and D_{in} contributes $0.6285^2 \approx 40\%$, $0.5899^2 \approx 35\%$ and $0.4927^2 \approx 25\%$ of the variance.

Table 1. Linear Regression Model Coefficients and Fit Quality.

Sequence	r	v_{in}	D_{in}	D_{ex}	β_{ex}	R^2	RMSE
PGSE (y1)	-0.0316	0.0932	0.0043	-0.0938	-0.0007	0.9095	0.0427
OGSE-n1 (y2)	-0.0813	0.0589	-0.0235	-0.0896	-0.0056	0.8373	0.0599
OGSE-n2 (y3)	-0.0381	0.0258	-0.0262	-0.0608	-0.0066	0.8231	0.0373

Coefficients are for standardized parameters (z-scores)

Table. 2: SVD Principal Directions.

Measurement	r	v_{in}	D_{in}	D_{ex}	β_{ex}	σ	$pVar$
1st principal direction	-0.4397	0.5393	-0.1130	-0.7084	-0.0331	0.20	93.2%
2nd principal direction	0.6285	0.5899	0.4972	-0.0248	0.0956	0.05	6.2%
3rd principal direction	0.6397	-0.2436	-0.5155	-0.4933	-0.1499	0.02	0.6%

DISCUSSION

Our SVD analysis reveals a fundamental information-theoretic limit on IMPULSED parameter estimation at clinical SNR. Despite excellent regression fits ($R^2 > 0.82$), only **two of the five degrees of freedom are detectable** above the noise floor, directly demonstrating that goodness-of-fit metrics can be misleading: high R^2 reflects the model's ability to explain measurement variance collectively, not its ability to disentangle individual parameters.

The dominant principal direction (93.2% variance) is composed of D_{ex} (50%), v_{in} (29%), and r (19%), indicating strong collinearity. These parameters' effects on the signal lie nearly along a single direction in measurement space, making simultaneous estimation ill-conditioned. The signed weights show that v_{in} moves opposite to r and D_{ex} along this direction, so any parameter combination that leaves this composite fixed produces nearly indistinguishable signals. This provides a principled explanation for the estimation errors observed in our prior optimized-protocol study, where small-cell and high-v_{in} regions showed the largest RMSE. The second principal direction (6.2% variance) is the only one carrying D_{in} sensitivity but sits only marginally above the noise floor, while β_{ex} contributes negligibly to both detectable directions and is therefore unidentifiable.

Because the analysis is grounded in the sensitivity matrix rather than a specific fitting algorithm, these identifiability limits apply uniformly across NLLS, Bayesian, and deep-learning estimators. The results recommend fitting only {r, v_{in}, D_{ex}} with informative priors from histology or literature, while fixing D_{in} and β_{ex} to reduce estimation variance without sacrificing biological specificity for the parameters most relevant to monitoring radiation-induced microstructural change.

CONCLUSIONS

Using SVD on the parameter–signal sensitivity matrix, we showed that the Bayesian-optimized IMPULSED protocol at $SNR = 20$ supports only two resolvable degrees of freedom despite high goodness-of-fit. The dominant direction (93.2% variance) is a strongly collinear combination of cell radius (r), intracellular volume fraction (v_{in}), and extracellular diffusivity (D_{ex}) — the only reliably identifiable quantities at clinical SNR. D_{in} is weakly identifiable, β_{ex} is not. We recommend fitting {r, v_{in}, D_{ex}} with informative priors while fixing D_{in} and β_{ex}, enabling more reliable cellular-scale dMRI biomarkers for tumor characterization and radiation treatment response monitoring.

REFERENCES

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