MRSCloud: a Cloud-based MR Spectroscopy Tool for Basis Set Simulation

Steve C.N. Hui, PhD,1,2 Muhammad G. Saleh, PhD,3 Helge J. Zöllner, PhD,1,2 Georg Oeltzschner, PhD,1,2 Hongli Fan 1,4, Yue Li 5, Yulu Song, MD,1,2 Hangyi Jiang, PhD,1,2 Jamie Near, PhD,6 Susumu Mori, PhD,1,2 Hanzhang Lu, PhD,1,2 Richard A.E. Edden, PhD,1,2\*

1 Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

2 F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA

3 Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

4 Department of Biomedical Engineering, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

5 AnatomyWorks, LLC, Ellicott City, Maryland, USA

6 Sunnybrook Research Institute and Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

\* Corresponding author. Division of Neuroradiology, Park 367H, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287, USA.

Email address: raee2@jhu.edu

**Acknowledgement**

This work was supported by NIH grants R01 EB016089, R01 EB023963, R21 AG060245, R00 AG062230, K99 DA051315, P41 EB015909 and P41 EB031771

**Running Title**

Cloud-based MRS Simulation

MRSCloud: a Cloud-based MR Spectroscopy Tool for Basis Set Simulation

**Abstract**

BACKGROUND

PURPOSE

The aims of the proposed cloud-based spectral simulation tool, the MRSCloud, are: 1) to implement HERMES and HERCULES in addition to the un-edited and MEGA sequences, 2) to allow the simulation of using different localization methods (PRESS and semi-LASER), 3) to simulate vendor specify (GE, Philips, Siemens) basis sets.

STUDY TYPE (retrospective/prospective/longitudinal/case control/cohort etc.)

POPULATION or SUBJECTS or PHANTOM or SPECIMEN or ANIMAL MODEL (type and numbers)

FIELDSTRENGTH/SEQUENCE

Simulations can be achieved in 3T using unedited, MEGA, HERMES and HERCULES with PRESS and semi-LASER localizations.

ASSESSMENT (what? By whom? How? What criteria?)

STATISTICAL TESTS (please list the significance level)

RESULTS (must have numerical data and statistical testing for each phrase)

DATA CONCLUSION (conclusion is based on the author’s results only)

Keywords: magnetic resonance spectroscopy, simulation, basis set, coherence pathway filtering, one dimensional projection

Research Articles: up to 20 manuscript pages (5,000 words), 40 references, 10 figures and tables.

**Introduction**

Magnetic resonance spectroscopy (MRS) is a non-invasive method that measures the in vivo concentration of brain metabolites. It has a broad range of preclinical and clinical applications included detection of metabolite changes in neurodegenerative diseases and psychiatric disorders (1-3) as well as determination of biomarkers for brain tumors and its corresponding treatment response (4,5). Although MRS can be preform using existing clinical scanners and RF coils without hardware modification, it has not been widely adopted clinically as a tool for medical diagnosis. The requirement of spectral knowledge in data acquisition and analysis have been the limiting factor for utilizing MRS. Unlike having radiologists to interpret MR imaging, non-academic local hospitals seldom have site spectroscopist, as the counterpart for analyzing spectral data, to support the use of MRS. There is a need to increase the accuracy and reliability of the spectral data and to decrease the complexity of data analysis in order to implement MRS in clinical setting. A recent consensus paper has pointed out that the use of semi-LASER and simulated basis set are crucial for both acquisition and quantification (6).

Accurate quantification requires modeling of spectral data using a linear combination of known metabolite basis functions. Basis sets are most commonly generated by numerical simulation because preparation of a full set of metabolite phantoms and experimental acquisition is time-consuming, expensive and extremely demanding technically. Simulations based on the quantum mechanical density-matrix formalism (7) can be carried out in a number of application tools and software packages (8-14). However, they may require a significant learning curve, and only a minority of groups applying MRS have the detailed sequence knowledge to implement accurate basis-set simulations locally. Therefore, most analyses rely upon basis sets generated off-site, often with approximate, rather than exact-match parameters. This approach is feasible for fitting single large and well-separated metabolite resonances such as NAA, choline and creatin in unedited experiments. However, fitting editing experiments for coupled and overlapping resonances must be incorporated basis set into the analysis. It is necessary to apply optimal acquisition parameters to generate accurate basis set as prior knowledge for data modeling. To generate basis sets based on realistic parameters, experimentally applied RF pulses, gradients and timings should be employed, rather than using ideal or hard pulses with different timings from the scanner for general approach. A customized tool that provides realistic parameters for basis set simulation would benefit data modeling and quantification, and that allows online generation would also reduce the expertise requirement for non-academic or non-research units to carry out spectral analysis and quantification. Furthermore, spectral editing sequences have recently been added to product for the major vendors. Users now require basis sets both for conventional and scans edited for *J*-coupled metabolites, such as GABA, and for more advanced Hadamard-encoded sequences (15,16).

MRSCloud is an online-based spectral simulation tool for brain metabolites which contains a number of unique features. It allows users to generate density-matrix-simulated basis sets through a simple web interface for up to 32 metabolites for linear combination modeling. The 1D projection method (17), coherence pathway filters (18) and pre-calculation of propagators have been implemented to accelerate the simulation process and to run on a high-performance cloud server. Parameters specified include localization method (PRESS (19) or semi-LASER (20,21)), vendor (GE, Philips, Siemens), sequence (unedited, MEGA (22), HERMES (15), HERCULES (16)), metabolite list, spatial resolution, echo time (TE) and editing pulse frequencies. It allows community users to generate vendor, sequence, editing experimental-specific basis sets that are appropriate for their studies.

Apart from presenting the functionality of MRSCloud, evaluation of simulated basis sets among MRSCloud, FID-A (8) and LCModel (23) is also performed. Modeling strongly coupled metabolites with multiplet pattern such as Lac and GABA is challenging due to the inhomogeneity of magnetic field gradient that causes imperfect editing and application of the intended selective RF pulses to the spin system. That rises the chances of getting signal loss and eventually causes subtraction error. Recent consensus papers (6,24) have recommended the use of semi-LASER localization to mitigate the effect of chemical shift displacement error (CSDE). As the offset of CSDE is governed by

where denotes difference between spins Larmor frequency (MHz), BW denotes RF pulse bandwidth (Hz) and denotes slice thickness (m), it is increased with strongly coupled metabolites with large difference in spin Larmor frequency and is decreased using RF with higher BW (25). Previous studies on basis set analysis are more focused on STEAM and PRESS (26,27) and little work has been done on semi-LASER (11,28). The second purpose of this study was to compare basis set between unedited PRESS and semi-LASER and to the extent of the MEGA version of them.

**Methods**

MRSCloud, the GUI for which is shown in Figure 1, is built upon FID-A functionality. Up to 32 metabolites can be simulated, of which 25 use FID-A spin-system definitions (8), augmented by other metabolites including cystathionine, ethanolamine, homocarnosine, lysine, phosphorylethanolamine, threonine and valine (25,29,30). Other input parameters include localization method (PRESS or semi-LASER), sequence options (Unedited, MEGA, HERMES or HERCULES (15,16,22)), and vendor (GE, Philips and Siemens). TE can be defined for Unedited and MEGA simulations, and is fixed at 80 ms for HERMES and HERCULES. Editing frequencies of ON and OFF scans are user defined for MEGA (default edit-on/-off: 1.9/7.5 ppm) and fixed for HERCULES (1.9/4.18/4.58 ppm) and GABA/GSH-edited HERMES (1.9/4.56 ppm).

It has recently been demonstrated in MARSS (11) that density-matrix simulations can be substantially accelerated by using the 1D projection method (17) and applying coherence pathway filters (18,31). MRSCloud includes these functionalities, and makes additional savings by pre-calculating the propagators for all RF pulses. Cloud-based simulations allow exact simulation of proprietary vendor-specific RF pulse shapes, e.g. GTST (32) slice-selective refocusing pulses (bandwidth 1.3 kHz, duration 6.90 ms) for Philips PRESS sequences. GOIA pulses (bandwidth 10 kHz, duration 4.5 ms) are simulated for sLASER localization. Editing pulse durations for MEGA sequences are determined from TE, using a vendor-appropriate shape. A spatial array of simulations (of 101×101 resolution, by default) is carried out across a field of view that extends 50% larger than the voxel size in the two dimensions defined by refocusing pulses.

All code was written in MATLAB (R2020b, MathWorks, Natick, USA), and compiled as an executable file to run on the server with MATLAB Runtime. User inputs are stored in a declaration file (.json) that is loaded into the simulation. The pipeline for generating a basis set and the simulation module are shown in Figure 2.

For validation, simulations of GABA using MEGA, HERMES and HERCULES at TE 80 ms with PRESS in 21×21, 41×41 and 101×101 spatial points were performed using MRSCloud. For comparison, MEGA-PRESS of GABA in 41×41 spatial points was simulated using the local FID-A.

Comparison between LCModel, FID-A and MRSCloud

**Results**

MRSCloud has been successfully established, offering web-based basis set simulation for the community through the <https://braingps.anatomyworks.org/mrs-sim> portal. Simulation time varies somewhat depending on the usage of the third-party server. MEGA-PRESS simulations of GABA using MRSCloud are comparable to FID-A simulations, as shown in Figure 3, with a run time that is reduced by a factor of 9. MEGA-PRESS, HERMES and HERCULES simulations on GABA at 21×21, 41×41 and 101×101 spatial points are shown in Figure 4. GABA integrals at 3 ppm were slightly larger with a larger number of spatial points. Simulation time of 1012 spatial points for GABA, a strongly coupled 6-spin system, was less than 1 minute for all three sequences and MEGA-PRESS simulations for a basis set of 25 common metabolites, as shown in Figure 5, was ~4 minutes.

**Discussion**

MRSCloud provides fast and accurate simulation for MRS metabolites and generation of basis sets for linear-combination modeling. This improves access to basis sets across the community, and should result in more modeling being performed with basis sets that exactly represent the timing and RF pulse shapes of specific vendor sequences. Substantial reductions in runtime have been achieved by implementing the 1D projection method, coherence-order filtering, and pre-calculation of propagators, as well as implementation on a high-performance cloud server.

Discrepancies in lineshape between MRSCloud and FID-A are driven by the better coherence transfer pathway selection offered by direct filtering of the density matrix, as compared to incomplete phase-cycling of refocusing pulses. This advantage comes in addition to the 4x acceleration of not repeating simulations for the phase cycle. Changes of signal amplitude as the spatial resolution of the simulation changes are largely driven by raster effects (with a larger/smaller fraction of simulated points within the voxel).

**Summary (250 characters)**

MRSCloud is an online-based spectral simulations tool for the community to have fast and reliable basis set generation for up to 32 common and disease-related metabolites for linear combination modeling.

**Figures**

Figure 1: GUI of MRSCloud

Background pattern

Description automatically generated

Figure 2: Flowchart for a) MRSCloud pipeline and b) simulation module along the sequence diagram



Figure 3: Comparison between local FID-A and MRSCloud for simulated GABA spectra using MEGA-PRESS for 41x41 spatial points



Figure 4: a) Simulated GABA spectra using MEGA, HERMES and HERCULES with PRESS in 21x21, 41x41 and 101x101 spatial points and b) slight differences can be observed at the edited GABA signal at 3 ppm.



Figure 5: Basis set components for MEGA-PRESS GABA-editing at TE 68 ms simulated using MRSCloud



**References**

1. Murray ME, Przybelski SA, Lesnick TG, et al. Early Alzheimer's disease neuropathology detected by proton MR spectroscopy. J Neurosci 2014;34(49):16247-16255.

2. Martin WR. MR spectroscopy in neurodegenerative disease. Mol Imaging Biol 2007;9(4):196-203.

3. Maddock RJ, Buonocore MH. MR spectroscopic studies of the brain in psychiatric disorders. Curr Top Behav Neurosci 2012;11:199-251.

4. Choi C, Ganji SK, DeBerardinis RJ, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18(4):624-629.

5. Weinberg BD, Kuruva M, Shim H, Mullins ME. Clinical Applications of Magnetic Resonance Spectroscopy in Brain Tumors: From Diagnosis to Treatment. Radiol Clin North Am 2021;59(3):349-362.

6. Wilson M, Andronesi O, Barker PB, et al. Methodological consensus on clinical proton MRS of the brain: Review and recommendations. Magn Reson Med 2019;82(2):527-550.

7. Fano U. Description of States in Quantum Mechanics by Density Matrix and Operator Techniques. Reviews of Modern Physics 1957;29(1):74-93.

8. Simpson R, Devenyi GA, Jezzard P, Hennessy TJ, Near J. Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. Magn Reson Med 2017;77(1):23-33.

9. Young K, Matson GB, Govindaraju V, Maudsley AA. Spectral simulations incorporating gradient coherence selection. J Magn Reson 1999;140(1):146-152.

10. Naressi A, Couturier C, Castang I, de Beer R, Graveron-Demilly D. Java-based graphical user interface for MRUI, a software package for quantitation of in vivo/medical magnetic resonance spectroscopy signals. Comput Biol Med 2001;31(4):269-286.

11. Landheer K, Swanberg KM, Juchem C. Magnetic resonance Spectrum simulator (MARSS), a novel software package for fast and computationally efficient basis set simulation. NMR Biomed 2021;34(5):e4129.

12. Bak M, Rasmussen JT, Nielsen NC. SIMPSON: a general simulation program for solid-state NMR spectroscopy. J Magn Reson 2000;147(2):296-330.

13. Veshtort M, Griffin RG. SPINEVOLUTION: a powerful tool for the simulation of solid and liquid state NMR experiments. J Magn Reson 2006;178(2):248-282.

14. Soher B, Semanchuk P, Todd D, Steinberg J, Young K. Vespa: Integrated applications for RF pulse design, spectral simulation and MRS data analysis. 19th Meeting ISMRM. Montreal; 2011.

15. Chan KL, Puts NA, Schar M, Barker PB, Edden RA. HERMES: Hadamard encoding and reconstruction of MEGA-edited spectroscopy. Magn Reson Med 2016;76(1):11-19.

16. Oeltzschner G, Saleh MG, Rimbault D, et al. Advanced Hadamard-encoded editing of seven low-concentration brain metabolites: Principles of HERCULES. Neuroimage 2019;185:181-190.

17. Zhang Y, An L, Shen J. Fast computation of full density matrix of multispin systems for spatially localized in vivo magnetic resonance spectroscopy. Med Phys 2017;44(8):4169-4178.

18. Bodenhausen G, Kogler H, Ernst RR. Selection of coherence-transfer pathways in NMR pulse experiments. 1984. J Magn Reson 2011;213(2):276-294.

19. Bottomley PA. Spatial localization in NMR spectroscopy in vivo. Ann N Y Acad Sci 1987;508:333-348.

20. Scheenen TW, Heerschap A, Klomp DW. Towards 1H-MRSI of the human brain at 7T with slice-selective adiabatic refocusing pulses. MAGMA 2008;21(1-2):95-101.

21. Garwood M, DelaBarre L. The return of the frequency sweep: designing adiabatic pulses for contemporary NMR. J Magn Reson 2001;153(2):155-177.

22. Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R. Simultaneous in vivo spectral editing and water suppression. NMR Biomed 1998;11(6):266-272.

23. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30(6):672-679.

24. Oz G, Deelchand DK, Wijnen JP, et al. Advanced single voxel (1) H magnetic resonance spectroscopy techniques in humans: Experts' consensus recommendations. NMR Biomed 2020:e4236.

25. de Graaf RA. In Vivo NMR Spectroscopy – Static Aspects. In Vivo NMR Spectroscopy; 2019. p. 43-128.

26. Cudalbu C, Cavassila S, Rabeson H, van Ormondt D, Graveron-Demilly D. Influence of measured and simulated basis sets on metabolite concentration estimates. NMR Biomed 2008;21(6):627-636.

27. Wilson M, Davies NP, Sun Y, et al. A comparison between simulated and experimental basis sets for assessing short-TE in vivo (1)H MRS data at 1.5 T. NMR Biomed 2010;23(10):1117-1126.

28. Jalnefjord O, Pettersson P, Lundholm L, Ljungberg M. Simulated basis sets for semi-LASER: the impact of including shaped RF pulses and magnetic field gradients. MAGMA 2021;34(4):545-554.

29. Govindaraju V, Young K, Maudsley AA. Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed 2000;13(3):129-153.

30. Branzoli F, Pontoizeau C, Tchara L, et al. Cystathionine as a marker for 1p/19q codeleted gliomas by in vivo magnetic resonance spectroscopy. Neuro Oncol 2019;21(6):765-774.

31. Mitschang L, Ponstingl H, Grindrod D, Oschkinat H. Geometrical representation of coherence transfer selection by pulsed field gradients in high-resolution nuclear magnetic resonance. The Journal of Chemical Physics 1995;102(8):3089-3098.

32. Murdoch JB, Lent AH, Kritzer MR. Computer-optimized narrowband pulses for multislice imaging. Journal of Magnetic Resonance (1969) 1987;74(2):226-263.