An Exegesis of Advanced Normalization Tools (ANTs)

Brian B. Avants, Nicholas J. Tustison, Hans J. Johnson & the ITK and registration community

Contents

Background

Big picture

- Differentiable maps with differentiable inverse + *statistics in these spaces*

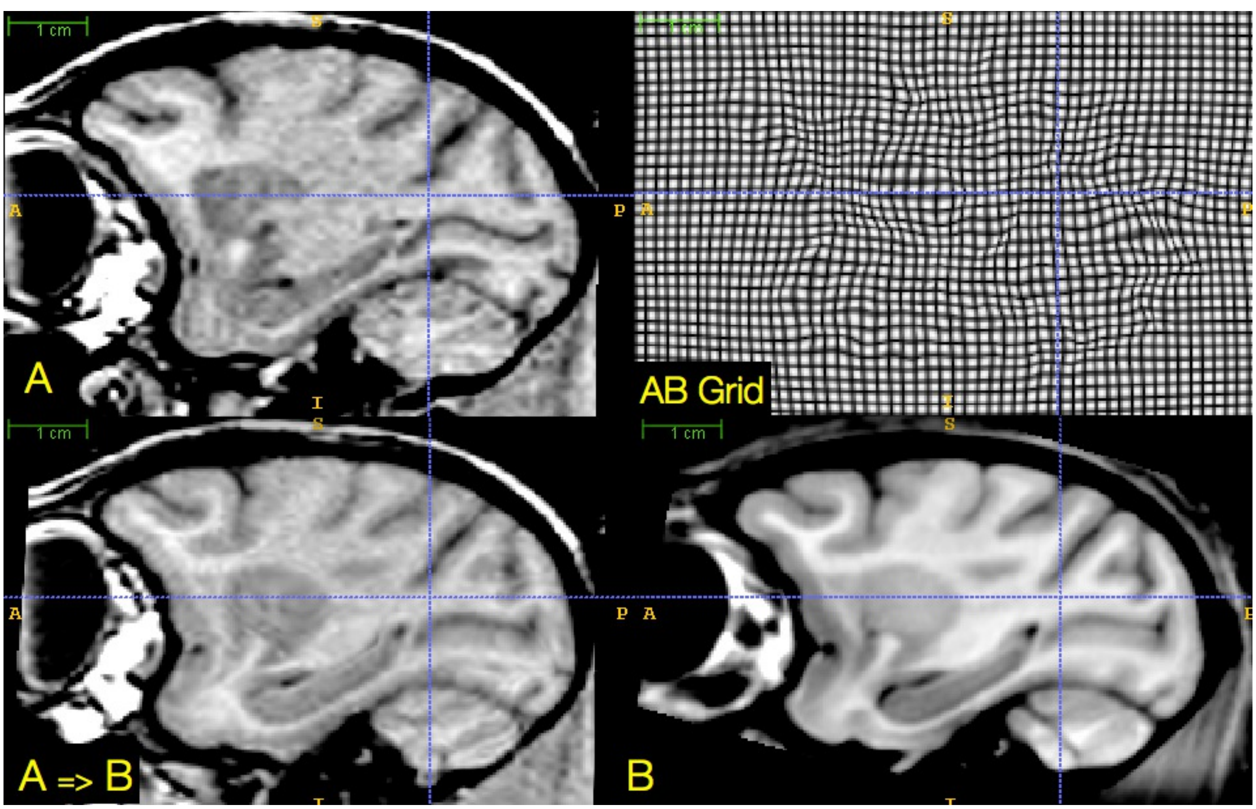
- Customizable multivariate segmentation & registration
- High-dimensional statistics in low-dimensional spaces
- Borg philosophy: from I/O, to processing to statistical methods
- Open source, testing, many examples, consistent style, multiple platforms, active community support ...

Tools you can use for imaging science

- Core developers: *B. Avants, N. Tustison, H. J. Johnson, J. T. Duda*
- Many contributors, including users ...
- Multi-platform, multi-threaded C++ stnava.github.io/ANTs
- Developed in conjunction with http://www.itk.org/
- R wrapping and extension stnava.github.io/ANTsR
- rapid development, regular testing + many eyes → bugs are shallow

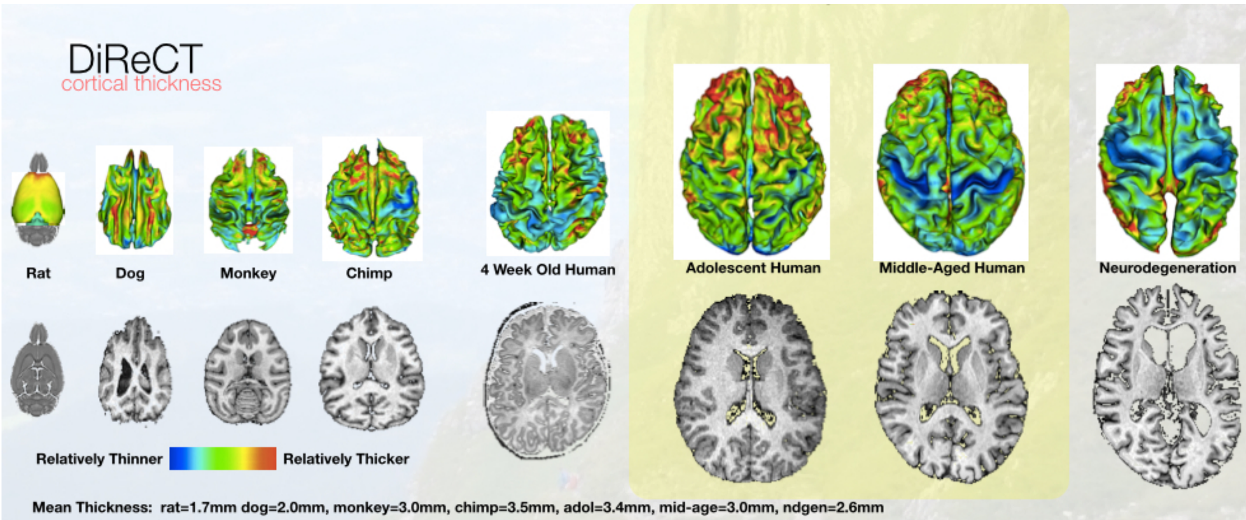
General theory tunable to specific domains: *no-free lunch*

Fine-grained and flexible



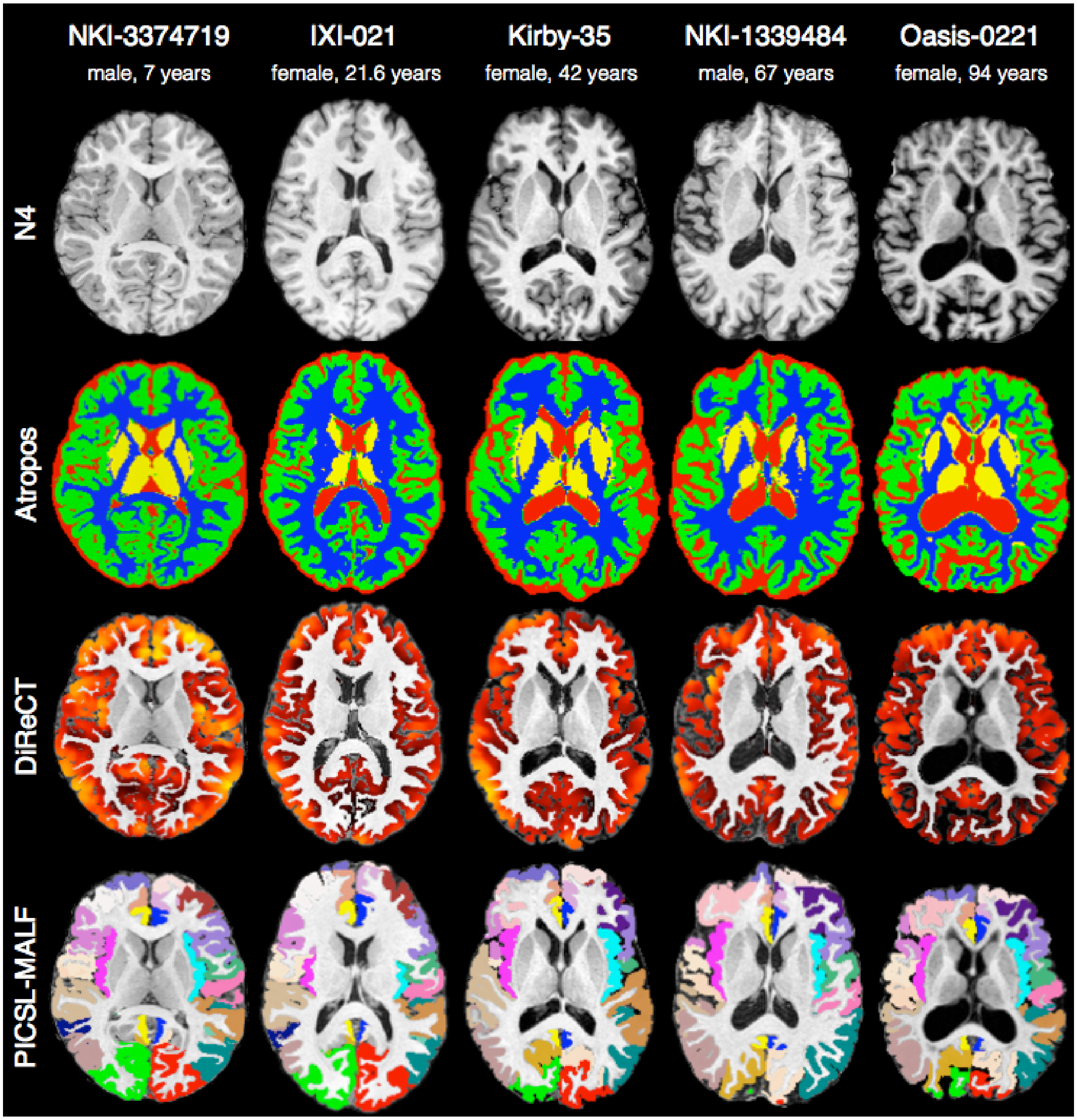
Use prior knowledge to broaden performance

Mammalian cortical thickness computed with ANTs

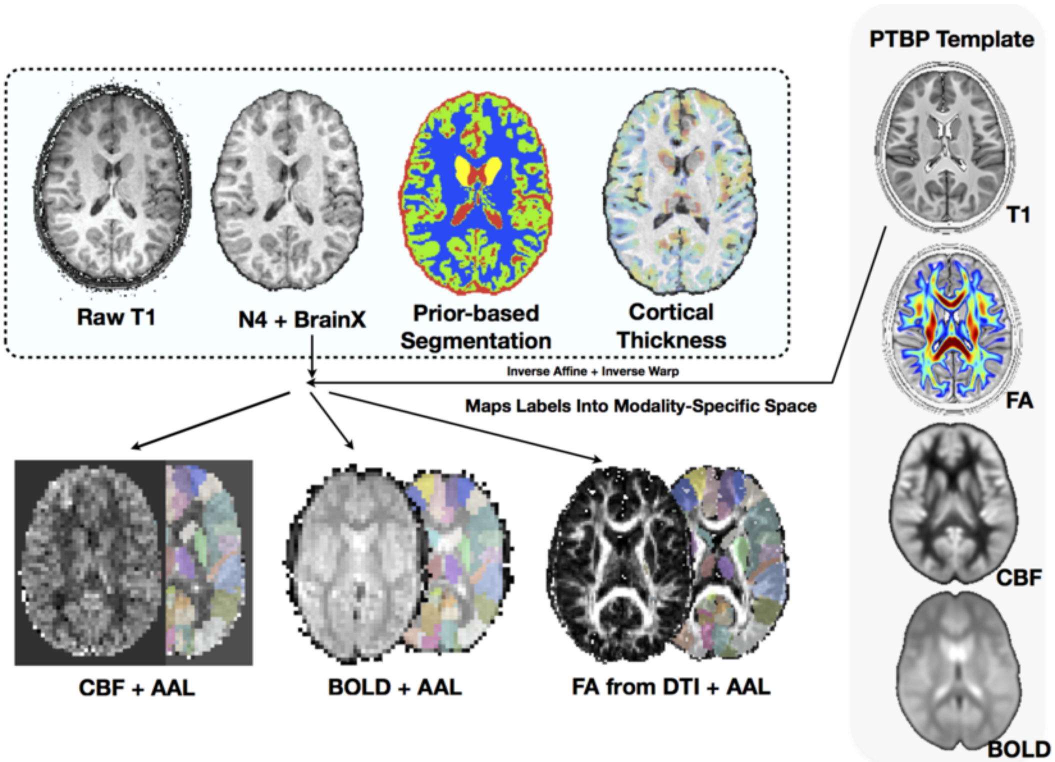


Library for multivariate image registration, segmentation & statistics

Anatomical quantification

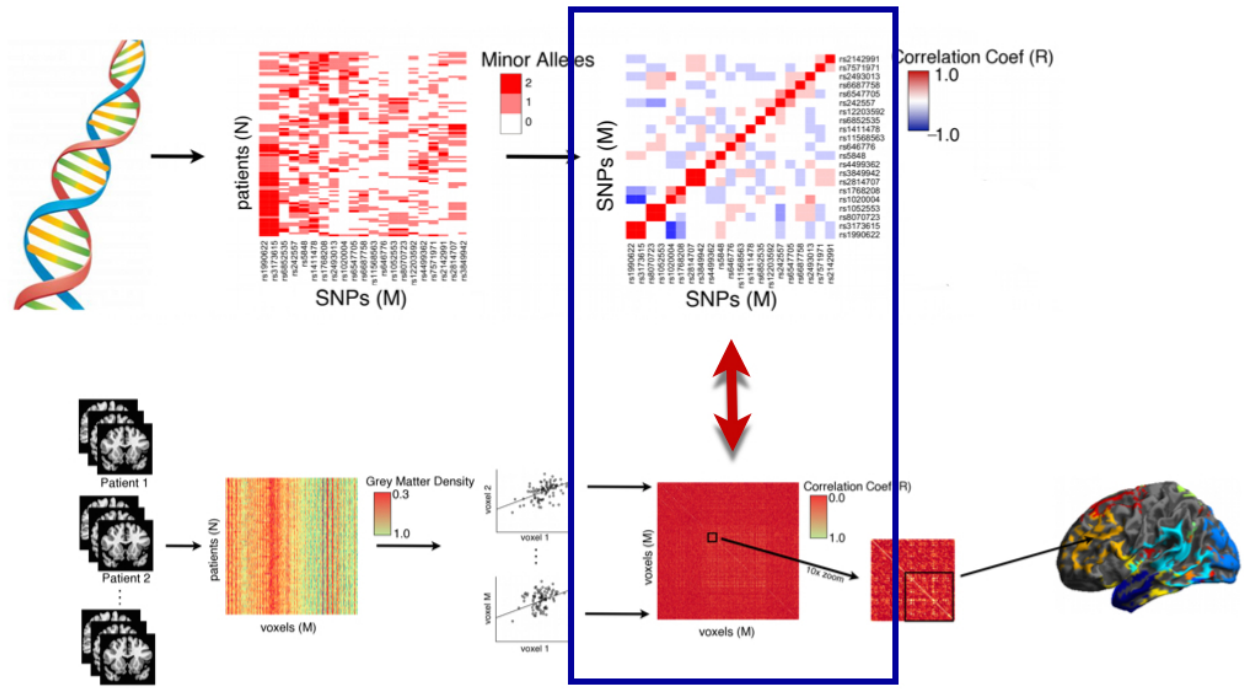


Modality integration



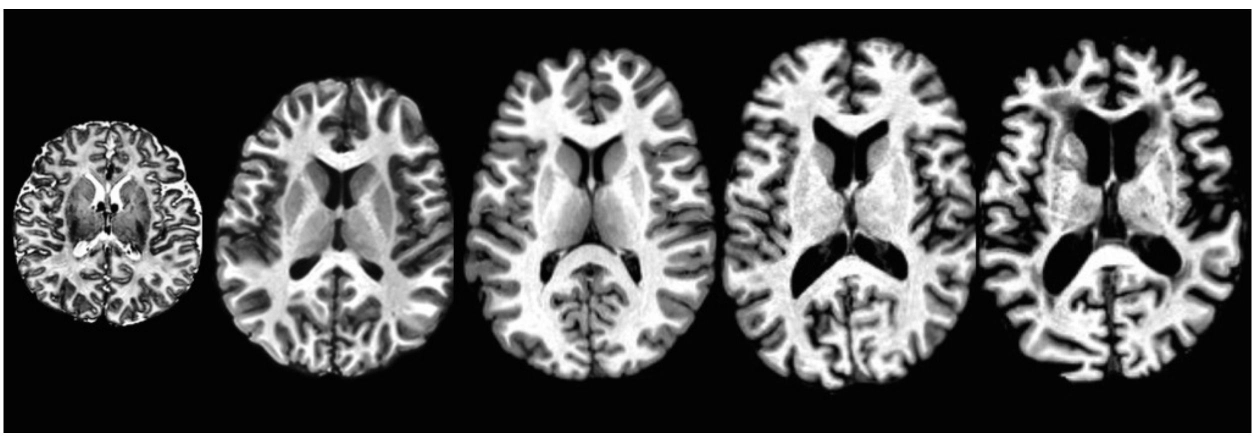
ITK+ANTs+R = ANTsR

Agnostic statistics



(McMillan et al, *NoA*, 2014)

How do we quantify *life span* brain health in individuals and in populations?



How do we integrate modalities and organ systems?

need unbrain example here

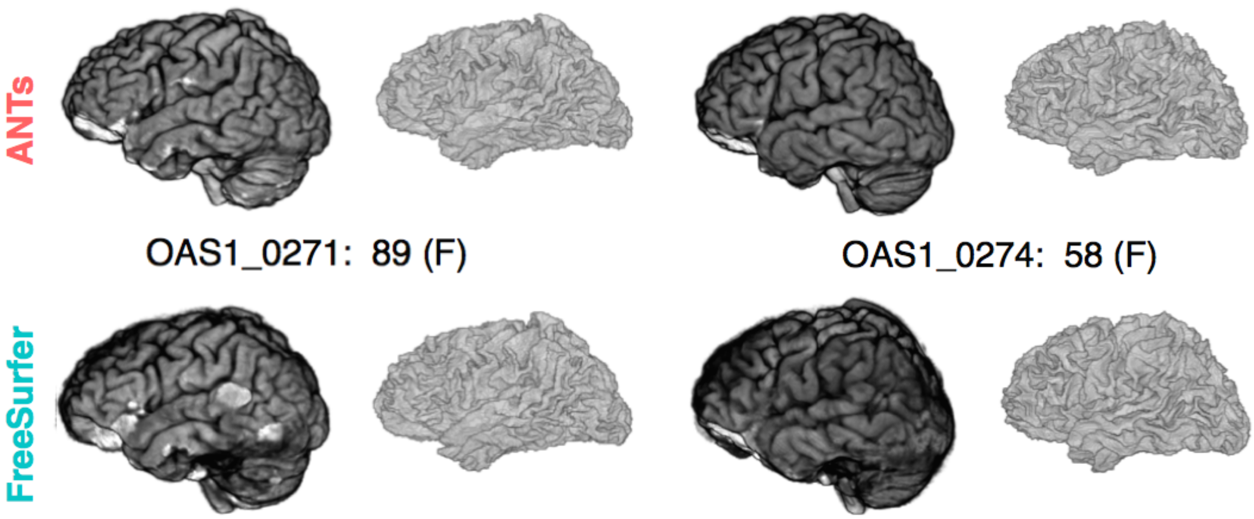
ANTs*R* → new insight via quantification

Good software should fade into the background . . . however . . .

As is common in science, the first big breakthrough in our understanding . . . [came from] an improvement in measurement.

> Daniel Kahnemann, *Thinking, Fast and Slow* (2011)

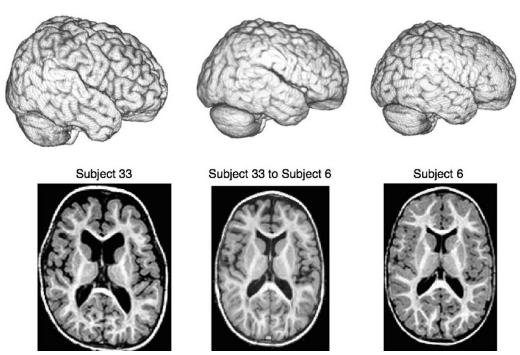
ANTs v Freesurfer



SyN Example

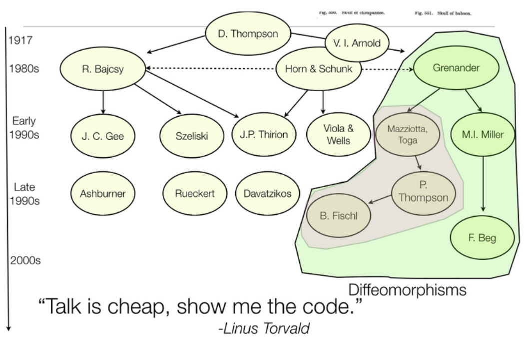
SyN video

Theory + evaluation + reproducibility



Founding Developers

A long history of research



Rigorous transformation definition is key

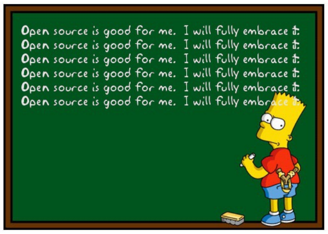
ANTs and ITK are developed together: see B. B. Avants et al. (2014), Tustison and Avants (2013), Tustison et al. (2010) and more …

Key definitions

- physical space
- transformation definition aware of physical space
- optimization space consistent with above
- unit testing

Merit Badges

bart



open source

built on ITK—probably the most well-vetted medical image analysis package in the world B. B. Avants and Tustison (2014)

competitions

- Klein 2009: Brain Registration (ANTs)
- Murphy 2010: Lung Registration (ANTs)
- SATA 2012: Multi-Atlas Segmentation (ANTs+JointLabelFusion)
- SATA 2013: Multi-Atlas Segmentation (ANTs+JointLabelFusion)
- BRATS 2013: Multivariate Brain Segmentation (ANTsR)
- Yushkevich's Hipp Atlas: (hippocampusubfield.com)
- TBA: BOLD decoding (ANTsR)
- Substantial work with DTI (Camino developer in house)
- STACOM2014 ?

papers

- registration : ANTs vs. everything else Klein et al. (2009)
- segmentation : Atropos vs. SPM, etc.
- bias correction : N4 vs N3
- cortical thickness : ANTs vs. FreeSurfer Tustison et al. (2014)
- compatibility with R

The stories behind ANTs development

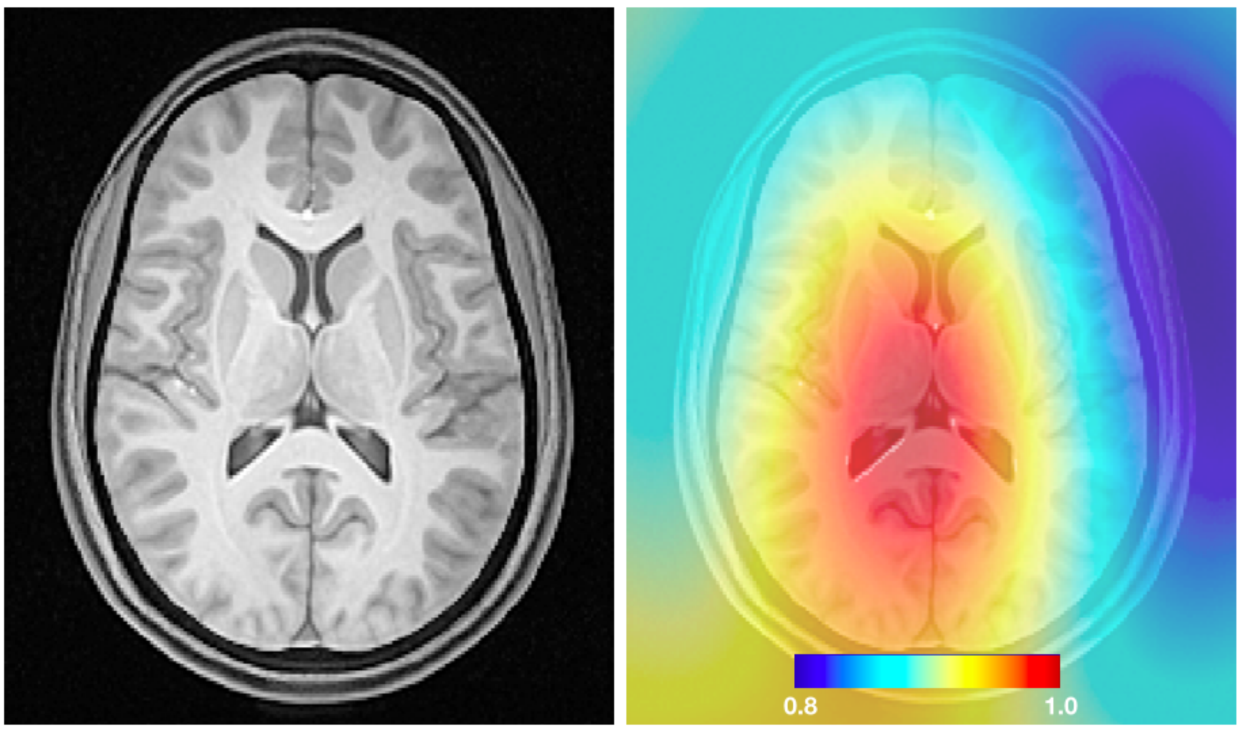
(we can comment this out but I think it would be good to make some notes for posterity)

Registration

N4

- N3 (developed at the Montreal Neurological Institute) has been the gold standard for bias correction—used in important projects such as ADNI
- N3 is a set of perl scripts that works natively with the MINC file format which we tried to incorporate into an ANTs processing pipeline.
- We had so much trouble converting back and forth between ITK-compatible Nifti format and MINC that Brian suggested we try to implement N3 in ITK.
- I had some experience with B-splines and added some other tweaks giving birth to N4.

N4 Introduction



T1 Axial Brain Image   Bias Field

Nonparametric nonuniform intensity normalization (N3)

Sled et al., “A nonparametric method for automatic correction of intensity nonuniformity in MRI Data,” *IEEE-TMI*, 17(1), 1998.

Boyes et al., “Intensity non-uniformity correction using N3 on 3-T scanners with multichannel phased array coils,” *NeuroImage*, 39(4), 2008.

> In a comparison of several correction techniques N3 performed well (Arnold et al., 2001). Also, the algorithm and software are in the public domain (http://www.bic.mni.mcgill.ca/software/N3/) and is probably the most widely used non-uniformity correction technique in neurological imaging.

Zheng et al., "Improvement of brain segmentation accuracy by optimizing non-uniformity correction using N3," *NeuroImage*, 48(1), 2009.

> Among existing approaches, the nonparametric non-uniformity intensity normalization method N3 (Sled et al., 1998) is one of the most frequently used... High performance and robustness have practically turned N3 into an industry standard.

Vovk et al., "A Review of Methods for Correction of Intensity Inhomogeneity in MRI," *IEEE-TMI*, 26(3), 2007.

> A well-known intensity inhomogeneity correction method, known as the N3 (nonparametric nonuniformity normalization), was proposed in [15]... Interestingly, no improvements have been suggested for this highly popular and successful method... The nonparametric nonuniformity normalization (N3) method [15] has obviously become the standard method against which other methods are compared.

Code

```
COMMAND:
     N4BiasFieldCorrection

OPTIONS:
     -d, --image-dimensionality 2/3/4
     -i, --input-image inputImageFilename
     -x, --mask-image maskImageFilename
     -w, --weight-image weightImageFilename
     -s, --shrink-factor 1/2/3/4/...
     -c, --convergence [<numberOfIterations=50x50x50x50>,<convergenceThreshold=0.0>]
     -b, --bspline-fitting [splineDistance,<splineOrder=3>]
                           [initialMeshResolution,<splineOrder=3>]
     -t, --histogram-sharpening [<FWHM=0.15>,<wienerNoise=0.01>,<numberOfHistogramBins=200>]
     -o, --output correctedImage
                  [correctedImage,<biasField>]
     -h
     --help
```

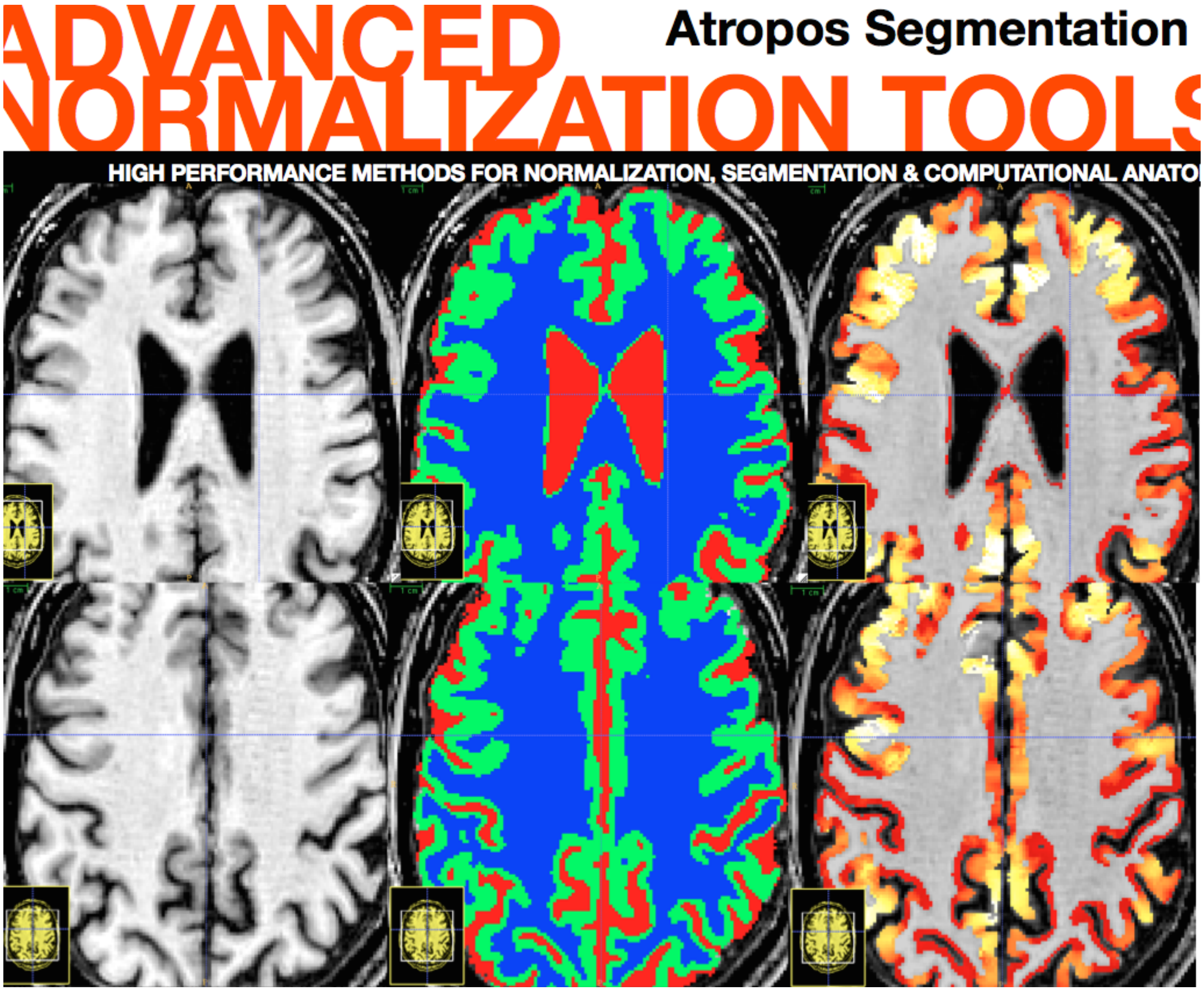
> Talk is cheap, show me the code.

Atropos

- Similar to our experience with N3, we tried to incorporate FAST (from the FMRIB at Oxford) into an ANTs processing pipeline.
- Phil (?) pointed out the difficulty of incorporating priors into FAST.
- Related, Brian went to a segmentation-related worksop at MICCAI and aired publicly his disappointment that so much of what had been developed in the community over the last 20+ years has not been made publicly available. "What's wrong with you people!"
- 3-tissue algorithm in ImageMath —> multivariate, n-class Atropos

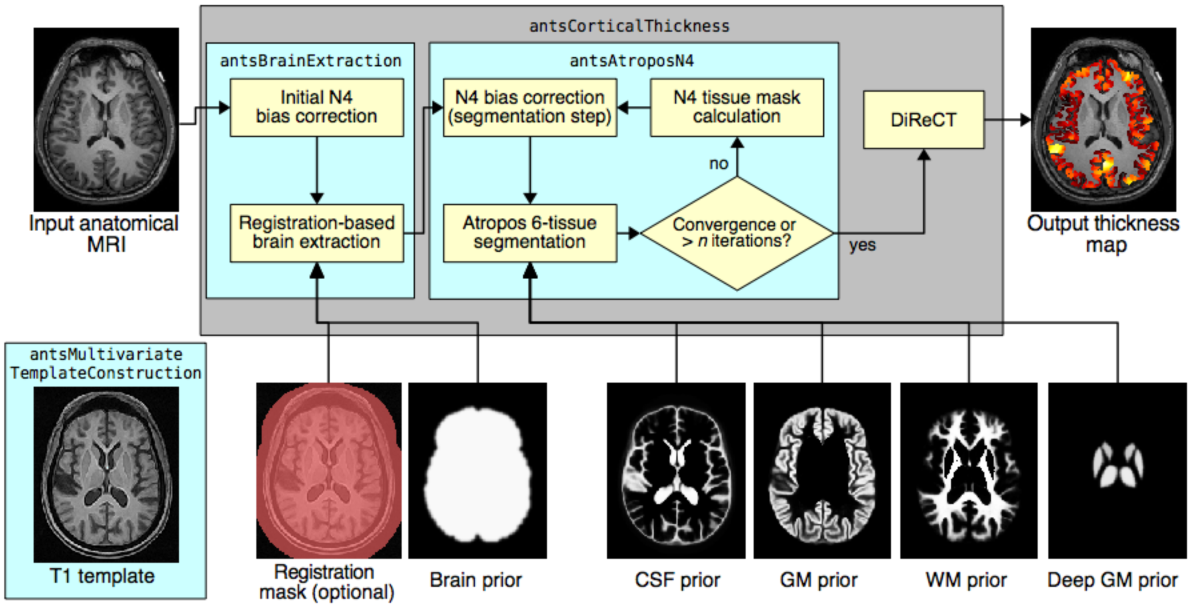
KellySlater –> KellyKapowski

Atropos + KK Example



Putting it all together

The ANTs cortical thickness pipeline



Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements, NeuroImage 2014.*

All software components are open source and part of the Advanced Normalization Tools (ANTs) repository.

Basic components of the pipeline

1. template building (offline)
2. brain extraction
3. cortical thickness estimation
4. cortical parcellation

Template building

Tailor data to your specific cohort

- Templates representing the average mean shape and intensity are built directly from the cohort to be analyzed, e.g. pediatric vs. middle-aged brains.
- Acquisition and anonymization (e.g. defacing) protocols are often different.

Template building (cont.)

Each template is processed to produce auxiliary images which are used for brain extraction and brain segmentation.

Brain extraction

Comparison with de facto standard FreeSurfer package. Note the difference in separation of the gray matter from the surrounding CSF. (0 failures out of 1205 scans)

Brain segmentation

Randomly selected healthy individuals. Atropos gets good performance across ages.

Cortical thickness estimation

In contrast to FreeSurfer which warps coupled surface meshes to segment the gray matter, ANTs diffeomorphically registers the white matter to the combined gray/white matters while simultaneously estimating thickness.

Evaluation

Question: In the absence of ground truth, how do we evaluate performance?

Answer: We use demographic information with known thickness sensitivity and correlate with measured thickness quantities. One of the most well-known, most easily obtained, and most confident measures available is "age." So we take 50% of the thickness data to train a model (e.g. linear regression) and then calculate the model's age prediction error on the other 50%. We do this for n=1000 permutations to build a distribution. Similarly, we can do this for gender.

A couple notes on usage

- Out of the many cortical thickness algorithms that have been proposed, FreeSurfer dominates. And rightfully so, because it works well and has been the only publicly available tool (until reccently).
- In the same spirit, we have made our tools publicly available. Usage is similar to that of FreeSurfer (see below). We also make several templates available.

"Talk is cheap, show me the code." —Linus Torvald

Components

Software engineering

ants gource

Analysis philosophy and published opinions

Voodoo in voxel-based analysis

Instrumentation bias in the use and evaluation of software

Discussion

Problems

There are several problems and shortcomings to this analysis.

- Customizable for specific problems but not too specific
- Latest theoretical advances in registration not yet wrapped for users

Strengths

Some strengths include relatively few assumptions, a flexible implementation and open-science approach.

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