Smooth network inference from neural tracing data

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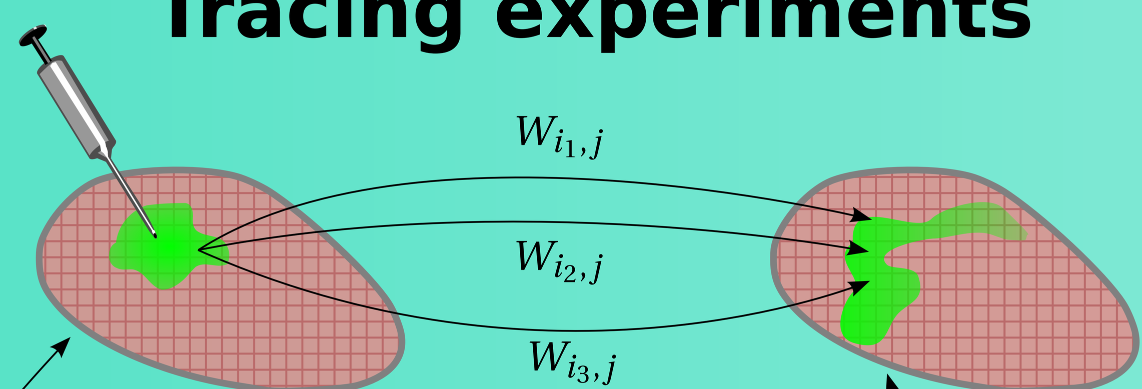
Motivation

Broadly, understand interplay of brain **structure** and **information representation**

Improve the resolution of the connectivity weight matrix to voxel scale: underconstrained w/o regularization

Tracing experiments

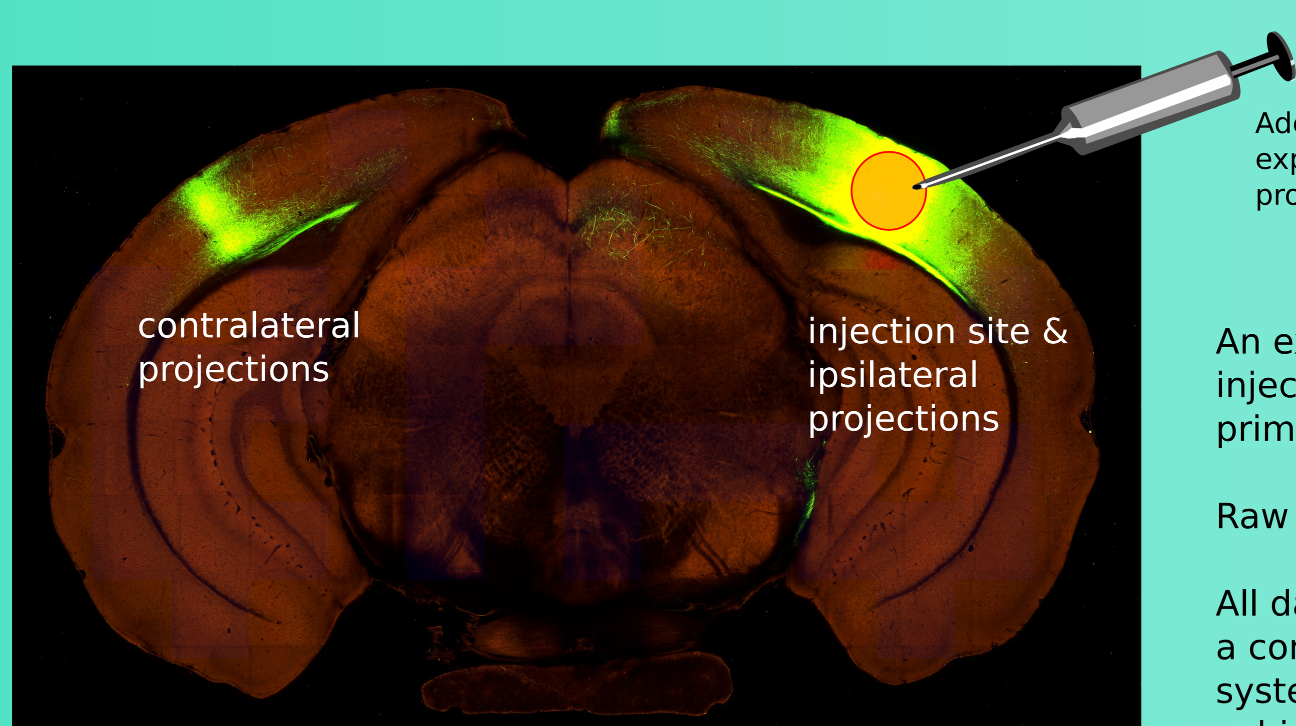


x: source expression (n_x x 1), n_x is # voxels in source regions

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

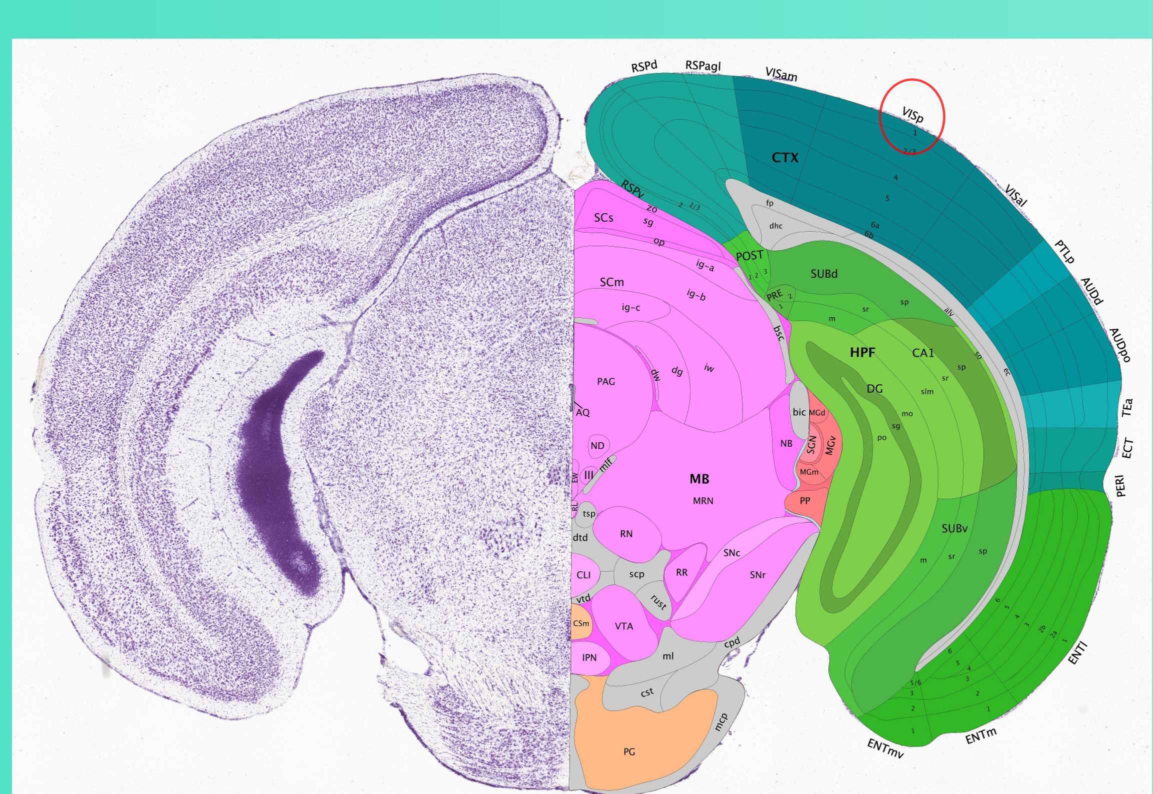


Adeno-associated virus expressing green fluorescent protein

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, which are organized in a heirarchy

Other information:
- 100-1000 neurons/voxel
- 5 x 10^5 voxels
- each injection covers 30-500 voxels, 240 avg
- projections identifiable at voxel scale
- approx 400 injections in current version of data (many more planned)

Above images: Allen Institute for Brain Science

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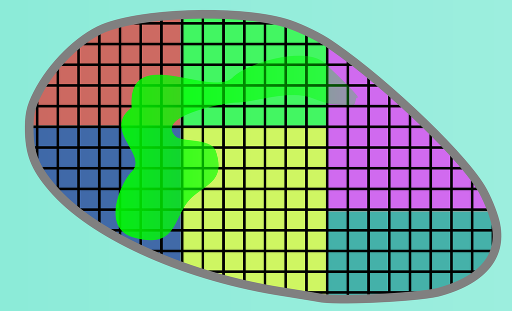
Previous work: regional model

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



colors indicate regions

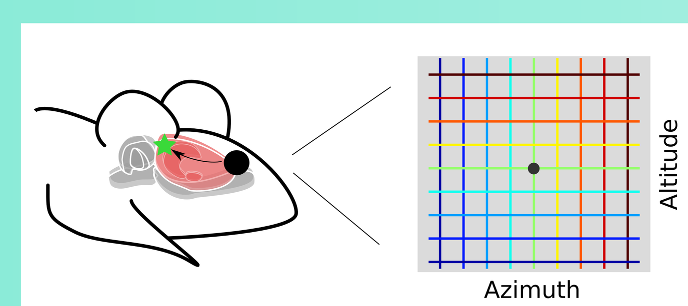
Integrate source and target expression over regions to produce regional vectors of expression $\mathbf{x}^{(r)}$ and $\mathbf{y}^{(r)}$
(n_r x 1) (n_r x 1)

Then fit the (n_r x n_r) weight matrix $W^{(r)}$ via least squares by solving

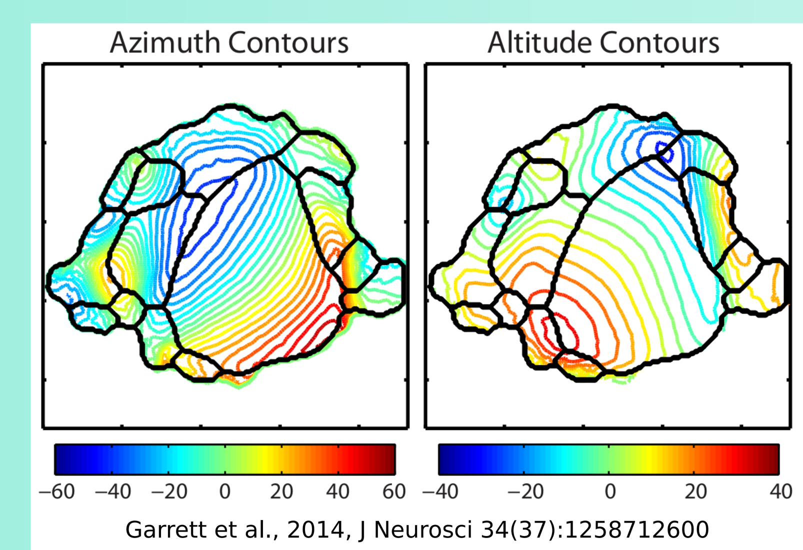
$$\min_W \left\| Y^{(r)} - W^{(r)} X^{(r)} \right\|_F^2$$

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

Evidence for smoothness



What the mouse sees



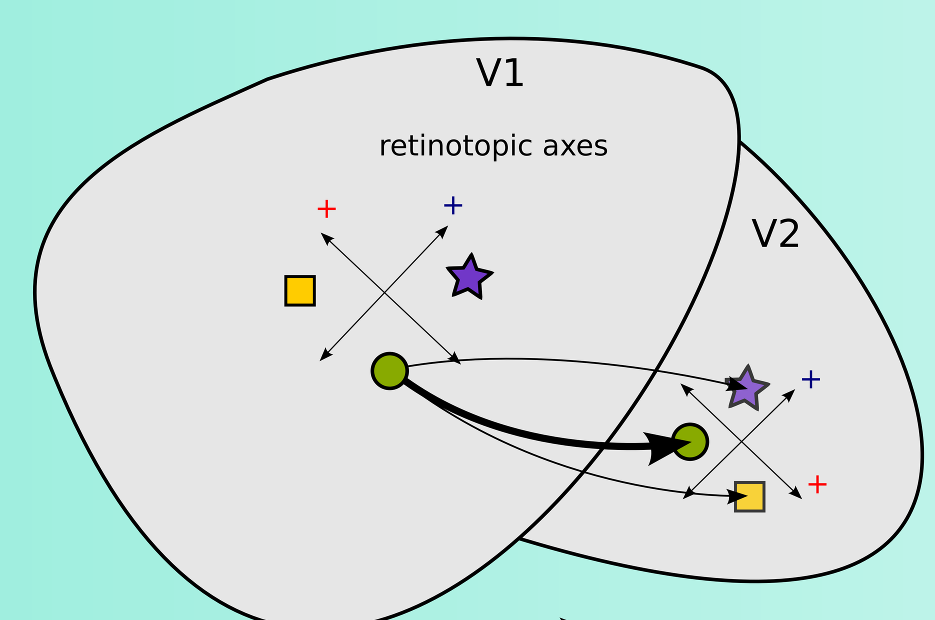
... and it's cortical representation

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.

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

Above items taken together suggest connections will vary smoothly in space



Smoothness regularized model

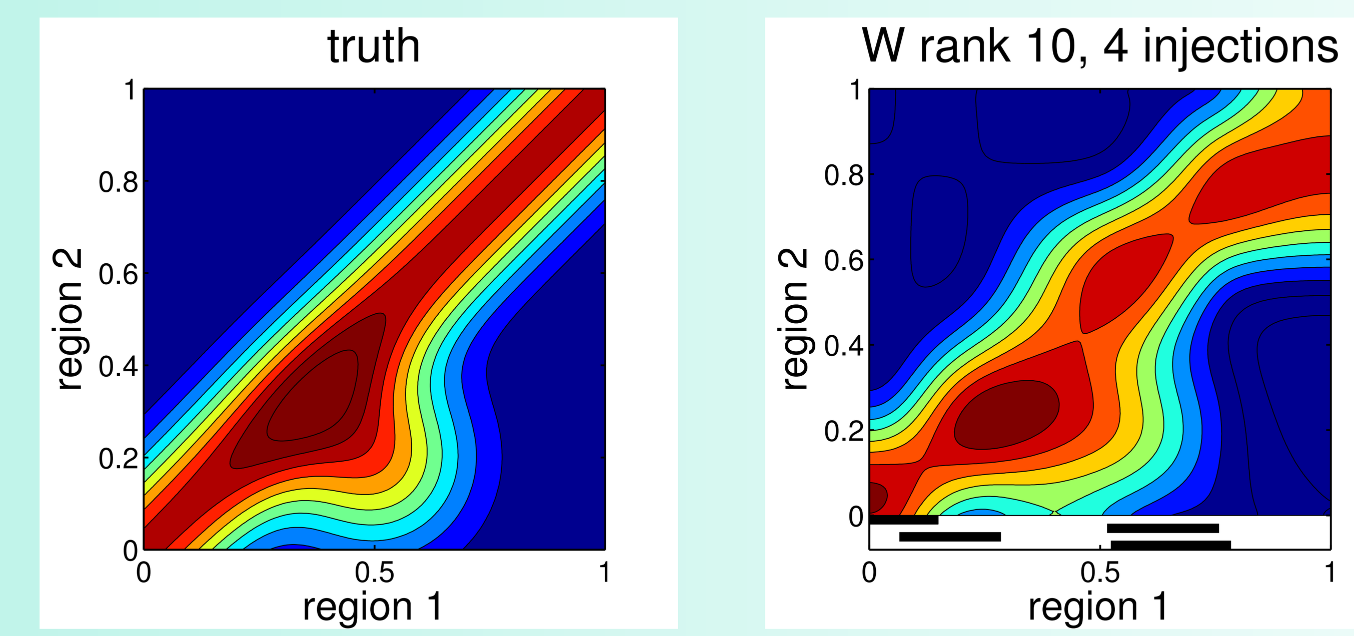
Find the voxel-resolution connection matrix W that balances goodness of fit and smoothness:

$$\min_W \|Y - WX\|_F^2 + \lambda \left\| W L_x^T + L_y W \right\|_F^2 \quad *$$

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

Laplacian matrices (smoothness terms), Neumann boundary conditions

The choice of a Laplacian penalty in this regression is analagous to so-called "thin-plate splines" for curve fitting or interpolation



Reconstruction of a smooth matrix in a test problem, λ=2

Method must be scalable to work with O(10^5) voxels in dataset

Result: With n_{inj} small (relative to n_x, n_y) a low rank (≈3 x n_{inj}) solution $W=UV^T$ works well in our 1-dimensional test problem

Require: $U_0 \in \mathbb{R}^{n_y \times r}$, $\epsilon > 0$ (and X, Y, L_x, L_y, λ to evaluate J)
Ensure: $W = USV^T$ rank r solution to the regularized problem
$k \leftarrow 0$
repeat
$k \leftarrow k+1$
$\tilde{V}_k = \operatorname{argmin}_V J(U_{k-1}, V)$
$[V_k, S_k] = \operatorname{svd}(\tilde{V}_k)$
$\tilde{U}_k = \operatorname{argmin}_U J(U, V_k)$
$U_k = \operatorname{orth}(\tilde{U}_k)$
until $\|U_k - U_{k-1}\|_F < \epsilon$ **and** $\|V_k - V_{k-1}\|_F < \epsilon$
return $W = U_k S_k V_k^T$

Solve a generalized Sylvester equation of the form AXB + CXD + XE + FX = G for X (J is cost function *)

Algorithm: Alternating least-squares low-rank solution

Challenges and future work

- Algorithmic bottleneck is Sylvester equation solve
- Regularization parameter & goodness of fit w/ cross-validation
- Does this work equally well in higher dimensions?
- How much injection coverage is needed?
- Hope to recover **retinotopy correlation from connectivity**
- Fit entire mouse visual system... fit entire mouse brain