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

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**Running Title**

Cloud-based basis-set Simulation

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**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, density matrix.

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

**Introduction**

[Introducing MRS and quantification]

Proton magnetic resonance spectroscopy (MRS) is a non-invasive method that uses an MRI scanner to detect radiofrequency (RF) signals from endogenous brain metabolites. Quantitative MRS has a broad range of preclinical and clinical research applications, as changes in metabolite levels can be observed in neurodegenerative, psychiatric and neurodevelopmental disorders (1-3) and offering biomarkers for brain tumor phenotyping and tracking treatment response (4,5). A key challenge in MRS has been bridging from detection to quantification, that is, access to robust, reproducible, and transparent analysis workflows that convert the acquired spectrum into measured metabolite levels. Although the signals derived from each metabolite change linearly with concentration, resolution between the signals of the large number of metabolites that are present in brain tissue is very limited. Inferring the concentration of individual metabolites from the complex mixture of signals that make up the in vivo spectrum is therefore challenging.

[Introducing LCM]

The most widely accepted approach to analyze MR spectra is linear combination modeling (LCM). In LCM, the acquired spectrum is modeled as a sum of weighted metabolite basis functions and other terms to describe background signals from mobile lipids and macromolecules and the spectral baseline. Metabolite basis sets can either be generated by numerical simulation or experimental acquisition of spectra from a set of single-metabolite phantoms. The latter is time-consuming, expensive and extremely demanding technically. Simulations based on the quantum mechanical density-matrix formalism (6) have become easier over time, with increased compute power and broadened access to simulation tools (7-13).

[Parameters that affect good and bad simulations]

Accurate simulated basis sets can only be generated by simulation using accurate acquisition parameters, including experimentally applied vendor-appropriate RF pulse shapes, correct timings and sufficient spatial resolution, rather than using ideal or hard pulses with different timings from the scanner for general approach. RF pulse shape determines the efficiency of the refocusing and editing power. A proper pulse shape fully refocused metabolite signal to avoid signal loss, and generation of the pulse depends on various parameters including B0, B1 power, waveforms, phase, amplitude and timesteps which vary across different vendors and sequences. Correct timings allow appropriate evolution of the metabolite signal between exciting, refocusing and editing pulses and signal acquisition. For instant, in a typical MEGA PRESS experiment, the first editing pulse is halfway between excitation and the second refocusing pulse while the second editing pulse is halfway between the second refocusing pulse and the start of acquisition. The TE, TE1 and TE2 timings have to be correct in order to generate accurate basis functions for each metabolite whereas TE and duration of the pulses could be user-defined and varied across different vendors or experiments. Sufficient spatial resolution allows accurate simulation for locations relative to the voxel as the efficiency of the pulse depends on the shapes and bandwidth and simulated spectra prone to have reduced intensity toward the edge of the pulse. Simulation with high spatial resolution guarantee the simulated spectra after averaging look as close as possible to the real data.

[Access to current LCM fitting tools]

Although there are numbers of existing simulation tools available (7-13), generating an appropriate LCM basis set to analyze a given experiment involves 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 the large, relatively well-separated singlet resonances of NAA, choline and creatine in short-TE spectra. However, using approximated basis sets is less tolerable for lower-concentration coupled spin systems and for more complex (i.e. longer-TE and edited) experiments. Two substantial shifts have recently occurred in MRS analysis. The predominant software product in the field ‘LCModel’ (14) is no longer actively supported, and at the same time a new generation of fuller-function analysis software has been released, including FSL-MRS (15), Tarquin (16), Osprey (17) etc. Most of these tools perform some form of LCM but access to appropriate basis-sets is one remaining hurdle in broadening access to stat-of-the-art MRS analysis tools.

[Aim of the study]

FID-A is an open-source software package using density matrix simulation in Matlab to generate basis functions of metabolites for MRS experiments as well as designing and analyzing RF pulses (7). It simulates metabolite functions with formulated timings and pre-defined phase cycling scheme for OVS suppression. It allows precise simulations for general unedited and MEGA PRESS experiments using ideal and hard pulses but not particularly optimized for vendors and simulation speed especially for the repetitive propagator calculation. Also, it has recently been demonstrated in MARSS (10) that density-matrix simulations can be substantially accelerated by using the one-dimensional (1D) projection method (18) and applying coherence pathway filters (19,20).

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, i.e. MEGA (21) 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 (22,23). Based on FID-A and the accelerating features mentioned, a cloud-based simulation tool is proposed.

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 (18), coherence pathway filters (20) 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 (24) or semi-LASER (25,26)), vendor (GE, Philips, Siemens), sequence (unedited, MEGA (21), HERMES (22), HERCULES (23)), 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.

**Methods**

**Development of Simulations**

This cloud implementation builds upon the simulation tools of FID-A. In order to accelerate the simulations, three improvements have been implemented, which are described in the following sections.

**1D projection method**

Spatially resolved simulations are time-consuming. In the original FID-A implementation of spatial simulations, each spatial direction was governed by a loop, and the full sequence was simulated for each spatial location. Simulating , , and spatial points in the x-, y- and z-direction, respectively amounts to performing x x simulations of the sequence. Zhang et al. (18) demonstrated that a more efficient way to achieve three-dimensional simulations is to average across each spatial dimension after simulating each one-dimensional frequency-selective RF pulse.

In PRESS localization, for example, the first spatial averaging can be performed after simulation of the slice-selective excitation pulse (and the appropriate accompanying rephase gradient). In the MRSCloud implementation, the excitation pulse is not explicitly simulated, but approximated by an ideal excitation. An additional spatial averaging step is performed after the first slice-selective

refocusing pulses, and then finally after the second slice-selective refocusing pulse. The total simulation time decreases from the order of ( x x ) to ( + + )/3.

**Coherence pathway filters**

Slice-selective refocusing relies upon coherence pathway selection to suppress signals from outside the intended slice. In the sequence itself, this is usually achieved both by phase cycling (20) and the coherence transfer pathway selection gradient scheme. Typically, simulations are not performed with sufficient spatial resolution for simulated gradients (8) alone to accurately suppress out-of-voxel signal, and simulations rely upon phase cycling. The commonly used EXORCYCLE (27) scheme is a suitable four-step phase cycle; independent EXORCYCLE of the two refocusing pulses results in a 16-step phase cycle (i.e. the simulation is repeated 16 times with different RF pulse phases and simulated receiver phase). In FID-A, it is common to approximate this with a half-EXOCYCLE on each pulse, resulting in a four-step phase cycle.

The MRSCloud implementation removes the need for phase cycling by applying coherence pathway filters (8,10,11). The different elements of the density matrix can each be classified in terms of their coherence order, and unwanted elements can be zeroed (equivalent to perfect coherence transfer pathway selection). Each simulated RF pulse in the sequence is immediately followed by a coherence-order filters, so that only density-matrix elements of the intended order are propogated further in the simulation.

**Pre-calculation of propagators**

Within FID-A, shaped pulses are applied elementwise each time they are applied. For example, a 256-point shaped refocusing pulse is simulated as 256 individual rotations. This involves a substantial amount of redundant calculation that can be avoided by pre-calculation of the pulse propagators. Simulating each pulse then becomes a matter of applying the appropriate propagator, rather than serially claultating and then applying 256 individual propagators. The saving arises both because refocusing and editing pulses are repeated within the sequence and, in cases where the previos two accelerations have not been implementated, for phase cycling and spatial purposes.

Figure 1a illustrates the MRSCloud simulation for the example of MEGA-PRESS, in terms of its constituent propagation operations.

**GUI Specification of simulation parameters**

Figure 1b outlines the pipeline for a given MRS Cloud simulation. Firstly, the user specifies the metabolites to be simulated, from a list of thirty-two. Of those, 25 use FID-A spin-system definitions (7), many of which are parameterized from (28,29), augmented by other metabolites including cystathionine, ethanolamine, homocarnosine, lysine, phosphorylethanolamine, threonine and valine (28,30,31). Next the user specifies the vendor (GE, Philips and Siemens), sequence options (Unedited, MEGA, HERMES or HERCULES (21-23)) and localization method (PRESS or semi-LASER). 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 HERMES (GABA/GSH 1.9/4.56 ppm). The GUI for MRSCloud is shown in Figure 2. Once the user presses submit, the user inputs are stored in a declaration file (.json) that is loaded into the precompiled simulation executable to execute the desired simulation. Thhe basis-set output is then saved on the server and the user can download it.All code was written in MATLAB (R2020b, MathWorks, Natick, USA), and compiled as an executable file to run on the server with MATLAB Runtime.

MRSCloud simulations allow exact simulation of proprietary vendor-specific RF pulse shapes, e.g. GTST (32) slice-selective refocusing pulses for Philips (bandwidth 1.35 kHz, duration 6.20 ms), GE (bandwidth 1.38 kHz, duration 5.20 ms) and Siemens (bandwidth 1.34 kHz, duration 7.0 ms) for PRESS sequences (33). For sLASER, GOIA-WURST pulse (bandwidth 8 kHz, duration 4 ms, B1 15uT) is simulated for Philips and slice-selective AFP 180° refocusing pulses (bandwidth 5.1 kHz, duration 5 ms, B1 27uT) for Siemens (34). Since pulse shape and detailed parameters are unknown for GE, sLASER simulation for GE has been carried out using the GOIA-WURST. RF pulses were generated using Bloch simulation. B0 field strength was 3.0 T for Philips, GE and universal pulses and 2.89 T for Siemens. Therefore, Larmor frequency was 127.7 MHz for Philips, GE and universal pulses and 123.0 MHz for Siemens pulses given the gyromagnetic ratio for hydrogen (42.577 MHz/T). Details of pulses for localization and editing are shown in Table 1. 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.

For validation, simulations of GABA using MEGA, HERMES and HERCULES at TE 80 ms with PRESS and sLASER 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

Validation was performed using basis sets from LCModel and MRSCloud for PRESS at TE 30 ms. (Can we perform any statistical analysis?)

**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 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.

Various improvement that we have made in MRSCloud.. Now doing 41+41 instead of 40\*40 times. Or 1\*40. Get rid of the phase cycling 4 times to prefrom suppression of OVS slice selection of the 180 pulse with Gradient. Now we use pfilter to obtain spatial, 3: pre-calculate the propagator for the individual pulse 1600 times now 1 time and apply it for 40 times]

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).

Table 1: Summary of pulses for simulation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Name of pulse | Simulated vendor | Localization/editing | Duration (ms) | Bandwidth/ sweep width (kHz) | B1max (µT) | Target (ppm) |
| gtst | Philips | PRESS | 6.19 | 1.354 | 13.5 | - |
| Siemens | 7.0 | 1.342 | 13.5 | - |
| GE | 5.2 | 1.384 | 17.6 | - |
| Universal | 7.0 | 1.342 | 13.5 | - |
| GOIA-WURST | Philips/GE | sLASER | 4.0 | 2.97/8.0 | 15.0 | - |
| Siemens-AFP | Siemens | 5.0 | 5.1/TBC | 27.0 | - |
| sg100 | Philips/GE | Editing pulse | 14/20\* | 1.33 | - | Arbitrary |
| sl\_univ | Siemens/Universal | 14/20\* | 1.33 | - | Arbitrary |
| dl\_456 | Philips/GE | 20 | 0.0605 | - | 4.56,1.9 (HERMES) |
| dl\_458 | Philips/GE | 20 | 0.0605 | - | 4.58,1.9 (HERCULES) |
| dl\_418 | Philips/GE | 20 | 0.0605 | - | 4.18,1.9 (HERCULES) |
| dl\_Siemens\_456 | Siemens/Universal | 20 |  | - | 4.56,1.9 (HERMES) |
| dl\_Siemens\_458 | Siemens/Universal | 20 |  | - | 4.58,1.9 (HERCULES) |
| dl\_Siemens\_418 | Siemens/Universal | 20 |  | - | 4.18,1.9 (HERCULES) |

\*TE dependent as for MEGA (If TE <80 ms, Duration =14 ms; if TE=80 ms, Duration=20 ms). Fixed at 20 ms for HERMES and HERCULES

**Figures**

Figure 1: GUI of MRSCloud

Background pattern

Description automatically generated

Figure 1: 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

Replace with short-TE 41x41 for ~10 major metabolites. (NAA, Cr, Cho, Glu, Gln, mI, Lac GABA, GSH, Gly?)



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



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