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**

**1D projection method**

Three implementations were applied into MRSCloud to accelerate the speed of simulation. Zhang et al. (18) demonstrated that a conventional three-dimensional simulation could be achieved using three one-dimensional frequency selective RF pulses approach as shown in the following equations for simulating full density matrix of spins.

[1]

[2]

[3]

where , and denote the evolution propagators corresponding to the excitation RF pulse along the z-direction and the two refocusing pulses along x and y directions respectively. In a PRESS localization example, resulted from the free evolution between the excitation and the first refocusing pulse; resulted from the evolution of the first crusher gradient in the x-direction and the evolution between the first and second refocusing pulses; resulted from the evolution of the crusher gradient in the y-direction and the evolution between the second refocusing pulse and the signal acquisition. The density operators were summed at the end for acquisition for all spatial points. The same principle was being used for semi-LASER as shown in equations 4 and 5 in which the and propagators denote the evolution for the first pair of adiabatic full-passage (AFP) pulses in the x-direction and and propagator denote the evolution of the second pair of AFP pulses in the y-direction.

[4a]

[4b]

[5a]

[5b]

With the 1D projection method, the number of simulations decreased from a multiple of number of spatial points in x-, y- and z-directions (i.e. x x ) to the sum of them (i.e. + + ), where n is the number of spatial points.

**Coherence pathway filters**

The second implementation applied to accelerate simulation was the coherence pathway filters (19,20). Coherence is a collection of spins from detectable transverse magnetization and coherence selection is to indicate and detect the desire coherence component and to simultaneously separate unwanted signals. Traditionally, phase cycling of the EXORCYCLE [ref] is one of the most common method of choices for selecting desired and removing unwanted signals after experiencing any RF pulse. It is a four-step phase cycle of 180o pulses being applied on the ±x- and ±y- axes resulting cancellation of unwanted signal. In order to replace phase cycling in simulation for running a pre-defined phase cycling scheme which multiples the number of simulations by a factor of 4 for every RF pulse being applied, the coherence pathway filters (8,20) was implemented. It was applied on the density matrix each time after experiencing a RF pulse followed by the RF evolution for the correct timing. It is governed by equation 6

dout = din .\* (HP\_filter) [6]

where dout denotes the output density matrix which is a Hadamard product of the input density matrix, din, and the filter matrix in Hamiltonians, Hp\_filter, which is a pre-defined value as either +1 or -1. (Try to explain what this +1/-1 is, and how p-filter accelerate the simulation) Proton with a spin of system, has 3 possible coherence pathways evolve (-1, 0, +1) after application of a pulse. Therefore, the number of coherence pathway would be the multiply of 3 and the number of pulses applied (i.e. 3 x n, where n is the number of pulses). For instant, a PRESS localization would have 9 possible pathways due to its excitation pulse and 2 refocusing pulses. However, for most MR receiving coils, only signals in the -1 coherence can be detected which limited the number of total coherences that evolve. Previous simulation tool applied pre-defined phase cycling scheme each time when there is a RF pulse being applied to minimize or remove outer voxel signals.

**Pre-calculation of propagators**

dout = Q1' \* din \* Q1 [7]

where Q1 is the pre-calculated propagator for RF pulse and Q1' is the transpose of it and din denotes the input density matrix.

The pipeline of MRSCloud is shown in Figure 1.

**GUI and RF pulses**

MRSCloud, the GUI for which is shown in Figure 2, is built upon FID-A functionality. Up to 32 metabolites can be simulated, of which 25 use FID-A spin-system definitions (7), augmented by other metabolites including cystathionine, ethanolamine, homocarnosine, lysine, phosphorylethanolamine, threonine and valine (27-29). Other input parameters include localization method (PRESS or semi-LASER), sequence options (Unedited, MEGA, HERMES or HERCULES (21-23)), 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).

MRSCloud simulations allow exact simulation of proprietary vendor-specific RF pulse shapes, e.g. GTST (30) 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 (31). 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 (32). 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.

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 is shown in Figure 1.

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 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



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