High resolution neural connectivity from incomplete tracing data using nonnegative spline regression

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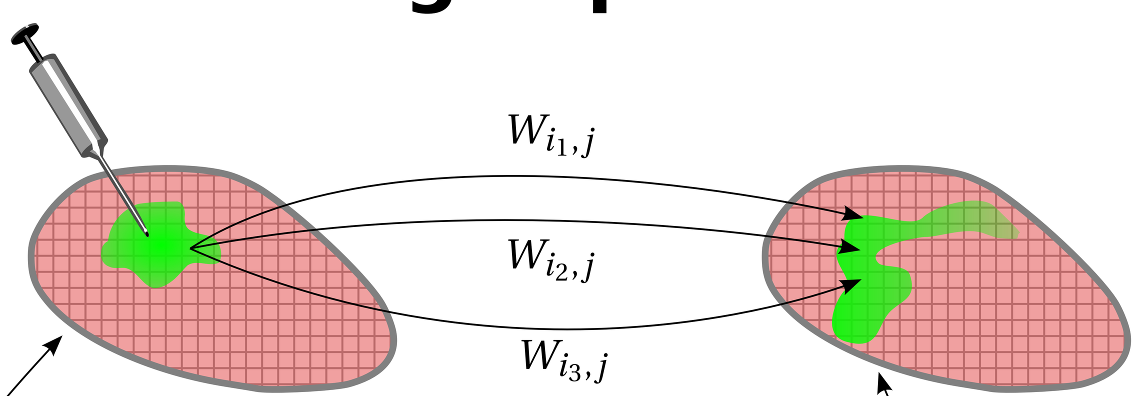
Code, movies, and more!
github.com/kharris/high-res-connectivity-nips-2016

Motivation

Scientific: Understand interplay of brain **network structure** and **information representation** (coding). Examine functional correlations such as spatial maps in relation to structural connectivity.

Mathematical: Develop tractable methods for analyzing high-dimensional structural connectivity data from next-generation experiments.

Tracing experiments

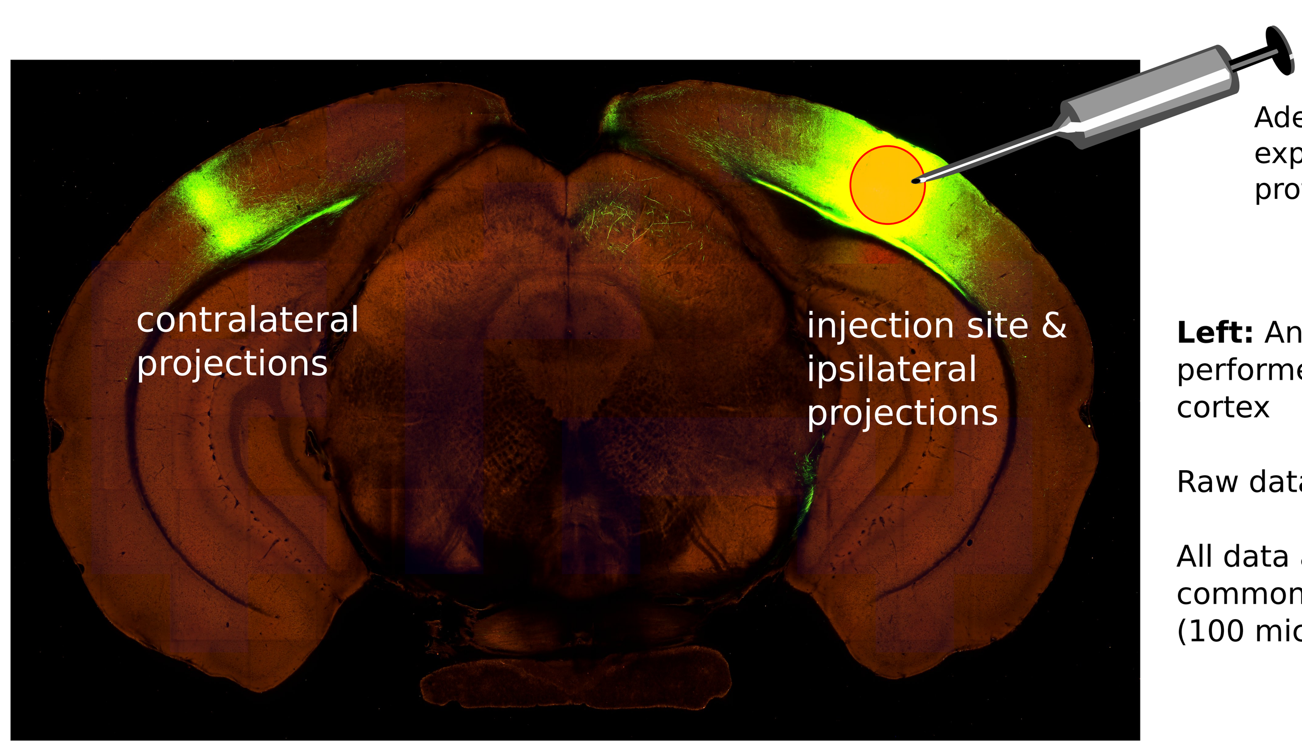


x: source expression (n_x x 1), n_x is # voxels in source regions

y: target expression (n_y x 1), n_y is # voxels in target regions

$$\mathbf{y} \approx W\mathbf{x}$$

Goal: fit unknown (n_y x n_x) weight matrix

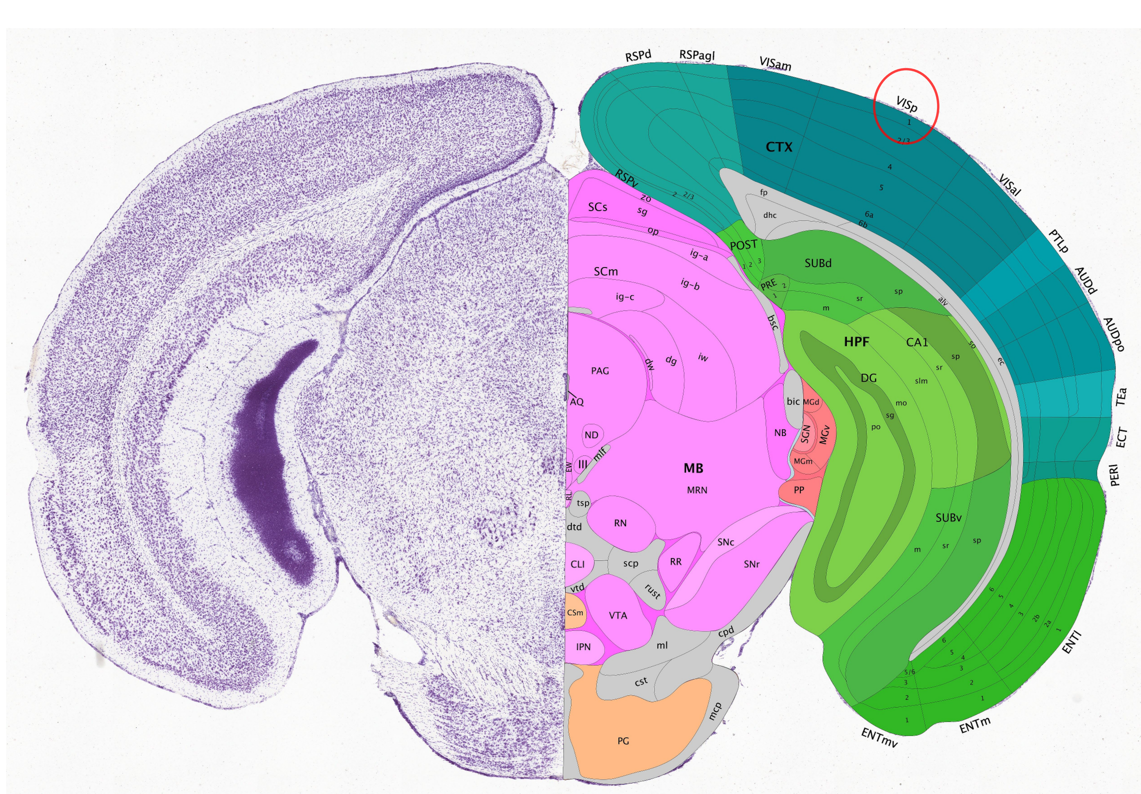


Adeno-associated virus expressing green fluorescent protein

Left: An example of an injection performed in primary visual cortex

Raw data (images) 2 PB

All data are aligned onto a common coordinate system of (100 micron)^3 cubic voxels



The reference atlas labels voxels belonging to known regions (**left**), which are organized in a heirarchy

Data summary

1) Mesoscale: 100-1000 neurons/voxel, averages over neurons. Each injection covers 30-500 voxels, 240 avg.
2) Still, projections are identifiable at voxel scale and all regions are targeted by at least 1 injection.
3) Connectome fitting is very underconstrained: 5 x 10^5 voxels and only ~1000 injections.

Above images: Allen Institute for Brain Science

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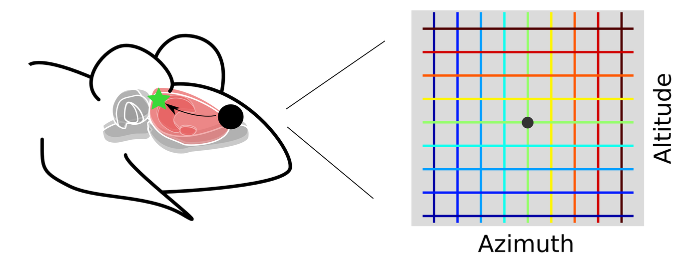
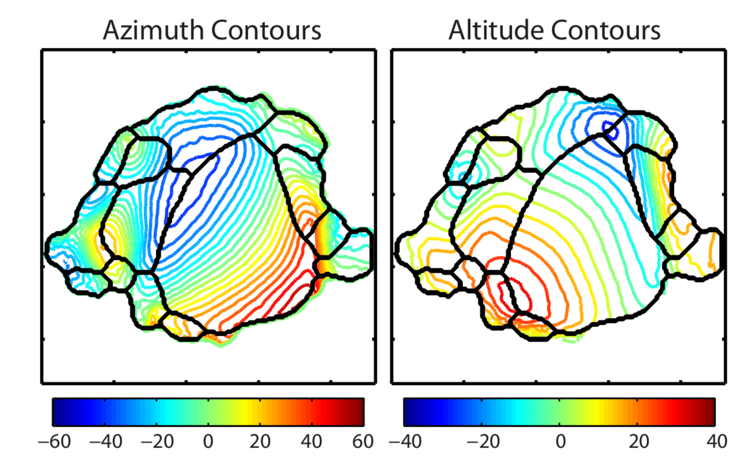
Voxel model strategy: assume smoothness



What the mouse sees

... and it's cortical representation

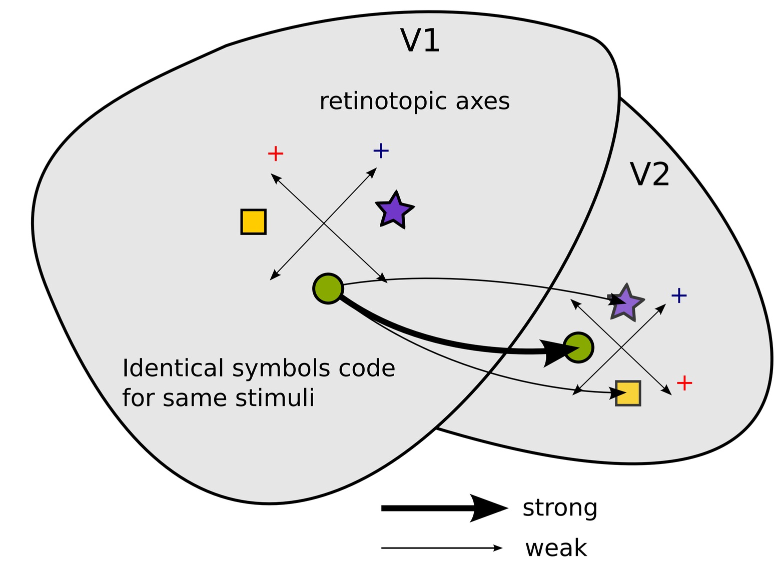


Garrett et al., 2014, J Neurosci 34(37):1258712600

Retinotopy (map representation of visual field) in primary visual cortex is maintained from V1 into deeper areas analagous to V2, etc.

Assumptions:
- like connects strongest to like
- connection strength decreases as similarity decreases
- retinotopy (hence similarity) is smooth

Taken together, suggests connections vary smoothly in space



Smoothness regularized model

Find the voxel-resolution connection matrix W that balances goodness of fit and smoothness:

$$W^* = \arg\min_{W \succeq 0} \underbrace{\|P_\Omega(WX - Y)\|_F^2}_{\text{Goodness of fit (loss) term}} + \underbrace{\lambda \frac{n_{\text{inj}}}{n_x} \left\|L_y W + W L_x^T\right\|_F^2}_{\text{Smoothness (regularization) term}}$$

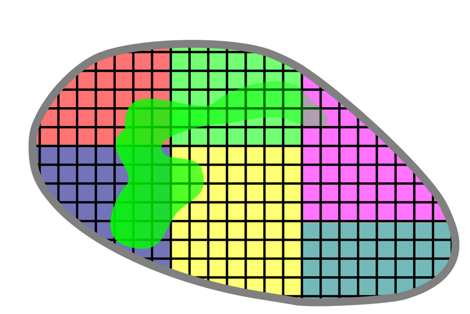
Data matrices:
$Y = [\mathbf{y}_1, \ldots, \mathbf{y}_{n_{\text{inj}}}]$
$X = [\mathbf{x}_1, \ldots, \mathbf{x}_{n_{\text{inj}}}]$

P_Ω: Loss is summed only over voxels outside injection site, as in "matrix completion"

L_x, L_y: finite difference Laplacian matrices. Regularization is analogous to so-called "thin-plate splines" radial basis functions for regression or interpolation

Previous work: regional model

Oh et al., 2014, Nature 508(7495):207-214



colors indicate regions

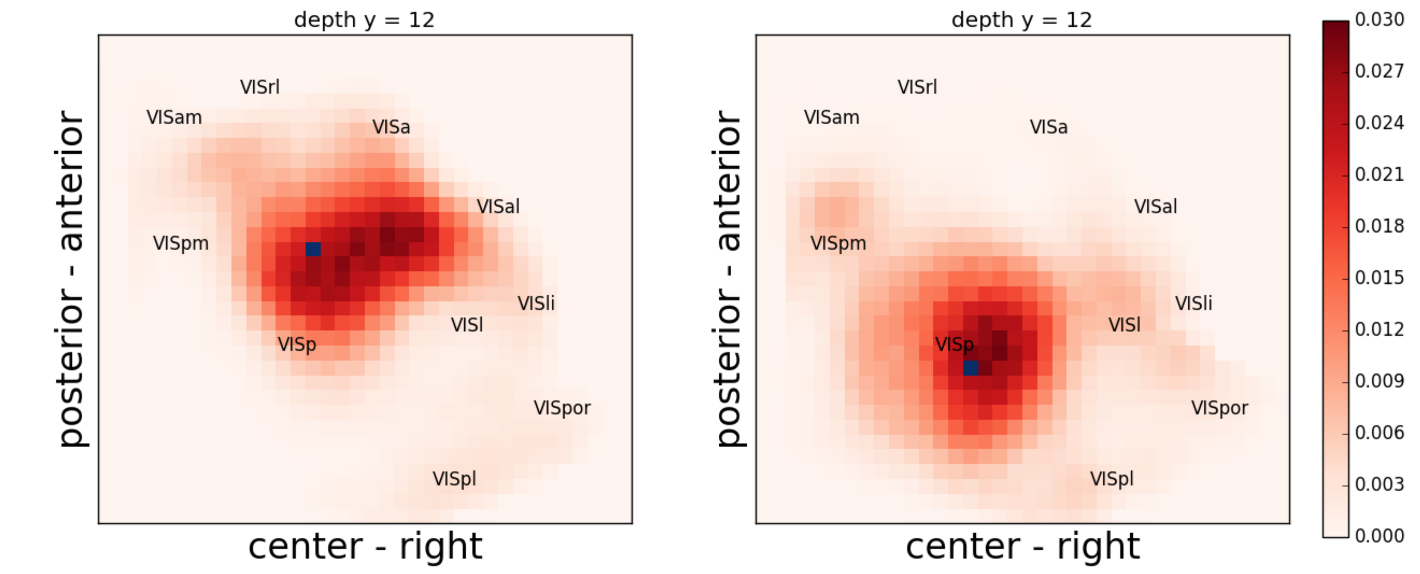
Fit the weight matrix $W^{(r)}$ via non-negative least squares

$$\min_W \left\| Y^{(r)} - W^{(r)} X^{(r)} \right\|_F^2$$

$y^{(r)}_{i,j} = \int_{\text{region } i}$ target signal of experiment j
$x^{(r)}_{i,j} = \int_{\text{region } i}$ source signal of experiment j

This is the same as choosing a voxel scale W where W_{ij} is constrained to be constant for all voxels *i* in region A and *j* in region B, for all regions A and B

Voxel approach begins to reveal spatial connectivity maps



Results of 2 "virtual" injections into VISp, visualizing columns of W

Spatial connectivities are more predictive in cross-validation

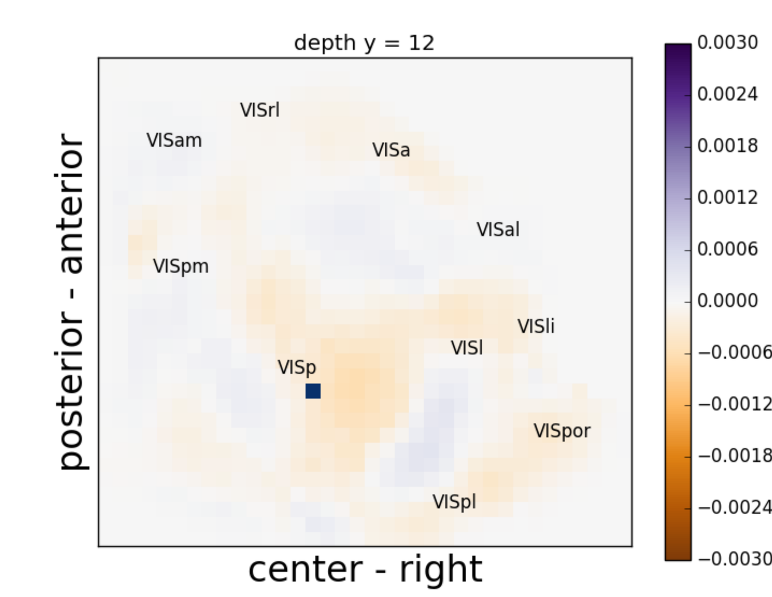
Model	Voxel MSE_{rel}	Regional MSE_{rel}
Regional	107% (70%)	48% (6.8%)
Voxel	**33% (10%)**	**16% (2.3%)**

$$\text{MSE}_{\text{rel}} = \frac{2\|P_\Omega(WX - Y)\|_F^2}{\|P_\Omega(WX)\|_F^2 + \|P_\Omega(Y)\|_F^2}$$

Low rank approximation enables inference that scales

Non-convex, low-rank version of previous spatial model:

$$(U^*, V^*) = \arg\min_{U,V \succeq 0} \|P_\Omega(UV^T X - Y)\|_F^2 + \lambda \frac{n_{\text{inj}}}{n_x} \left\|L_y UV^T + UV^T L_x^T\right\|_F^2$$



Left: Residuals between the full-rank and a rank-160 nonnegative approximation are an order of magnitude less than connectivity.

This corresponds to 23-fold compression of the 7497 x 7497 matrix, with error:

$$\frac{\|U^* V^{*T} - W^*_{\text{full}}\|_F}{\|W^*_{\text{full}}\|_F} = 13\%$$

Factorized matrix provides NMF-like "clustering" of voxels by projections.

- Whole brain: number of voxels is 5 × 10^5
- Same 23-fold compressibility means rank 10^4
- This is still a problem in O(10^9) unknowns
- Compresses W matrix from 1.9 TB to 75 GB

Challenges and future work

- Basis function representations: better than low rank?
- Compare *Cre* cell type-specific connectivity
- Compare spatial maps of retinotopy to connectivity
- Fit entire mouse brain, requires massive parallelization