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A separable least squares approach for intravoxel incoherent motion (IVIM) MRI

Introduction

Intravoxel incoherent motion (IVIM) MRI[1] allows measuring pseudo perfusion as an extension to diffusion weighted imaging (DWI) measures such as the apparent diffusion coefficient (ADC). Recent applications in oncology[2] makes it an attractive addition to the traditional ADC measurements which could help capturing potential microstructural alterations in disease. However, the use of two compartments model, such as in IVIM, is susceptible to numerical issues[3] and are traditionally solved using nonlinear least squares method. We investigate the stability and precision of recovered IVIM parameters by making use instead of separable nonlinear least squares[4,5] and optionally the addition of a constant compartment.

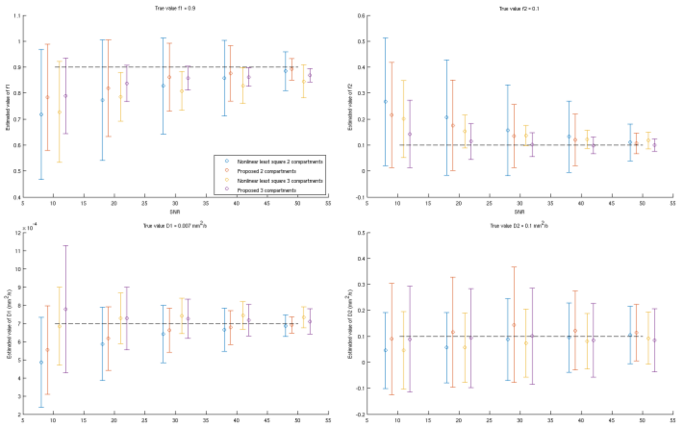

Figure 1 : Mean and standard deviation of 500 trials for a two (resp. three) compartments fit using nonlinear least squares (blue, resp. yellow) and the proposed separable least squares approach (red, resp. purple). Both method generally see an increase in precision and accuracy with higher SNR. The fractions (top) gain in precision and accuracy for a three compartment model fit. For the diffusivities (bottom), the precision is increased for D1 when using a three compartments fit while the accuracy is only increased until SNR 30. The proposed fitting method provides the largest precision increase for the fractions.

Theory

The IVIM model is characterized by a fast diffusing compartment accounting for perfusion and a slower diffusing compartment which represents the traditional definition of diffusivity in tissues. This can be written as

$$S_b / S_0 = f_1 \exp(-b^*D_1) + f_2 \exp(-b^*D_2)$$

with S_b the diffusion attenuated signal, S_0 the non diffusion weighted signal, b the b-values, f_1, f_2 are the signal fractions balancing each compartment of the model and D_1, D_2 are the associated diffusivities. While the IVIM model is non linear in itself, it contains a linear part in f_1, f_2 and a non linear part in D_1, D_2. The IVIM model can be solved using separable nonlinear least squares, which enables solving only non linearly for the diffusivities D_1, D_2 and using linear least squares methods for the fractions f_1, f_2. The key idea lies in replacing the linear parameters by a function of the nonlinear parameters only; assuming D_1, D_2 would be known, the solution to f_1, f_2 can be expressed as the pseudoinverse of the linear system. This expression can be plugged-in implicitly in the original problem[4,5], which now only depends on the nonlinear parameters D_1 and D_2.

Data

To properly capture the IVIM effect, one subject underwent a DWI sequence on a 3T Philips scanner comprised of 7 b0s volumes, 3x DWI of [5, 10, 20, 50, 100, 150, 300, 500] s/mm², 6x 750 s/mm², 20x 1000 s/mm², 10x 1400 s/mm² and 30x 2500 s/mm² for a total of 97 volumes. The acquisition was optimized for angular coverage on all shells. Multiband and SENSE acceleration with a factor of 2 were both employed with TE/TR = 113 ms / 7.1 s and a voxelsize of 2 mm isotropic.

A synthetic dataset was also generated 500 times using the same diffusion weighting as the invivo scan with parameters $f_1 = 0.9$, $f_2 = 0.1$, $D_1 = 0.007$ mm²/s and $D_2 = 0.1$ mm²/s. Data was simulated at SNR 10, 20, 30, 40 and 50 by adding Rician noise where SNR = S_0 / σ with σ the noise standard deviation.

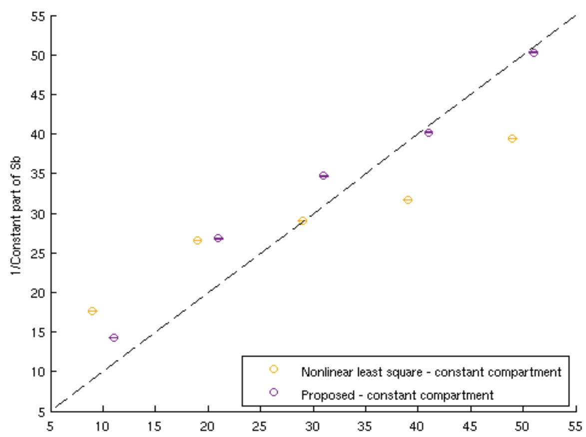

Figure 2: Mean and standard deviation of the signal as computed by the constant compartment and fraction no. 3 for the synthetic experiments. Note how the signal value scales with the SNR in both cases as it captures the Rician noise floor part of the signal. The proposed separable least squares method also follows linearly the SNR while classical nonlinear least squares under represents the noise floor at higher SNR.

Methods

We compared the use of a two compartments IVIM model using both nonlinear least squares and separable nonlinear least squares. We additionally added a constant compartment with a diffusivity close 0 mm²/s to account for the noise floor and non gaussian diffusion present in our datasets[2,6]. We used constraints on each variable to discourage poor solutions due to the nonconvexity of the model3. All fractions f_i were constrained to $0 \leq f_i \leq 1$ while the diffusivities were constrained to $1e\text{-}5 \leq D_1 \leq 2e\text{-}3$, $2.5e\text{-}3 \leq D_2 \leq 1$, $0 \leq D_3 \leq 1e\text{-}5$. We also used starting values of $f_1 = 0.8$, $f_2 = 0.2$, $f_3 = 0$ and $D_1 = 1e\text{-}3$, $D_2 = 5e\text{-}2$, $D_3 = 0$. Note that f_3 and D_3 are the constant parts which were only used for the three compartments model experiments. The separable least square approach also did *not* require starting estimates of f_i, while it can still make use of bounds during optimization.

Discussion & Conclusion

Figure 1 shows the mean and standard deviation of parameters for the synthetic experiments across the 5 tested SNRs. Using a three compartments model to capture the non gaussianity/noise floor effect reduces the variance of the recovered parameters. The use of separable least squares also improves estimation of the fractions. **Figure 2** shows the signal which is captured by adding a third compartment - even though the true underlying model has only two compartments. As expected, the inverse of this captured constant signal part follows approximately the SNR level due to the reduced noise floor with increasing SNR. **Figure 3 and 4** show results on the invivo dataset using two and three compartments. For the two compartments case, both nonlinear and separable least square seems to perform equally with the fast diffusion D_2 being more homogeneous for the separable least square. In the three compartment cases, both method recover plausible diffusivities in the ventricles, unlike the two compartments case. Moreover, the constant compartment captures the non gaussianity and noise floor part as expected. **Figure 5** shows the signal part represented by this third compartment, which is mostly constant across all b-values.

The separable least squares approach reduces the parameters space to only the nonlinear components by implicitly including the linear variables in the optimization procedure.

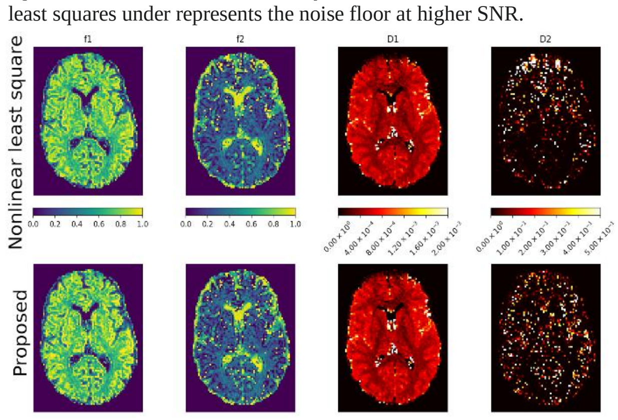

Figure 3 A two compartments model fit with the nonlinear least squares method (top row) and the proposed separable least squares (bottom row). The fractions for the signal part (left) is similar for both cases, but the diffusivities (right) for the IVIM signal are more homogeneous for the proposed method. The nonlinear least squares is underrepresenting the back of the brain while the frontal part exhibits higher diffusivity.

References

1. Le Bihan, D; Breton, E; Lallemand, D; Grenier, P; Cabanis, E; Laval-Jeantet, M (1986). "MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders". *Radiology*. 2. Le Bihan, D., 2017. What can we see with IVIM MRI? *NeuroImage*, (December 2017), pp.1–12. 3. Novikov DS, Kiselev VG, Jespersen SN. On modeling. *Magn Reson Med*. 2018 4. G. H. Golub and V. Pereyra, The Differentiation of Pseudo-Inverses and Nonlinear Least Squares Problems Whose Variables Separate SIAM Journal on Numerical Analysis 1973 5. Golub, Gene & Pereyra, Victor. (2003). Separable Nonlinear Least Squares: the Variable Projection Method and its Applications. Inverse Problems. 6. Jbabdi, S. et al., 2012. Model-based analysis of multishell diffusion MR data for tractography: How to get over fitting problems. Magnetic Resonance in Medicine

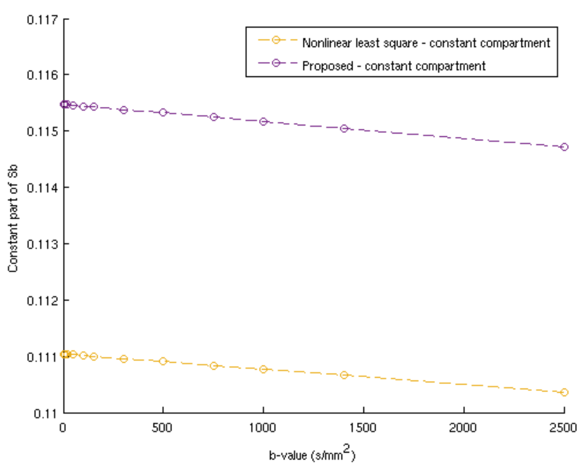

Figure 5: Average signal intensity as captured by compartment f3 and D3 for both methods ordered by b-values for a single slice of the invivo dataset. A decrease of approximately 0.1% in the value representing the noise floor is observed for both case. This is in line with the assumption that this (constant) compartment should be stable across b-values as the noise floor affects equally every acquired volume.

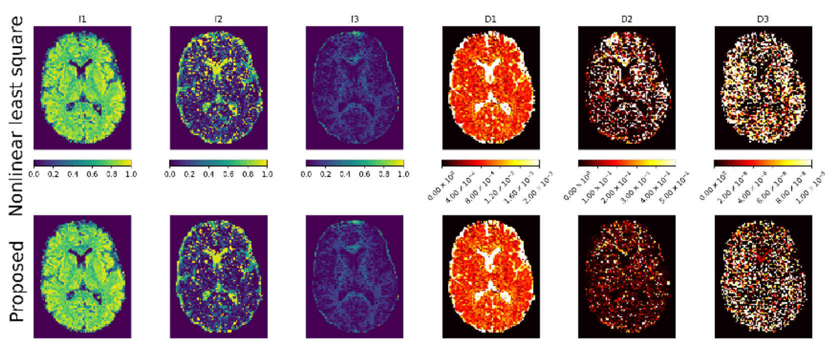

Figure 4: A three compartments model fit with the nonlinear least squares method (top row) and the proposed separable least squares (bottom row). The three fractions for the signal part are on the left while the diffusivities are shown on the right. As in figure 2, the IVIM signal and combined noise floor and kurtosis effect are more homogeneous for the proposed method. Nevertheless, the estimated fraction f1 and diffusivity D1, which comprises the major part of the brain, is similar in both cases.