

MIX Setup Instructions and Examples

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1. Software Requirements:

- a. MATLAB with optimization toolbox.
- b. For reading/writing 'nifti' files in MATLAB, download 'niftilib-1.2' (<https://sourceforge.net/projects/niftilib/files/niftimatlib/>). For 'nifti' libraries details see (<http://niftilib.sourceforge.net/>).
- c. Download MATLAB based Genetic Algorithm Toolbox 'gatbx' (<http://www.acse.dept.shef.ac.uk/cgi-bin/gatbx-download>). Please note that on LINUX/ UNIX platform or with MATLAB 2015, *.M files in the '~\gatbx\genetic' folder will need to be renamed as *.m files.
- d. Download and install CVX: MATLAB Software for Disciplined Convex Programming (<http://cvxr.com/cvx/doc/install.html>).
- e. Copy the downloaded folders 'gatbx', 'niftimatlib-1.2', to MIX_toolbox folder. And add all the folders (including ActiveAx and NODDI, which are already present in the MIX_toolbox) in MATLAB search path as shown in Fig. 1.

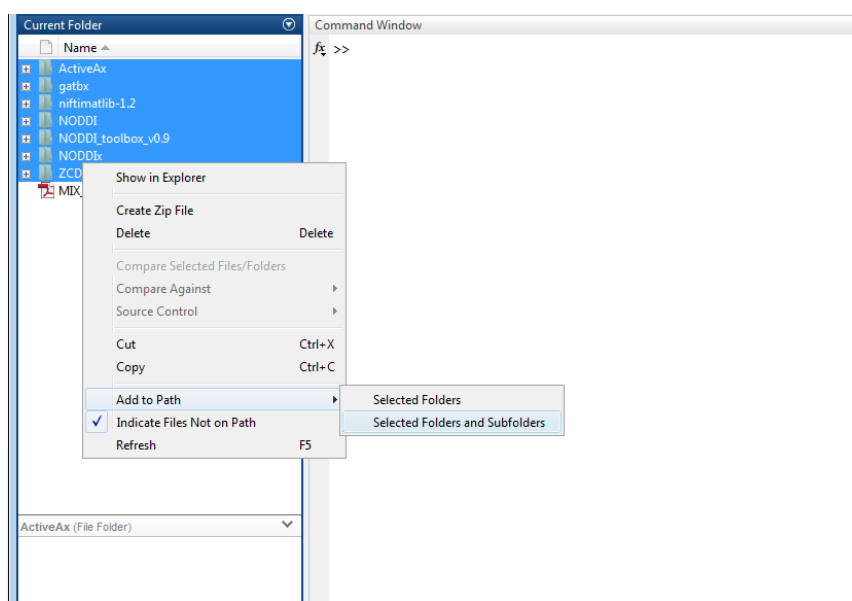


Figure -1. Add 'gatbx', 'niftimatlib-1.2', 'ActiveAx', 'NODDI', 'NODDIx' and ZCDx folders to MATLAB path.

2. ActiveAx Examples

- a. **Example # 1:** ActiveAx parameter estimation using synthetic dataset

- i. A sample synthetic data file 'Aax_synth_data.nii', the mask file 'synth_mask.nii' and 'nifti' files for the true parameter values have been placed in the '~\MIX_toolbox\ActiveAx' folder. Please see **Supplementary Note 2** for details of the synthetic data experiment setting.
- ii. Go to Example1 folder (cd ~\MIX_toolbox\ActiveAx\Example1).
- iii. Run 'MIX_Aax_synth_data.m'. While the code is running 'current folder' should be Example1.
- iv. Two output files will be created, 'R_MIX_synth_Aax.nii' and 'DI_MIX_synth_Aax.nii'. Plots shown in Fig 2 will also be generated for ease of comparison between the estimated and the true Radius Index and Density Index values.
- v. Estimation time can vary from 1 to 20 minutes depending upon availability of parallel pools and computing power of the machine.

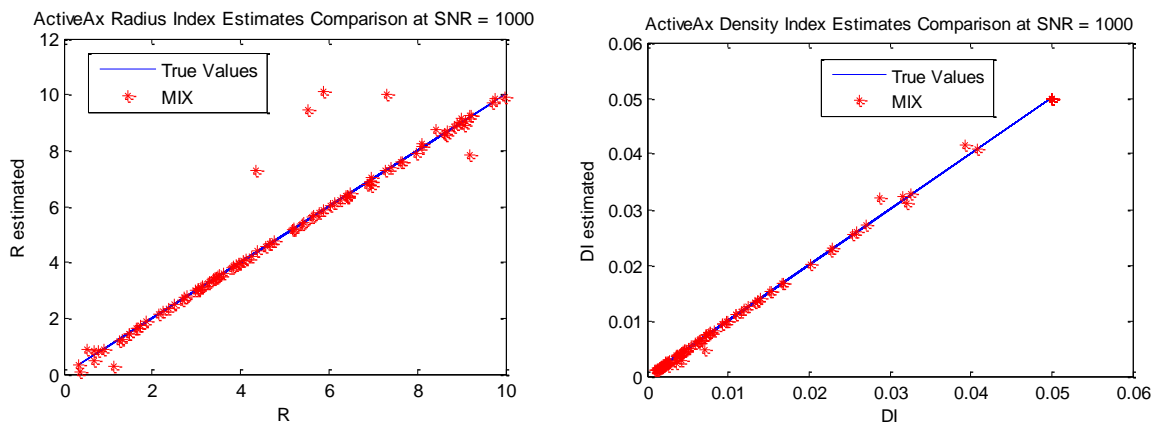


Figure -2. Example 1 output plots. Radius Index and Density Index estimation comparison for ActiveAx synthetic data.

- b. **Example # 2:** ActiveAx parameter estimation using ActiveAx dataset used in the original study
 - i. Download original DWI dataset from DRCMR website (<http://dig.drcmr.dk/activeax-dataset/>).
 - ii. Data file: Convert data files into a single file 'All.Bfloat' as given at CAMINO website (<http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.ActiveAx>) OR create 'DWI.nii' using 'fslmerge' as described in AMICO ActiveAx tutorial website (<https://github.com/daducci/AMICO/tree/master/matlab/doc/demos/ActiveAx>).
 - iii. Mask file: Download mask file (MidSagCC.img and MidSagCC.hdr) from CAMINO ActiveAx tutorial website (<http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.ActiveAx>).
 - iv. Scheme file. Text format of the scheme file (ActiveAx_xdata.txt) has already been provided with the toolbox. (~\MIX_toolbox\ActiveAx\ActiveAx_files\ActiveAx_xdata.txt).
 - v. Copy the data file 'All.Bfloat' or 'DWI.nii', mask files MidSagCC.img and MidSagCC.hdr, to the Example2 folder (~\MIX_toolbox\ActiveAx\Example2).
 - vi. Go to Example2 folder (cd ~\MIX_toolbox\ActiveAx\Example2).
 - vii. File 'MIX_Aax_data.m' assumes that 'All.Bfloat' has been created and placed in the current folder, if you use 'DWI.nii', as described in AMICO tutorial, please amend 'MIX_Aax_data.m' accordingly.
 - viii. Run 'MIX_Aax_data.m'. While the code is running 'current folder' should be Example2.

- ix. Seven output files will be generated, for axon radius index (R_MIX_Aax.nii), density index (DI_MIX_Aax.nii), fiber orientation (dir_MIX_Aax.nii) and the volume fractions estimates files.
- x. It can take about two hours depending upon the number of parallel pools available/ computational power of the machine.

3. **NODDI Examples**

- a. **NODDI Toolbox:** In addition to the software requirements given in paragraph1, download 'NODDI Matlab Toolbox' from (<http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDI matlab>), and add the folder to the MATLAB search path.
- b. **Example # 3:** NODDI parameter estimation using synthetic dataset
 - i. A sample synthetic data file 'NODDI_synth_data.nii', the mask file 'synth_mask.nii' and 'nifti' files for the true parameter values have been placed in '~\MIX_toolbox\NODDI' folder. Please see **Supplementary Note 2** for details of the synthetic data experiment setting.
 - ii. Go to Example3 folder (cd ~\MIX_toolbox\NODDI\Example3).
 - iii. Run 'MIX_noddi_synth_data.m'. While the code is running 'current folder' should be Example3.
 - iv. Four output files will be generated i.e., 'OD_MIX_synth.nii', 'v_iso_MIX_synth.nii', 'v_ic_MIX_synth.nii' and 'dir_MIX_synth.nii'. Plots shown in Fig 3 will also be generated for the comparison between estimated and the true parameter values.

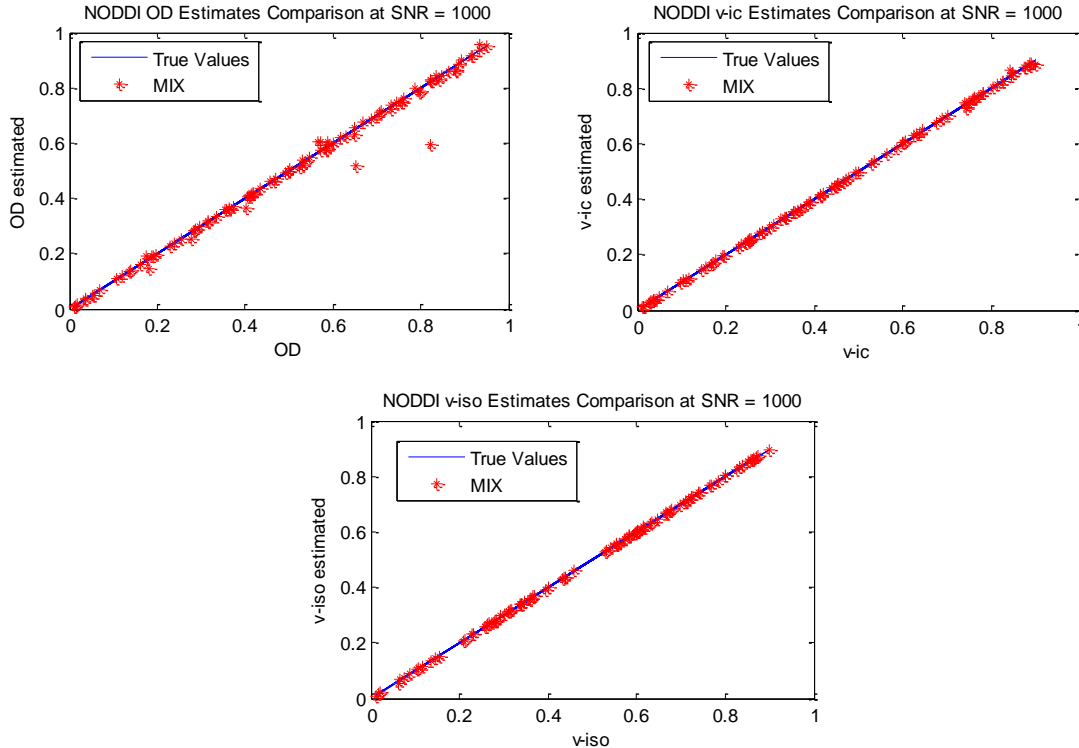


Figure -3. Example 3 output plots. OD, v_ic and v_iso estimation comparison for NODDI synthetic data.

- c. **Example # 4:** NODDI parameter estimation using in-vivo dataset used in the original NODDI study
- Dataset for NODDI.** Download dataset from NODDI website (<http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDI matlab>). The dataset will include NODDI_DWI.hdr/img, brain_mask.hdr/img, roi_mask.hdr/img and NODDI_protocol.bval/bvec files as described on the website. Copy all the downloaded files to Example4 folder (~MIX_toolbox\NODDI\Example4).
 - Scheme file.** Text format scheme file for the example is included in the MIX toolbox as `noddi_scheme.txt`.
 - Go to ActiveAx folder (`cd ~MIX_toolbox\NODDI\Example4`).
 - Run '`MIX_noddi_data.m`'. While the code is running 'current folder' should be Example4.
 - Four output files will be generated i.e., '`OD_MIX.nii`', '`v_iso_MIX.nii`', '`v_ic_MIX.nii`' and '`dir_MIX.nii`'.
 - Depending upon the MATLAB version, (please see discussion at NODDI Google group: [https://groups.google.com/forum/#!searchin/noddi/Avoid\\$20MATLAB\\$202013b\\$20onwards/noddi/oPkZamvpZ3Q/FRHpN0-hFCgl](https://groups.google.com/forum/#!searchin/noddi/Avoid$20MATLAB$202013b$20onwards/noddi/oPkZamvpZ3Q/FRHpN0-hFCgl)), and the computational power of the machine, estimation time can be around 11 hours for the data set.
- d. **Example # 5:** NODDIx parameter estimation using Human Connectome Project (HCP) dataset
- Dataset for HCP.** Download dataset from the HCP website (<http://www.humanconnectome.org/documentation/S900/>). The dataset is for 900 subjects. Choose a data file and rename as '`HCP_data.nii`' and rename mask file as '`HCP_brain_mask.nii`'. Alternatively, change the data and mask file names in '`MIX_noddi_HCP.m`'.
 - Scheme file.** Text format scheme file for the HCP data is included in the MIX toolbox as `HCP_scheme.txt`.
 - Go to NODDIx folder (`cd ~\MIX_toolbox\NODDIx`).
 - Run '`MIX_noddi_HCP.m`'. While the code is running 'current folder' should be 'NODDIx'.
 - Five output files will be generated i.e., '`OD1_MIX.nii`', '`OD2_MIX.nii`', '`v_ic1_MIX.nii`', '`v_ic2_MIX.nii`' and '`v_iso_MIX.nii`'.
 - Depending upon the MATLAB version, (please see discussion at NODDI Google group: [https://groups.google.com/forum/#!searchin/noddi/Avoid\\$20MATLAB\\$202013b\\$20onwards/noddi/oPkZamvpZ3Q/FRHpN0-hFCgl](https://groups.google.com/forum/#!searchin/noddi/Avoid$20MATLAB$202013b$20onwards/noddi/oPkZamvpZ3Q/FRHpN0-hFCgl)), and the computational power of the machine, estimation time can be around 5- 6 hours for the slice shown in Figure 4 of the manuscript or 6-11 seconds/voxel for the HCP data set.
4. **ZCDx Example:** ZCDx parameter estimation using synthetic dataset
- A sample synthetic data file '`ZCDx_synth_data.nii`', the mask file '`synth_mask.nii`' and '*nifti*' files for the true parameter values (of axon radius indices in the three orientations) have been placed in the '~\MIX_toolbox\ZCDx' folder. Please see **Supplementary Note 2 (Experiment 4)** for details of the synthetic data experiment setting.
 - Scheme file.** Protocol used for this experiment has been used from the White Matter Modeling Challenge (<http://cmic.cs.ucl.ac.uk/wmmchallenge/>). Text format scheme file is included in the MIX toolbox as '`scheme_wmm.txt`'.
 - Go to the 'ZCDx' folder (`cd ~MIX_toolbox\ZCDx`).

- iv. Run 'ZCDx_main.m'. While the code is running 'current folder' should be 'ZCDx'.
- v. Three output files will be created, 'R1_ZCDx.nii', 'R2_ZCDx.nii' and 'R3_ZCDx.nii'. Plots shown in Fig 4 will also be generated for ease of comparison between the estimated and the true Radius Indices in the three orientations.
- vi. Estimation time can vary from 1 to 2 hours depending upon availability of parallel pools and computing power of the machine.

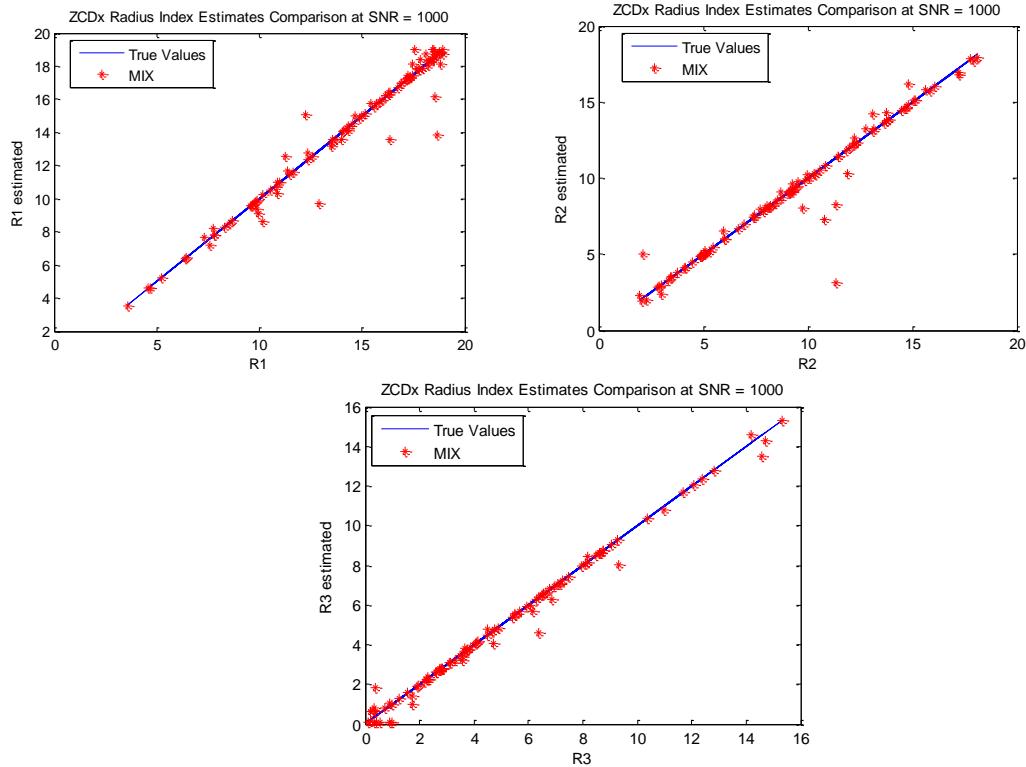


Figure -4. ZCDx output plots. R1, R2 and R3 estimation comparison for ZCDx synthetic data.

5. Instructions for fitting NODDI/ ActiveAx/ NODDIx/ ZCDx to any other dataset using MIX

- i. Copy data, mask and scheme ('nifti' / 'hdr') files in the relevant folder (i.e. ActiveAx /NODDI /NODDIx /ZCDx) folder.
- ii. Provide scheme file 'scheme.nii'. Please note that scheme file has to be in **Stejskal-Tanner** format.
- iii. Rename data file as 'data.nii' and mask file as 'mask.nii' or amend the relevant *.m file (i.e. 'MIX_Aax_generic.m' / 'MIX_noddi_generic.m' / 'Noddix_generic.m' / 'ZCDx_generic.m') accordingly.
- iv. Go to the relevant folder (i.e. ActiveAx /NODDI /NODDIx /ZCDx) depending upon which model you want to fit.
- v. Run the relevant *.m file (i.e. 'MIX_Aax_generic.m' / 'MIX_noddi_generic.m' / 'Noddix_generic.m' / 'ZCDx_generic.m').

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