

The influence of acquisition parameters on the metrics of the bi-exponential IVIM model

Gabrielle Fournet, Jing-Rebecca Li, Denis Le Bihan, Luisa Ciobanu

▶ **To cite this version:**

Gabrielle Fournet, Jing-Rebecca Li, Denis Le Bihan, Luisa Ciobanu. The influence of acquisition parameters on the metrics of the bi-exponential IVIM model. 2016. hal-01429508

HAL Id: hal-01429508
https://hal.science/hal-01429508

Preprint submitted on 8 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Title Page

Title: The influence of acquisition parameters on the metrics of the bi-exponential IVIM model

Authors: Gabrielle Fournet[1,2], Jing-Rebecca Li[2], Denis Le Bihan[1] and Luisa Ciobanu[1]

Institution information: [1]Neurospin, CEA Saclay-Center, Gif-sur-Yvette, France, [2]INRIA Saclay, Palaiseau, France.

Corresponding author: Dr. Luisa Ciobanu, luisa.ciobanu@cea.fr, phone/fax: +33 1 69 08 67 38/79 80, NeuroSpin, I^{2}BM, Bâtiment 145, CEA Saclay-Center, 91191 Gif-sur-Yvette, France.

Word count : 2318

Running title: Acquisition parameters influence the IVIM outputs

Key words: IVIM; microvasculature; inflow effects; pulse sequence; diffusion encoding time

Abstract (maximum: 200 words, word count: 200 words)

Purpose: The IntraVoxel Incoherent Motion (IVIM) MRI signal, typically described as a mono-exponential decay, can sometimes be better modeled as a bi-exponential function accounting for two vascular pools, capillaries and medium-size vessels. The goal of this work is to define precisely in which conditions the IVIM signal shape becomes bi-exponential and to understand the evolution of the IVIM outputs with different acquisition parameters.

Methods: Rats were scanned at 7T and 11.7T using diffusion-weighted pulsed-gradient spin-echo (SE) and stimulated-echo (STE) sequences with different repetition times (TR) and diffusion encoding times. The obtained IVIM signals were fit to the mono- and bi-exponential models and the output parameters compared.

Results: The bi-exponential and mono-exponential models converge at long diffusion encoding times and long TRs. The STE is less sensitive to inflow effects present at short TRs, leading to a smaller volume fraction for the fast pool when compared to the SE sequence.

Conclusion: The two vascular components are more easily separated at short diffusion encoding times, short TRs and when using SE sequences. The volume fractions of the two blood pools depend on the pulse sequence, TR and diffusion encoding time while the pseudo-diffusion coefficients are only affected by the diffusion encoding time.

Key words: IVIM; microvasculature; inflow effects; pulse sequence; diffusion encoding time

INTRODUCTION

Intravoxel Incoherent Motion (IVIM) magnetic resonance imaging (MRI) is getting momentum as an imaging modality capable of non-invasively extracting perfusion related parameters without the need for tracers or contrast agents. Initially, a mono-exponential model was proposed to describe the IVIM signal, taking into account only the smallest blood vessels, i.e. the capillaries (1). To provide a more accurate description of the IVIM signal, we recently introduced (2) a bi-exponential IVIM model consisting of two components representing two distinct vascular pools. One pool is associated with slow flowing blood in small vessels such as capillaries (as in the standard mono-exponential IVIM model) while the other pool corresponds to faster flowing blood in medium-size vessels, such as arterioles and venules (**Erreur ! Source du renvoi introuvable.**). In this manuscript, we establish under which experimental conditions the two pool model should be considered and study the evolution of its outputs with various acquisition parameters. In addition, we compare the IVIM outputs obtained with two different sequences often used in IVIM imaging: spin-echo and stimulated-echo. Ultimately, the results presented here will facilitate the interpretation of IVIM data acquired on different platforms and under different experimental protocols.

METHODS

Animals

Dark Agouti male rats (number of animals, n = 8, 232-349 g, 5-20 months, Janvier, Saint Isle, France) were used in this study. All animal experiments were conducted according to recommendations of the EU Directive 2010/63/EU for care and use of laboratory animals. The protocol was approved by the Comité d'EThique en Expérimentation Animale Commissariat à l'Energie Atomique et aux énergies alternatives Direction des Sciences du Vivant Ile de France (CETEA CEA DSV IdF) under protocol IDs 10_032 and 15_040.

MRI acquisitions

The acquisitions were performed on horizontally oriented 7T and 11.7T small animal MRI scanners (Biospec, Bruker Biospin, Etlingen, Germany) equipped with 760 mT/m gradient coil systems. 3 x 3 cm² four-element phased-array receiver coils and 7.2 cm (inside diameter) volume transmit coils (Bruker BioSpin, Etlingen, Germany) were used on both systems.

Coronal images were obtained using diffusion-weighted (Dw) pulsed-gradient spin-echo (PG-SE) or stimulated-echo (PG-STE) echo planar imaging (EPI) sequences. The common parameters to all trials were: 30 b-values (20 ranging from 5 to 500 s/mm² and 10 from 500 to 2500 s/mm², slice thickness 1.5 mm, field of view 20 x 20 mm^2, 1 segment, 2 slices, diffusion gradient duration time δ = 3 ms, gradient direction [X=0, Y=1, Z=0] (considering diffusion anisotropy is not present in the cortex at this resolution) and NR=6 repetitions. The other parameters were varied according to:

(a) For investigating the influence of TR (experiments performed at 7T): Dw-PG-SE-EPI sequence with TE = 45 ms, TR = 1000 and 3000 ms, diffusion gradient separation time Δ = 14 ms, in-plane resolution 250 x 250 µm², 6 averages and n=4.
(b) For investigating the influence of the pulse sequence (experiments performed at 7T): Dw-PG-SE-EPI and Dw-PG-STE-EPI sequences with TE= 45ms , TR=1000 and 3500 ms, Δ = 14 ms, in-plane resolution 400 x 400 µm², matrix size 50 x 50, 6 averages and n=6 and 4 for the two TRs, respectively.
(c) For investigating the influence of the diffusion encoding time (experiments performed at 11.7T): Dw-PG-STE-EPI sequence with TE/TR = 18/1000, Δ = 14, 30 and 60 ms, in-plane resolution 400 x 400 µm², 4 averages and n = 6.

Data analysis

The images were processed using an in-house software written in MATLAB (MathWorks, Massachusetts, USA) as described in (2). Briefly, the data were averaged over the different repetitions in an ROI drawn manually on the cortical gray matter of the left hemisphere (shown in white in **Erreur ! Source du renvoi introuvable.**.A).

The signal attenuation, $S(b)$, including both the diffusion, $F_{diff}(b)$, and the IVIM, $F_{IVIM}(b)$, components, can be expressed as:

$$S(b) = S_{0diff}F_{diff}(b) + S_{0IVIM}F_{IVIM}(b), \quad [1]$$

where b signifies the amount of diffusion weighting, S_{0diff} and S_{0IVIM} are the diffusion and IVIM components at b=0, with $S_{0diff} = S_0(1 - f_{IVIM})$ and $S_{0IVIM} = S_0 f_{IVIM}$, f_{IVIM} being the total flowing blood volume fraction and S_0 the overall signal when b=0.

The diffusion parameters were first obtained by fitting $S(b)$ for b-values > b_{lim} to the diffusion Kurtosis model (3),

$$F_{diff}(b) = e^{-bADC_0+(bADC_0)^2\frac{K}{6}}, \quad [2]$$

where ADC_0 is the apparent diffusion coefficient obtained when b approaches 0 and K is the Kurtosis parameter characterizing the deviation from the exponential decay.

The diffusion component was extrapolated for b-values < b_{lim} and subtracted from $S(b)$. The remaining IVIM component was fit to the standard mono-exponential IVIM model (1),

$$F_{IVIM}(b) = e^{-b(D_b+D^*)}, \quad [3]$$

where D_b is the diffusion coefficient of water in blood and D^* the pseudo-diffusion coefficient and to the recently proposed bi-exponential IVIM model (2),

$$F_{IVIM}(b) = e^{-bD_b}\left(f_{slow}e^{-bD^*_{slow}} + f_{fast}e^{-bD^*_{fast}}\right), \quad [4]$$

where f_{slow} and f_{fast}, D^*_{slow} and D^*_{fast}, are the relative blood volume fractions and pseudo-diffusion coefficients of the slow and fast pools, respectively. D_b was set to 1.75 10^{-3} mm²/s (4). For experiments performed at 7T b_{lim} was set to 500 s/mm^2 as in reference (2), however for the data acquired at 11.7T we used b_{lim} = 300 s/mm^2 as we found that there was no IVIM signal left past this value probably due to the shortening of the T_2 of blood with the increase in the strength of the magnetic field.

Statistical methods

To determine the best model to fit the IVIM signal, the corrected Akaike information criterion, AICc, was calculated using MATLAB (5),

$$AICc = N_b \ln(MSE) + \frac{2k(k+1)}{N_b-k-1}, \quad [5]$$

where N_b is the number of b-values used to fit the signals, MSE the mean squared error and k the number of parameters in the model. Taking into account that the Gaussian noise hypothesis for the signal residuals counts as 1 parameter according to the AIC theory we obtain k = 3 and 5 for the mono- and bi-exponential models, respectively.

The difference in AICc between the two models, $AICc_{mono} - AICc_{bi}$, was used as estimation of the bi- versus the mono-exponential behavior of the IVIM signal; a positive difference indicating that the bi-exponential model performs better.

Using the R software (R Foundation for Statistical Computing, Vienna, Austria) (6), Welch's t-tests (7) were performed to assess whether the output parameter means were significantly different from each other while varying the acquisition parameters. A *P*-value < 0.05 was considered statistically significant. The minimum sample size to perform the statistical tests was also estimated and established to be respected for all IVIM parameters found significant in this study.

RESULTS

(a) Influence of TR

Erreur ! Source du renvoi introuvable. gathers the results obtained for TR = 1000 ms and 3000 ms. Both f_{IVIM} and f_{fast} show a significant increase with decreasing TR, with f_{IVIM}*f_{fast} significantly higher at short TRs. The other IVIM parameters do not vary significantly. The difference in AICc decreases with increasing TR, suggesting that the bi-exponential behavior is more present at short TRs.

(b) Influence of the pulse sequence

The two pulse sequences, SE and STE, were compared for two TR values, 1000 and 3500 ms. The results are displayed in **Erreur ! Source du renvoi introuvable.**. At short TRs, f_{IVIM}, f_{fast} and f_{IVIM}*f_{fast} are significantly smaller for the STE sequence. Although not significantly different between the two sequences, the difference in AICc is smaller for STE, suggesting that the bi-exponential behavior is less visible with this sequence compared to the SE sequence.

At TRs of 3500 ms, the difference in AICc becomes negative and the IVIM signal is better fit to a mono-exponential model for both sequences. There is no significant difference in f_{IVIM}, D* and the difference in AICc between the two pulse sequences at this value of TR.

(c) Influence of the diffusion encoding time

The STE sequence was employed with three different Δ–values: 14, 30 and 60 ms. The IVIM signal is better fit to the bi-exponential IVIM model for all three Δ-values, but f_{IVIM} and the difference in AICc between the two IVIM models are not significantly different between the different Δ-values although the latter decreases with increasing Δ. f_{fast} significantly decreases between Δ = 30 and 60 ms. D^*_{slow} is significantly smaller for Δ = 14 ms compared to both Δ = 30 and 60 ms (Table 3). Finally, D^*_{fast} is shown to significantly decrease with increasing Δ-value.

DISCUSSION

By decreasing TR, we observe an increase in f_{IVIM}. This increase is coherent with inflow effects which are present at short TRs in 2D sequences employing a small number of slices (8). The volume fraction of the slow pool, $f_{IVIM}*f_{slow}$, does not vary significantly with TR while the volume fraction of the fast pool, $f_{IVIM}*f_{fast}$, is significantly larger at short TRs. This is consistent with inflow effects being more important for faster flows. Note that the inflow effects will be significantly reduced in studies employing multi-slice or 3D acquisitions.

The bi-exponential behavior of the IVIM signal seems to be less visible at long TRs as the difference in AICc between the two IVIM models decreases. This implies that, at longer TRs, the two models converge, most likely because the fast flowing pool is harder to detect than at short TRs where its contribution is enhanced by inflow effects.

At short TRs, the two pulse sequences used, SE and STE, present different sensitivities to inflow effects with the STE sequence being less affected as the values measured for f_{IVIM} and f_{fast} are significantly lower than for the SE sequence. This is due to the fact that the signal from inflowing spins is decreased in the STE compared to the SE sequence due to the higher first moments of the slice-selection gradients (9). This differential sensitivity to inflow is further confirmed by the fact that $f_{IVIM}*f_{slow}$ does not differ significantly with the pulse sequence whereas $f_{IVIM}*f_{fast}$ decreases significantly between the SE and STE sequences. Additionally, as the fast pool, exhibiting stronger inflow effects, is less visible with the STE sequence the difference in AICc between the two IVIM models is significantly lower for the STE sequence than for the SE sequence.

At long TRs for which inflow effects are negligible, the IVIM signal becomes mono-exponential for the two pulse sequences. This was predictable from the evolution of the IVIM signal with TR as discussed in the previous paragraph. Without inflow effects, the IVIM parameters are not significantly different for the two pulse sequences.

The dependence of the IVIM parameters on the diffusion encoding time has already been partly discussed previously (2). To further be able to increase the diffusion encoding time without increasing the echo time, the STE sequence was used instead of the SE sequence in this study.

As observed previously, a decrease in the difference in AICc is observed when increasing Δ suggesting that the two IVIM models, mono- and bi-exponential, converge at long diffusion encoding times. Accordingly, the fraction of fast flowing blood vessels decreases for the longest Δ. The pseudo-diffusion coefficients of the two pools are also affected. D^*_{slow} increases between Δ = 14 and 30 ms implying that the slow pool is likely to be in the sinc regime at the shortest Δ for which D* can be expressed as $D^* = V^2\Delta/6$ (where V is the mean blood velocity). As Δ, increases, D^*_{slow} reaches the exponential regime for which D* = LV/6 (where L is the mean vessel length). In this regime, D* is independent of Δ. On the contrary, D^*_{fast} was found to decrease with Δ. Indeed, as Δ increases, the fastest spins cannot be detected anymore leading to a decrease in D^*_{fast}.

Erreur ! Source du renvoi introuvable. summarizes the impact of different combinations of acquisition parameters studied in this work on the IVIM signal behavior and the IVIM outputs. At short TRs, with both pulse sequences, the IVIM signal behavior is bi-exponential with f_{IVIM} and f_{fast} overestimated for the SE sequence at all diffusion encoding times and for the STE sequence only at short diffusion encoding times. At long TRs, the mono- and bi-exponential models converge, with the mono-exponential model being a better fit at long diffusion encoding times. D^*_{slow} and D^*_{fast} are only impacted by the diffusion encoding time.

When inflow effects are present the signal contribution from blood in the fast pool is artificially increased. One should also consider that the flowing blood fractions of the IVIM model (f_{IVIM}, f_{fast} and f_{slow}) are T_1 and T_2 weighted. Hence, in order to estimate the correct values for f_{fast}, f_{slow} and f_{IVIM} from the measured values one should take into account the relaxation times, T_1 and T_2, of blood and tissue. While the influence of the echo time was not investigated in this study, it is expected to be significant for the estimation of the volume fractions of the two pools. An extended bi-exponential IVIM model correcting for the TE and TR dependences, paralleling the extended mono-exponential model recently proposed and applied to other organs [10], will certainly increase the reliability of the IVIM measurements.

CONCLUSIONS

This study confirms the contribution to the IVIM signal of flow within both small vessels (capillaries) and larger vessels (on the scale of arterioles and venules). We have shown that, in the case of 2D spin-echo acquisitions with a small number of slices, the main factor influencing the behavior, bi- or mono-exponential, of the IVIM signal as well as the measured volume fractions is the repetition time. Shorter repetition times allow for an easier separation of the two

pools. However, they can lead to an overestimation of f_{IVIM} and $f_{fast.}$ As expected, the IVIM output parameters depend less on the repetition time for sequences less sensitive to inflow effects such as the stimulated echo sequence. The diffusion encoding time also influences the IVIM metrics. For very long diffusion encoding times, the behavior tends to become mono-exponential. For certain ranges, this parameter can also influence the values obtained for the pseudo-diffusion coefficients of the slow and fast pools.

To conclude, certain acquisition parameters can have an effect on the IVIM outputs and therefore care should be taken when comparing results obtained under different experimental protocols.

ACKNOWLEDGMENTS

The authors thank Brad Sutton and Alex Cerjanic for useful discussions and Boucif Djemai and Erwan Selingue for their excellent technical assistance in the animal experiments. The research was supported by the ANR Grant ANR-13-NEUC-0002-01.

REFERENCES

1. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497-505.

2. Fournet G, Li J, Cerjanic A, Sutton B, Ciobanu L, Le Bihan D. A two pool model to describe the IVIM cerebral perfusion. J Cereb Blood Flow Metab 2016; Published on line November 30, 2016, DOI: 10.1177/0271678X16681310.

3. Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 2010; 23: 698-710.

4. Li JG, Stanisz GJ, Henkelman RM. Integrated analysis of diffusion and relaxation of water in blood. Magn Reson Med 1998;40:79-88.

5. Information theory and an extension of the maximum likelihood principle. Second international symposium on information theory 1973.

6. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

7. Welch B. L. The generalization of "Student's" problem when several different population variances are involved. Biometrika 1947; 34: 28–35.

8. Gao J, Liu H. Inflow effects on functional MRI. Neuroimage 2012;62:1035-1039.

9. Caprihan A, Griffey R H, Fukushima, E. Velocity imaging of slow coherent flows using stimulated echoes. Magn Reson Med 1990; 15: 327–333.

10. Jerome NP, d'Arcy JA, Feiweier T, Koh D-M, Leach MO, Collins DJ, Orton MR. Extended T2-IVIM model for correction of TE dependence of pseudo-diffusion volume fraction in clinical diffusion-weighted magnetic resonance imaging. Phys. Med. Biol. 2016; 61: N667–N680

Figure Captions:

Figure 1. The bi-exponential model reflects two vascular pools: capillaries and larger vessels. (A) MRI image showing a coronal section of the rat brain. (B) Drawing of the architecture of the microvasculature consisting of arterioles, venules and capillaries.

Tables:

Table 1. IVIM parameters for the SE sequence and two TRs (mean ± SD, n = 4). *P*-values < 0.05 are highlighted in bold.

Output parameters	TR = 1000 ms	TR = 3000 ms	*P*-value
f_{IVIM} (%)	13.41 ± 0.55	6.36 ± 1.06	**0.000076**
f_{fast} (%)	75.61 ± 10.84	42.06 ± 10.36	**0.0021**
f_{IVIM}*f_{slow} (%)	3.25 ± 1.45	3.76 ± 0.92	0.29
f_{IVIM}*f_{fast} (%)	10.16 ± 1.51	2.60 ± 0.77	**0.00026**
D^*_{slow} (10^{-3} mm²/s)	2.21 ± 0.33	2.16 ± 0.70	0.45
D^*_{fast} (10^{-3} mm²/s)	27.48 ± 1.97	25.96 ± 3.21	0.23
$AICc_{mono}$ - $AICc_{bi}$	19.04 ± 13.18	4.35 ± 7.57	0.057

Table 2. IVIM parameters for SE and STE pulse sequences at two TRs (mean ± SD). *P*-values < 0.05 are highlighted in bold.

Output Parameters	TR = 1000 ms (n = 6)			TR = 3500 ms (n = 4)		
	SE	STE	*P*-value	SE	STE	*P*-value
f_{IVIM} (%)	10.84 ± 1.16	6.34 ± 1.88	**0.00046**	3.41 ± 0.56	3.27 ± 1.19	0.42
f_{fast} (%)	59.50 ± 14.29	29.98 ± 19.88	**0.0080**	-	-	-
f_{IVIM}*f_{slow} (%)	4.42 ± 1.63	4.67± 1.92	0.41	-	-	-
f_{IVIM}*f_{fast} (%)	6.42 ± 1.69	1.67 ± 1.21	**0.00016**	-	-	-
D^*_{slow} (10^{-3} mm²/s)	2.37 ± 1.62	2.37 ± 0.13	0.50	-	-	-
D^*_{fast} (10^{-3} mm²/s)	21.45 ± 4.19	17.02 ± 5.04	0.065	-	-	-
D^* (10^{-3} mm²/s)	-	-	-	6.37 ± 1.19	6.72 ± 2.64	0.41

$AICc_{mono}$ - $AICc_{bi}$	12.95 ± 15.82	3.26 ± 17.59	0.17	-0.92 ± 22.47	-2.65 ± 17.34	0.45

Table 3. IVIM parameters for the different diffusion encoding times (mean ± SD, n = 6). *P*-values < 0.05 are highlighted in bold.

Output parameters	Δ = 14 ms (1)	Δ = 30 ms (2)	Δ = 60 ms (3)	Comparison group	*P*-value
f_{IVIM} (%)	5.47 ± 0.85	5.17 ± 0.56	5.03 ± 0.60	All	> 0.05
f_{fast} (%)	56.77 ± 10.52	63.16 ± 5.40	49.95 ± 11.81	1 vs. 2	0.11
				1 vs. 3	0.16
				2 vs. 3	**0.021**
D^*_{slow} (10^{-3} mm²/s)	3.97 ± 0.53	7.40 ± 1.91	7.10 ± 1.46	1 vs. 2	**0.0030**
				1 vs. 3	**0.0011**
				2 vs. 3	0.38
D^*_{fast} (10^{-3} mm²/s)	33.81 ± 4.04	28.95 ± 3.31	24.68 ± 2.66	1 vs. 2	**0.024**
				1 vs. 3	**0.00070**
				2 vs. 3	**0.017**
$AICc_{mono}$ - $AICc_{bi}$	11.01 ± 9.71	7.56 ± 11.04	2.52 ± 9.27	All	> 0.05

Table 4. Summary of the influence of TR, the diffusion encoding time (Δ) and the pulse sequence on the behavior and output parameters of the IVIM signal.

TR	Δ	SE sequence				STE sequence			
		Behavior	f_{IVIM}, f_{fast}	D^*_{slow}	D^*_{fast}	Behavior	f_{IVIM}, f_{fast}	D^*_{slow}	D^*_{fast}
Short	Short	Bi-exp.	++	=	=	Bi-exp.	+	=	=
Long	Short	Bi-exp./ Mono-exp.	=	=	=	Bi-exp./ Mono-exp.	=	=	=
Short	Long	Bi-exp.	NA	NA	NA	Bi-exp.	=	+	-

Note. The symbols =, - , + and ++ signify, respectively, equal, smaller, higher or much higher values compared to those obtained for long TR and short Δ.