Convolutional neural networks for fast and accurate 3D reconstruction of histological sections

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Introduction

While *in vivo* imaging offers an excellent view of the intact brain's 'macro' structure, it lacks the resolution and intensity markers required to accurately identify details of interest to many neuroscientists (e.g., certain subregions of the brain or identification of some types of pathology). Histological sectioning offers excellent in-plane resolution and the ability to identify chemical and cytoarchitectural markers, but does not maintain the structure of the intact brain. In recent years, interest in reconstructing histological sections and placing them into their original 3D geometry has grown. Histological reconstruction offers the ability to provide a 'ground-truth' in order to accurately identify subregions or other loci of interest in *in vivo* images and thus is of considerable interest to clinicians and researchers. A significant remaining challenge is to find reconstruction methods that are automated, efficient, and accurate. Here we develop a new automated approach for reconstructing histological sections using *in vivo* MRI. Our approach leverages recent advancements in artificial neural networks to construct an intensity-based reconstruction scheme that uses convolutional 'spatial transformer networks' (STNs) to perform image registration.

Spatial Transformer Networks (STNs)

The Spatial Transformer Network (STN) was introduced by Jaderberg et al. (2015) as a fully differentiable ANN module capable of affine and non-rigid deformations. Here, we use this module to construct two convolutional neural networks (CNNs) that perform 'rigid' and 'Thin-plate Spline' (TPS) registration. Each network utilizes two convolutional layers of rectified linear unit (ReLUs) followed by one fully-connected ReLU layer, and a fully-connected linear output layer. These networks estimate parameters for the rigid and TPS STN modules which resample the moving image accordingly. The networks can then be trained using stochastic gradient descent on the output parameters (supervised) or an error function based on similarity or squared error between the fixed and resampled moving image (unsupervised). Our initial observations suggest that networks are most efficiently trained using supervised followed by unsupervised learning for the rigid network and fully-unsupervised learning for the TPS network. The TPS network is easily regularized by including common regularizer terms in the error function (e.g., curl, divergence, determinant of Jacobian).

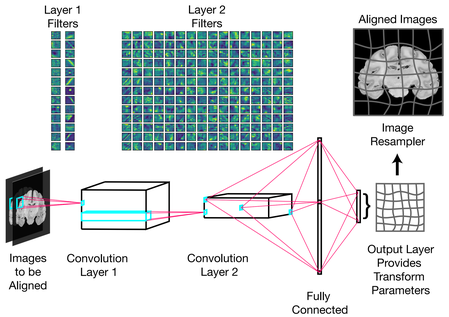
Materials

256x256x80 coronal T1-weighted radio frequency spoiled gradient recalled echo sequence (3D SPGR) whole brain images were collected *in vivo* at 0.625mm x 0.625mm x 1.0mm. *Ex vivo* brain tissue was coronally sectioned at 30 µm on a sliding microtome. Sections were collected in four series, one of which was Nissl-stained for the entire extent of the brain. Nissl-stained slides through the hippocampal region were scanned using an Olympus VS 110 Virtual Slide Microscope system. Scans were performed with an Olympus PlanSApo 10X/0.40 lens and an Olympus XC10 camera. Nissl-stained sections were scanned at a resolution of 644.16 by 644.16 nm and .24 mm between sections but down-sampled to 0.244mm x 0.244mm x 0.24mm for processing. Tissue was segmented from image background using an implementation of fully convolutional networks for semantic segmentation (Long et al., 2015).

All analysis was conducted in Windows 10 on a 6 core intel i7- 5930k @ 4 GHz and an Nvidia Quadro M4000 with 8gb ram with 1664 cuda cores and a memory bandwidth of 192 GB/s.

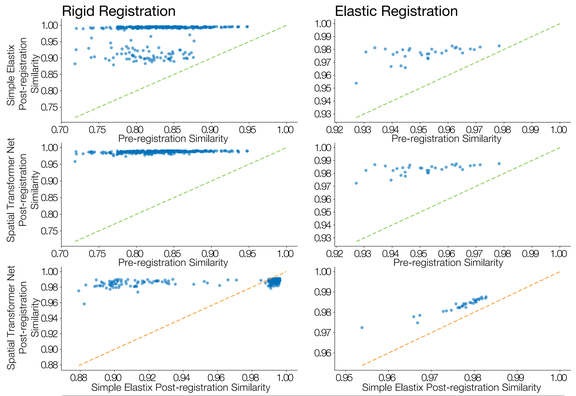
All analysis was conducted in Python version 3.5 and TensorFlow version 1.0.

STN Network Architecture



Spatial transformer network. A series of filters are swept across images that are to be brought into alignment. A second bank of filters is swept across the output of the first. Finally, two fully connected layers convert the activations of the filter layers into parameters that define how the moving image should be resampled. The filters and network weights can be learned without supervision by backpropagating the registration error terms. This network registers images in a single forward pass, avoiding the time-consuming iterations involved in standard image registration algorithms.

Registration Accuracy

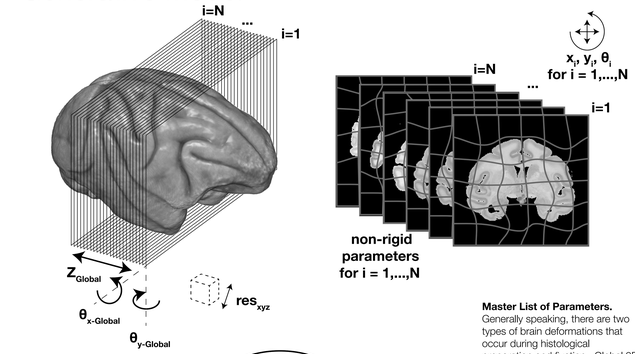


Before vs. after registration comparison. Rise above diagonal indicates iregistration improvement.
Registration method comparison. Diagonal indicates equal performance between methods, above favors STN, below favors SimpleElastix.

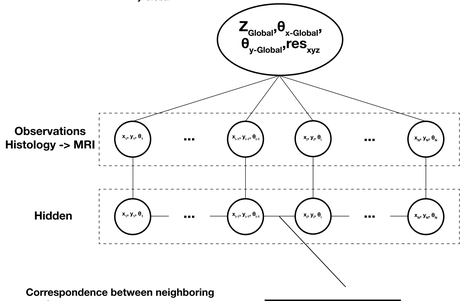
Comparison to SimpleElastix software package for rigid and elastic registration. We compared the compute time and accuracy of the STN versus the SimpleElastix Python library using default parameter maps for rigid and B-spline registration. 320 rigid registrations took **2610 seconds in SimpleElastix** and many images failed to reach convergence within the default 256 iteration limit. Conversely, the **Spatial Transformer Network took 2.3 seconds for a speed improvement of 1100x.** In SimpleElastix 32 B-spline registrations took 3796 seconds. The STN took a total of 0.94 seconds for a **speed improvement of 4000x** and displayed slightly better registration accuracy due to SimpleElastix's default iteration limit being insufficient.

The neural network-based approach registered images 1000+ times faster with little or no sacrifice in accuracy.

Generative Model



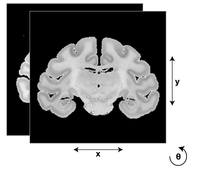
Master List of Parameters. Generally speaking, there are two types of brain deformations that occur during histological preparation and fixation. Global 3D deformation and section-specific 2D deformations. We define 3D parameters: Z_{Global}, $\theta_{x\text{-}Global}$, and $\theta_{y\text{-}Global}$, which account for the position of the block face during sectioning and res_{xyz} which accounts for shrinkage due to cerebrospinal fluid loss and global dehydration. We define section specific 2D parameters: x_i, y_i, θ_i, and non-rigid warp parameters to account for each section's unique placement on a slide and any additional section specific warping during the mounting process.



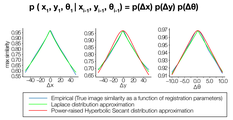
Correspondence between neighboring sections. Our previous attempt of histological reconstruction used *Graph-Theoretic Slide Stacking* which attempted to align each section to a central section via an optimal series of transformations (Kyle et al., 2017). Alternatively, here we estimate the full distributions of similarity values for rigid registrations between neighboring sections, giving distributions across parameters Δx, Δy, and $\Delta\theta$ for each pair of neighbors. Notably, after observing that *Graph-Theoretic Slide Stacking* results in poor fits in the y-direction, we intentionally underfit the Δy distribution using a power-raised hyperbolic secant distribution. Using these distributions we can approximate the probability of a mapping of histology to mri with

$$p_{Hist\text{->}MRI}(Z_{Global}, \theta_{x\text{-}Global}, \theta_{y\text{-}Global}, res_{xyz}) \sim \prod_{i=1} p(\Delta x_i, \Delta y_i, \Delta\theta_i)$$

across pairs of neighboring sections.

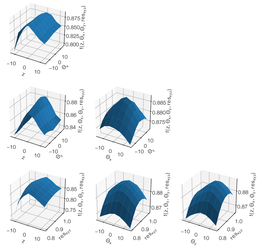


$$p(x_i, y_i, \theta_i \mid x_{i-1}, y_{i-1}, \theta_{i-1}) = p(\Delta x)\, p(\Delta y)\, p(\Delta\theta)$$



Graph-Theoretic Slide Stacking produces large Inferior-Superior axis localization errors

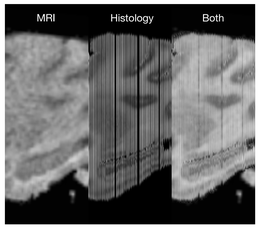
Results



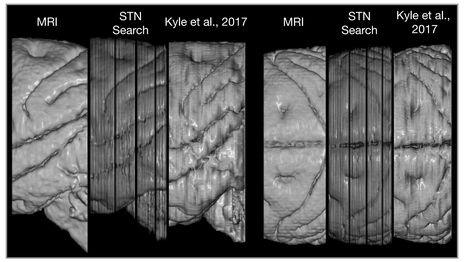
Searching the Global Parameter Space. Here we utilize grid-search to find the combination of global parameters that maximizes our objective function:

$$0.4^{*}\mathrm{Corr}(\mathrm{Hist,MRI}) + 0.6^{*}p_{Hist\text{->}MRI}(Z_{Global}, \theta_{x\text{-}Global}, \theta_{y\text{-}Global}, res_{xyz}) - \mathrm{Cost}_{Regularization}$$

We found the objective function to be convex within our relatively large search space indicating our result was globally optimum and that in the future we can consider faster optimization methods.



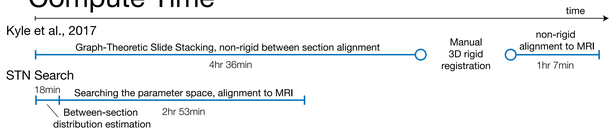
MRI - Histology Alignment. The maximum global search parameters demonstrate good agreement between MRI and histology. As a final registration step, histology is rigidly warped to the MRI, then each section of histology undergoes non-rigid weighted multi-image diffeomorphic registration with equal weighting to the MRI image, and each of the neighboring histological sections.



Comparison to Kyle et al., 2017. In comparison to our previous method of histological reconstruction, the STN search method results in better agreement of images. The current method's improved data model requires no redundant warping or interpolation steps. Finally, our improved pipeline finds accurate reconstructions automatically, eliminating the need for user supervision and introduction of human error.

Note: the current method respects the precise z location of each histological section and allows for missing data (black lines), while in Kyle et al., 2017, neighboring sections were duplicated to construct a contiguous volume. Rendering software produces striped artifact.

Compute Time



Conclusions

- CNN rigid and Thin-plate Spline Spatial Transformer Networks accurately register images orders of magnitudes faster than conventional registration methods.
- We present a simple model that efficiently utilizes information from neighboring sections to automatically and accurately reconstruct histological data.

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