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Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package

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Abstract
The software package jMRUI with Java-based graphical user interface enables user-friendly time-domain analysis of magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) and HRMAS-NMR signals. Version 3.x has been distributed in more than 1200 groups or hospitals worldwide. The new version 4.x is a plug-in platform enabling the users to add their own algorithms. Moreover, it offers new functionalities compared to versions 3.x. The quantum-mechanical simulator based on NMR-SCOPE, the quantitation algorithm QUEST and the main MRSI functionalities are described. Quantitation results of signals obtained *in vivo* from a mouse and a human brain are given.

Keywords: MR spectroscopy, MRS, MRSI, HRMAS-NMR, jMRUI software package, Java, plug-ins, quantitation

1. Introduction

Magnetic resonance spectroscopy (MRS) and spectroscopic imaging (MRSI) play an increasing, important role in diagnosing major diseases, and in monitoring the effect of therapies. The challenge is to quantify spectra which exhibit many metabolites, and to estimate their concentrations. To that effect, the software package jMRUI with a Java-based graphical user interface (GUI) [1, 2] is being developed for user-friendly time-domain analysis of MRS, MRSI and HRMAS-NMR signals. In this paper, we describe the essential components of the GUI of version 4.x which has an extensible architecture based on plug-ins, and the recent and new functionalities. The jMRUI software package offers:

- Black box quantitation algorithms based on singular-value decomposition (SVD): the state space methods HSVD [3, 4], HLSVD [5], and HTLS [6] and the linear prediction method LPSVD [7]. These non-interactive black box techniques are efficient for quantitating signals with good signal-to-noise ratios. They are also helpful in parametrizing signals of unknown composition and shape, but they cannot make use of all available prior knowledge.
- Nonlinear least-squares (NLLS) quantitation algorithm: AMARES [8] and QUEST [9, 10]. AMARES is an improved version of VARPRO [11] enabling us to impose prior knowledge on the model-function parameters. QUEST is based on the availability of a metabolite signal basis set.

- Preprocessing algorithms such as rapid removal of dominant signals using HLSVD [5, 12] and HLSVD-Pro [13], or time–frequency analysis [14], the Cadzow enhancement procedure for noise reduction [15], the ER-filter [16] for frequency selection, and Gabor tools for peak extraction and dynamic phase correction [17].
- Estimation of spectral parameters with their confidence intervals (Cramér–Rao lower bounds) [18–21].
- Conversion routines for data files from most manufacturers (Bruker, General Electric, Philips, Siemens, Varian, etc). Moreover, the software package jMRUI handles the new advanced DICOM format for MRS, MRSI and MRI.
- Signal simulations from a model function.
- Quantum-mechanical signal simulator based on NMR-SCOPE [22] that can handle various measurement protocols and enables the simulation of metabolite signal basis sets.

The jMRUI software package works with Windows 2000, XP, Vista and Linux.

This software package is presently developed in the context of the European Marie Curie project 'FAST', *Advanced Signal Processing for Ultra-Fast Magnetic Resonance Spectroscopic Imaging, and Training*. It is free for Academia and has been distributed in more than 1200 groups or hospitals worldwide. Figure 1 shows its increasing impact. See http://www.fast-mariecurie-rtn-project.eu and http://www.mrui.uab.es/mrui. Note that the previous version, based on Matlab, mMRUI [23], has not been maintained since 2001 but the source code can still be downloaded.

This paper is set up as follows. First, we give an overview of the software architecture of version 4.x based on plug-ins. Next, we present the recently implemented functionalities, namely the quantum-mechanical simulator and the quantitation algorithm QUEST needed for quantitation of short echo-time signals, and the MRSI functionalities.

2. Plug-in platform

Version 3.x of the jMRUI software package has been completely refactored. The plans within the context of the project 'FAST' are to go from the jMRUI to the eMRUI software package by adding a collaborative training layer. We will go from a single-user application to a collaborative application involving several users worldwide. The client–server interface will enable Web distance-collaboration between remote clinical experts as well as researchers. Then, multiple clients worldwide will be able to learn, train, interpret interactively through their computers by remote real-time sharing signal processing/visualization actions.

In a first step, version 3.x has been refactored as a plug-in platform; see figure 2. This was a major programming task. The plug-in platform enforces a modular approach to software development. As a result, it is more maintainable and upgradeable. In other words, it facilitates the development and integration of new features, while keeping a robust application kernel. The plug-in configuration tools will also enable filtering and rearranging the loaded features, providing a more personalized experience or simply a lighter and more focussed application.

2.1. Architecture

Version 4.x offers new main features:

- It is a ***plug-in platform*** and one of its aims is to give the users more power to adapt it to their taste. Plug-in templates (conversion routines for data files, preprocessing, quantitation, custom) are provided; see figure 3. The users can then extend/simplify the GUI. A configuration window enables activating, deactivating or reordering the plug-ins. Those operations will have a direct impact on the main menu, thus achieving a more personalized and optimized experience with the application. New features can easily be added by implementing the desired plug-in interface. Any Java programming platform can be used, but we provide 'ready-to-go' project templates for the Eclipse platform (http://www.eclipse.org).

  eMrui as a plug-in platform is based on some basic and advanced object-oriented concepts such as abstraction, inheritance, custom class loading and reflection. In a normal Java application, a class calling the methods of another class must have a direct reference to it during programming. In order to enable adding and using plug-in libraries without altering the application code, a custom class loader was implemented for loading classes during runtime. Plug-ins must implement plug-in interfaces to enable generic method calls.
- The function calls are generic.
- Memory has been optimized for processing of large MRSI/time-series data sets. An improvement by a factor of 6 has been achieved.

2.2. Implementation of plug-ins

Plug-ins can be implemented using Eclipse and the provided jMRUI plug-in template project enabling the users to extend the software. A template enables the users to easily add their own favoured applications like file-conversion, preprocessing in their own copy of jMRUI. Even addition of alternative quantitation algorithms is possible enabling future integration in jMRUI of European quantitation software packages. As an example, a plug-in for temperature mapping based on chemical shift variations is being implemented; see figure 4. The users who would like to share their own plug-ins can post them in a dedicated repository on the FAST and jMRUI Web sites and leave a message in the FAST or jMRUI Wiki. Some plug-ins could even be integrated and provided with the jMRUI software package.

In combination with the collaborative training layer, new unforeseen developments are then to be expected.

3. New functionalities

3.1. NMR-SCOPE

Within the context of the FAST European project, partners are developing a 'virtual scanner' based on quantum-mechanical

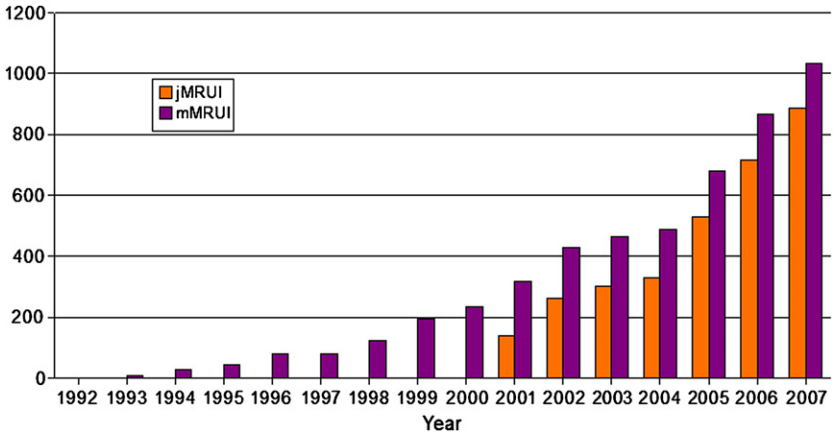

Figure 1. Number of research groups and hospitals using jMRUI worldwide and number of mMRUI downloads.

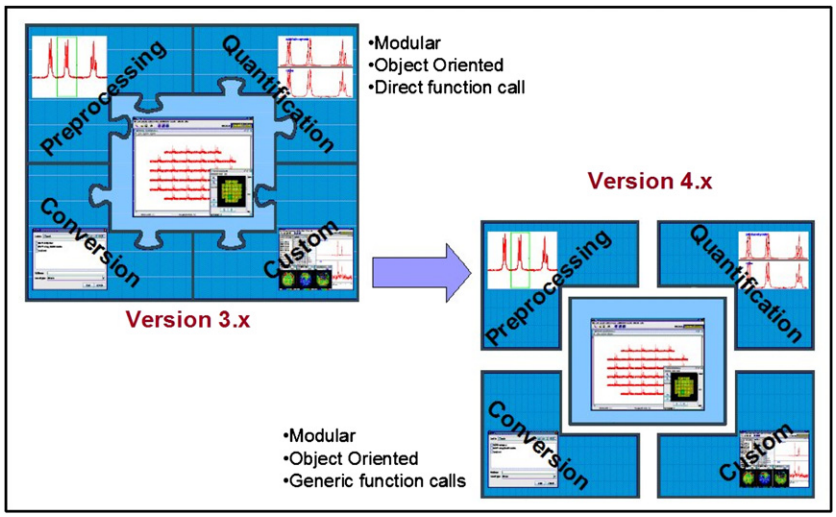

Figure 2. Changes in the architecture of the jMRUI software package from version 3.x to the new version 4.x.

simulation, enabling the design of novel, complex, user-adaptable MRS(I) scan protocols and simulation of the ensuing signals. The quantum-mechanical simulator used is the NMR-SCOPE algorithm [22]. The latter is based on the density matrix and the product-operator (super operators) formalism and handles a product-operator description of strongly coupled spin 1/2 systems. It enables us to simulate signals of the metabolites in response to a MR sequence. It can handle various pulse sequences such as STEAM and PRESS, and provides the time-domain signals directly. It is applicable to ^{1}H, ^{13}C, ^{19}F, ^{15}N, ^{31}P, ... nuclei, and arbitrary field strength.

The simulation scheme can be summarized as follows:

(i) Loading of a pulse sequence with its parameters,
(ii) Loading of the spin-system parameters (chemical shifts and *J*-couplings) of a given molecule (metabolite),
(iii) Generation of the 4^N Cartesian-basis product operators, For each sequence event,
(iv) Automatic generation of the considered Hamiltonian (radio-frequency pulse or free-precession),
(v) Evolution of the density matrix product-operators. Steps IV and V are repeated for each event of the NMR pulse-sequence.
(vi) Detection period: generation of the sampled signal directly in the time domain.

Compared to the GUI of recent versions 3.x of jMRUI, the GUI of NMR-SCOPE has been refactored (see figure 5) and offers more possibilities:

- Handling of more spins (up to 12 spins can be handled using the conventional quantum-mechanics approach (one pulse sequence), 8 and 6 spins in the weak and strong coupling approaches, respectively (multi-pulse sequence),
- Saving of spin and sequence files as text files,
- Direct simulation of series of signals as a function of MR pulse-sequence parameters,
- Phase cycling,
- Viewing of the simulated signals in the 1D mode window enabling the possibility of directly using the preprocessing and quantitation functionalities.

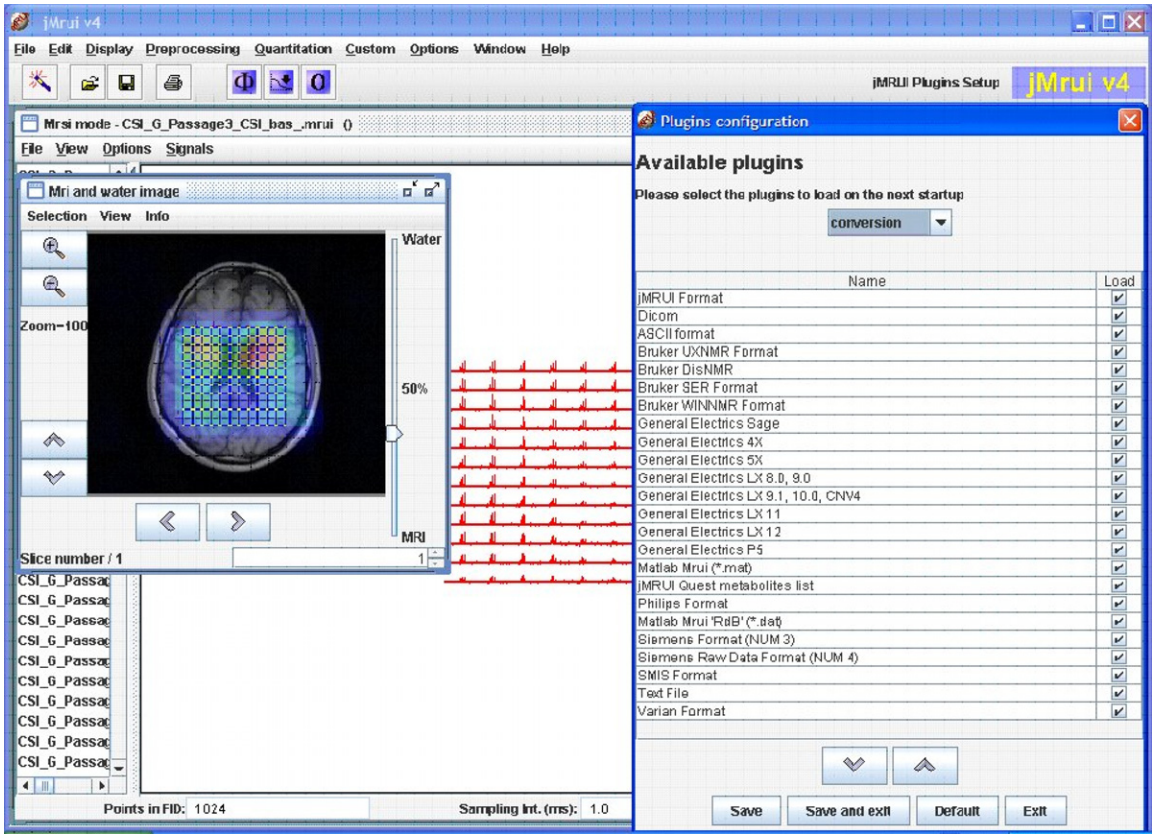

Figure 3. jMRUI version 4.x. The list of the available conversion plug-ins is shown in the right-hand window.

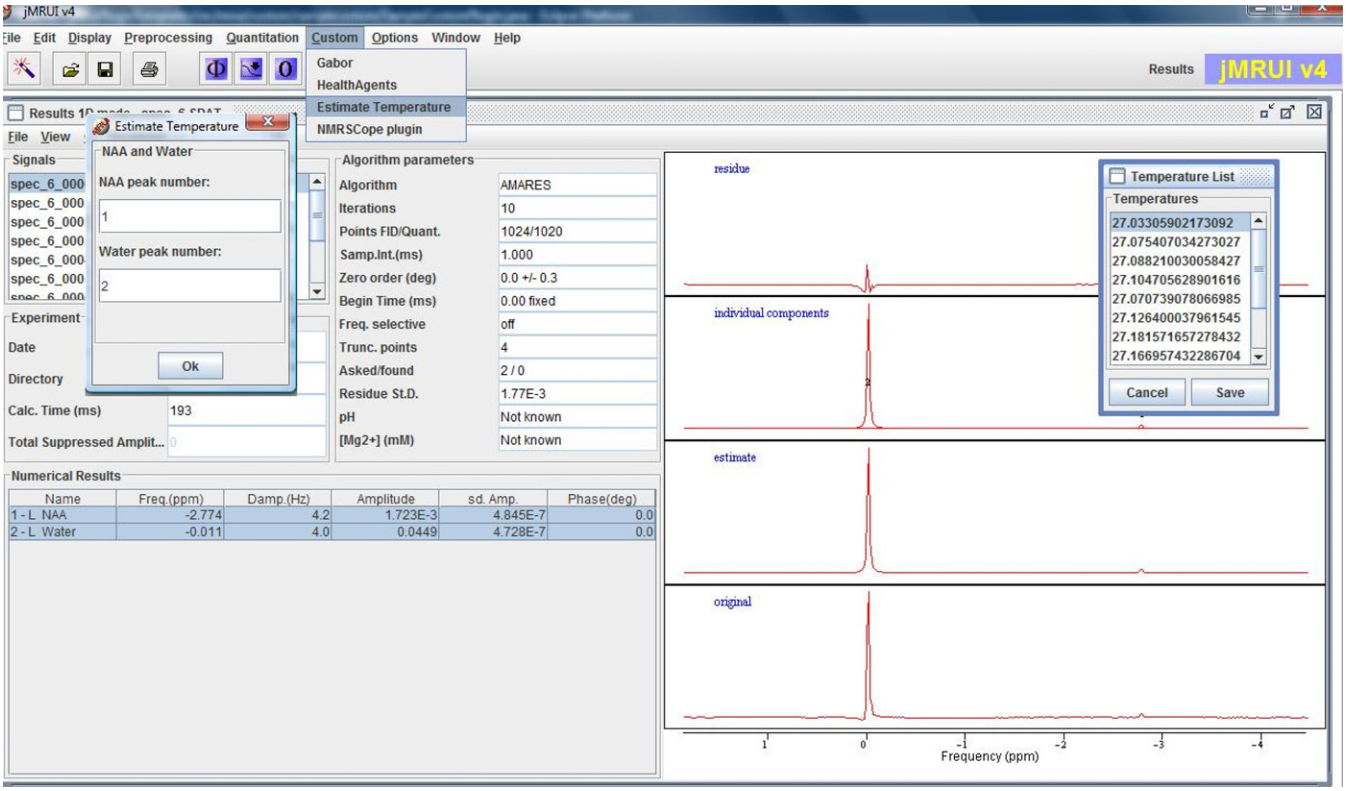

Figure 4. jMRUI version 4.x. The plug-in for *in vivo* temperature estimation under development, set-up from the custom template. The temperature is estimated using the frequency difference between the peaks of water and NAA for time-series signals.

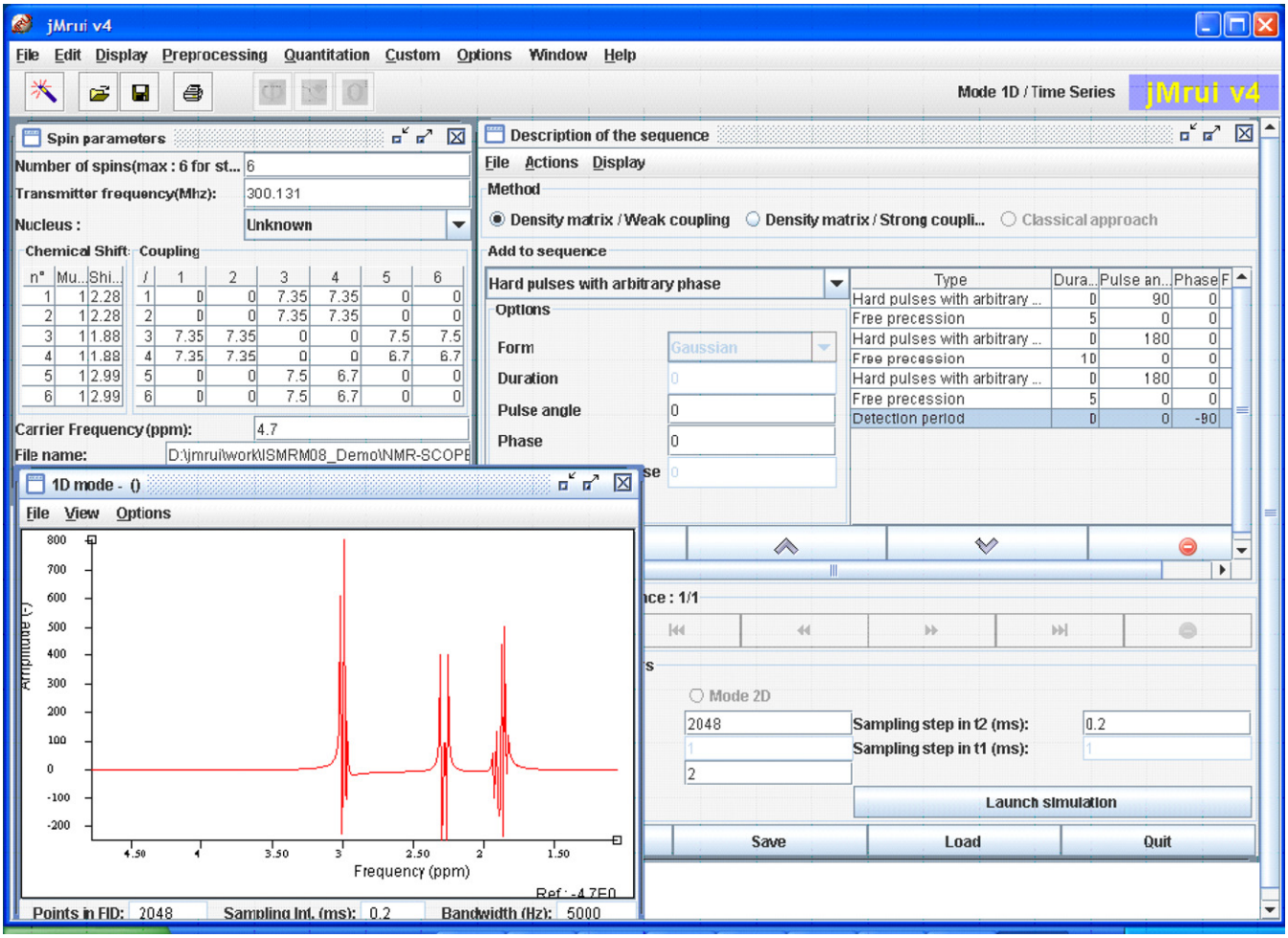

Figure 5. jMRUI version 4.x: new design of the NMR-SCOPE window. The top left window corresponds to the spin parameters of a given metabolite (in this case GABA). The window on the right enables us to handle various magnetic resonance pulse-sequences including phase-cycling. A PRESS sequence with an echo-time of 20 ms is displayed (each line corresponds to an event of the sequence). The simulated signal of GABA at 7 T in response to the PRESS sequence is directly obtained in the 1D mode window.

Simulation of 2D experiments, possible with NMR-SCOPE [22], will be implemented in the GUI of version 4.1. Relaxation is being incorporated in the quantum-mechanics formalism too.

NMR-SCOPE enables us, for instance, to build the ^{1}H basis-set signals for about 40 metabolites. Spin parameters were initially taken from [24] and refined with the aid of 2D NMR experiments, and NMR-SCOPE. The corresponding files are provided with the software package.

As an example, 23 metabolites—acetate (Ace), alanine (Ala), aspartate (Asp), creatine (Cr), choline (Cho), cysteine (Cys), ethanolamine (Eth), γ-amino-butyric acid (GABA), glucose (Glc), glutamate (Glu), glutamine (Gln), glycine (Gly), glycero-phosphoryl-choline (GPC), lactate (Lac), myo-inositol (mI), N-acetylaspartate (NAA), phosphoryl-choline (PC), phosphocreatine (PCr), phenylalanine (Phe), scyllo-inositol (sI), serine (Ser), succinate (Suc), taurine (Tau)—were included in the basis set used for quantitation of HRMAS signals. Such a basis set used in QUEST for quantitation of rodent brain HRMAS signals is shown in figure 6.

3.2. Quantitation with QUEST

Quantitation of ^{1}H *in vivo* signals obtained at short echo-time or HRMAS signals is highly challenging because these signals contain several hundreds of overlapping spectral components from many metabolites. Quantitation can be achieved using the algorithm QUEST based on a metabolite basis set [9, 10, 25]. The latter can be simulated with NMR-SCOPE as previously mentioned. The algorithm QUEST, for optimal fitting of metabolite basis-set signals to (contaminated) data is based on a *semi-parametric* approach. Subtract-QUEST sequentially uses (1) untangling of the background from the metabolite signal, (2) separate modelling and (3) a parametric nonlinear least-squares fitting of the untangled metabolite signal knowing the background [10, 25].

The 'QUEST quantitation' window in figure 7 shows how a metabolite basis set can be user-friendly set-up in QUEST.

An example of a mouse brain spectrum obtained at 7 T using a PRESS sequence with an echo-time of 20 ms, and quantitated with QUEST is shown in figure 8. The 20 initial data-points were used to disentangle the metabolite from the background signals.

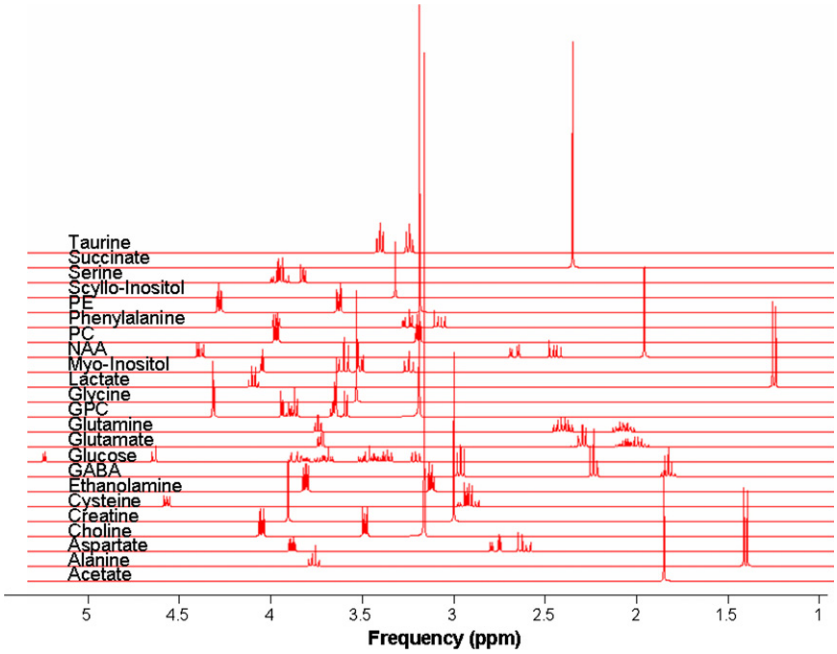

Figure 6. Fourier transform of a metabolite signal basis set at 9.4 T, simulated by quantum mechanics with NMR-SCOPE for a one pulse sequence. This basis set was used in QUEST for quantitation of HRMAS signals. Lorentzian line shapes were used.

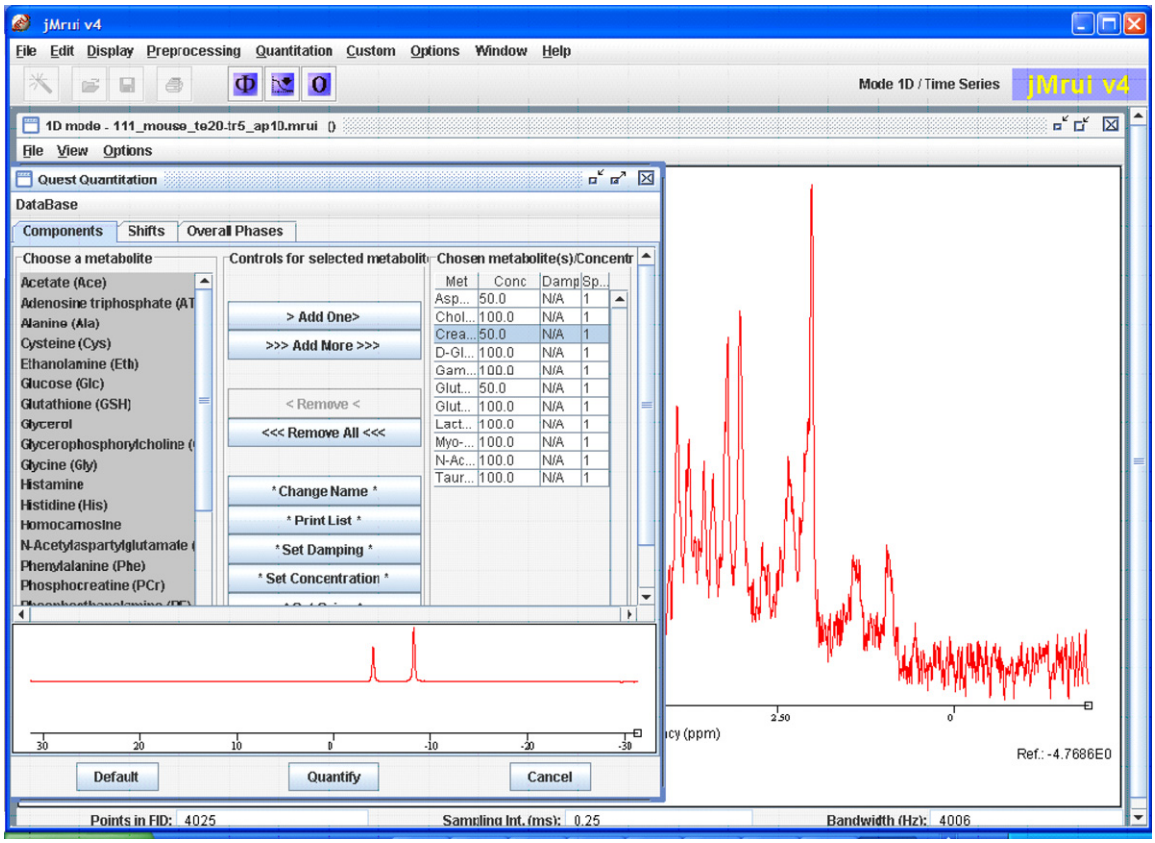

Figure 7. First window-tab of the 'QUEST quantitation' window used to set up a metabolite basis set. Users select from the list on the left the metabolites that will be included in the basis set. The corresponding signals previously simulated with NMR-SCOPE or measured from *in vitro* solutions are then loaded.

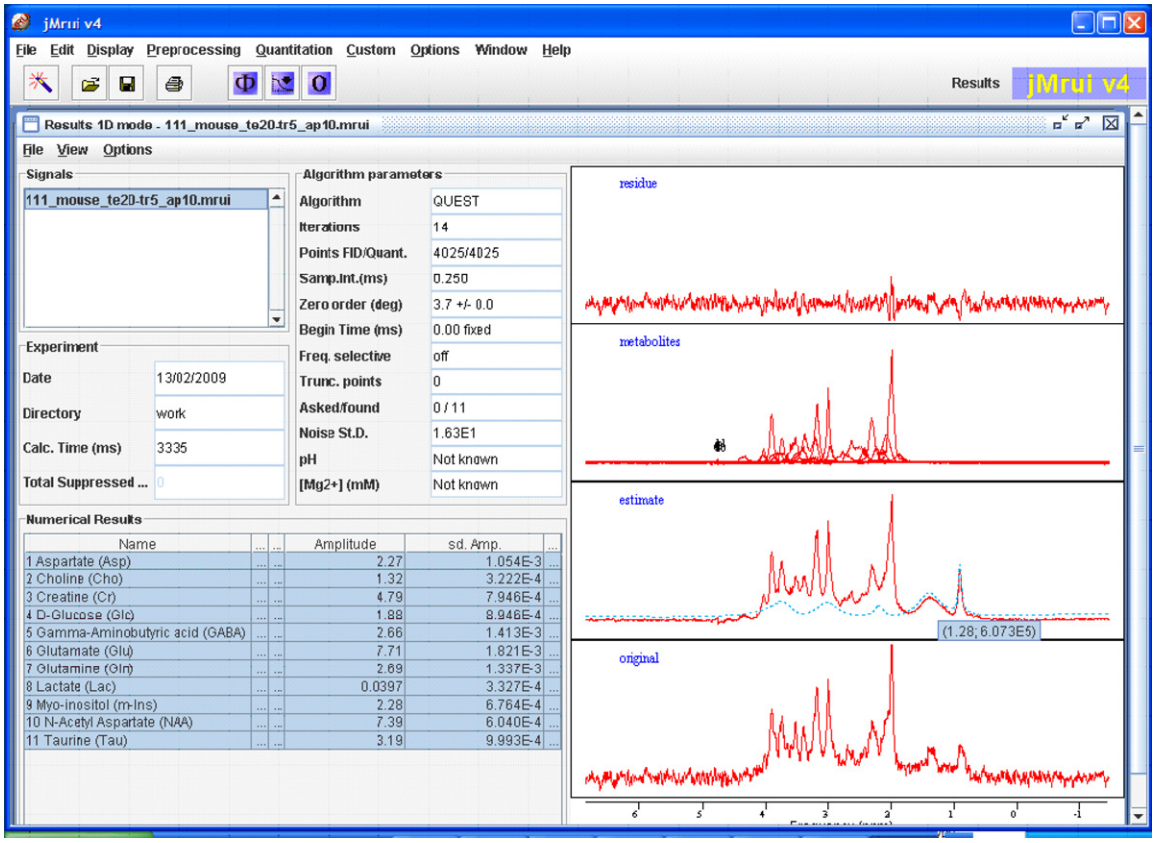

Figure 8. ^{1}H spectrum of a mouse brain at 7 T obtained using a PRESS sequence with an echo-time of 20 ms, quantitated with QUEST. From bottom to top, raw spectrum, estimated spectrum and background (dashed line), individual spectra of the metabolites and the residue. Note that the lipids at 0.9 and 1.3 ppm are well retrieved in the background.

3.3. Magnetic resonance spectroscopic imaging (MRSI)

A specific user-friendly GUI for processing of MRSI data has been designed.

When processing MRSI data, one faces: (1) a large amount of data, (2) a water signal a hundred times larger than metabolite signals, (3) macromolecule signals overlapping metabolite peaks and (4) low signal-to-noise metabolite signals. A user-friendly GUI is highly needed for handling the data as well as fast and non-interactive algorithms. With the jMRUI-MRSI GUI, all functionalities of the 1D/time-series mode are available including, (1) preprocessing: filter-HLSVD for water/macromolecule suppression, eddy current correction, correction of frequency shifts due to field heterogeneities (based either on the use of water MRSI data, when available, or on the correlation between the spectrum obtained without spatial encoding gradient and the spectrum in each voxel), (2) time-domain quantitation: SVD-based algorithms, NLLS-based methods AMARES and QUEST. In addition, the GUI offers some more specific functionalities:

- Customization of *k*-space sampling enabling the users to handle their own sampling strategies.
- Preprocessing in *k*-space.
- Automatic selection of relevant localized signals; see the window on the left in figure 3.
- Viewing of the anatomic images and *interactive* construction of the metabolite images (interpolated or not), maps for the damping factors (transverse relaxation times), frequencies, ratio maps, error maps on spectral parameters computed from the Cramér–Rao lower bounds.
- Direct comparison between the estimated metabolite concentrations in different regions (i.e., pathological versus healthy regions).
- Exports of the results in DICOM format for viewing on PACS.

An example of quantitation results obtained with the algorithm QUEST [9, 10, 26] of ^{1}H MRSI data of a human brain (32 × 32 voxels, PRESS pulse sequence with an echo-time of 136 ms), obtained at 1.5 T is given in figure 9. The data were obtained from a patient with multiple sclerosis. Metabolic images of N-acetylaspartate (NAA), creatine (Cr), as well as the map of the concentration ratio NAA on Cr are displayed with quantitation results in a voxel selected in plaques. The absence of metabolites in the ventricles is clearly visible.

4. Conclusion

Version 4.x of the jMRUI software package based on Java is a plug-in platform offering advanced signal processing for medical magnetic resonance spectroscopy. It gives more power to the users and provides advanced new features.

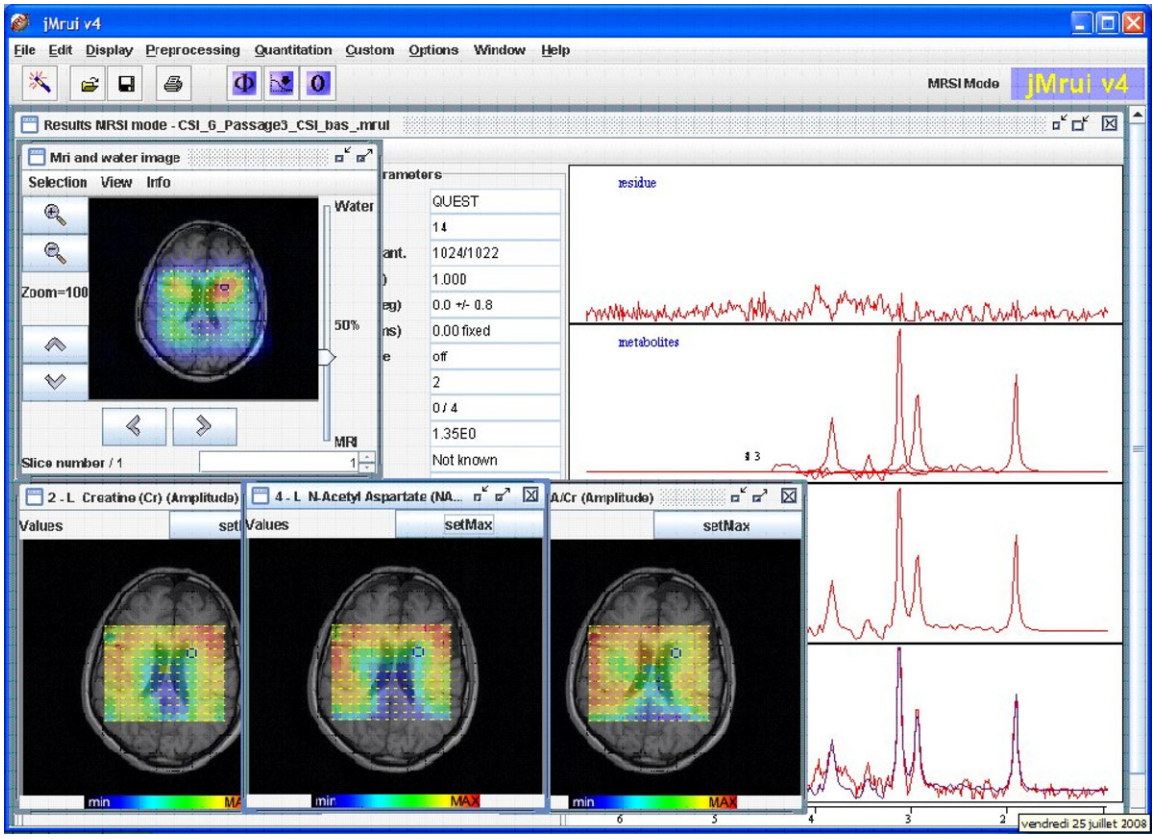

Figure 9. Quantitation with QUEST of ^{1}H MRSI data (32 × 32 voxels, PRESS sequence with an echo-time of 136 ms) of a human brain of a patient with multiple sclerosis, obtained at 1.5 T. Metabolic images of NAA and Cr, and of the ratio NAA on Cr superimposed on the anatomic image, and quantitation results in a selected voxel in plaques; from bottom to top, raw (red) and estimated (black) spectra, estimated spectrum, individual metabolites and the residue. The residue can be improved by fitting more metabolites. Data were in the new advanced DICOM format.

FAST's plans are to go from the jMRUI to the eMRUI by adding a collaborative training layer enabling distance interaction between the users for training and consultation.

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Figures 1, 2, 3 and 9 have been presented at the 2008 IEEE Workshop on Imaging Systems and Techniques and published in its proceedings.

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