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To the editor

Magnetic Resonance

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Dear Dr. Geoffrey Bodenhausen,

Firstly, the authors would like to thank the reviewers for the contributions to improve the quality of the manuscript by posing important questions and making useful comments. We believe that all the considerations made by the reviewers were very important to improve this manuscript in all aspects.

Therefore, all comments of the reviewers were taken into account to elaborate the revised version of the manuscript, which is submitted to Magnetic Resonance. In the following, a point-by-point list of answers to the reviewer´s questions and comments is presented.

Response to reviewers

Editor comments:

Editor: I wish to encourage the authors to submit a revised manuscript that should incorporate the changes they promised to make in their replies to the reviews.

Authors: We are grateful to the editor and reviewers suggestions and comments. We have carefully considered all remarks and implemented the appropriate revisions in the manuscript, which are highlighted in the revised version. In our opinion they improved the quality of the work. In the following, a point-by-point list of answers to the reviewer´s questions and comments is presented.

Referees' Comments:

Reviewer #1:

General: The manuscript reports the availability, access, and use of an open-access, on-line platform to convert NMR relaxation data into distributions or relaxation times. Despite the availability of different open-access ‘Laplace-transform’ algorithms, this platform provides a useful tool for research and teaching, as it is easy to use. The authors review the non-negative least squares algorithm with Tikhonov regularization and singular value decomposition and provide helpful advice for the beginner to

achieve best results. I value this work, as it will benefit a growing community attracted to diverse incarnations of time-domain NMR. Moreover, this manuscript is well written, albeit it would still benefit from the language editing service of Copernicus Publishers. Nevertheless, I see this work outside the scope of Magnetic Resonance as it does not report a significant advance in magnetic resonance: “To be suitable for publication in MR, articles must describe substantial advancements in magnetic resonance. They should include significant innovation regarding new insights into magnetic resonance methodology, or into systems studied by magnetic resonance techniques, or expand the applicability of magnetic resonance. Routine applications of established techniques and minor technical advances are considered to be outside its scope.” Therefore, I recommend it to be submitted to a different Journal.

Authors: We sincerely thank the reviewer for the careful evaluation of our manuscript and for the very positive assessment of our work, particularly highlighting its usefulness for research and teaching and its potential benefit to the growing time-domain NMR community. We respectfully acknowledge the reviewer’s concern regarding the journal scope. However, according to the journal’s Aims & Scope, Magnetic Resonance explicitly welcomes “innovative advances in techniques supporting magnetic resonance experiments that may range from sample preparation to computational techniques” and also welcomes “educational articles that provide informative and original insights into topics of current interest.”

The inverse Laplace transform is a fundamental computational step in TD-NMR relaxometry, directly supporting magnetic resonance experiments by enabling the interpretation of relaxation data. The main contribution of this work is the development of a fully open-access, web-based computational platform specifically designed to support magnetic resonance data analysis, improving accessibility, reproducibility, and reliability of TD-NMR relaxometry. Furthermore, this WebApp was specifically designed not only as a computational tool but also as an educational platform, allowing users to interactively explore the effects of inversion parameters and better understand inverse Laplace transform analysis in magnetic resonance. By making TD-NMR relaxometry more accessible and easier to use, this work helps extend the use of magnetic resonance techniques to a broader audience.

We respectfully hope that the reviewer may reconsider the suitability of this contribution within the scope of Magnetic Resonance. Also, the detailed comments provided by the reviewer are greatly appreciated and was fully addressed in the revised version of the manuscript.

Detailed comments

Line 119: Equation number missing. The text reads “like equation ??”.

Authors: We thank the reviewer for pointing this out. The sentence has been corrected. Line 120.

Line 240 (dito lines 270, 280): A validation of the algorithm with only 1% RMS Gaussian white noise added to the noise-free simulation data is a very benevolent test. It would be helpful to illustrate the limits of the algorithm, by showing how the distributions of relaxation times change with decreasing signal-to noise ratio. This would guide the unexperienced user in producing experimental data of sufficient quality.

Authors: We thank the reviewer for this suggestion. In the revised manuscript, we modified Figure 6 including additional simulations with different noise levels (0%, 1%, 2% and 5% RMS) and showing how the relaxation time distributions are affected. This helps illustrate the limits of the method and provides guidance for experimental data quality. Lines 250-258 and caption Figure 6 Lines 261-265.

We are grateful to the reviewer for their careful evaluation of our work. We are hopeful that the changes highlighted in the resubmitted manuscript will effectively address the questions that have been raised.

Reviewer #2:

General comments: This manuscript presents an open-source, free, web-based app for the analysis of different types of time-domain NMR relaxation data in terms of distribution of relaxation times. Overall, the manuscript reads well, although some sentences could be shorten to improve clarity. The web interface is straightforward to understand and use, and presents an improvement to the existing software. The approach for the analysis of this type of data has already been used by the authors in numerous previous studies, such that we can expect its implementation to be used by other researchers in the field. However, as such, I believe it does not present a 'significant advancement in magnetic resonance', an important aspect of manuscripts published in MR and I would recommend submission in another journal.

Authors: We sincerely thank the reviewer for the careful reading of the manuscript and for the constructive comments. We appreciate the positive evaluation of the web interface and the recognition that the platform provides an improvement over existing software tools for the analysis of time-domain NMR relaxation data.

Regarding the reviewer's concern about the scope of the journal, we respectfully note that, according to the Aims & Scope of Magnetic Resonance, the journal welcomes innovative advances in techniques supporting magnetic resonance experiments, including computational methods. The inverse Laplace transform is a central computational step in TD-NMR relaxometry, enabling the interpretation of relaxation measurements. Thus, the main contribution of this work is the development of a fully open-access, web-based platform

designed to support the analysis of magnetic resonance relaxation data. In addition to providing a practical computational tool, the platform was also designed with an educational perspective, allowing users to interactively explore the effects of inversion parameters and better understand the principles behind ILT analysis in magnetic resonance.

We appreciate the reviewer's suggestions and believe they will help improve the clarity of the manuscript. All the detailed comments provided by the reviewer were carefully addressed and incorporated in the revised version of the manuscript.

Detailed comments

Eq. 2: ck(0) should likely read ci(0)

Authors: We thank the reviewer for identifying this typographical error. The correction has been made in the revised manuscript. Lines 127 to 145.

Eq. 4 does not show a time-dependence of the noise value (en instead of en(t)).

Authors: We thank the reviewer for this observation. The notation has been corrected to include the time dependence of the noise term in the revised manuscript. Lines 136-138, (equation 4).

I find Eq. 5 inconsistent with the previous notations. I believe the experimental data should not be labelled c as c is the function modelling the behaviour of the experimental data (for example, as in Eq. 4). Some phrasing should also be changed in that regard, as the functions written in Eq. 1 to 4 are not experimental data, but functions modelling experimental data.

Authors: We thank the reviewer for this comment. We agree that the notation could lead to confusion. The notation and corresponding phrasing have been revised in the manuscript to clearly distinguish between experimental data and the model functions. Lines 125-126, 128 (equation 2), 132 (equation 3), lines 135-137, lines 143 (equation 5) and line 144.

As highlighted by reviewer 1, the effect of the noise should be discussed more thoroughly, especially as the authors note that the SNR heavily affects the ILT spectrum (line 279). The experimental data leading to the results shown in Fig. 7 should also be included.

Authors: We thank the reviewer for this important suggestion. In the revised manuscript, we expanded the discussion on the influence of signal-to-noise ratio on the ILT spectrum in Figure 6, including additional simulations with different noise levels (0%, 1%, 2% and 5% RMS) and showing how the relaxation time distributions are affected. This helps illustrate the limits of the method and provides guidance for experimental data quality. Lines 250-258 and caption Figure 6 Lines 264-265.

The experimental CPMG data corresponding to Fig. 7 have been included to better support the results. See Figure 7 and caption. Lines 286-288.

A discussion on the effect of the regularization parameter α is included, but should be extended. For example, it is not clear what guides the decision toward choosing a value over another.

Authors: The discussion regarding the selection of the regularization parameter alpha was expanded in the revised manuscript, including additional explanation of how the parameter affects the resolution and smoothness of the relaxation time distributions. Lines 238-245.

The 3D plot in Fig 5 does highlight the broadening of the distribution from the increasing value of α, but I suggest showing a contour plot instead to make the evolution more readable.

Authors: We thank the reviewer for this suggestion. A contour representation has been adopted in Fig. 5 to improve readability. Figure 5. Lines 249.

We thank the reviewer again for the thoughtful comments and suggestions. We believe that addressing these points will significantly improve the clarity and completeness of the manuscript in the final revised version.

Reviewer #3:

In this very well-written manuscript a new open-access WebApp is presented that performs Inverse Laplace Transform (ILT) analysis of time-domain NMR relaxation data in a transparent and user-friendly way. The tool implements a non-negative least squares inversion with Tikhonov regularization and singular value decomposition. It supports common TD-NMR experiments such as CPMG, inversion recovery, and saturation recovery from instruments of any manufacturer. Validation with simulated and experimental datasets is shown, demonstrating that the resulting relaxation time distributions agree with established ILT approaches.

The ILT / NNLS approach is well established and in the sense of NMR or data analysis do not “do” anything new, as other reviewers correctly remarked. However, what is new is that both the manuscript and the web app offer an excellent introduction to ILT for novice users. I feel this is an important contribution that will help students and first-time users to get into ILT TD-NMR. A multitude of other open source packages are available, as also is discussed in the manuscript, but these still represent a significant hurdle for new users of TD-NMR. Most, if not all existing packages do not only require prior knowledge of ILT, but also programming skills and a significant time investment to get them to run. The data analysis itself in most cases also is not without its pitfalls. For most TD-NMR users who do not yet have a background in NMR this is too much of a hurdle to overcome, in my experience. I therefore feel that the paper does, in fact, represent a substantial contribution within the scope of Magnetic Resonance and most certainly represents a novel tool that will change the approaches used by other groups: it will open ILT to novice users who do

not happen to have access to an easy to use ILT tool embedded in their proprietary spectrometer software.

Author: We sincerely thank the reviewer for the careful reading of the manuscript and for the very positive and encouraging assessment of our work. We are particularly grateful for the recognition that the WebApp and manuscript provide a clear and accessible introduction to inverse Laplace transform (ILT) analysis for novice TD-NMR users. We fully agree with the reviewer that the accessibility of ILT tools remains a barrier for many researchers entering the field, and one of the main motivations of this work was precisely to lower this barrier.

We also greatly appreciate the reviewer's comment that the work represents a meaningful contribution within the scope of Magnetic Resonance. The goal of this platform is to make TD-NMR relaxometry analysis more accessible, transparent, and reproducible for the broader magnetic resonance community.

We thank the reviewer for the constructive suggestions to further improve the manuscript. All the points raised below will be carefully addressed and incorporated in the revised version of the manuscript when requested by the editor.

Detailed comments:

1) Sec. 3: It would be nice to see the actual function that is minimized for (including the regularization term) to get a better understanding of the concept of the ILT algorithm

Authors: We thank the reviewer for this valuable suggestion. The mathematical formulation of the ILT problem, including the objective function with the regularization term, is indeed fundamental for a deeper theoretical understanding of the method. However, the primary focus of the present work is to provide a user-friendly and accessible WebApp aimed at facilitating ILT analysis for a broad audience, including users without a strong background in inverse problem theory.

For this reason, we intentionally opted to keep the manuscript focused on practical implementation and application aspects, while relying on well-established formulations of the ILT problem that are extensively described in the literature cited throughout the manuscript, particularly in Borgia et al. (1998), where the full mathematical details are presented. We believe that including a detailed mathematical derivation would go beyond the scope and intended audience of this contribution.

Nevertheless, we appreciate the reviewer's suggestion and will consider incorporating a more explicit formulation in future developments or complementary documentation of the WebApp.

2) Lines 151-152: For readers that are new to this type of analysis it might be nice to briefly discuss the general concept of regularization and already mention the effect of large and small alphas on the solution (is briefly mentioned later in text). This way the regularization concept might become less abstract at this stage.

Authors: We appreciate this suggestion. The discussion regarding the regularization parameter alpha was expanded in the revised manuscript, including additional explanation of how the parameter affects the resolution and smoothness of the relaxation time distributions. Also a contour representation has been adopted in Fig. 5 to improve readability. Lines 249-258. Figure 5.

3) I would like to compliment the authors with the clear “look” of the WebbApp, it appears very user friendly.

Authors: We sincerely thank the reviewer for this encouraging comment. Ease of use and accessibility were central goals during the development of the WebApp, particularly to support students and researchers who are new to TD-NMR relaxometry.

4) It is not clear what happens to the data after it is uploaded. Is it stored or logged, or deleted? Please clarify

Authors: We thank the reviewer for pointing this out. A clarification was added to the manuscript describing how uploaded data are handled by the platform: The uploaded dataset is temporarily transmitted to the server, where the ILT processing is performed and the results are generated. After the analysis is completed and the user session is closed, the server hosted at the University of São Paulo automatically discards the uploaded data. The data are not stored, logged, or used for any other purposes. Lines 179-180.

5) line 26-27: please add some references of applications of TD-NMR in research and industry

Authors: Additional references illustrating the applications of TD-NMR in research and industrial contexts was included in the revised manuscript: (Lines 27-28)

https://doi.org/10.1016/S0066-4103(10)69003-5

https://doi.org/10.1111/1750-3841.70839

https://doi.org/10.1016/j.meatsci.2018.08.020

https://doi.org/10.1016/j.jmr.2012.11.010

https://doi.org/10.1016/j.colsurfa.2019.04.080

https://doi.org/10.1016/j.jmr.2023.107522

https://doi.org/10.1016/j.pnmrs.2013.09.001

6) line 59: it is not necessarily the homogeneity of the magnetic field of permanent magnets that limits spectral resolution, as Magritek has demonstrated in the last decade or so with their sub-ppm Halbach magnets. Rather, it is the lower field strength. (Although even that limitation has been overcome in the aforementioned systems).

Authors: We thank the reviewer for this observation. The corresponding sentence was revised. Lines 59-60.

7) Please check typos, missing equation numbers, clarity, or English in the following lines: L119; L206, L215, L249, L251, L257, L260, L274.

Authors: We appreciate the reviewer's careful reading. The manuscript was thoroughly revised to correct typographical errors and improve clarity in the indicated sections. Line 199; Lines 203-208; Lines 209-214; Lines 218-219; Lines 247-250; Lines 256-257; line 259, line 273

8) Regularization and Alpha are discussed, in similar wording, at least twice in the MS. Please remove redundancy

Authors: We thank the reviewer for identifying this redundancy. The relevant sections were revised to remove repetition and improve the overall flow of the manuscript.

We thank the reviewer again for the very positive evaluation and the constructive suggestions provided. We believe these comments will help improve the clarity and pedagogical value of the manuscript in the final revised version.