Dear Editor and reviewers,

Thank you for your critical assessment of our manuscript. Below we provide replies to your comments, and describe all the minor changes done as requested. We also included a few other minor changes that, although not requested, improve, in our view, the final version of the manuscript.

Editor comments:

The Proton Detected Local Field Experiment is used, together with a modified data evaluation scheme (including considering the effect of the rf-inhomogeneity) to determine order parameters. Based on the comments of referee 1 ("In particular my main concern was the claim that time domain analysis is better than freq. domain analysis. After reading the letter, it is clear that this was not the intended claim. However, there is still once instance where I think the phrasing is problematic in this regard. page 4 line 112:'Time-domain analysis can be used to circumvent the limitations outlined above entirely'. Rather, considering RF inhomogeneity is important and time domain analysis is convenient/ efficient.") and ,my own reading, the manuscript needs a further revision to make it clear that the time-domain fitting is more CONVENIENT but does not provide more information or needs less measurement time) than a frequency-domain FIT based on the same model (including rf inhomogeneity). The comparison with a by eye inspection of the Fourier transform is not an adequate comparison and falsely suggests that the time-domain method is superior. also, the time domain method does not need shorter rf irradiation periods as claimed.

We have tried to clarify that there is no advantage of using TD fits over FD fits. We have introduced for instance the following new sentences:

- (in Abstract) “In comparison to the analysis of dipolar splittings without any fitting procedure, the accurate modelling of PDLF measurements makes possible…”

- “Analysing the measured data with a fitting model (in either the time or frequency domains) can be used to circumvent the limitations outlined above”

We stress again that the comparison of TD fits with FD fits was never our intention, as also emphasised by reviewer 1, and we were actually surprised for this issue to come up. Our intention was to compare the result of fitting a model with the result of “reading off” the dipolar splitting from the spectrum (with no fitting) since the latter approach is often used including by us. Therefore, when we state that the methodology enables to use shorter experiments, this is in connection to the “read off” method that requires more points in the indirect dimension for determining a dipolar coupling.

Furthermore, as suggested by referee 1, the hype should be tuned down and words like "unprecedented level of detail" and the extensive use of new or novel (in particular in the abstract) should be avoided.

We have tried to remove these instances and tried to cool down our excitement over the proposed strategy.

Reviewer 1

The second submission of this article is substantially improved, addressing the points raised in review. In particular my main concern was the claim that time domain analysis is better than freq. domain analysis. After reading the letter, it is clear that this was not the intended claim. However, there is still once instance where I think the phrasing is problematic in this regard. page 4 line 112:'Time-domain analysis can be used to circumvent the limitations outlined above entirely'. Rather, considering RF inhomogeneity is important and time domain analysis is convenient/efficient.

We have now replaced the sentence “Time-domain analysis can be used to circumvent the limitations outlined above entirely” by “Analysing the measured data with a fitting model (in either the time or frequency domains) can be used to circumvent the limitations outlined above”.

The claim of improved fitting accuracy is addressed via synthetic data adequately. It might also be interesting to show fits that do not consider RF inhomogeneity in Table 1. This could further strengthen the argument since the current presentation comparing with 2H data does not quantify the improvement.

We thank the reviewer for this suggestion. We now included the result of the fits performed without considering RF inhomogeneity (the ideal model) in table 1 and in Figure 4, and show the minimum chi^2 for these fits in the supplementary information. We also briefly discussed this new information in the text.

'new' and 'new method' is overused in the abstract for my taste, but fine if it fits the style of the journal.

We agree about the overuse and tried to reduce the use of these instances throughout the text.

These suggested changes are so minor that I do not see a need to review another version.

Reviewer 2

The authors' responses to concerns raised are mainly deflection rather than substance. Some of the responses strain credulity, and appear to reflect fundamental misunderstanding of the nature of inverse problems and the role of model fitting.

For example,

"RF inhomogeneity is not an uncertainty subject to statistical treatment, it is an objective experimental fact..."
"We do not consider any model order selection because the model is always the same: spin-pair simulations of the R-PDLF NMR experiment including RF inhomogeneity. We only fit two-components in cases for which we know that there exist two-components (two distinct acyl chains). Please note that this is not an assumption. "
"... a TD fit enables to extract information from shorter data (indeed with an increase of error towards shorter data) for which FT processing does not yield any dipolar splitting."
The authors might consult a book such as Körner "Fourier Analysis". It reprints an essay by Haldane on error analysis.

While the second reviewer is to be commended for the extensive editing, it is not the responsibility of reviewers to edit manuscripts for grammar or syntax.

We have tried to optimise further our error analysis which was the concern of reviewer 2 in his first report. Namely, we now used $\chi 2$ boundaries for defining our maximum and minimum confidence bounds as described in detail in the supplementary information.

List of the changes made:

- We tried to remove words like new and novel as suggested.
- Figure 4D was updated to include results from the ideal model.
- Table 1 was updated with results from the ideal model including a brief discussion of these results in the text.
- The experimental errors were modified to correspond to the standard deviation instead of the previous maximum error (which were used previously). For the confidence bounds, $\chi 2$ is used now as described in detail in the SI.
- Figure 7 in the main text was updated according to the preceding item.
- The figures S2 to S8 were modified in accordance to the more simple and standard analysis of fitting errors used now.
- A figure with the $\chi 2$ dependence for the analysis of myelin carbons was added to the supplementary information (Figure S9).
- Table 1 and Table 2 were updated with the new fitting error estimations.
- The last paragraph of section 2.3 was removed since it was incorrectly stated that POPE membranes gave a higher line broadening than the DMPC/DMPCd membranes. This was a mistake as could be seen in the previous SI plots for these samples.

Again, thanks to all Reviewers and Editor for their evaluation of our manuscript.

Sincerely,
Tiago Mendes Ferreira,
On behalf of all the co-authors.