Longitudinal TRACULA

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Longitudinal FreeSurfer

- Detecting changes in brain structure with time (development, aging, effects of treatment):
  - Cross-sectional studies are hampered by between-subject variability, which may dominate the longitudinal effect of interest
  - Longitudinal studies measure within-subject changes directly - each subject is her own control

- Applying cross-sectional image analysis methods to longitudinal data:
  - Performance of methods may degrade as disease progresses
  - Giving a time point special status (mapping other points to it) leads to bias

- **Longitudinal stream of FreeSurfer:** Unbiased analysis of longitudinal T1 data, relying on robust within-subject template [Reuter ‘12]

- **Longitudinal stream of TRACULA:** Unbiased tractography on longitudinal dMRI data, using the within-subject template from above
Why longitudinal?

- Between-subject variability is often greater than the longitudinal effects of interest
Why longitudinal?

• Within-subject percent change of measure (thickness, volume, etc.) may be more sensitive than absolute values of measure
Robust registration

- **Symmetric**
  - Treats source and target image the same
  - Registering source to target results in the inverse of the registration from target to source
  - Resample both source and target to an unbiased half-way space in intermediate steps (square root of registration matrix)

- **Robust**
  - Cost function that does not penalize large intensity differences
  - Outlier voxels in the images are detected and iteratively filtered out
Robust registration

Reuter et al., 2010

Target

Target
Robust registration

Source, registered by FSL FLIRT

Source, registered by robust

Reuter et al., 2010
Robust registration

- Tumor patient data, registered to the first time point
- Overlay shows regions detected as outliers, which did not contribute to the robust registration

Tumor data courtesy of Greg Sorensen
1. Create a robust, unbiased, within-subject base template (iterative registration of time points to median)

2. Process base template as a regular scan

3. Transfer information to time points

4. Let processing evolve from there
   - All time points are treated the same
   - No over-regularization, time points evolve freely

Reuter et al., 2012
Longitudinal FreeSurfer stream

- Assume a subject, bert, with $T_1$ scans at multiple time points:
  bert_tp1, bert_tp2, ...

- **Step 1: CROSS** (run independently for each time point 1, 2, ...)
  recon-all -subjid bert_tp1 -all
  recon-all -subjid bert_tp2 -all
  ...

- **Step 2: BASE** (run once for this subject, creates base template)
  recon-all -base bert_base -tp bert_tp1 bert_tp2 ... -all

- **Step 3: LONG** (run for each time point 1, 2, ..., also specifying the base)
  recon-all -long bert_tp1 bert_base -all
  recon-all -long bert_tp2 bert_base -all
  ...

Biased vs. unbiased

- Test-retest scans, treat either test or retest as the base
- Biased information transfer from follow-up to base ([BASE1], [BASE2]) vs. unbiased longitudinal stream ([FS-LONG], [FS-LONG-rev])

Reuter et al., 2012

Subcortical

Cortical
Simulated atrophy

- Simulated 2% atrophy in left hippocampus only
- Longitudinal stream significantly improves precision

Reuter et al., 2012
Test-retest reliability

- 115 subjects, ME-MPRAGE, 2 scans, same session
- Longitudinal stream significantly improves reliability

Subcortical

Cortical
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Reuter et al., 2012
Increased power

- Longitudinal processing requires a fraction of the subjects needed by cross-sectional processing to detect differences

Reuter et al., 2012
Huntington’s Disease (3 visits)

Reuter et al., 2012

- Longitudinal processing leads to higher precision and better discriminating power between groups (specificity and sensitivity)

Independent processing

Longitudinal processing

[Diagram showing data for different regions of the brain over time, comparing cross-sectional and longitudinal processing.]
Huntington’s Disease (3 visits)  
Reuter et al., 2012

- Putamen atrophy rate is significantly different between controls (CN) and pre-HD far from onset (PHDfar).
- Baseline volume is not

**Rate of atrophy**

**Baseline volume (normalized)**

![Graph showing rate of atrophy and baseline volume in Huntington's Disease.](image)
Longitudinal tractography

- Goal: Reconstruct a WM pathway consistently among a subject’s time points
- Challenging to do when processing time points independently, as if they were cross-sectional data sets
  - Different parts of the pathway may be reconstructed in each time point, due to noise or WM degeneration
    - Changes in average anisotropy/diffusivity may be underestimated
    - Point-to-point correspondence difficult to establish for along-the-path analysis of anisotropy/diffusivity
Longitudinal TRACULA

Yendiki et al., In prep

- Reconstruct a subject’s pathways simultaneously in all time points:
  - Perturb path in the space of the base template
  - Map to each time point
  - Compute likelihood (fit to the dMRI data) at all time points
  - Anatomical prior info based on aparc+aseg from all time points

- Ensures point-to-point correspondence between time points
- Unbiased, treats all time points the same way
Usage

- Processing steps of trac-all do not change for longitudinal:
  trac-all -prep -c dmrirc
  trac-all -bedp -c dmrirc
  trac-all -path -c dmrirc

- Only configuration file changes:
  set subjlist = (bert_1 bert_2 elmo_1 elmo_2 elmo_3)
  set baselist = (bert_b bert_b elmo_b elmo_b elmo_b)

- Sample configuration file for longitudinal TRACULA:
  $FREESURFER_HOME/bin/example.dmrirc.long

Longitudinal
- Define baselist in config file
- Paths saved under dpathlong/

Cross-sectional
- Do not define baselist
- Paths saved under dpath/
Test-retest reliability

Yendiki et al., In prep

- 9 healthy subjects, scanned twice each (1.5T, 2mm iso, b=700)
- For each subject, pathways reconstructed:
  - Independently from each scan (“cross-sectional”)
  - Jointly from both scans (“longitudinal”)
- Find FA along the path, compare point to point b/w test-retest
Sensitivity to WM changes

Yendiki et al., In prep

- 43 HD patients, scanned 2-5 times each (3T, 2mm iso, b=700)
- For each subject, pathways reconstructed:
  - Independently from each scan (cross-sectional)
  - Jointly from both scans (longitudinal)
- Find FA along the path, fit linear slope at each point
Sensitivity to WM changes

Yendiki et al., In prep

- Longitudinal changes plotted along each pathway in freeview