Brain mapping tools for neuroscience research

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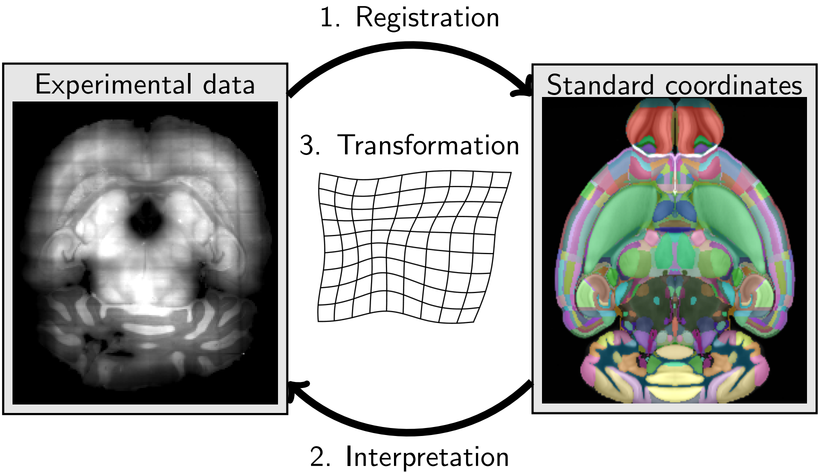
Workshop Outline

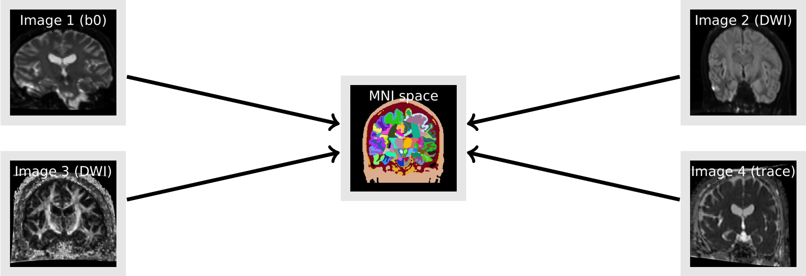
1. Focused look at registration algorithms
2. Running code on real data
3. Discussion of issues affecting the community

The goal of brain mapping



1. Registration

Align images into a standard coordinate system



- Enrich information by fusing modalities
- Analyze different specimens statistically
- Build databases of information indexed to spatial coordinates

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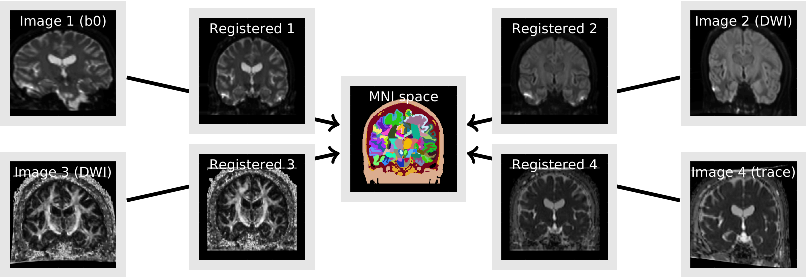

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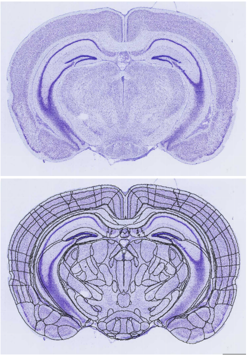
- Analyze different specimens statistically
- Build databases of information indexed to spatial coordinates

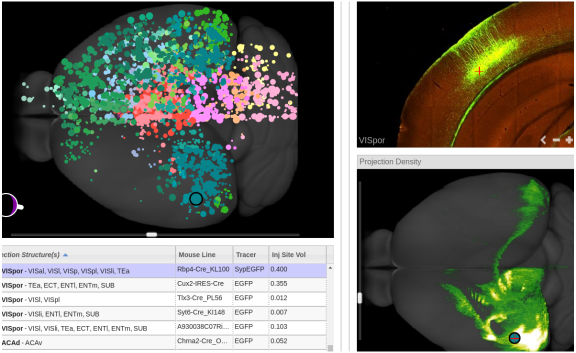
2. Interpretation

Leverage information stored in atlas coordinates.[1]

MBA



ARA

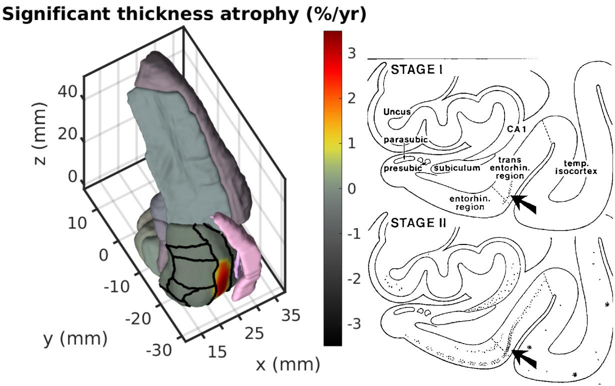


- Label images with standard ontologies
- Index to gene expression, cell types, tractography, etc.

[1] MBA: Mouse brain architecture brainarchitecture.org, ARA: Allen reference atlas connectivity.brain-map.org/

3. Transformation

Studying transformations quantifies growth or atrophy



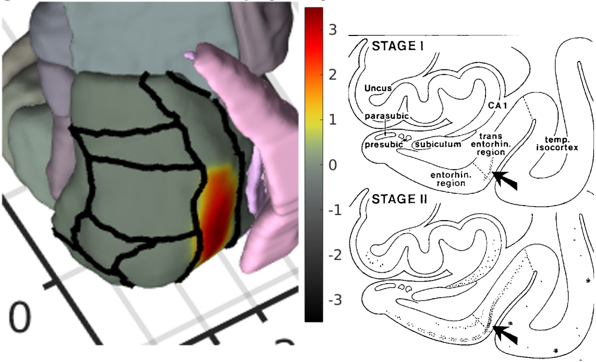
- Here thickness change in transentorhinal region measured from longitudinal MRI[2]
- Previously only observed at autopsy

[2] Tward, Daniel J., et al. "Entorhinal and transentorhinal atrophy in mild cognitive impairment using longitudinal diffeomorphometry." Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 9 (2017): 41-50.

3. Transformation

Studying transformations quantifies growth or atrophy

Significant thickness atrophy (%/yr)



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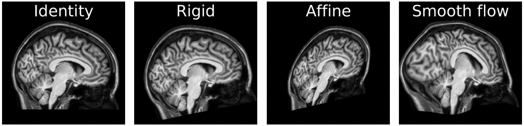
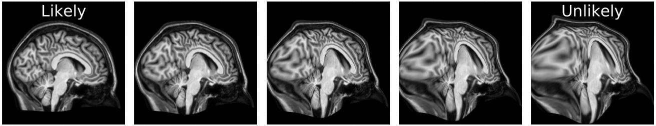
The ingredients of a brain mapping tool

Mappings are calculated from optimization problem with 3 parts.

Transformation model: What types of mappings do we consider?



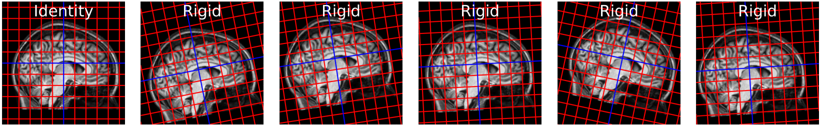
Regularization: How likely is a given transformation?



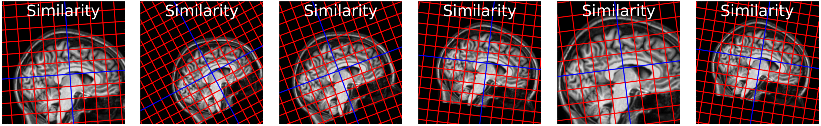
Similarity: How good is an alignment?

Transformation models: Matrix groups

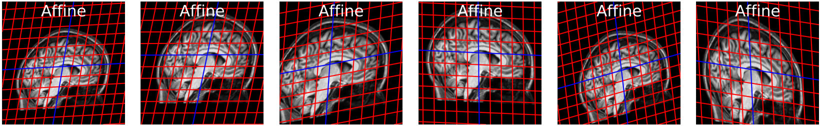
Euclidean (6 degrees of freedom): Encodes position and pose



Similarity (7 DOF): Include scale, more flexible, no shape change



Affine (12 parameters): Include shear and nonuniform scale

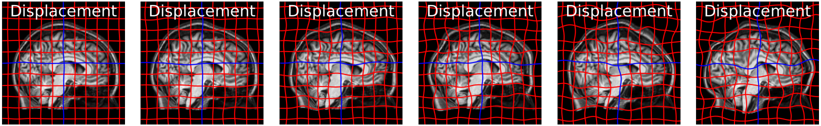


Pros: Simple to compute, easy to enforce invertibility, good for within-subject, often used in conjunction with deformations

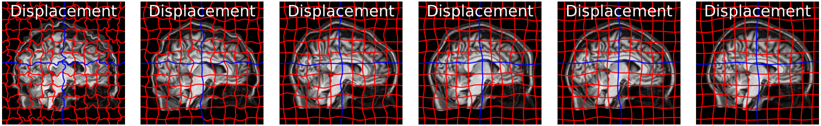
Cons: Cannot model distortions or realistic biological variability

Transformation models: Displacement fields

Can vary in magnitude

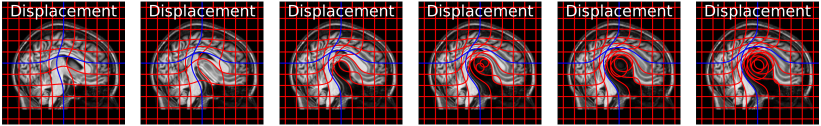


or in smoothness



Pros: Can model a wide range of biological variability.

Cons: Large transforms fail to be invertible no matter how smooth



Transformation models: Flow fields

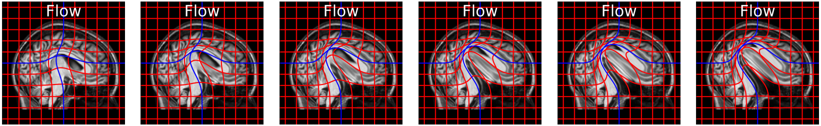
Composition of invertible transforms is invertible.
We use this to move from displacement to velocity.
If $\Delta t v_i$ is a small displacement field, then the composition

$$\varphi_n = (id + \Delta t v_n) \circ \cdots \circ (id + \Delta t v_2) \circ (id + \Delta t v_1)$$

becomes a flow

$$\frac{1}{\Delta t}(\varphi_{n+1} - \varphi_n) = v_n(\varphi_n) \to \frac{d}{dt}\varphi_t = v_t(\varphi_t)$$

which gives Euler's equation in the limit.



These diffeomorphisms form the basis of Computational Anatomy, as well as state of the art image registration algorithms.

Pros: Geometric and statistical advantages (discussed below).

Cons: Computational complexity.

Regularization

High dimensional transformations are not unique, regularization allows us to choose most favorable.

Early approaches used (e.g.) elastic energy. For φ a transform:

$$\int \frac{1}{2} |D(\varphi - id)(x)|_F^2 dx$$

Computational Anatomy[3] uses kinetic energy Lagrangian:

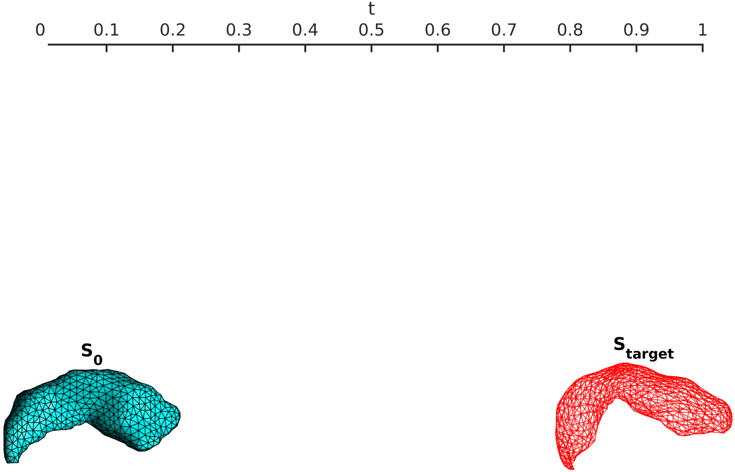
$$\int_0^1 \frac{1}{2} \int |Lv_t(x)|^2 dx dt$$

where L is an inertial (differential) operator.

Choosing L with sufficient derivatives guarantees diffeomorphisms.

[3] Beg, M. Faisal, et al. "Computing large deformation metric mappings via geodesic flows of diffeomorphisms." International journal of computer vision 61.2 (2005): 139-157.

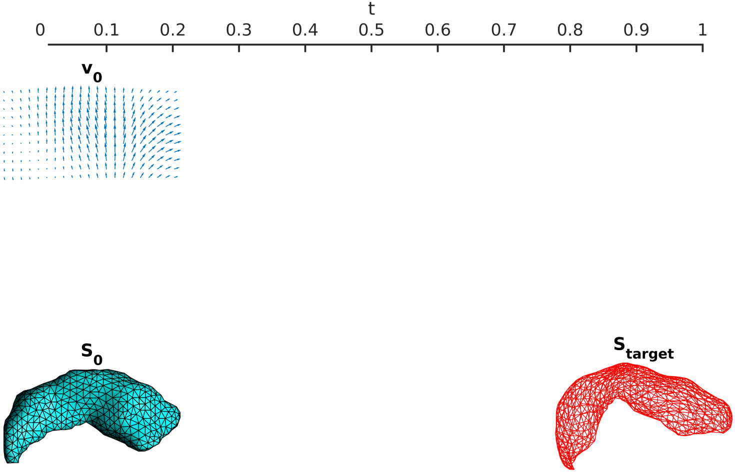
Regularization



Puts shapes and diffeomorphisms in a Reimannian metric space.

Allows statistical concepts such as averages or regression.

Regularization



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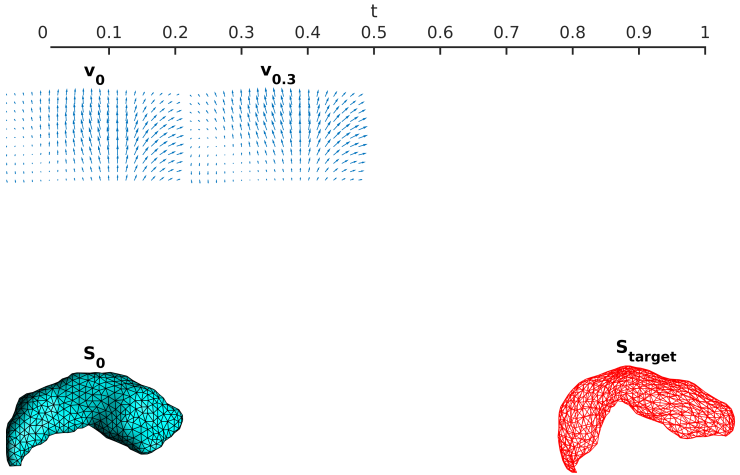

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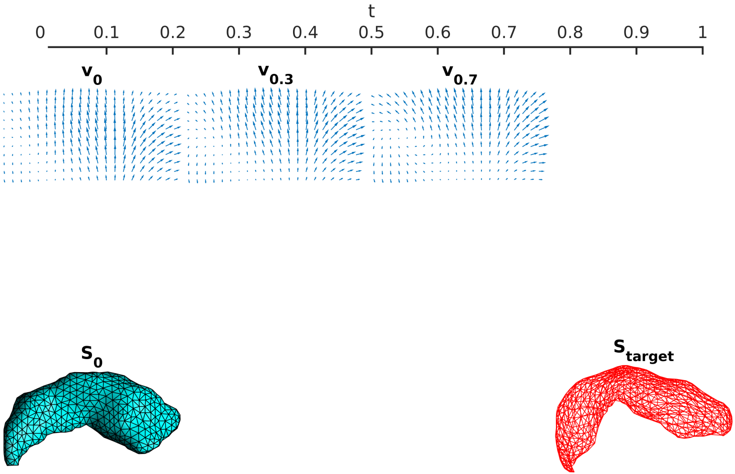

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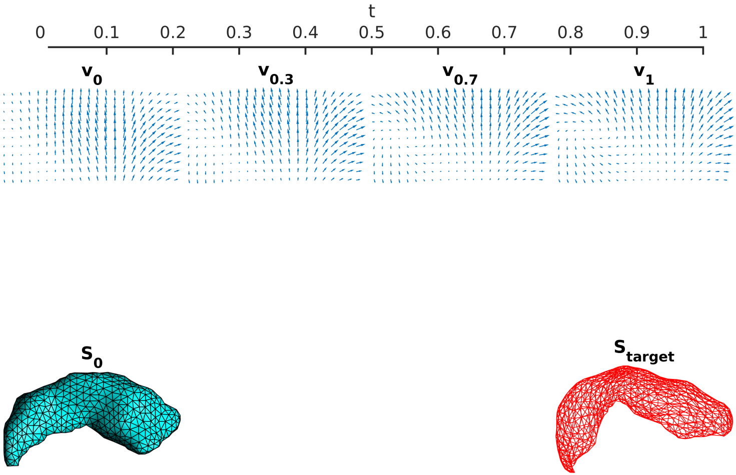

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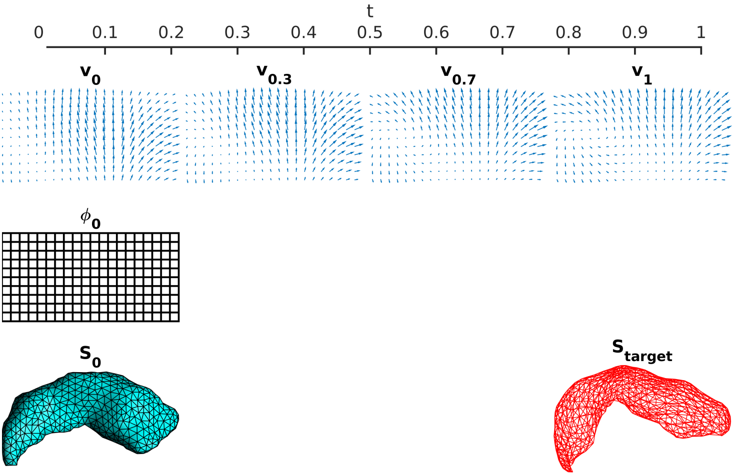

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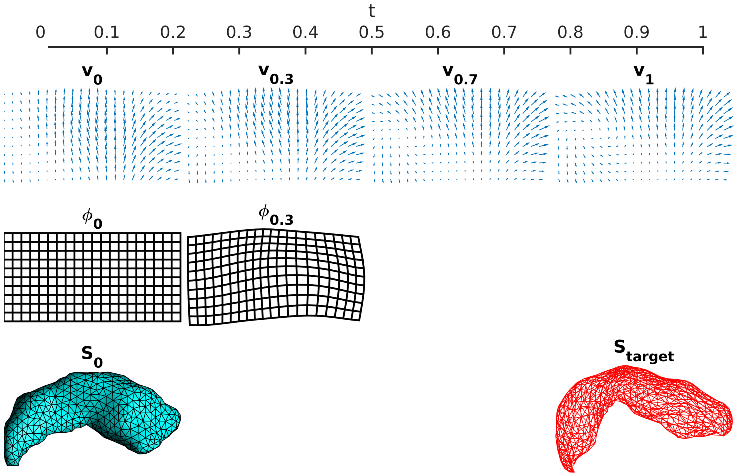

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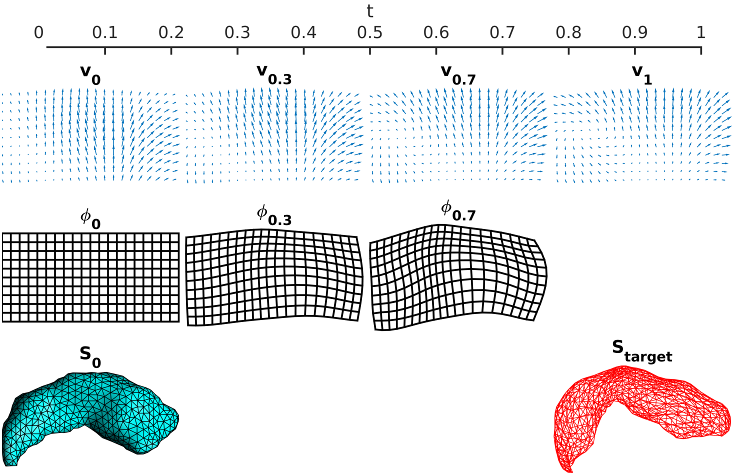

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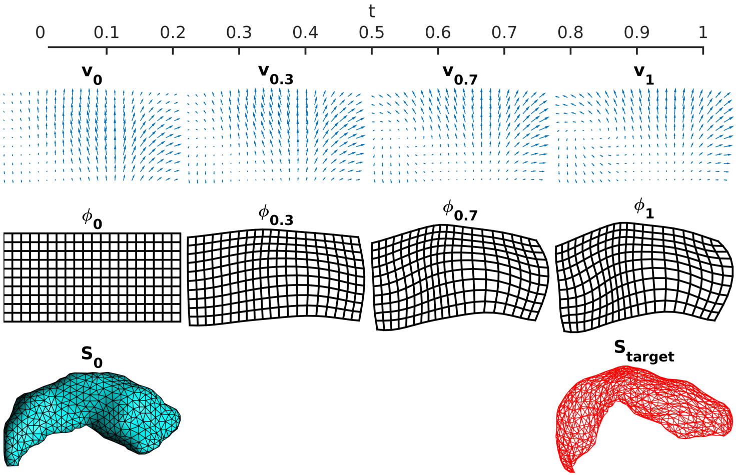

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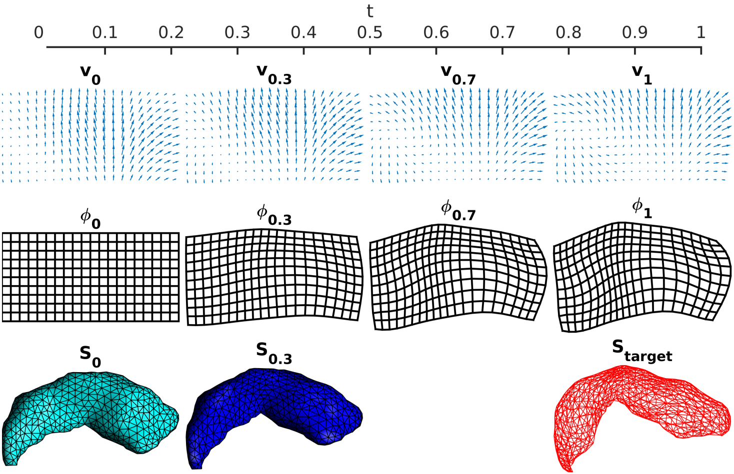

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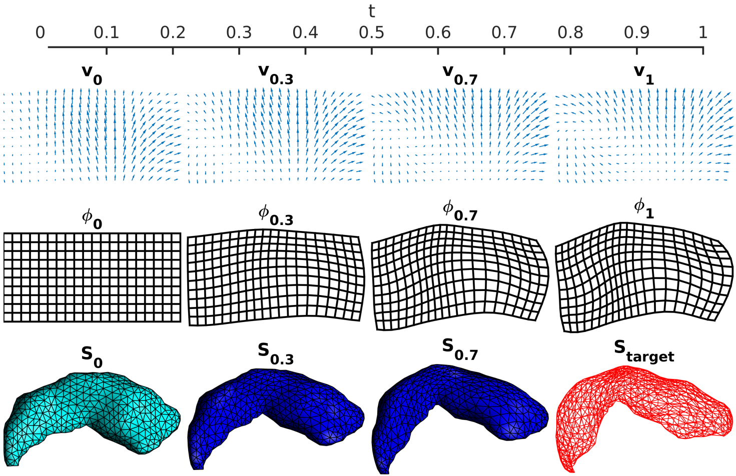

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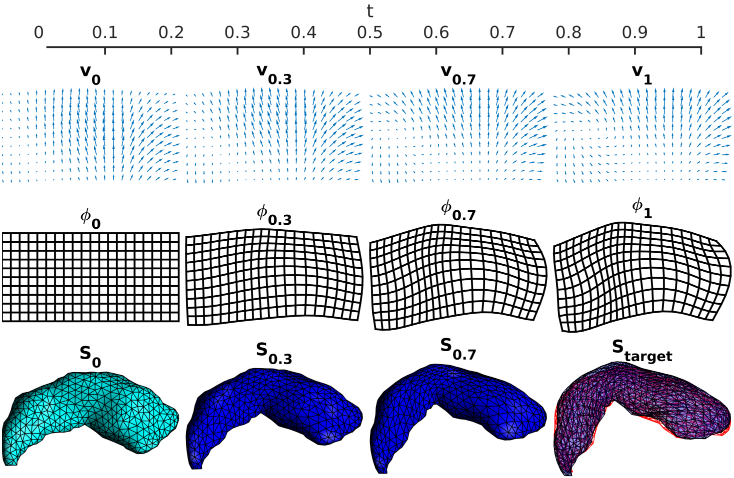

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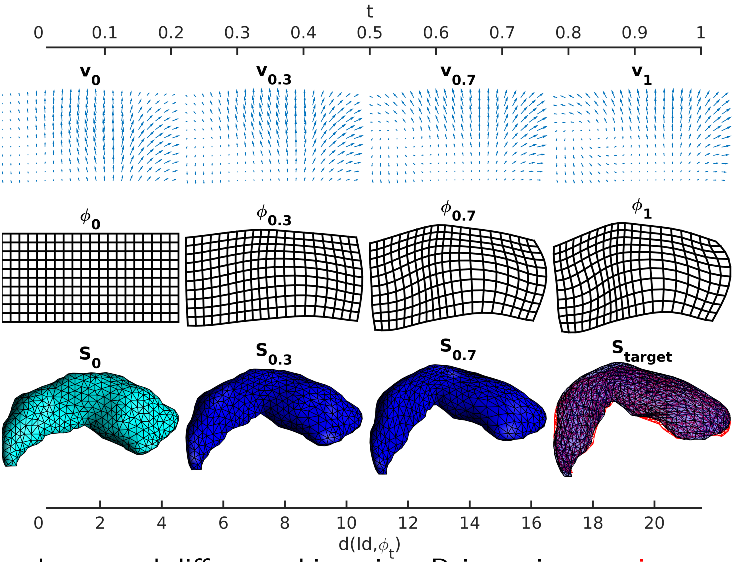

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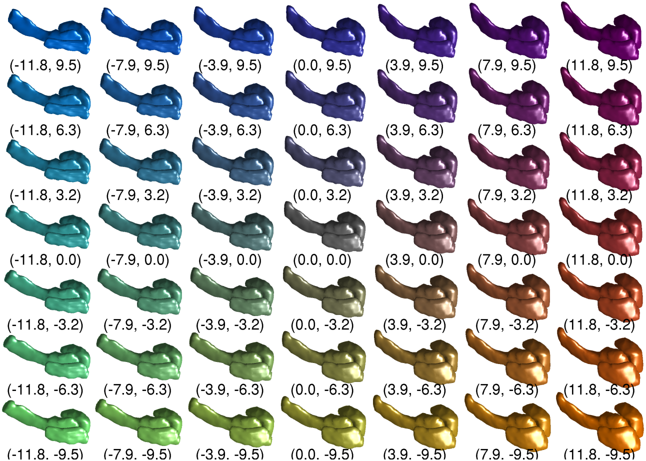
Regularization

Energy minimizing flows admit sparse solutions, key for overcoming bias variance tradeoff in high dimensions

Regularization based on low dimensional priors for MAP estimates[4]



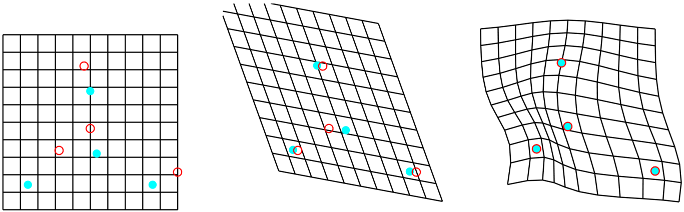
[4] Tward, Daniel, et al. "Parametric surface diffeomorphometry for low dimensional embeddings of dense segmentations and imagery." IEEE transactions on pattern analysis and machine intelligence (2016).

Similarity: Feature point based

Matching corresponding pairs of fiducial landmark points, X to Y, via sum of square error admits closed form solutions:

$$\left.\begin{aligned}\varphi(x) &= Ax \\ A &= \mathrm{Cov}(X,X)^{-1}\mathrm{Cov}(X,Y)\end{aligned}\right\} \quad \text{(affine)}$$

$$\left.\begin{aligned}\varphi(x) &= x + \textstyle\sum_i K(x,X_i)P_i \\ P &= K(X,X)^{-1}(Y-X)\end{aligned}\right\} \quad \text{(spline displacement)}$$



Unlabeled points curves and surfaces via currents or varifolds.

Points require manual selection, only ensures accuracy nearby.

Similarity: Image based

Common cost functions for comparing atlas $I(\varphi^{-1})$ to target J:

Voxel based (intra modality), e.g. sum of square error

$$\int \frac{1}{2}|I(\varphi^{-1}(x)) - J(x)|^2 dx$$

conditional likelihood of J given φ in a Gaussian white noise model. Other robust similarities can be used such as L1 or Huber.

Neighborhood based (inter modality), e.g. MIND[5] or other local structure, local cross correlation.

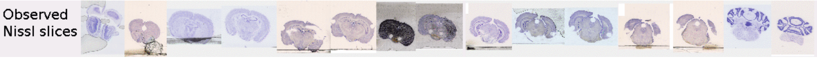
Histogram based (inter modality), e.g. mutual information.

[5] Heinrich, Mattias P., et al. "MIND: Modality independent neighbourhood descriptor for multi-modal deformable registration." Medical image analysis 16.7 (2012): 1423-1435.

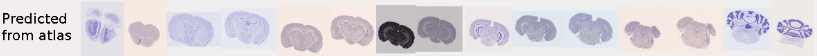
Challenges and solutions

Most brain mapping techniques were developed for medical imaging, but neuroscience data faces unique challenges:

- Incomplete or sliced data
- Artifacts or damaged tissue
- Multiple different modalities or appearance



We use machine learning to predict one image from another, while jointly performing registration and artifact detection[6]



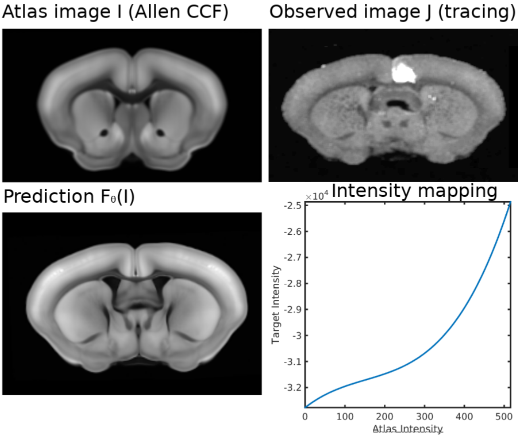
[6] Tward, Daniel Jacob, et al. "Diffeomorphic registration with intensity transformation and missing data: Application to 3D digital pathology of Alzheimer's disease." BioRxiv (2019): 494005.

Intensity mapping: Grayscale to grayscale

Expand optimization problem to include an intensity transform F_θ

$$\int \frac{1}{2}|F_\theta[I(\varphi^{-1}(x))] - J(x)|^2 dx$$

and optimize jointly over φ and θ.



Calibration curve: reduce contrast at low intensity, increase at high.

Intensity mapping: Grayscale to RGB

Expand optimization problem to include an intensity transform F_θ

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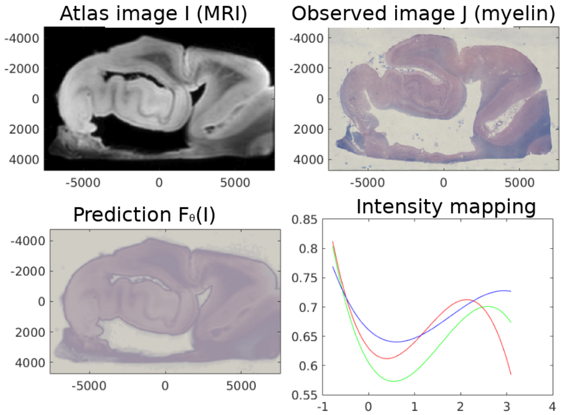

Nonmonotonic: swaps order of “grey”, “white”, “background”.

Intensity mapping: RGB to RGB

Expand optimization problem to include an intensity transform F_θ

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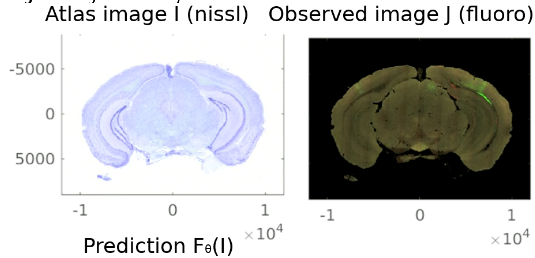
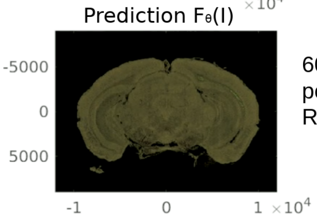




60 parameter cubic polynomial map from R^3 to R^3

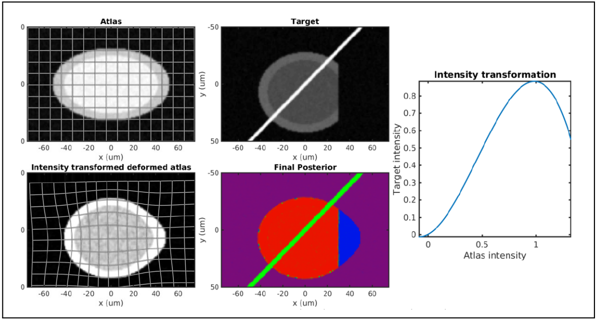
Mix powers of RGB, fairly high dimensional, flexible transforms.

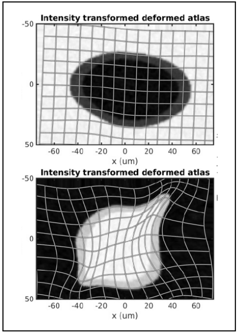
Artifacts

Allows multimodality registration with simple Gaussian likelihood.
Handle artifacts with Expectation Maximization algorithm

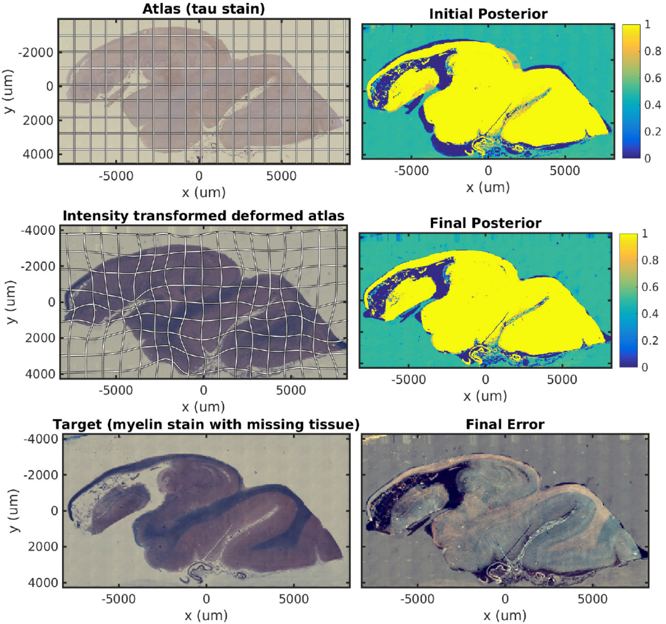
$$\int \frac{1}{2}|F_\theta[I(\varphi^{-1}(x))] - J(x)|^2 W(x) dx$$

E step: Compute W as posterior probability for fixed θ, φ.
M step: Compute optimal θ, φ for fixed W.

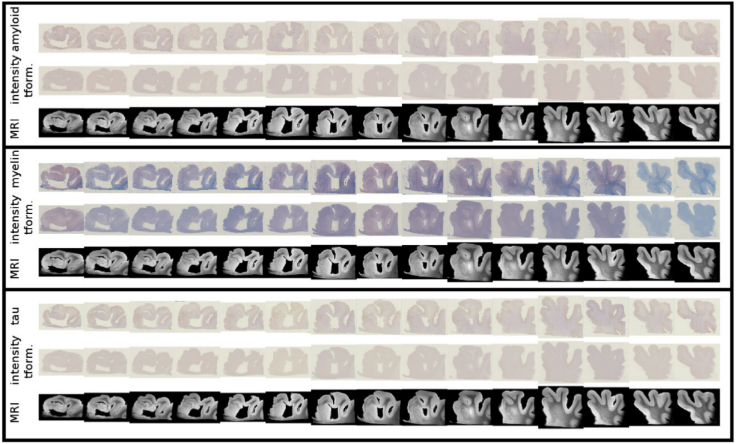




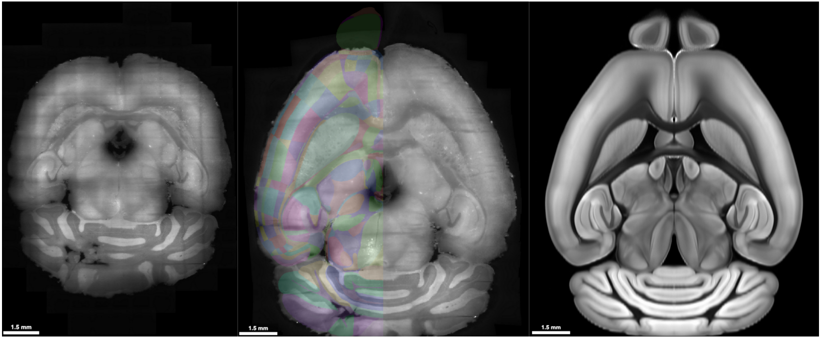
Multimodality and damaged tissue in digital pathology



Multimodal 2D histology slices to 3D atlas



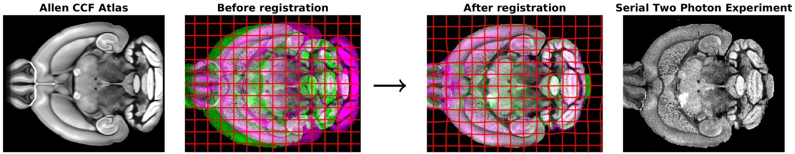
CLARITY cleared mouse brain registered to Allen Atlas



ARDENT[7]: NeuroData's open source brain mapping tool

Publications and code available online from `neurodata.io/reg`

Ingredient	Choice	Benefit
Transform	Diffeomorphism	Smooth invertible fluid transform
Similarity	Log likelihood	Enables statistical approaches to artifacts and multi-modality
Regularization	Kinetic energy	Enables sparse representations effective in high dimensional bias variance tradeoff[5,6]



[7]Affine and Regularized Diffeomorphic Numeric Transform. [8]Tward, Daniel, et al. "Parametric surface diffeomorphometry for low dimensional embeddings of dense segmentations and imagery. IEEE transactions on pattern analysis and machine intelligence (2016) [9]Tward, Daniel, et al. "Estimating diffeomorphic mappings between templates and noisy data: Variance bounds on the estimated canonical volume form. Quarterly of Applied Mathematics (2019).

Computation

Computational burden[7] includes interpolation:

- integrating flows
- deforming images

and Fast Fourier Transforms:

- applying differential operators
- inverting differential operators

both are very efficiently parallelized.

We use pytorch (`pytorch.org`) as interface to GPU computing.

Registration algorithm is about 200 lines of code.

Optimization with gradient descent.

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[7] Tward, Daniel J., et al. "Performance of Image Matching in the Computational Anatomy Gateway: CPU and GPU Implementations in OpenCL." Proceedings of the Practice and Experience in Advanced Research Computing 2017 on Sustainability, Success and Impact. ACM, 2017.

Acknowledgements

People

- Michael Miller (JHU)
- Joshua Vogelstein (JHU)
- Susumu Mori (JHU)
- Juan Troncoso (JHU)
- Marilyn Albert (JHU)
- Partha Mitra (CSHL)
- Brian Lee (JHU)
- Vikram Chandrashekhar (JHU)
- Devin Crowley (JHU)

Funding

NIH: P41EB015909, R01NS086888, R01EB020062, R01NS102670, U19AG033655, R01MH105660, P50AG05146

NSF: 16-569 NeuroNex contract 1707298, ACI1548562 (Extreme Science and Engineering Discovery Environment)

Kavli Neuroscience Discovery Institute, BrightFocus Foundation, Dana Foundation