

Preprocessing : MRtrix3 and FSL commands applied for each subject for fixel-based analysis (commands in grey are identical to those detailed in https://mrtrix.readthedocs.io/en/latest/fixel_based_analysis/mt_fibre_density_cross-section.html)

cd ../{subject}

– Selection voxels GM/WM for response function estimation:

dwi2response dhollander data_file.nii.gz response_dhollander_wm.txt response_dhollander_gm.txt response_dhollander_csf.txt -fslgrad bvec_file bval_file -shells 0,200,1700,4200 -mask mask.nii.gz -voxels voxels.nii.gz

– Selection voxels CSF for response function estimation:

5ttgen fsl t1_file 5tt.mif

mrtransform t1_file -linear epi1t1_matrix.txt -inverse 5tt_coreg.mif

dwi2response msmt_5tt data_file.nii.gz 5tt_coreg.mif response_5tt_wm.txt response_5tt_gm.txt response_5tt_csf.txt -fslgrad bvec_file bval_file -shells 0,200,1700,4200 -mask mask.nii.gz -voxels msmt_5tt_voxels.nii.gz

– Compute mean response function across all control subjects

cd ..

responsemean {list_paths_response_dhollander_wm} group_average_response_wm.txt

responsemean {list_paths_response_dhollander_gm} group_average_response_gm.txt

responsemean {list_paths_response_5tt_csf} group_average_response_csf.txt

– Compute FOD et apply normalization

cd /{subject}

dwi2fod msmt_csd -fslgrad bvec_file bval_file -shells 0,200,1700,4200 data_file.nii.gz group_average_response_wm.txt wmfod.mif group_average_response_gm.txt gm.mif group_average_response_csf.txt csf.mif -mask mask.nii.gz

mrconvert -coord 3 0 wmfod.mif - | mrcat csf.mif gm.mif - vf.mif

mtnormalise wmfod.mif wmfod-norm.mif gm.mif gm-norm.mif csf.mif csf-norm.mif -mask mask.nii.gz

– Create population FOD template

mkdir -p ../template/fod_dir

mkdir ../template/mask_dir

for 8 Alzheimer's disease patients, 8 presumed LATE patients and 16 controls randomly selected:

```
ln -sr wmfd_norm.mif ../template/fod_input/{subject}_wmfd-norm.mif
```

```
ln -sr mask.nii.gz ../template/mask_input/{subject}_mask.nii.gz
```

```
cd ../template
```

```
population_template fod_input -mask_dir mask_input wmfd_template.mif -voxel_size 1.3  
-nl_update_smooth 0.75 -nl_disp_smooth 0.75 -nl_niter  
10,10,10,10,10,10,10,10,10,10,10,10,10,10,10,10
```

– Register and transform FODs to the template

```
cd ../{subject}
```

```
mrregister wmfd-norm.mif -mask1 mask.nii.gz wmfd_template.mif -nl_warp  
subject2template_warp.mif template2subject_warp.mif -nl_scale 0.25,0.25,0.5,0.5,1 -nl_lmax 0,2,2,4,4  
-nl_niter 5000 -nl_update_smooth 0.8 -nl_disp_smooth 0.8
```

```
mrtransform wmfd-norm.mif -warp subject2template_warp.mif -reorient_fod no  
fod_in_template_space_NOT_REORIENTED.mif -nan
```

– Transform masks to the template and create template mask

```
mrtransform mask.nii.gz -warp subject2template_warp.mif -interp nearest -nan -datatype bit  
mask_in_template_space.nii.gz
```

```
mrmath {list_paths_masks} min ../template/template_mask.nii.gz -datatype bit
```

– Create fixel mask on template

```
cd ../template
```

```
fod2fixel -mask template_mask.nii.gz -fmls_peak_value 0.1 wmfd_template.mif fixel_mask_0.1
```

– Transform CSF compartment deconvolution to the template and create mean CSF compartment

```
cd ../{subject}
```

```
mrtransform csf_norm.mif -warp subject2template_warp.mif -reorient_fod no  
csf_in_template_space.mif -nan
```

```
mrmath -keep_unary_axes {list_paths_csf_compartments}  
mean ../template/mean_csf_in_template_space.mif
```

– Create “CSF fixel mask” on template

```
cd ../template
```

```
fod2fixel -mask template_mask.nii.gz -fmls_peak_value 0.027 csf_in_template_space.mif  
csffixel_mask_0.027
```

- **Edit template mask to exclude areas in which the confusion between white matter and CSF compartments among subjects is too large**

```
mrmath          fixel_mask_0.1/index.mif          csffixel_mask_0.027/index.mif          min
csffixel_mask_0.027/intercept.mif
```

```
mrconvert      csffixel_mask_0.027/intercept.mif  -coord      3      0      -axes      0,1,2
csffixel_mask_0.027/intercept_0.mif
```

```
mrcalc template_mask.nii.gz csffixel_mask_0.027/intercept_0.mif -subtract template_mask_edited.mif
```

```
mrconvert template_mask_edited.mif template_mask_edited.nii.gz
```

```
fslmaths template_mask_edited.nii.gz -thr 0 template_mask_edited_thr.nii.gz
```

- **Compute new fixel mask on template**

```
fod2fixel -mask template_mask_edited_thr.nii.gz -fmls_peak_value 0.1 wmfod_template.mif
fixel_mask_0.1_edited
```

- **Estimate fixels for each subject**

```
cd ../{subject}
```

```
fod2fixel          -mask          ../template/template_mask_edited_thr.nii.gz
fod_in_template_space_NOT_REORIENTED.mif          -fmls_peak_value          0.12
fixel_in_template_space_NOT_REORIENTED -afd fd.mif
```

- **Reorient fixels for each subject**

```
fixelreorient      fixel_in_template_space_NOT_REORIENTED      subject2template_warp.mif
fixel_in_template_space
```

- **Assign subject fixels to template fixels**

```
fixelcorrespondence fixel_in_template_space/fd.mif ../template/fixel_mask_0.1_edited ../template/fd
{subject}_fd.mif
```

- **Compute FC, log(FC) and FDC**

```
warp2metric subject2template_warp.mif -fc ../template/fixel_mask_0.1_edited ../template/fc
{subject}_fc.mif
```

```
cd ../template
```

```
mkdir log_fc
```

```
cp fc/index.mif fc/directions.mif log_fc
```

```
mrcalc fc/{subject}_fc.mif -log log_fc/{subject}_fc.mif
```

```
mkdir fdc
```

```
cp fdc/index.mif fdc/directions.mif fdc
```

mrcalc fd/{subject}_fd.mif fc/{subject}_fc.mif -mult fdc/{subject}_fdc.mif

– **Compute whole brain tractography and filter tractogram**

tckgen -angle 22.5 -maxlen 250 -minlen 10 -power 1.0 wmfd_template.mif -seed_image template_mask_edited_thr.nii.gz -mask template_mask.nii.gz -select 20000000 -cutoff 0.1 tracks_20_million.tck

tcksift tracks_20_million.tck wmfd_template.mif tracks_2_million_sift.tck -term_number 2000000

– **Generate fixel to fixel connectivity**

fixelconnectivity fixel_mask_0.1_edited/ tracks_2_million_sift.tck matrix/

– **Smooth fixel data using fixel to fixel connectivity**

fixelfilter fd smooth fd_smooth -matrix matrix/

fixelfilter log_fc smooth log_fc_smooth -matrix matrix/

fixelfilter fdc smooth fdc_smooth -matrix matrix/