

An Exegesis of Advanced Normalization Tools (*ANTs*)

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

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ANTsR is a platform for reproducible studies of high-dimensional data

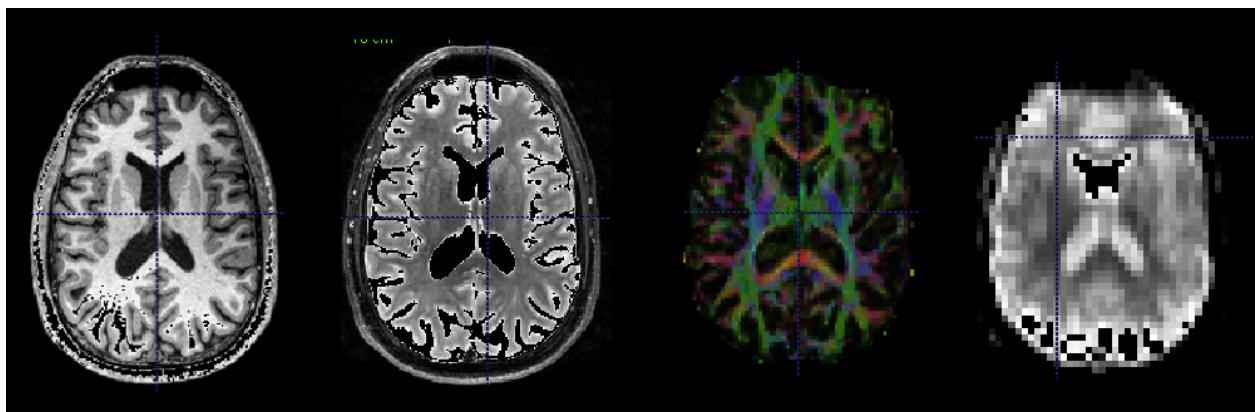
ANTsR is built from general mathematical and software engineering principles

Images are high-dimensional data (SNPs, demographics...)

[smile movie](#)

we map image pairs with a *transformation* and a *metric*

coordinated multivariate statistical fields arise from this mapping

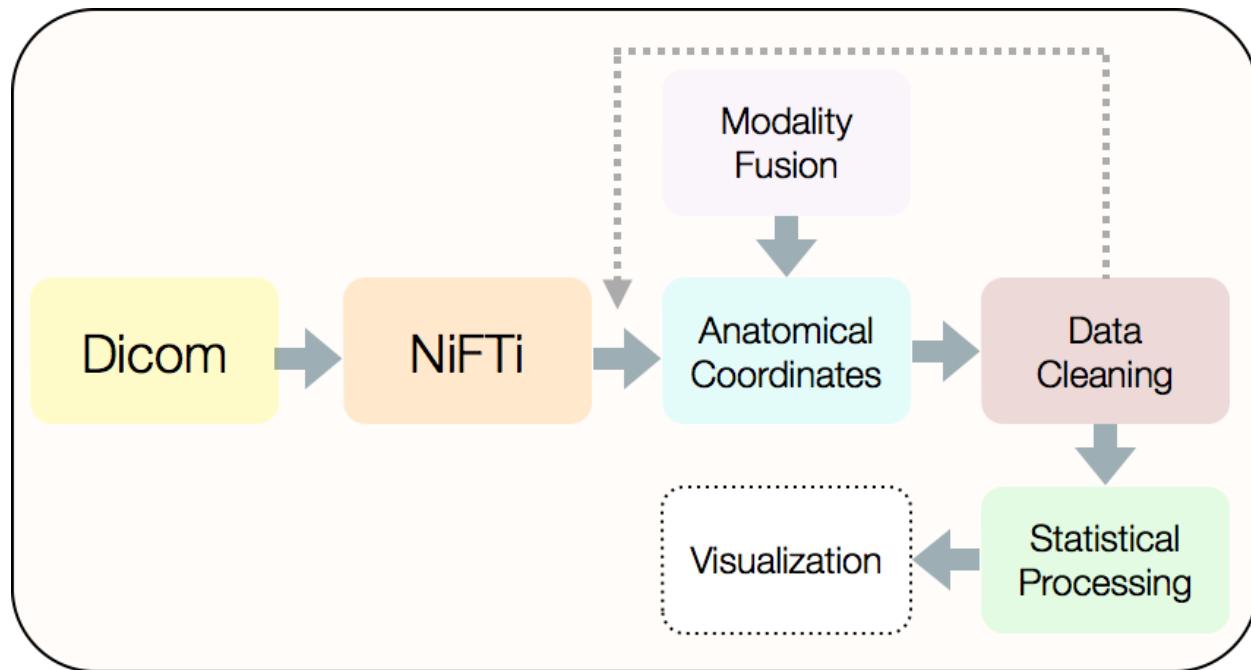


how do we map not just pairs but hundreds or thousands of pairs of images?

how do we cluster the statistical fields that arise from these maps?

how do we cluster these fields with supervision and associate clusters with outcomes?

ANTsR Platform for Medical Imaging

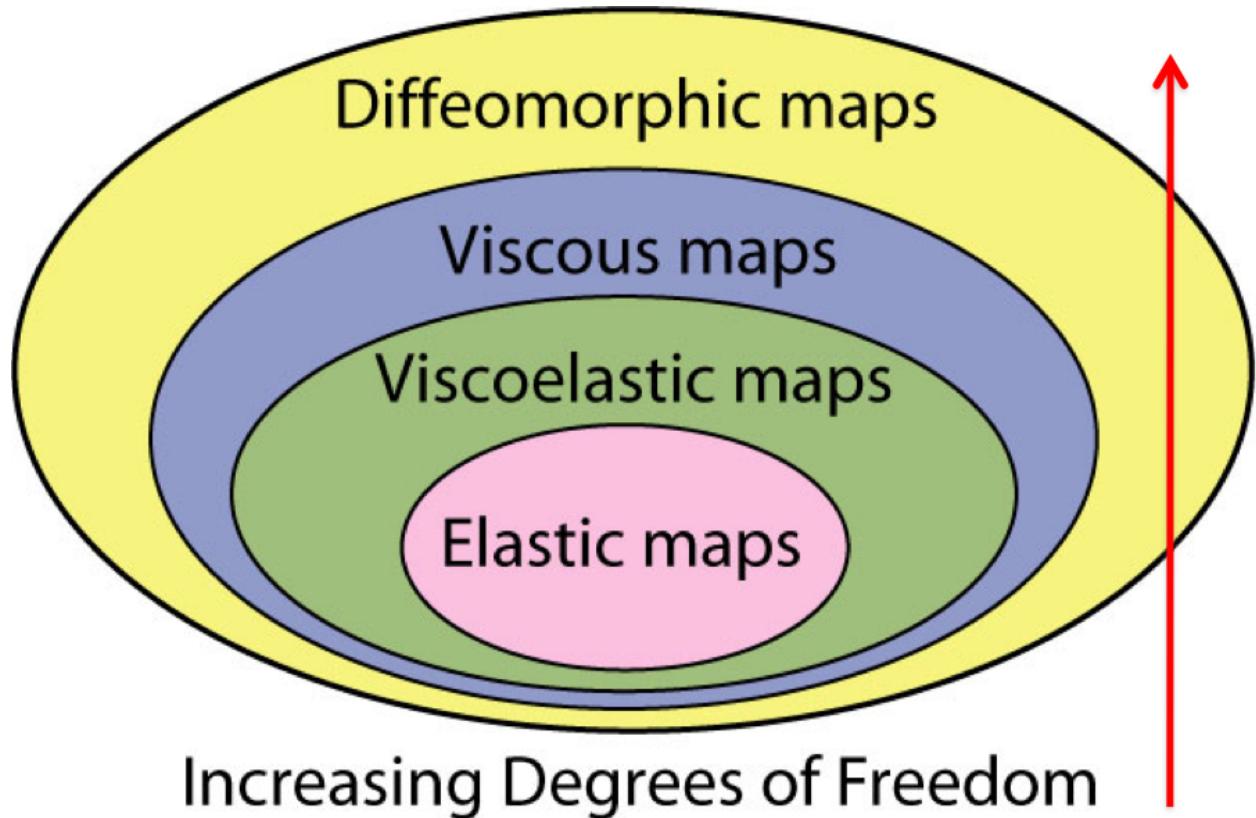


this document is another goal of ANTs as is [this one](#)

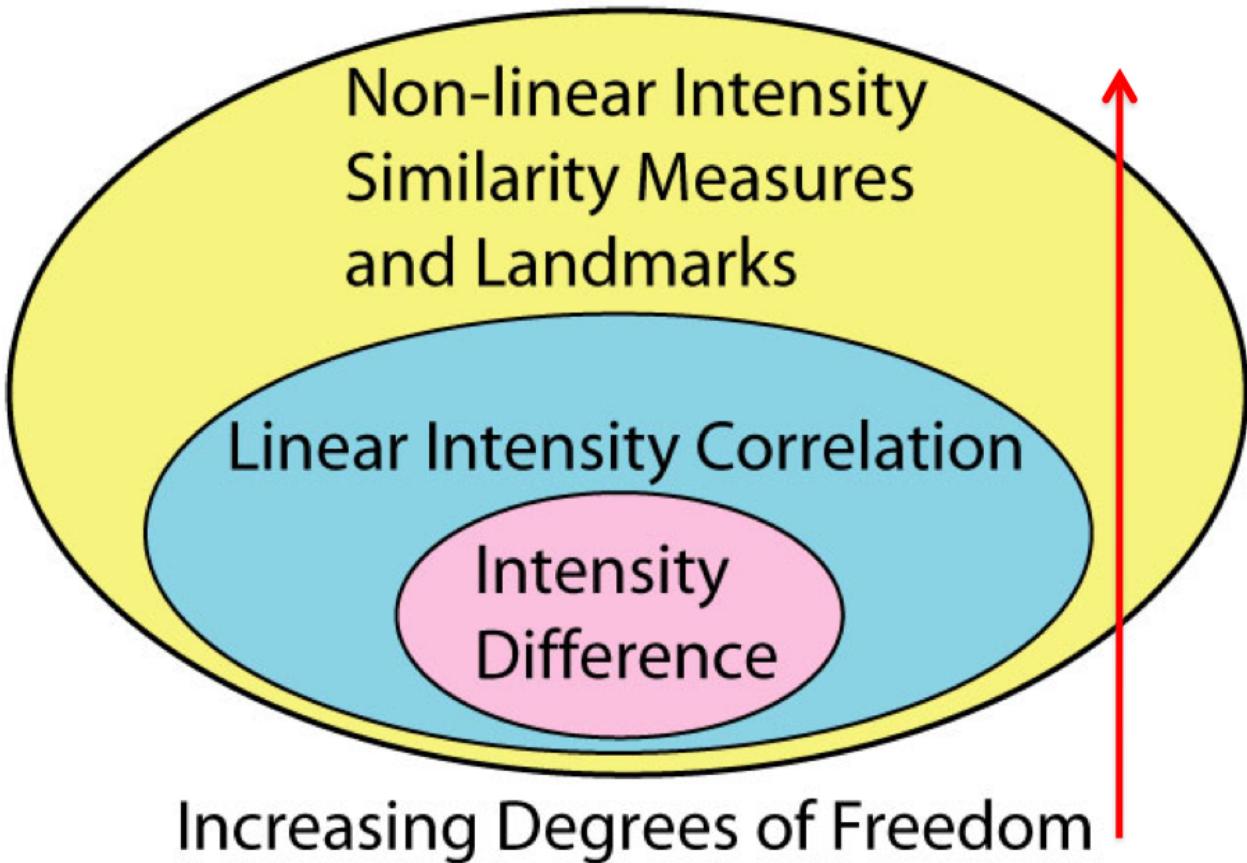
- Powerful, general-purpose, well-evaluated registration and segmentation.
- Differentiable maps with differentiable inverse + statistics in these spaces
- Evaluated in multiple problem domains via internal studies & open competition
- Borg philosophy: “best of” from I/O, to processing to statistical methods
- Open source, testing, many examples, consistent style, multiple platforms, active community support
...
- Integration with *R* + novel tools for prediction, decoding, high-to-low dimensional statistics.
- Collaborations with [neurodebian](#), [slicer](#), [brainsfit](#), [nipype](#), [itk](#) and more ...

Powerful, general-purpose automated or semi-automated registration and segmentation.

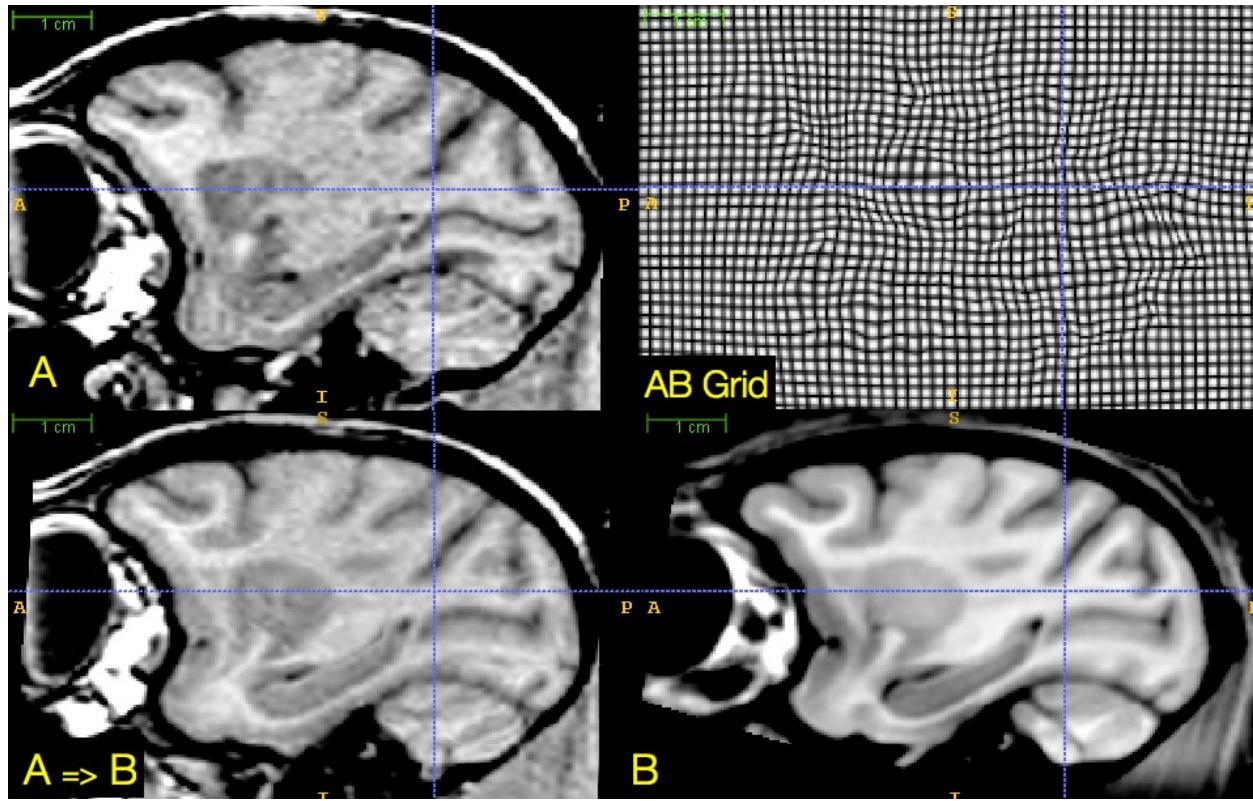
Geometric transformations



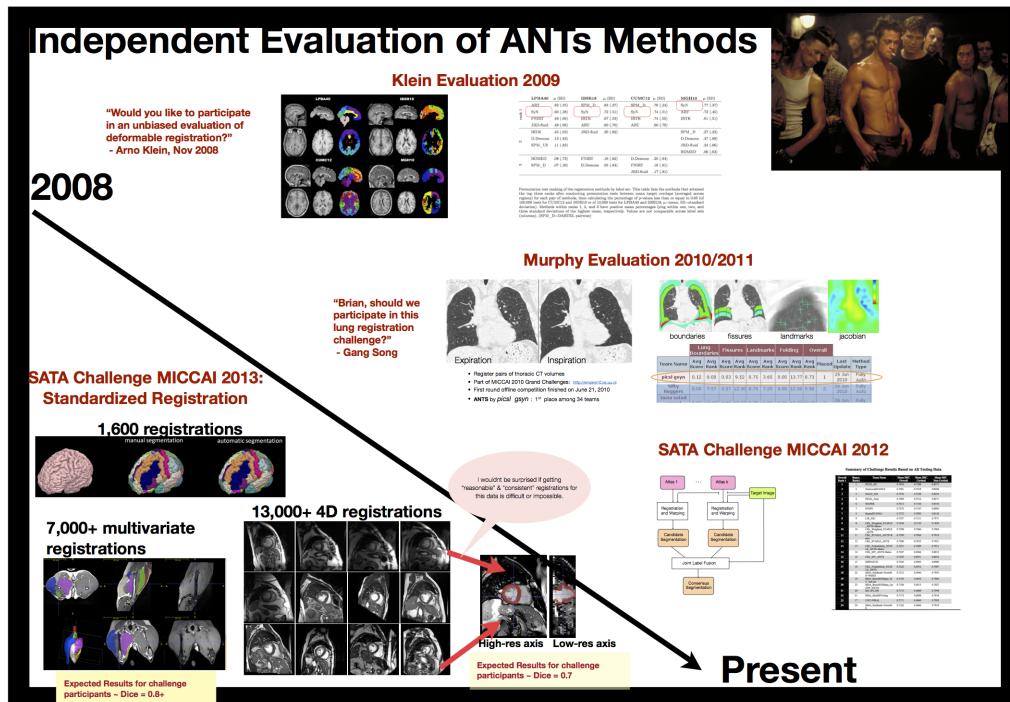
Intensity transformations



Fine-grained and flexible maps

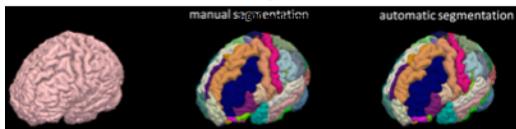


Evaluated on anatomical quantification



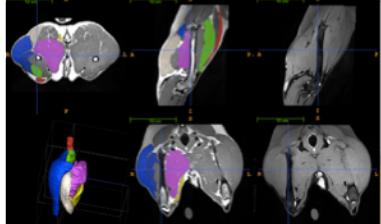
Sata 2013

1600 “easy” registrations



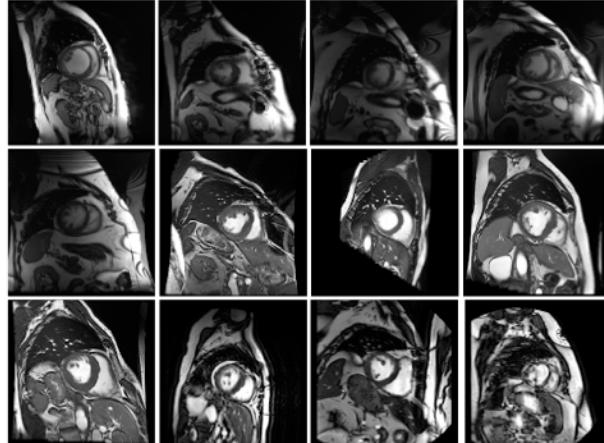
I wouldn't be surprised if getting "reasonable" & "consistent" registrations for this data is difficult or **impossible**.

7,000+ multivariate registrations (challenging)



Expected Results for challenge participants
~ Dice = 0.8+

13,000+ 4D registrations (very challenging)

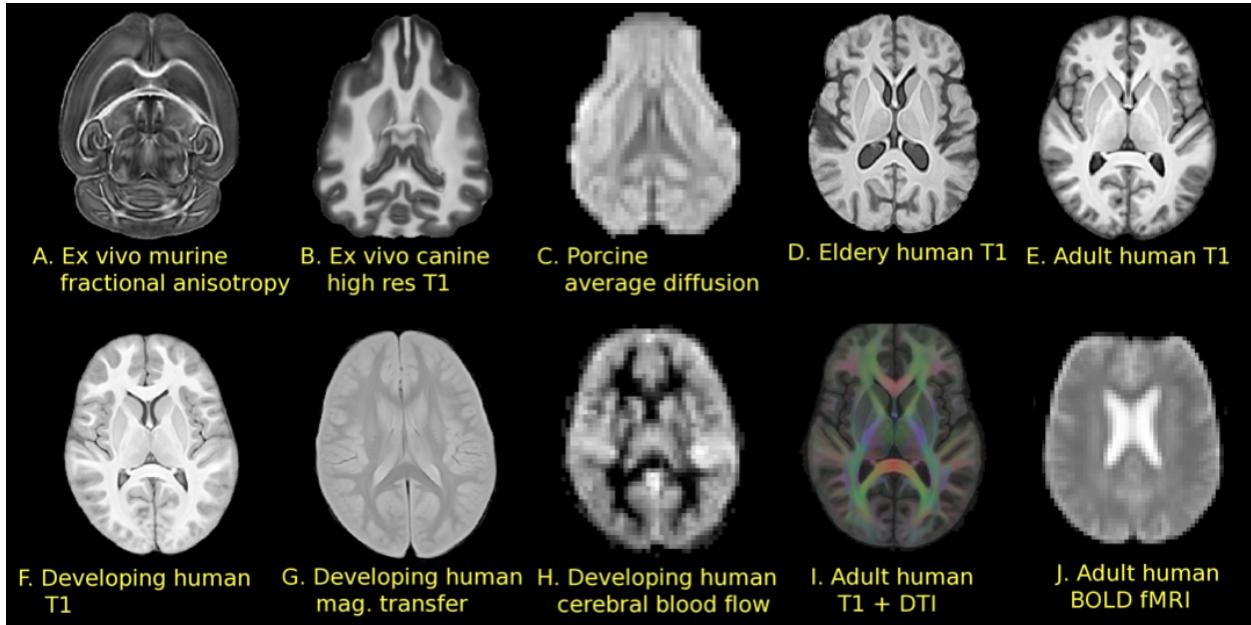


Heart orientation varies between individuals

we provided the *standard* registration results for > 20,000 image pairs at [SATA 2013](#)

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

Brain images as *high-dimensional data*

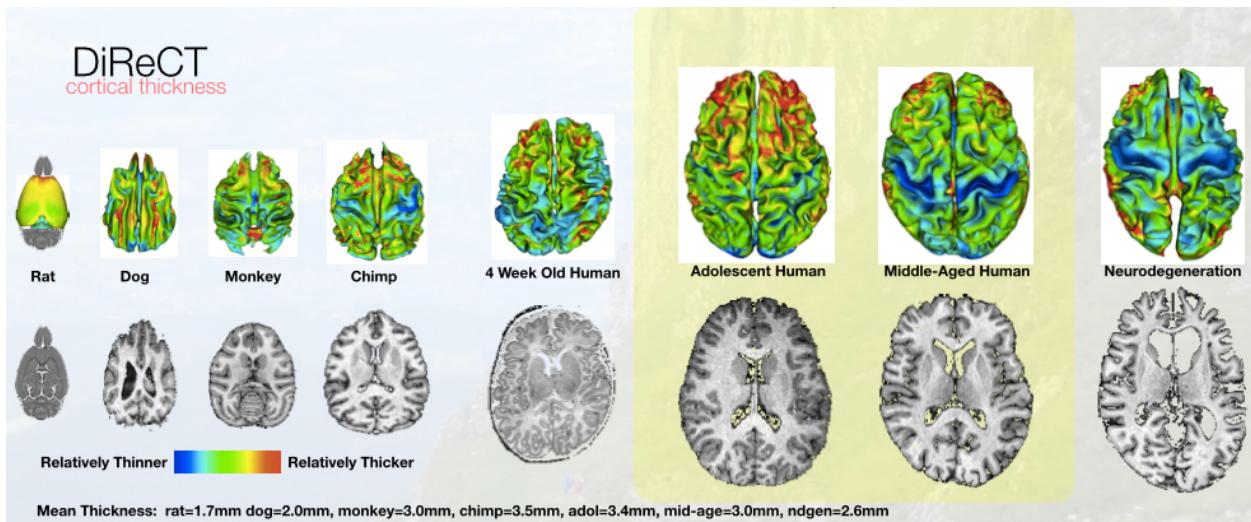


Political activism

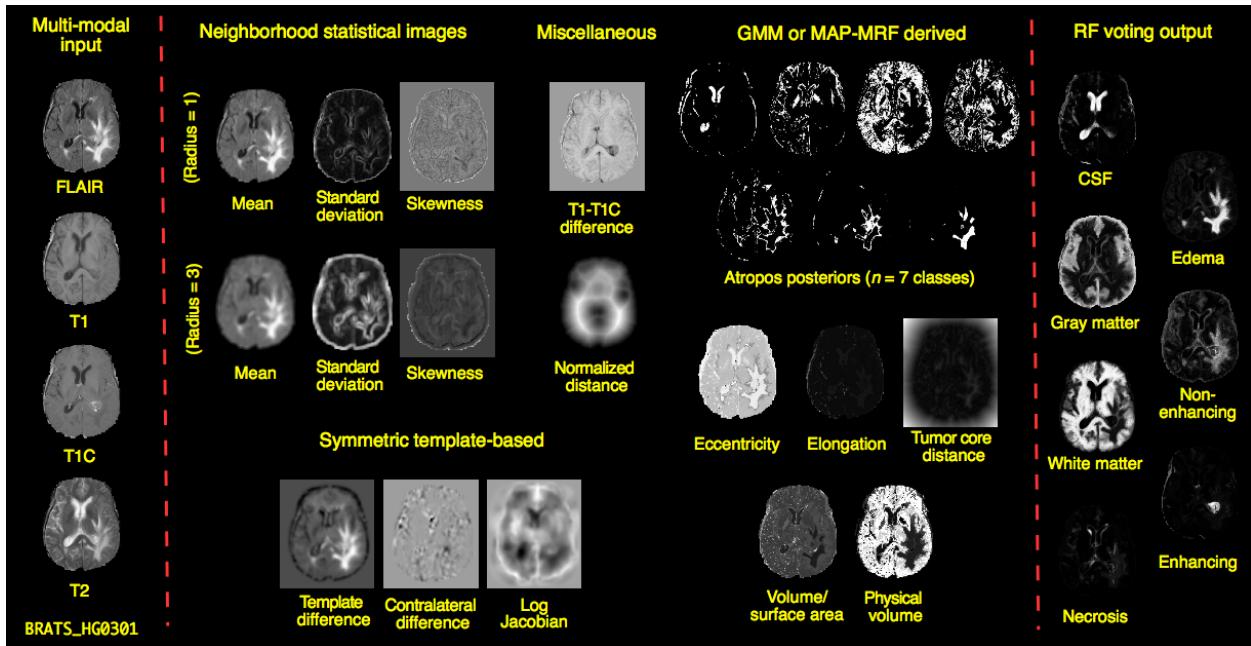
[congress commentary](#)

Customizable multivariate segmentation & registration

Mammalian cortical thickness computed with ANTs



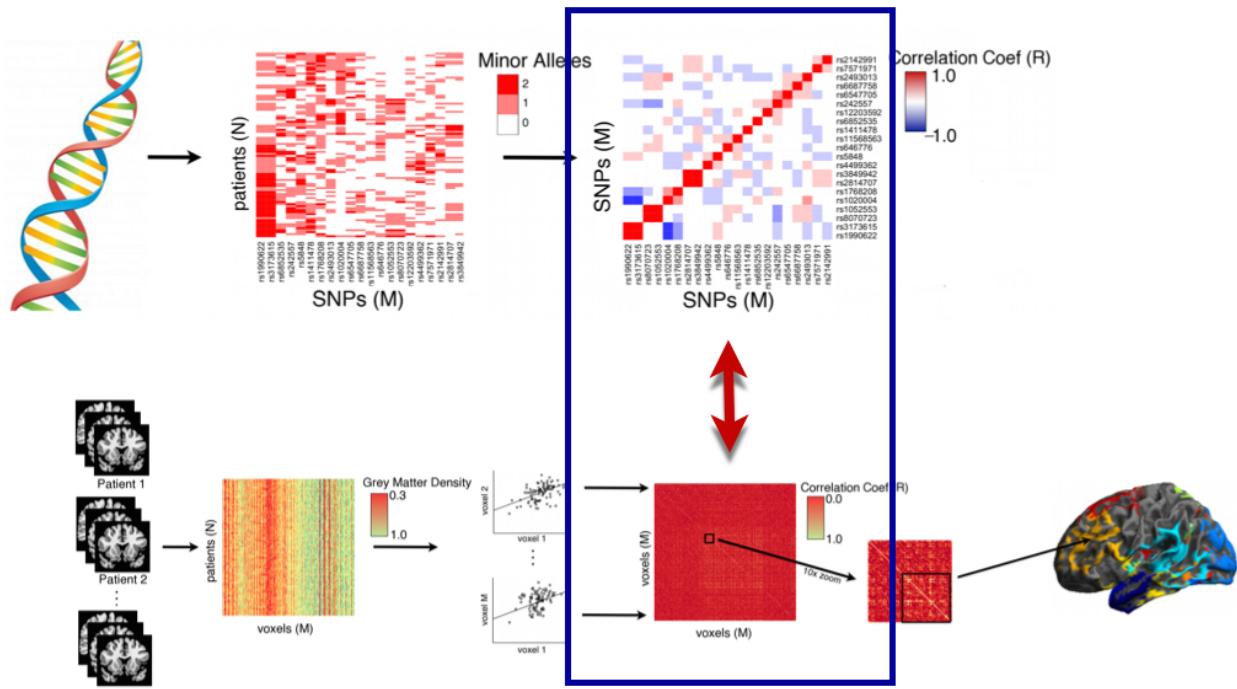
General theory tunable to specific domains: *no-free lunch*



Agnostic data integration: prediction, decoding, diagnosis

$$ITK+ANTs+R = ANTsR$$

Agnostic statistics



(McMillan et al, NoA, 2014)

McMillan et al.

ANTsR → new insight via quantification

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

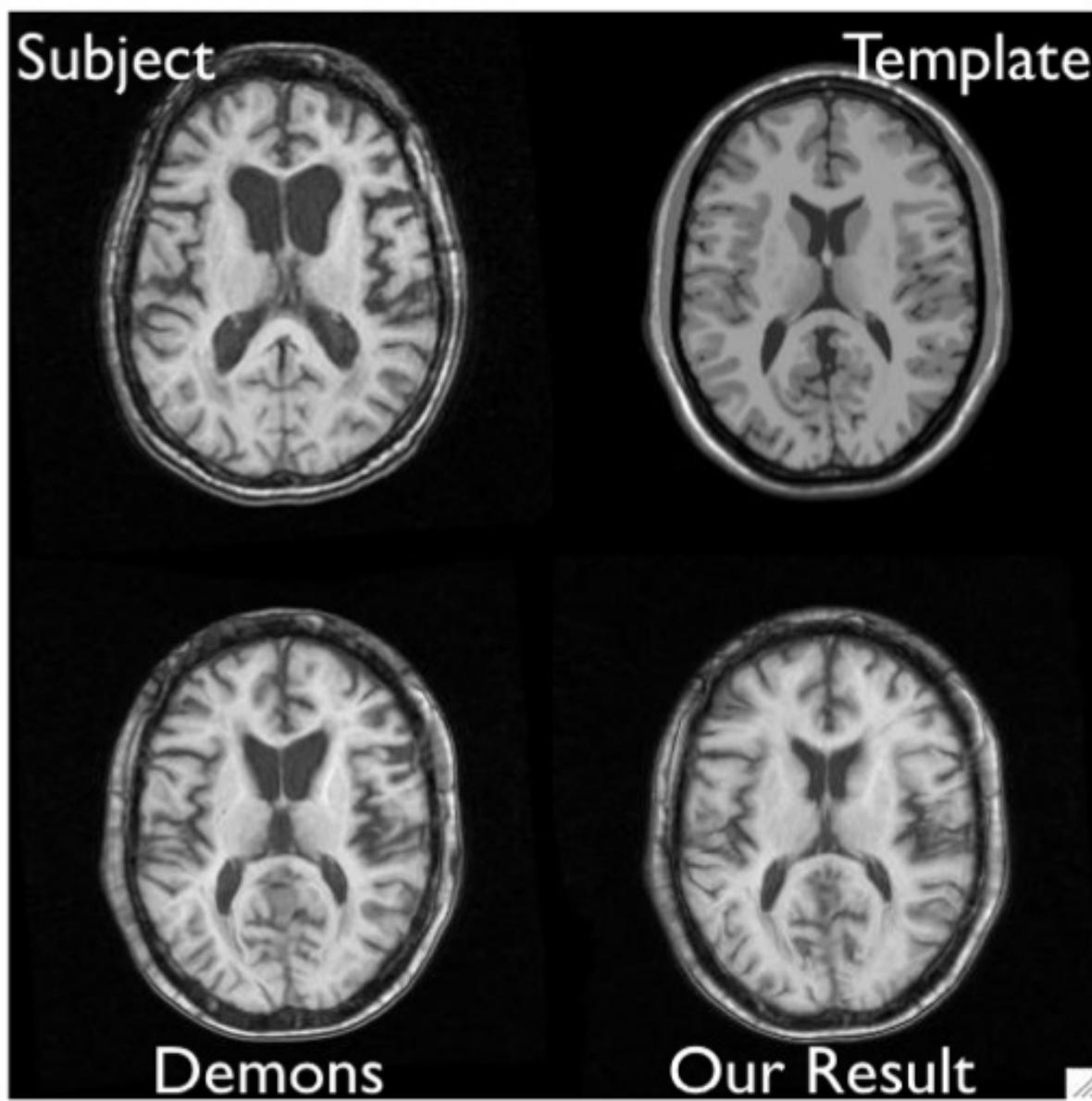
As is common in science, the first big breakthrough in our understanding ... [came from] an improvement in measurement.

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

Questions & ANTsRs

Can we do a better job of aligning these brains?

Brain mapping in the early 2000s was based on Matlab scripts or the *Demons* algorithm



These approaches over-penalized large deformations and were inadequate for several classes of problems

Compare chimpanzee and human prefrontal cortex



[LPF algorithm](#)

ANTs was begotten in SyN: “science is the belief in the ignorance of experts”

SyN formulation

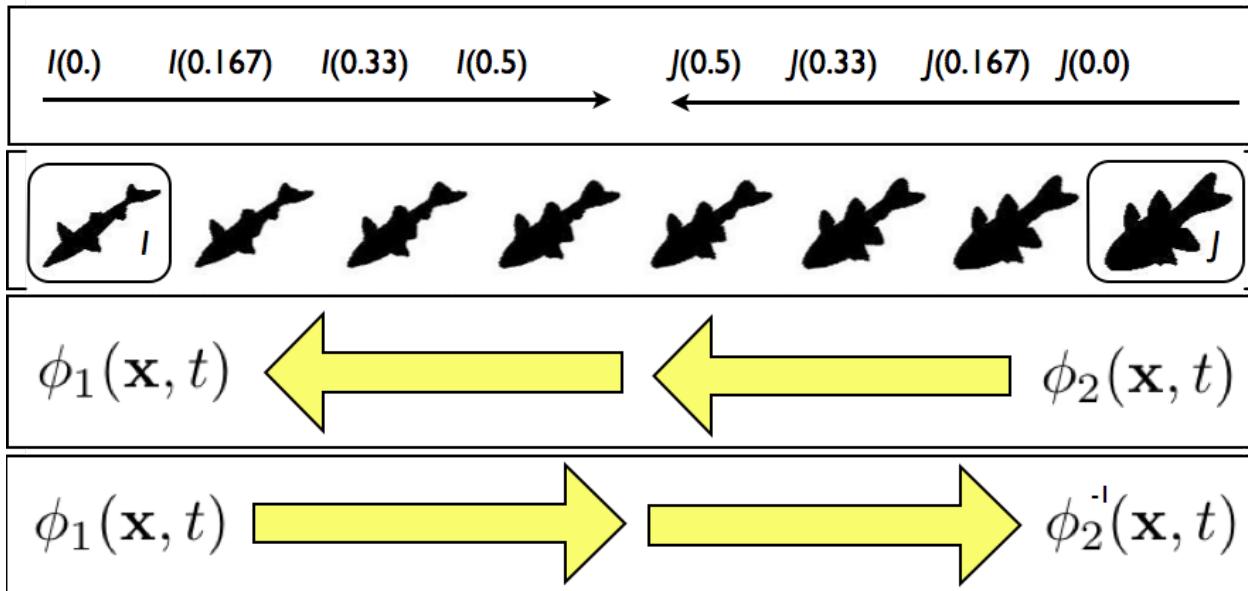
$$\inf_{\phi_1} \inf_{\phi_2} \left[\int_0^{0.5} (\|v_1(t)\|_L^2 + \|v_2(t)\|_L^2) dt + \int_{\Omega} \Pi_{\sim} (I \circ \phi_1^{-1}(\mathbf{x}, 0.5), J \circ \phi_2^{-1}(\mathbf{x}, 0.5)) d\Omega \right]$$

where

$$\frac{d\phi_i(\mathbf{x}, t)}{dt} = v_i(\phi_i(\mathbf{x}, t), t), \quad \phi_i(\mathbf{x}, 0) = \mathbf{Id}, \quad i \in \{1, 2\}$$

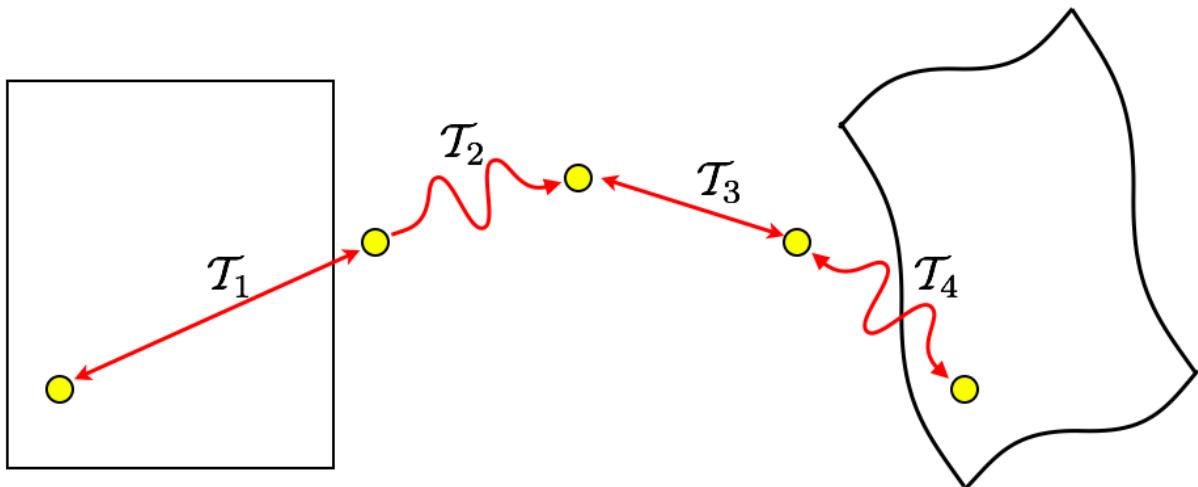
and Π_{\sim} is an arbitrary similarity metric (or metrics).

SyN for optimization symmetry



Images deform symmetrically along the shape manifold. This eliminates bias in the measurement of image differences.

Minimizing interpolations



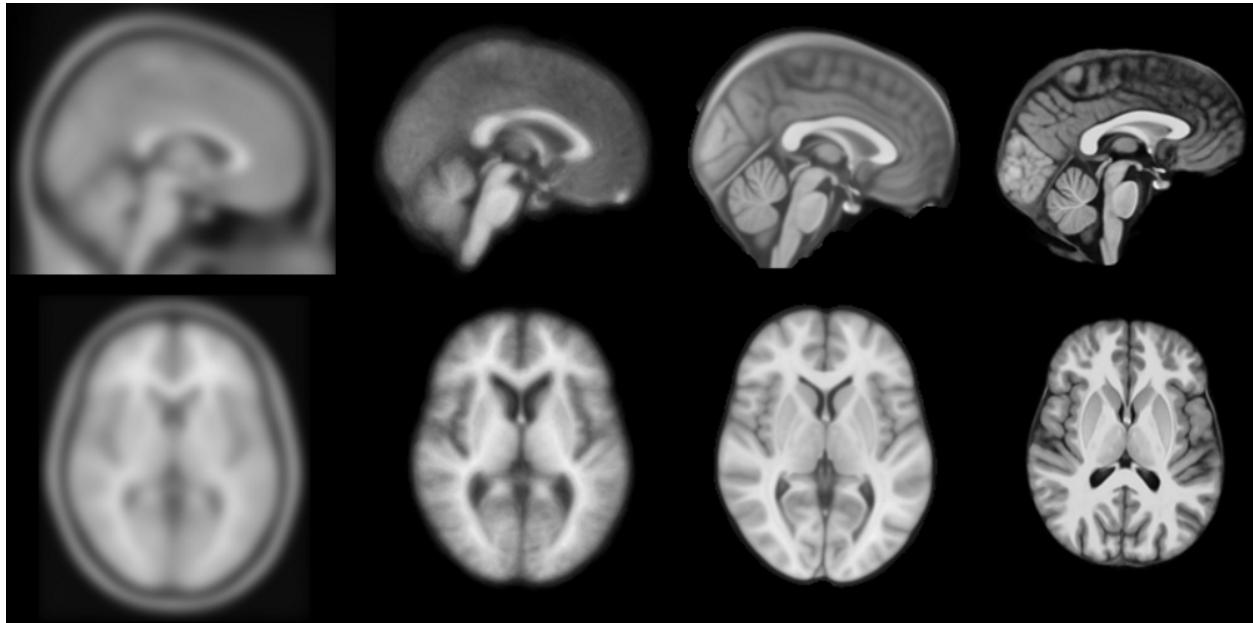
$$\mathcal{T}_{total} = \mathcal{T}_1 \circ \mathcal{T}_2 \circ \mathcal{T}_3 \circ \mathcal{T}_4$$

To avoid compounding interpolation error with the concatenation of transformations, ANTs never uses more than a single interpolation.

SyN Example

[SyN movie](#)

SyGN - templates and averages in deformation space



from [miykael](#)

geodesic image averages

optimal templates 2

canine template

chimpanzees

Can we improve segmentation in “challenging” populations?

Segmentation Framework

1. Bias correction (with optional priors)
2. Prior-based tissue segmentation
3. Prior-based anatomical labeling
4. Iteration through above steps (optional)

We tried N3 and FSL-FAST for these problems ... and *dislike* Matlab ...

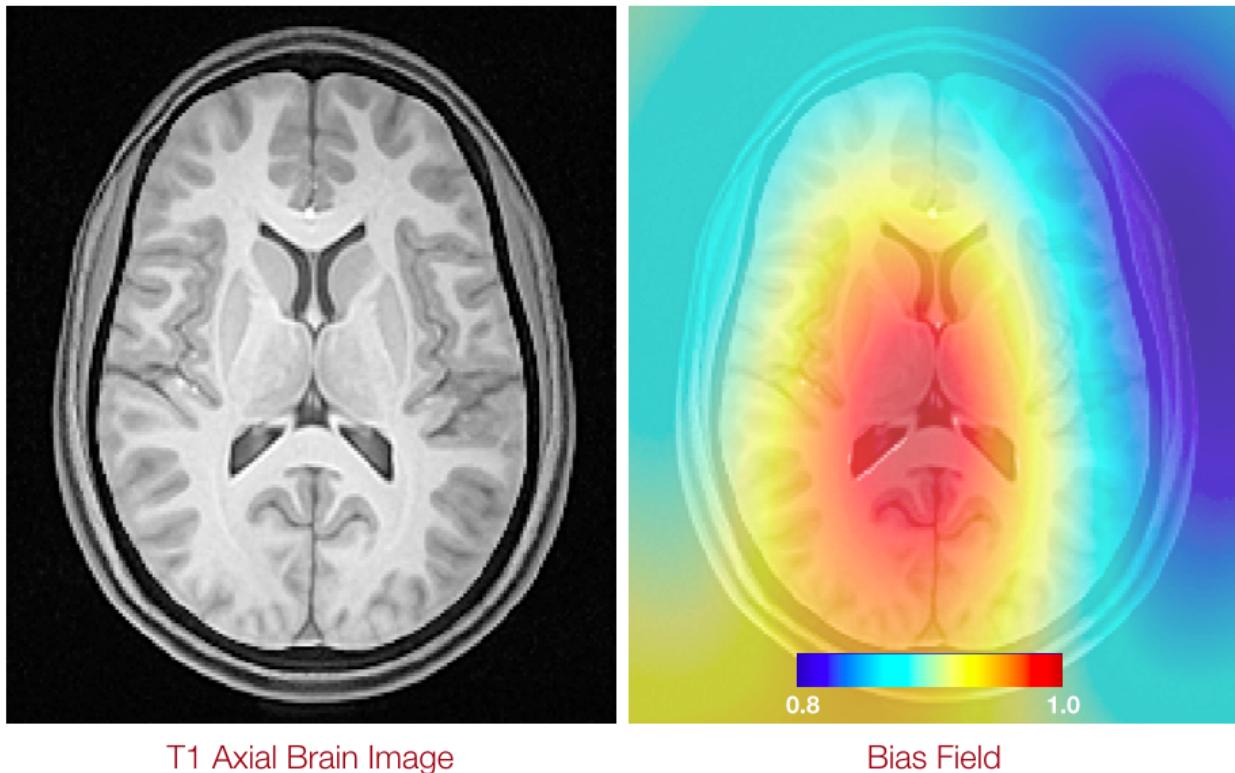
failed to locate well-implemented open-source resources for general purpose prior-based segmentation and inhomogeneity correction ...

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 BA suggested we try to implement N3 in ITK.
- NT had some experience with B-splines and added some other tweaks giving birth to N4.

N4 Introduction



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: Bayesian N -class multivariate segmentation

- Similar to our experience with N3, we tried to incorporate FAST (from the FMRIB at Oxford) into an ANTs processing pipeline.
- We failed to successfully incorporate priors into FAST.
- Related, BA went to a segmentation-related worksop at MICCAI and aired 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

Atropos components

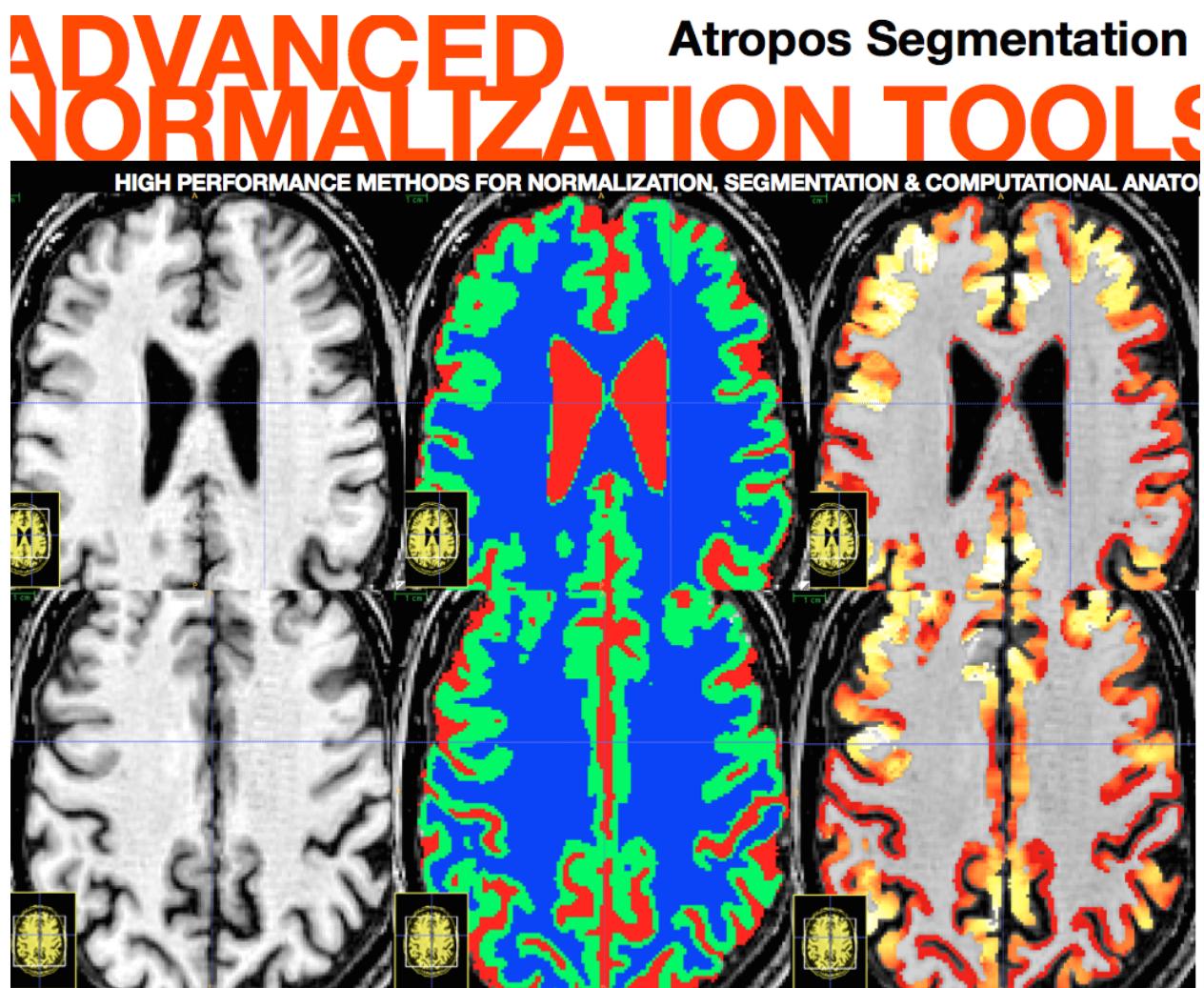
Can we accurately measure cortical thickness by DiReCTly using the image space?

KellySlater → KellyKapowski



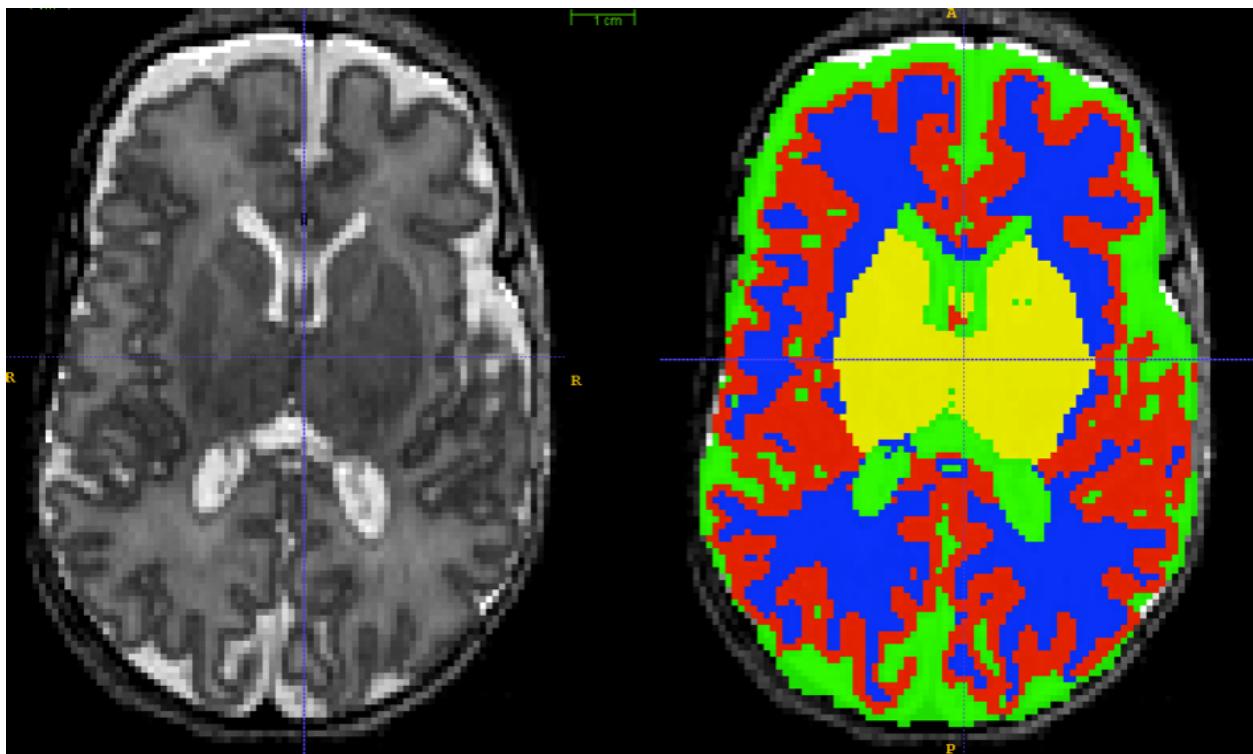
Several years of development by SR Das, BA, NT (KK fan)

Atropos + KK Example



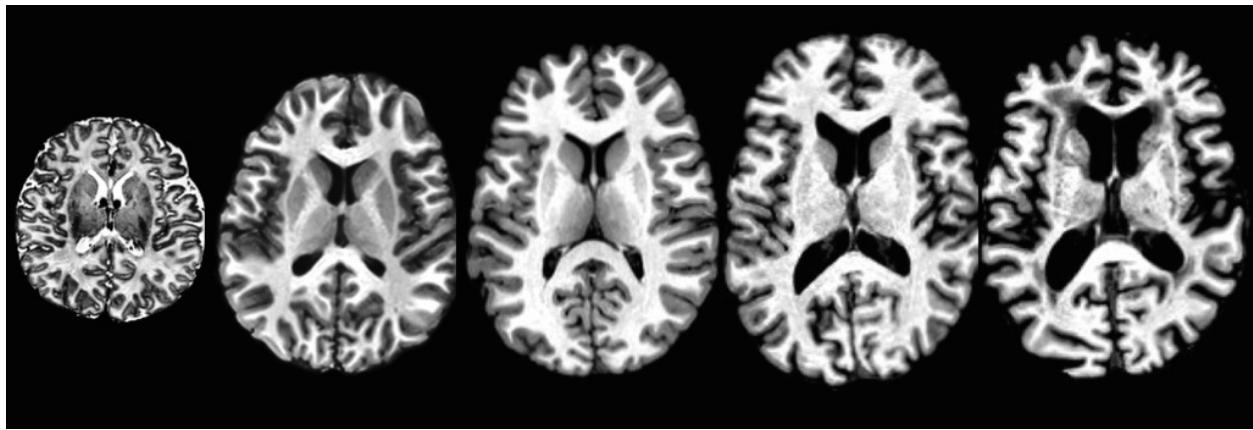
FTD

Babies



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

“Big data” problem from public resources



TOT, NKI, IXI, Oasis, ADNI . . . several thousand images

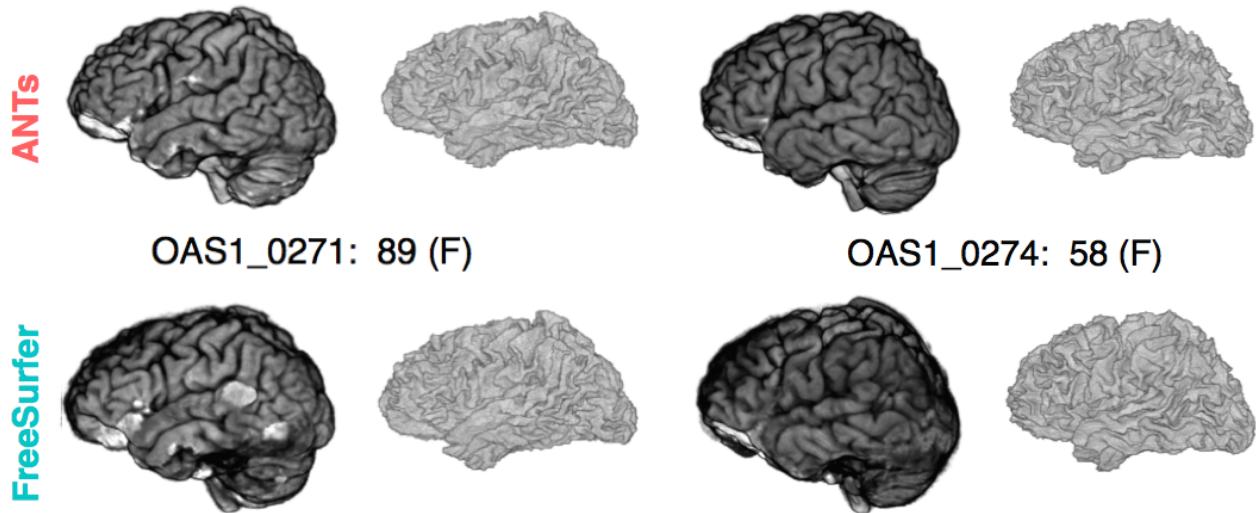
The Glove: Comparison with Freesurfer

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

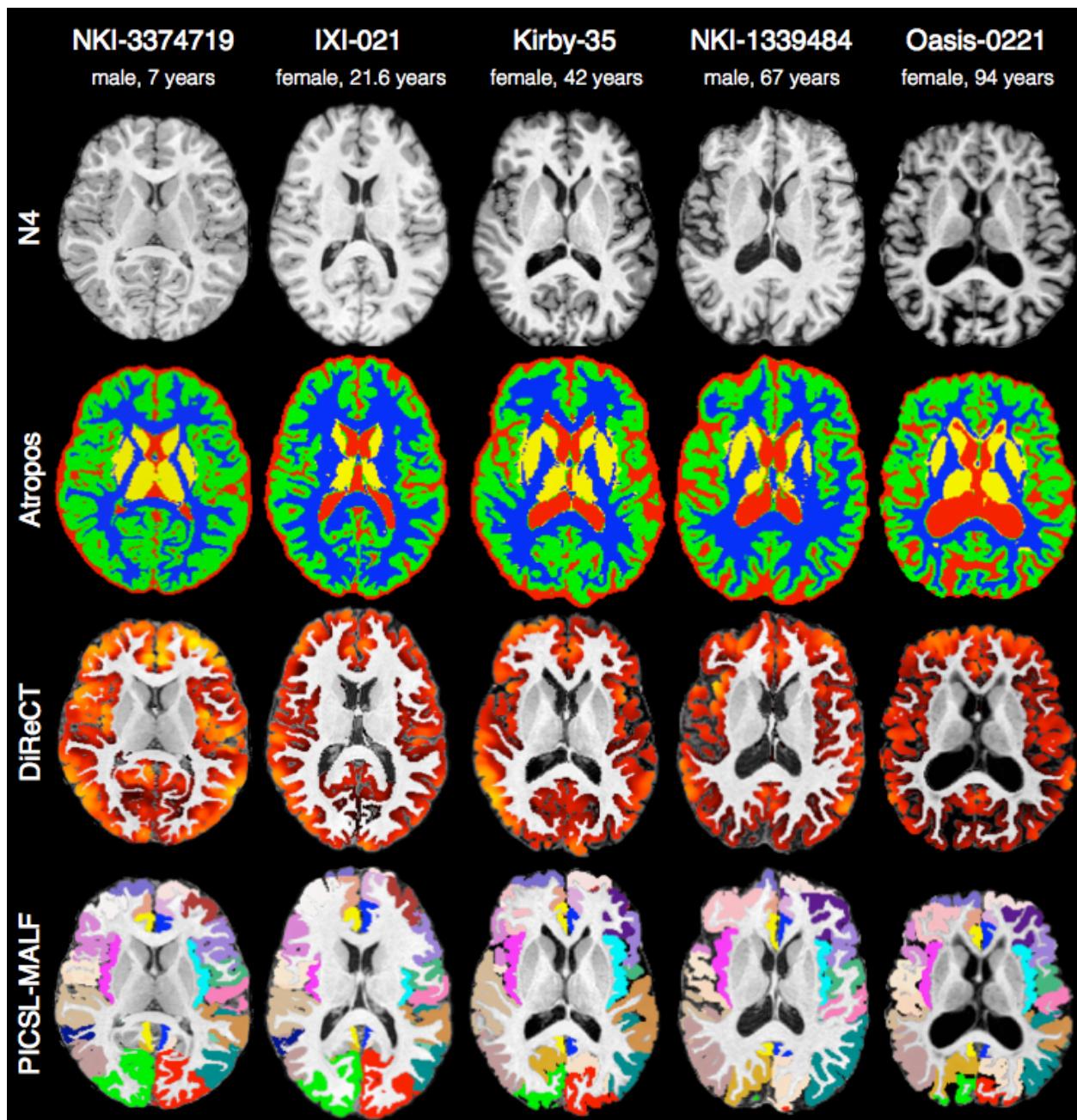
Answer: Use prediction of demographics from quantitative cortical thickness data as a reference for the power of our methods. One of the most well-known, most easily obtained, and most confident measures available is “age.” So we take 50% of the thickness data to train a model (e.g. linear regression) 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.

ANTs vs Freesurfer

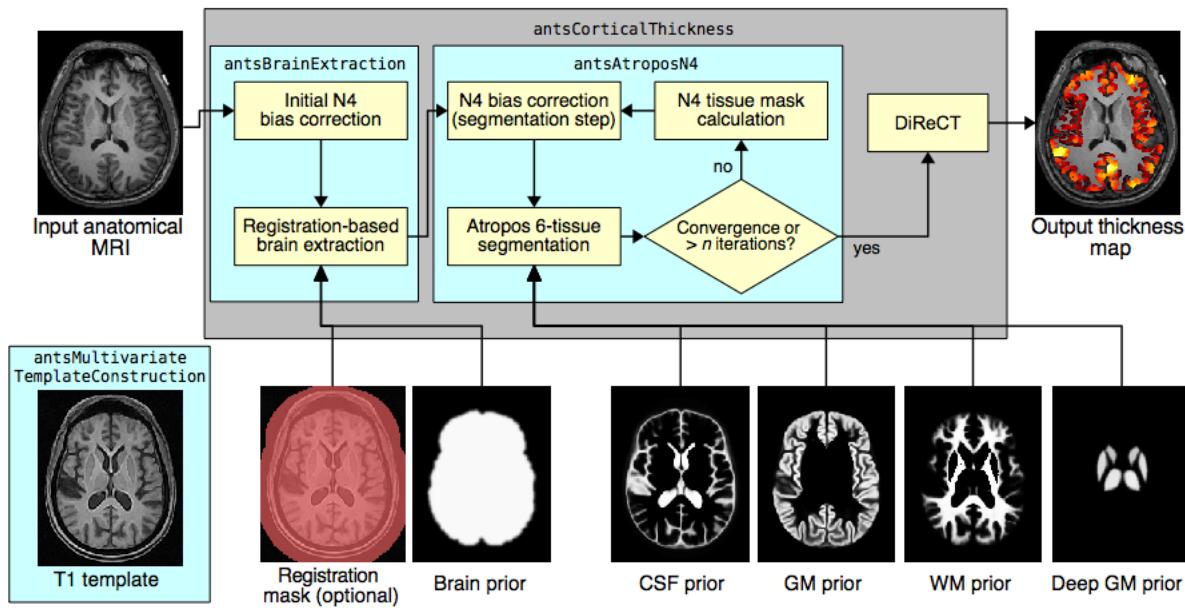
ANTs vs Freesurfer 2



ANTs MALF Labeling



The ANTs structural brain mapping 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

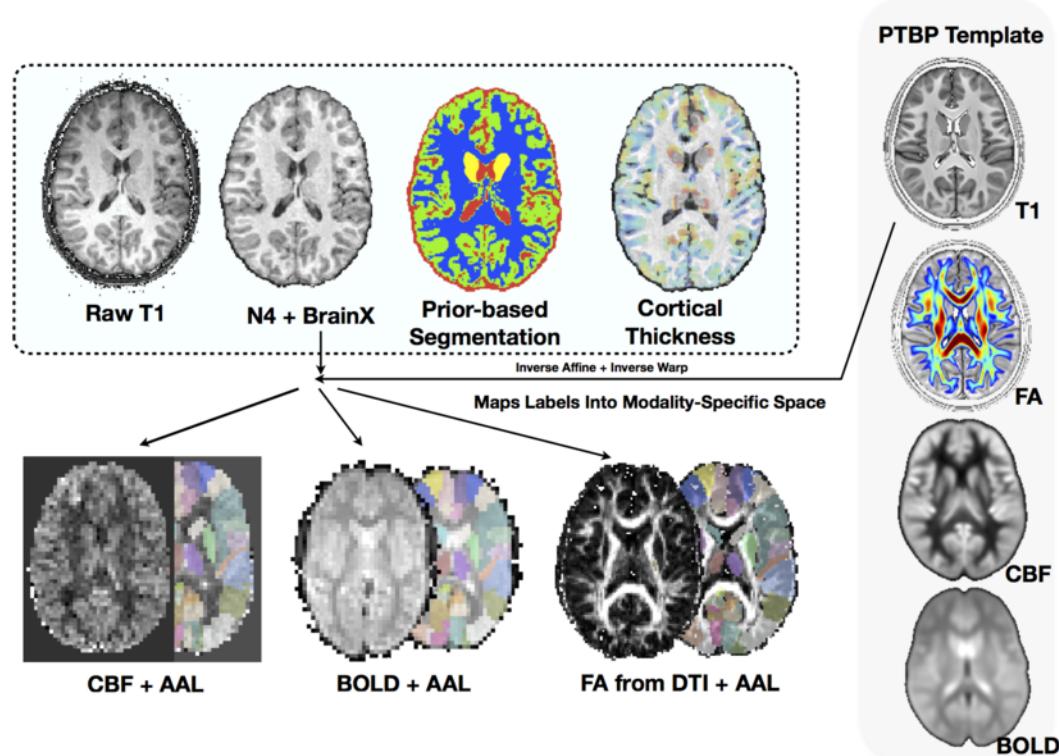
Randomly selected healthy individuals. Atropos gets good performance across ages.

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.

Can we implement and release, with provenance, a multiple modality MRI map of adolescent brain development from public MRI data?

Scientific Data 2014



Can we customize these methods for a challenging multivariate segmentation problem with clinical relevance?

BRATS 2013

Can we address subtle questions in brain and cognition via imaging-specific dimensionality reduction?

Eigenanatomy & SCCAN

Discussion

Problems

- Customizable for specific problems but not too specific
- Rapid development: still need familiarity with compilation for latest ANTs
- Latest theoretical advances in registration not yet wrapped for users
- Need more [Documentation & testing](#) ...

Solid Core Permits Broad Applications

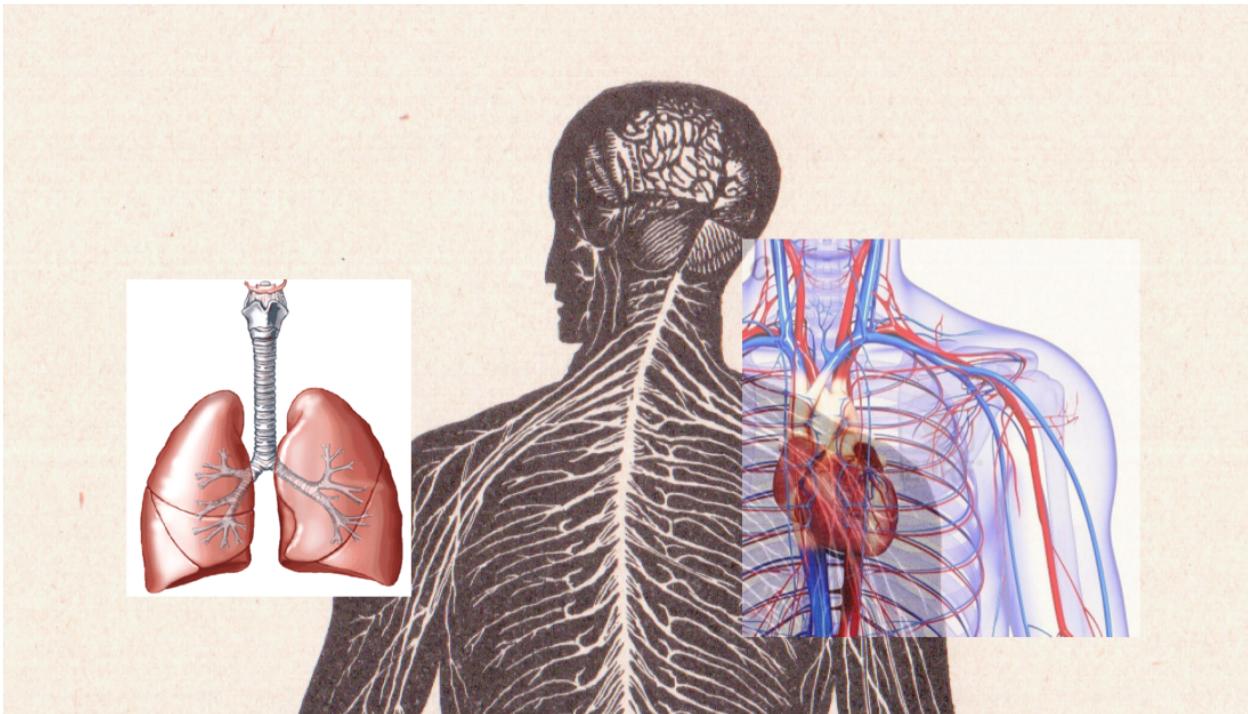
- microscopy
- satellite imagery
- interactive registration (see *Slicer*) and segmentation (see *ITK-SNAP*)

Community response

- Just wanted to let you know—ANTS worked for me! I seem to be getting interesting results along the line_s of what I was predicting my study would find in specific parts of the striatum. *—Patryk from Ireland*
- To put not to fine a point on it—ANTS rocks. *—Craig from California*
- The ANTS package is very, very cool! *—Jaime from Wisconsin*
- Thank you for sharing this work, and congratulations for a job well done. *—Alexandra from North Carolina*

Strengths

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



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

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: (hippocampussubfield.com)
- TBA: BOLD decoding (ANTsR)
- Substantial work with DTI (Camino developer in house)
- STACOM2014 ?



Data inspection w/ *ANTsR*

spider plots

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 recently).
- 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.

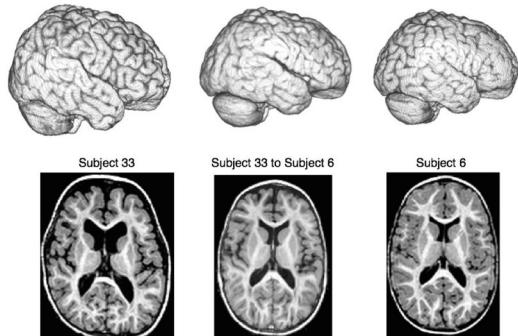
“Talk is cheap, show me the code.” —Linus Torvald

Software engineering

[ants source](#)

Library for multivariate image registration, segmentation & statistics

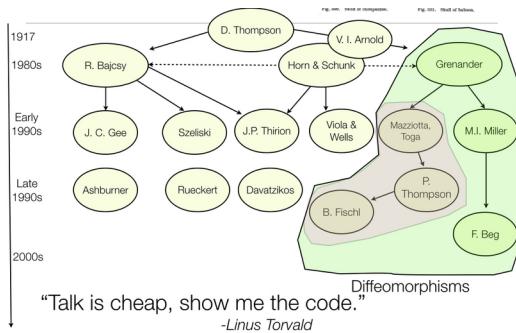
Theory + evaluation + reproducibility



Founding Developers



A long history of research



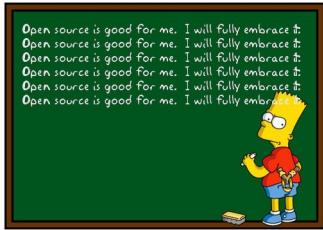
Rigorous transformation definition is key

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



open source

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

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

Analysis philosophy and published opinions

What is and *is not* image registration

not registration

Voodoo in voxel-based analysis

logical circularity VBA

Instrumentation bias in the use and evaluation of software

Instrumentation bias in the use and evaluation of software

References

Avants, Brian B., and Nicholas J. Tustison. 2014. “The ITK Image Registration Framework.” *Front Neuroinform* 7. Penn Image Computing; Science Laboratory, Department of Radiology, University of Pennsylvania Philadelphia, PA, USA.: 39. doi:[10.3389/fninf.2013.00039](https://doi.org/10.3389/fninf.2013.00039).

Avants, Brian B., Nicholas J. Tustison, Michael Stauffer, Gang Song, Baohua Wu, and James C. Gee. 2014. “The Insight ToolKit Image Registration Framework.” *Front Neuroinform* 8. Penn Image Computing;

Science Laboratory, Department of Radiology, University of Pennsylvania Philadelphia, PA, USA.: 44. doi:[10.3389/fninf.2014.00044](https://doi.org/10.3389/fninf.2014.00044).

Klein, Arno, Jesper Andersson, Babak A Ardekani, John Ashburner, Brian Avants, Ming-Chang Chiang, Gary E Christensen, et al. 2009. “Evaluation of 14 Nonlinear Deformation Algorithms Applied to Human Brain MRI Registration.” *Neuroimage* 46 (3). New York State Psychiatric Institute, Columbia University, NY, NY 10032, USA. arno@binarybottle.com: 786–802. doi:[10.1016/j.neuroimage.2008.12.037](https://doi.org/10.1016/j.neuroimage.2008.12.037).

Tustison, Nicholas J., and Brian B. Avants. 2013. “Explicit B-Spline Regularization in Diffeomorphic Image Registration.” *Front Neuroinform* 7. Penn Image Computing; Science Laboratory, Department of Radiology, University of Pennsylvania Philadelphia, PA, USA.: 39. doi:[10.3389/fninf.2013.00039](https://doi.org/10.3389/fninf.2013.00039).

Tustison, Nicholas J., Brian B. Avants, Philip A. Cook, Yuanjie Zheng, Alexander Egan, Paul A. Yushkevich, and James C. Gee. 2010. “N4ITK: Improved N3 Bias Correction.” *IEEE Trans Med Imaging* 29 (6). Department of Radiology, University of Pennsylvania, Philadelphia, PA 19140, USA. ntustison@wustl.edu: 1310–20. doi:[10.1109/TMI.2010.2046908](https://doi.org/10.1109/TMI.2010.2046908).

Tustison, Nicholas J., Philip A. Cook, Arno Klein, Gang Song, Sandhitsu R. Das, Jeffrey T. Duda, Benjamin M. Kandel, et al. 2014. “Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements.” *Neuroimage* 99 (Oct). Penn Image Computing; Science Laboratory, University of Pennsylvania, Philadelphia, PA, USA.: 166–79. doi:[10.1016/j.neuroimage.2014.05.044](https://doi.org/10.1016/j.neuroimage.2014.05.044).