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Sodium 3D COncentration MApping (COMA 3D) using ^{23}Na and proton MRI

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ABSTRACT

Functional changes of sodium 3D MRI signals were converted into millimolar concentration changes using an open-source fully automated MATLAB toolbox. These concentration changes are visualized via 3D sodium concentration maps, and they are overlaid over conventional 3D proton images to provide high-resolution co-registration for easy correlation of functional changes to anatomical regions. Nearly 5000/h concentration maps were generated on a personal computer (ca. 2012) using 21.1 T 3D sodium MRI brain images of live rats with spatial resolution of $0.8 \times 0.8 \times 0.8$ mm^3 and imaging matrices of $60 \times 60 \times 60$. The produced concentration maps allowed for non-invasive quantitative measurement of *in vivo* sodium concentration in the normal rat brain as a functional response to migraine-like conditions. The presented work can also be applied to sodium-associated changes in migraine, cancer, and other metabolic abnormalities that can be sensed by molecular imaging.

The MATLAB toolbox allows for automated image analysis of the 3D images acquired on the Bruker platform and can be extended to other imaging platforms. The resulting images are presented in a form of series of 2D slices in all three dimensions in native MATLAB and PDF formats. The following is provided: (a) MATLAB source code for image processing, (b) the detailed processing procedures, (c) description of the code and all sub-routines, (d) example data sets of initial and processed data. The toolbox can be downloaded at: http://www.vuiis.vanderbilt.edu/~truongm/COMA3D/.

1. Introduction

High-field MRI and localized MR spectroscopy (MRS) enable detection of dilute (millimolar concentration) metabolites [1,2]. 2D and 3D maps of proton metabolites can be obtained clinically [3]. Spatially localized spectra and 2D/3D multi-voxel proton MRS maps can be used for diagnosis of brain diseases [1] and cancer [4,5]. Furthermore, ^{13}C hyperpolarized MRS increases NMR sensitivity by orders of magnitude, and it can also gauge *in vivo* metabolism by MRS, disease associated abnormalities, response to treatment, but it has not yet been translated to a widespread use in clinical research [6].

Recent development of ultra-high field pre-clinical 21.1 T MRI [7] enabled high-resolution functional MRI studies of live rats [8], with sensitivity sufficient to generate high-resolution maps of dilute nuclei beyond protons and without the use of hyperpolarization techniques. High-resolution 2D ^{23}Na with sub-millimeter spatial resolution has been demonstrated and successfully used for functional changes of sodium in the rat model of migraine [9]. 3D ^{23}Na sub-millimeter MRI of brain cancer was also demonstrated [10]. Furthermore, ^{23}Na has also been advanced in clinical research use by the advent ultra-high field clinical MRI scanners [11–13].

However, the resolution and sensitivity improvements endowed by high magnetic fields create labor and information intense datasets, e.g. large multi-dimensional matrices that prove

Abbreviations: COMA, concentration map; FMRI, functional magnetic resonance imaging; GB, gigabytes; RAM, random access memory; NTG, nitroglycerin; FOV, field of view; CSF, cerebrospinal fluid; RF, radio frequency; Q, quality factor; SNR, signal-to-noise ratio; FID, free induction decay; ROI, region of interest.

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cumbersome for quantitative analysis. For example, previous functional ^{23}Na studies utilized voxel averaging of 2D projection images inside region of interest (ROI), and essentially comparison of individual ROIs [9]. Such analysis usually can be done manually by measuring individual ROIs' intensities and performing quantitative analysis, e.g. subtraction, division, etc. Similar analysis of 3D ^{23}Na MRI maps and potentially other nuclei is challenging, because it requires manual manipulation of thousands of individual voxels, which creates a new information challenge, because of the massive data being generated. Combined with the need for examining multiple animals and applying quantitative analytical and statistical tools, an automated image processing is indeed required.

While the standard intensity maps are of interest, the analysis and reporting of concentration and concentration changes of imaged nuclei and their relation to *in vivo* function [9] is a better approach to communicate findings across multiple fields of science. Here, we present an automated approach/software package for analysis of 3D ^{23}Na MRI with the goal of producing 3D concentrations maps. This software package is an open-source MATLAB toolbox that processes sodium MRI images and produces high-resolution 3D concentration or concentration difference maps on a voxel to voxel basis. The utility of this MATLAB toolbox was tested for detecting functional changes of sodium concentration in rat brain induced by migraine-like state. As previously reported, sodium concentrations changes in the brain and eyes, approximately 20 min after nitroglycerin (NTG) injection, in a rodent model of migraine triggered by NTG [9]. To the best of our knowledge, this is the first report of using ^{23}Na 3D MRI for imaging a change of brain function in this migraine model, and the first report of generating such 3D maps with sub-microliter isotropic spatial resolution.

2. Materials and methods

2.1. Program Execution: creating the input file

All image processing starts with a Sample.m script, containing the processing options and file targets for user's data set. As shown in Figs. 1 and 2, the operational workflow begins with creating an input file using the Sample.m template. Users input the file path that contains the raw imaging datasets and specify the file folders for four different types of data: (1) baseline functional MRI (FMRI) data, (2) experimental FMRI data, (3) co-registration data, and (4) a phantom data set used as a concentration standard. Additionally, the concentration of the phantom is specified in the input script. Once all of the information has been inputted, the user proceeds to the processing menu of the script, and chooses which processing functions will be applied to the datasets. There are five processing functions and the user can use one or all five of the processing functions by defining 'y' or 'n' in the processing list. The input file is ready after all the options have been defined, and can be executed in MATLAB (version R2013a) in its current form, or the user can use batch processing.

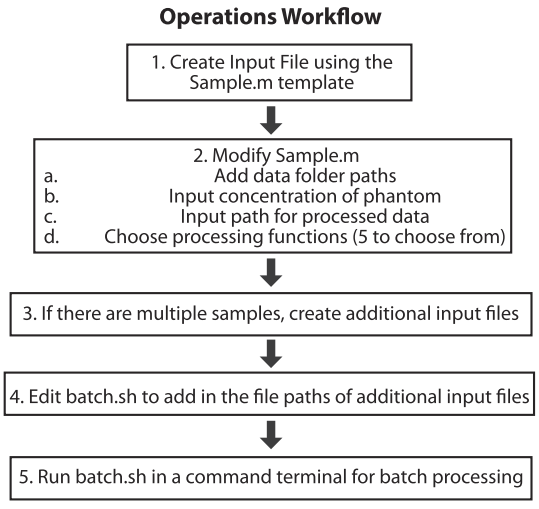

Fig. 1. Operational workflow for 3DCOMA toolbox. An instructional, graphical flowchart displaying the sequence of user actions needed to fully execute the 3DCOMA toolbox to process a complete imaging dataset.

2.2. Processing functions

Five different types of processing are available to users to analyze the 3D imaging datasets. The 3D data matrix is converted into 2D slices via the *x*, *y*, and *z* planar directions. The primary purpose of all the processing functions is to readily view intensity changes between an experimental 3D dataset and an established baseline dataset. The intensities and intensity changes are then converted into concentrations and changes of concentration, with values containing an explicit unit of measure that can easily be understood. The result (concentration map) is then overlaid onto a high-resolution image set, usually a ^{1}H image set, to provide anatomical registration. Four of the processing functions: *Diff_avg.m*, *Diff_full.m*, *Diff_avg3D.m*, and *Diff_full3D.m* incorporate simple interpolation methods to enhance the intensity changes, and thereby the concentration maps to highlight subtle features in the imaging experiments. The five processing functions are discussed in more detail below.

Overlay.m takes two imaging data sets and overlays them on top of each other, with the image intensities of the top layer converted into concentration values to produce a concentration map. The processed images from overlay.m provide a control in comparison to the other processing functions, since the top layer image is not interpolated. The default setting in the script is to plot the baseline 3D dataset as the top concentration map layer, however users can easily modify overlay.m to plot the experimental 3D dataset as the top layer image.

Diff_avg.m creates a difference matrix from the 3D baseline and experimental datasets and converts the difference matrix into slices of 2D matrices with dimensions of $m \times n(row \times column)$. For each slice or 2D matrix, the columns and rows of the matrix are averaged to create a new resulting matrix that is half the size of the original $\left(\frac{m}{2} \times \frac{n}{2}\right)$. The script first averages the columns of the matrix in groups of two as observed in Table 1 to create an intermediate intensity matrix.

Next the rows are also averaged in groups of two, shown in Table 2, to produce the final interpolated intensity matrix.

Diff_full.m creates a 3D difference matrix and converts the matrix into slices of 2D matrices. For each individual 2D image matrix, the columns are averaged to create an intermediate matrix, followed by the rows, however unlike *Diff_avg.m*, the dimension of the intermediate matrix and interpolated matrix remains the same as the original data set. Each column, *n*, of the matrix is averaged with the $n + 1$ neighboring column, except for the very last column, which is averaged with the first column, generating an intermediate matrix (Table 3). This normalizes the signal intensities and also limits the effects of noise spikes within the imaging dataset. The rows of the intermediate matrix are averaged in the same manner to produce the final interpolated matrix Table 4).

Diff_avg3D.m is a variation of *Diff_avg.m*, but interpolates the matrix cells through the slice dimension. The values of the same cell of each slice is averaged with the succeeding slice in a manner where slice 1 is processed with slice 2, slice 3 with slice 4, progressing through all of the slices of the data set. The resulting