MITK Diffusion Imaging

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Summary
Background: Diffusion-MRI provides a unique window on brain anatomy and insights into aspects of tissue structure in living humans that could not be studied previously. There is a major effort in this rapidly evolving field of research to develop the algorithmic tools necessary to cope with the complexity of the datasets.

Objectives: This work illustrates our strategy that encompasses the development of a modularized and open software tool for data processing, visualization and interactive exploration in diffusion imaging research and aims at reinforcing sustainable evaluation and progress in the field.

Methods: In this paper, the usability and capabilities of a new application and toolkit component of the Medical Imaging and Interaction Toolkit (MITK, www.mitk.org), MITK-DI, are demonstrated using in-vivo datasets.

Results: MITK-DI provides a comprehensive software framework for high-performance data processing, analysis and interactive data exploration, which is designed in a modular, extensible fashion (using CTK) and in adherence to widely accepted coding standards (e.g. ITK, VTK). MITK-DI is available both as an open source software development toolkit and as a ready-to-use installable application.

Conclusions: The open source release of the modular MITK-DI tools will increase verifiability and comparability within the research community and will also be an important step towards bringing many of the current techniques towards clinical application.

Methods Inf Med 2012; 51: 441–448
doi: 10.3414/ME11-02-0031
received: October 13, 2011
accepted: March 23, 2012
prepublished: September 28, 2012

1. Introduction

Diffusion-MRI provides a unique and sensitive probe for the architecture of biological tissues. The relationship between the diffusion-weighted signal and the molecular motion of water has made this technique indispensable for the reliable and early detection of cerebral ischemia. The diffusion tensor model, which was introduced in 1994 [1], characterizes the directional profile of water diffusion and made diffusion imaging the first and only non-invasive technique for assessing brain white matter integrity. As a result, scientific papers about the application of diffusion MRI to a variety of conditions in health and disease have exploded in recent years (e.g. see [2–5]). The underlying models have gained complexity and recent developments strikingly demonstrate how much more than a diffusion tensor can be exploited from the diffusion signal. Acquisitions of high angular resolution diffusion images (HARDI) and multiple diffusion weightings have mainly driven this development. Q-ball imaging (QBI), which has helped to overcome limitations of the tensor model in complex fiber configurations and partial volume [6], and the model for intra-voxel incoherent motion (IVIM), which allows for diffusion-based perfusion quantification mainly in tumor and body imaging, are only two significant examples of the advancement and also the increased complexity of information in each voxel.

This complexity makes it increasingly challenging to obtain reliable data and draw meaningful and robust inferences from it [7]. A major challenge for researchers is the long pipeline of image processing steps necessary to go from image acquisition to quantification of diffusion indices. While solutions to many of the problems have already been proposed, they are often not available as open-source and/or the corresponding tools are not compatible among each other. This biases researchers’ choice of methods away from the evaluation of their soundness or suitability and towards a choice on the basis of availability, operating system, licensing, or programming language (►Fig. 1, lower part). A second big obstacle for the development of robust and clinically applicable algorithms is the large amount of overhead work necessary to achieve proper visualization and interaction mechanisms for the algorithmic output. While most of the development work can be done using a console and batch processing approach, this does not hold true for application in a clinical setting. Thus, the research focus of most of the currently available tools creates a barrier for a direct clinical application of current techniques. In consequence, one important step in the cycle of development and refinement based on feedback is broken (►Fig. 1, upper part).

Several software toolkits like MedINRIA (www-sop.inria.fr/asclepios/software/MedINRIA), Camino (www.cs.ucl.ac.uk/research/medic/camino), SCIRun (http://
2. Objectives

MITK-DI aims at supporting cutting edge diffusion imaging techniques, extending the MITK framework in terms of data I/O, visualization, interaction, and processing of diffusion related images. It is publicly available under a BSD-style open-source license. In contrast to most other frameworks, MITK-DI addresses all aspects of application design including fluent workflows and full integration into the OSGi-based (www.osgi.org) CTK application platform that is the basis for all current MITK applications. While other diffusion imaging toolkits exclusively focus on providing diffusion-related functionalities, MITK-DI is tightly integrated into the grown-up platform MITK and therefore allows the complete cycle to be covered: from raw-data import to computer-aided diagnosis and statistics. MITK-DI offers exclusive processing algorithms that are not available elsewhere, including the global tractography, interactive IVIM, interactive FA clustering, TBSS results exploration, and others. Special focus was given to the interactive capabilities of MITK-DI and all the techniques it provides. As an example of application, two in-vivo datasets, one of the brain and one of the abdomen, were processed and visualized in order to underline the capabilities of the software.

3. Methods

Standardization is a key issue in medical imaging research and can only be successful with a consistent and flexible software design, the publication of source code and the use of development tools that allow integration in a clinical environment with reasonable effort. Only then can imaging techniques prove their relevance and, in the long run, improve health care. Specific care was taken to meet these requirements during the design of MITK-DI.

3.1 Software Design and Application-level Support

Like the Visualization Toolkit (VTK, www.vtk.org) and the Insight Toolkit (ITK, www.itk.org), MITK (including MITK-DI) is an object-oriented, cross-platform component implemented in C++. Most classes are derived from top-level classes of ITK, reusing mechanisms such as smartpointers, time-stamps, pipelines, and parallel processing. The component extends MITK using the module-mechanism provided. Application-level classes are implemented as bundles for the Common Toolkit (CTK) application platform (http://www.commonvtk.org/) that is the basis for all current MITK applications. Applications run on Windows, Mac OS X and Linux with native look and feel and 64-bit support. Executables can be easily built using a CMAKE superbuild process or can be downloaded as regularly released and precompiled binaries on the MITK website. The application front-end follows the MITK workbench concept, which was originally inspired by the eclipse project. Functional units are accessible via tabs (or “views”) which are organized in different task-oriented “perspectives”. For example,
the perspective for tractography includes several views for the different tracking approaches and tractography post-processing options.

Developers are supported by tools like the plugin-generator, the MITK tutorial steps, doxygen documentation, the MITK mailing list, and the bugzilla bug tracking system, all available via the MITK website (www.mitk.org).

### 3.2 Data Types and I/O

MITK-DI defines several new data types. Due to the MITK factory mechanism they all can be handled via drag and drop on the application level. The application uses the file extension to determine the data type. Internally, the files are organized according to widely used file formats such as NRRD\(^1\) (.dwi, .hdwi, .qbi, .hqbi, .dti, .hdti, .tbs) and VTK (.fib, .cnf). The following data types are defined:

- Diffusion weighted images (mitk::DiffusionImage, NRRD with file extension .dwi, .hdwi),
- Q-ball images (mitk::QBallImage, NRRD with file extension .qbi, .hqbi),
- Tensor images (mitk::TensorImage, NRRD with file extension .dti, .hdti),
- Tractography results (mitk::FiberBundle, VTK with file extension .fib),
- TBSS results (mitk::TbssImage, file extension .tbs), and
- Network graphs (mitk::ConnectomicsNetwork, VTK with file extension .cnf).

Diffusion weighted images can also be directly imported from and exported to FSL by changing the file extension from .nii or .ni.gz to .fsl or .fsl.gzr respectively. As in FSL, these files should be accompanied by a .bvecs and a .bvals file. Finally, MITK-DI also includes a direct DICOM import for Siemens diffusion weighted images. Support for other vendors is planned to be included.

### 3.3 Preprocessing and Model Reconstruction

MITK-DI supports a range of standard and advanced reconstruction algorithms for diffusion weighted images. It provides the options given by ITK (e.g. diffusion tensor reconstruction) and extends them by adding several different q-ball reconstruction methods for HARDI data sets: numerical reconstruction [9], analytical reconstruction using spherical harmonic basis functions [10], and solid angle reconstruction with single and multiple shells [11]. Pre-processing steps such as extraction of baseline images from vector valued diffusion images or gradient averaging for datasets with multiple repetitions are provided as well. Other optional preprocessing tasks such as correction of eddy current distortions, susceptibility-induced distortions, static magnetic field inhomogeneities, or patient movement are not yet covered by MITK-DI and must be performed externally if necessary. However, our policy of open source code and maximum compatibility to community standards (file formats, CTK, ITK, etc.) should induce other developers to contribute their tools in the future, or to use their tools for preprocessing and MITK-DI for further analysis of their images.

### 3.4 Visualization

An important feature of MITK is interactive and high-performance visualization of all existing data types in multiple planar views as well as in 3D. Interactive data exploration and high-performance visualization are of special significance in diffusion imaging, where datasets quickly become very large and unmanageable. Thus, MITK-DI implements several mappers and interaction mechanisms to cope with this challenge.

Mappers for concurrent visualization of colormaps and ODFs have been implemented that allow on-the-fly generation of the scene and thus avoid holding the whole image representation in memory. A level-of-detail (LoD) mechanism allows for fluent navigation in the datasets. Different options for normalization and scaling can be configured during runtime and allow the display e.g. of min-max normalized Orientation Distribution Functions (ODFs) or ODFs scaled by their Generalized Fractional Anisotropy (GFA) value. Close-up views and additional information about single ODFs are provided by the ODF detail view.

Tractography results can easily contain hundreds of thousands of fibers that need to be displayed in 3D and different 2D views at the same time. An efficient mapper was implemented that avoids data replication in memory and seamlessly generates cuts through the volume for 2D display. Additional track density imaging is supported by a filter that generates heat maps from given tract information [12]. Other mappers allow display and exploration of network graphs or TBSS results.

### 3.5 Quantification

MITK’s interactive segmentation framework [13] and the image statistics bundle provide powerful tools for performing statistics and conventional ROI analysis of scalar indices (FA, GFA, …) in 2D or 3D. Furthermore the Partial Volume Analysis view provides a very robust method for semi-automatic ROI analysis. It uses Expectation Maximization (EM) clustering to probabilistically segment fiber vs. non-fiber vs. partial volume [14].

### 3.6 Fiber Tractography

Tractography algorithms try to explicitly estimate the underlying fiber pathways from the given voxel-based information. There exists a wide variety of different tractography algorithms that can roughly be divided into the two subgroups of local and global methods. Local methods try to reconstruct each fiber individually by performing a step-by-step analysis of the voxel-wise information and successively adding segments to the fiber [15]. MITK-DI implements two local methods, namely fiber assignment by continuous tracking (FACT) and tensor deflection (TEND). While local methods are known to yield high processing speed, they often struggle with image artifacts or com-

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plex fiber configurations like crossing or kissing tracts. Global methods try to reconstruct all fibers simultaneously, searching for a global optimum [16]. While computationally much more challenging, global methods promise more robust results.

To our knowledge, MITK-DI is the first open source tool that implements a computationally efficient global tractography approach, the Gibbs Tracking [17]. While the algorithm is ready to use and embedded in the application, its ITK-style implementation allows convenient integration into other ITK compliant projects due to the standardized filter architecture. In addition to the Gibbs Tracking, MITK-DI provides a stochastic tractography method that was initially implemented in Slicer 3D (www.slicer.org). The fiber bundle operations view allows for interactive extraction, joining, and subtraction of bundles and provides tools like bundle envelope and tract density image calculation as well as visualization of the distribution of fiber endings.

3.7 Intra-voxel Incoherent Motion (IVIM)

The IVIM-approach, and especially the f-value as tissue perfusion fraction, yields perfusion related parameters that can be estimated from diffusion measurements at multiple b-values [18]. Among other applications, the f-value proved to be a valuable parameter in cancer imaging and may hold great promise for the non-invasive, non-contrast-enhanced imaging of lesions [19]. The IVIM view in MITK offers parameter estimation and interactive exploration of IVIM datasets with a choice of different fitting strategies for mixing parameter f and the diffusion (D) and pseudodiffusion (D*) coefficients.

3.8 Tract-based Spatial Statistics (TBSS)

TBSS, which is part of FSL [20], performs voxel-wise statistical analysis of scalar diffusion indices [21]). TBSS projects all subjects’ FA data onto a mean FA tract skeleton for voxel-wise cross-subject comparison. MITK-DI is not meant to replace TBSS, but builds on top of it by adding methods for interactive data exploration and interactive tract-based statistics. While TBSS uses FSLView for slice-based results visualization of t-statistics, MITK-DI aims at tract-based visualization of group averages and t-statistics. The user can create a mitk::TbssImage that includes all relevant data from a TBSS analysis. MITK-DI then allows the user to quickly define relevant tracts of interest with minimal mouse interaction. This is achieved by automatic computation of the shortest path on the skeleton that connects manually selected points of interest. Figures generated on-the-fly directly visualize the group-wise information along tracts and a link to the image information by image cross hair positioning through direct mouse interaction within the figure.

3.9 Connectomics

The connectomics module is the newest contribution to MITK-DI. It aims at providing graph-algorithmic data analysis of the brain’s neuronal network architecture. At its current state the module supports generation of network graphs from tractography output and calculation of basic graph indices like node degree distribution, betweenness centrality distribution, shortest path distribution, and others.

3.10 Supplemental Tools

MITK-DI takes advantage of a wide variety of supplemental image processing, visualization, and interaction tools. Some of the most relevant tools were directly included in the installable application MITK Diffusion. These include a module for easy-to-use and fast volume rendering, which allows for loading, saving, and interactive adaptation of transfer-functions. Further views are provided to capture high resolution screenshots as well as movies of the 3D screen.
Fig. 3  Coronal slices generated from the HARDI brain dataset: a) The base-line non-diffusion weighted image as it is produced by the scanner. b) The Generalized Fractional Anisotropy (GFA) calculated on the basis of the analytically reconstructed q-balls (ROI that is shown in Fig. 2 is indicated in red). c) The DTI-based colormap showing the principal diffusion direction with FA-modulated intensities. d) A 2D slice through the tracts generated by the Gibbs tracking algorithm. e) The track density image. f) Demonstration of the partial volume analysis module for quantification of the corpus callosum. The examiner draws a circular ROI, which is then automatically clustered in fiber (red), non-fiber (green), and partial volume (transparent). Quantitative measures (e.g. FA values) can then be extracted for the three classes separately. g) Volume visualization of the FA. h) Visualization of a network graph using the connectomics module. i) Tract-based TBSS results visualization of a part of the corpus callosum in an exemplary group study of 15 Alzheimer patients and 15 healthy controls that were enrolled in a DTI imaging study (for colored figures, please refer to the online version of this article).
3.11 Datasets and Experiments

Diffusion weighted MR images of the brain were acquired on a 3.0 T MR scanner (Magnetom TRIO, Siemens Medical Solutions, Erlangen, Germany) using a single-shot, spin-echo, echo-planar imaging sequence. Imaging parameters were: FOV = 240 × 205 mm², resolution = 2.5 × 2.5 × 2.5 mm³, TR = 5 s, TE = 120 ms, GRAPPA acceleration factor 2. Three repetitions of 64 diffusion weighted images at different gradient directions (b = 3500 s/mm²) and one b = 0 s/mm² baseline images were acquired (totaling 195 volumes).

Diffusion weighted MR images of the abdomen were acquired on a 1.5 T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) using a single-shot echo-planar imaging (SE-EPI) pulse sequence in expiratory breath-hold with the following imaging parameters: TR = 1300 ms, TE = 60 ms, FOV = 350 × 273 mm², matrix size = 100 × 78, 14 slices, slice thickness/gap = 5/0.25 mm, spectral fat saturation, 4 averages, bandwidth = 3000 Hz/pixel, k-space based parallel imaging technique (GRAPPA) acceleration factor of two, b-values = 0, 25, 50, 75, 100, 150, 200, 400, and 800 s/mm². The diffusion weighting was accomplished using a twice-refocused spin echo (TRSE) diffusion preparation and three orthogonal gradient directions (1,1,-1/2), (1,-1/2,1) and (-1/2,1,1) to obtain trace-weighted images. The acquisition was separated into blocks (b0, b25), (b0, b50)...(b0, b800), each acquired in a single breath-hold (TA = 26 s) to avoid motion artifacts.

3.12 Availability

The latest versions of the source code as well as executable installers of the MITK Diffusion Imaging App are available from the MITK web site: www.mitk.org.
4. Results

A Performance analysis was performed on an Intel(R) Core(TM) i7-2720QM Processor with 8 Gb of RAM. A linear diffusion tensor fit took 0.44 ± 0.04 s (image dimension 96 × 82 × 40, 64 directions). Q-ball reconstruction for the same volume took 2.31 ± 0.15 s for numerical, 1.13 ± 0.00 s for analytical, and 0.80 ± 0.03 s for solid angle reconstruction, generating ODFs with 252 directions. Please see Figure 2 for visualizations of the reconstructed data.

Fluent and interactive ODF visualization was achieved by the LoD-mechanism even for highly detailed and large datasets. Figure 2 shows renderings of the in-vivo acquisition, showing the significant advantages of q-ball imaging over DTI in complex fiber configurations.

High speed visualization was also achieved for the visualization and interactive exploration of tractography results (Fig. 3d). The mappers managed to display the whole brain tracking results shown in this work (37,031 fibers) with no noticeable stutter in four concurrent views. The same was achieved for the track density images that could be displayed using the ordinary image mappers (Fig. 3e).

In order to demonstrate the importance of robust interactive quantification approaches, we compared the results retrieved by conventional ROI analysis (mean FA inside a ROI) in the corpus callosum to the results retrieved by our partial volume analysis module using the same ROIs. Simulating ten different examiners, ten different ROIs were placed in a coronal view to quantify the FA in the corpus callosum (Fig. 4a). The results for the differently placed ROIs and the two approaches are reported in Figure 4b. While the results of the conventional methods are completely incomparable, the partial volume analysis module yields results that are quite independent of the exact ROI position.

Whole brain fiber tracking was performed on the proband using the Gibbs tractography. The fornix, the left cingulum, and the right corticospinal tract were extracted from whole brain fiber tracking result (Fig. 5). This was achieved by ROI-based tract selection using the interactive fiber extraction module (ROIs indicated in green in Fig. 5). The global tractography took about three hours.

The Intra-voxel Incoherent Motion (IVIM) module is demonstrated in Figure 6. The graph shows the eight different measurements normalized by the corresponding non diffusion weighted measurement at different b-values in the voxel selected by the crosshair in the image. The five squares in red (b >170 s/mm²) were used to fit D and f, indicated by the red line. D* was then fit using all measurements. The resulting model is shown using the black line. Interactive exploration of single voxels in the dataset and on-the-fly generation of complete f-, D-, and D*-Maps are both equally possible. The interactive Tract-based Spatial Statistics (TBSS) results explorer is shown in Figure 3i. A connectomics network computed from the dataset is visualized in Figure 3h.

5. Discussion

Image processing algorithms play a central role in diffusion imaging research. However, visualization and interaction mechanisms are equally important when it comes to integration of the developed methods in the clinical workflow. We have introduced a new set of tools for processing and interactive visualization of diffusion imaging related datasets. MITK-DI implements DTI, HARDI, and IVIM techniques and features the display of intricate details in combination with fluent interaction. The tools might help in further understanding aspects of diffusion imaging and bringing the techniques to clinical application. The design of the toolkit component allows for straightforward usage and extension of the developed framework by adding new CTK based plug-ins.

Many existing toolkits like ITK, DTI-TK, or FSL are powerful libraries for diffusion imaging processing, especially for segmentation, registration, and group analy-
sis. MITK and in particular MITK-DI, which is presented in this paper, can complement these toolkits by providing an open application framework dedicated to data visualization and exploration, where many useful processing algorithms for diffusion imaging datasets are implemented. New features and tools that might be required for a specific task can be rapidly developed and provided to the physician with very little overhead due to the plugin concept and the corresponding interfaces that are offered by MITK-DI.

In comparison to the tools provided by other groups, MITK-DI offers a variety of unique relevant features. All of these features are integrated into one shared application as opposed to being a collection of separate executables. The application supports DTI and HARDI imaging data and implements many state of the art processing algorithms like the global Gibbs tracking approach. A special strength of MITK-DI is the focus on seamless interactive data exploration and visualization even of complex datasets such as q-ball ODFs, large amounts of fiber tracts, TBSS results, or IVIM images.

As compared to other tools such as Slicer 3D or FSL, MITK-DI still has a rather small user community and fewer external contributions to the source code. Initiatives like CTK will promote increasing compatibility among different tools and will decrease the amount of duplicate work necessary to provide new tools. Hopefully, this trend will help to increase the visibility and participation in open source contributions like MITK-DI and further push the community’s and funding foundations’ commitment to open source and open data policy in medical image computing research.

6. Conclusions

Although primarily used as a research tool, diffusion weighted imaging is starting to find its way to clinical application. MITK-DI is an attempt to bundle and standardize current techniques in the field in a common framework and, following the open-source spirit, to enable other researchers to contribute and build upon it. Participation is most welcome.

References