Smooth kernel fitting to anterograde tracing data

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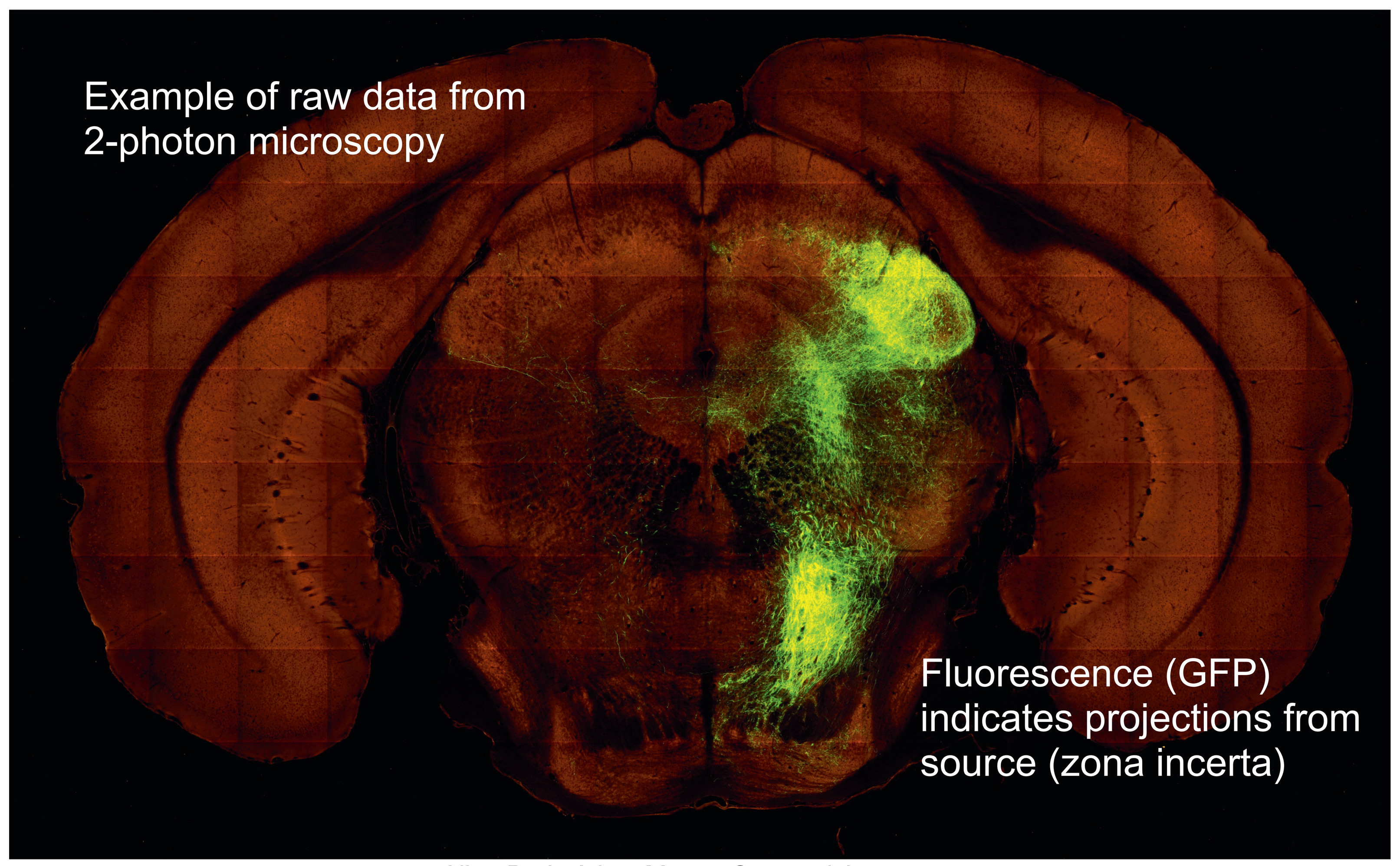
Motivation

- Connectome credo: network structure + dynamics → brain function
- Currently, Allen data is not used to full potential

Tracing Data



Allen Brain Atlas: Mouse Connectivity

500 injections of AAV tracer—anterograde, labels projections

Data are voxelized (100 x 100 x 100 μm)
- each voxel 100-1000 neurons
- 5 x 10^5 voxels in reference brain
- each injection covers 30-500 voxels, 240 on average
- projections identifiable at voxel scale

Brain is parcellated into heirarchy of regions
- each voxel assigned one region
- some injections overlap regions

Wildtype mice, Cre data soon for injections targeting specific neuron types

Regional Model

Signal is fluorescent fraction of voxel

Voxel data is integrated over each region to get region-resolution data

Linear observational model $$y_i^{(R)} = W^{(R)} x_i^{(R)}$$

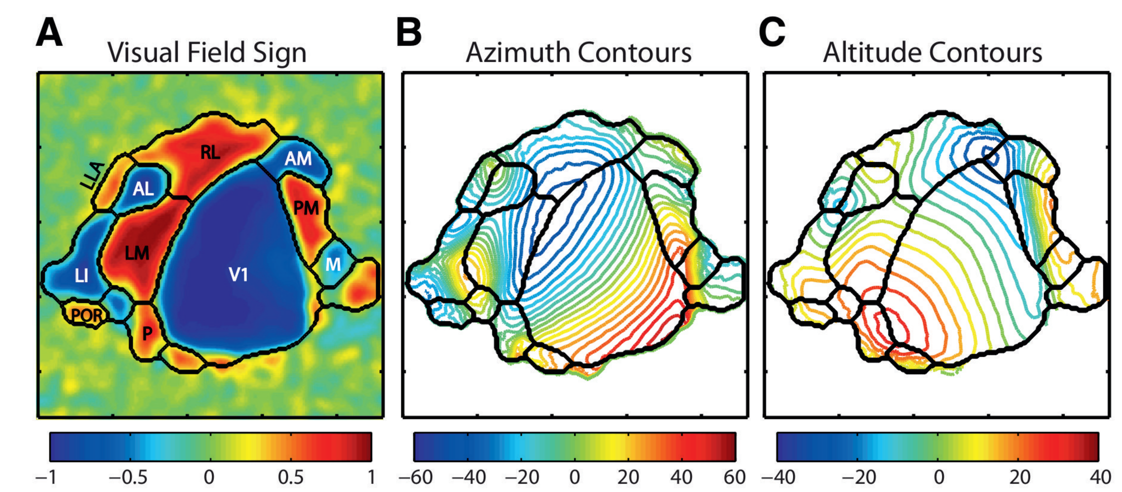
i=1, ..., # injections, via least squares

$$\hat{W}^{(R)} = \arg\min_W \left\| Y^{(R)} - W X^{(R)} \right\|_F^2$$

Smooth Voxel-scale Model

Lack of resolved source data means ill-posed, so **regularize** or use **priors**

Retinotopy: in some areas (at least) the connections are smooth



Garrett et al., 2014, J Neurosci 34(37):12587-12600

Smoothness can be likened to having derivatives with small norm (i.e. small Sobolev norm)

Laplacian operator on the weight connectivity matrix W:

$$\mathcal{L}(W) = W L_x^T + L_y W$$

Controlling the norm of this leads to the regularized problem

$$\hat{W} = \arg\min_W \|Y - WX\|_F^2 + \lambda \|\mathcal{L}(W)\|_F^2$$

Bayesian Interpretation

prior $$P(W) \propto \exp\left(-\lambda \|\mathcal{L}(W)\|_F^2\right)$$

With Gaussian posterior P(Y | X, W),
the optimization gives the maximum likelihood estimate for W

Other Regularizations

Different derivatives $$|\mathrm{grad}(W)|\,,\ \left|\mathcal{D}^{(m)}(W)\right|$$

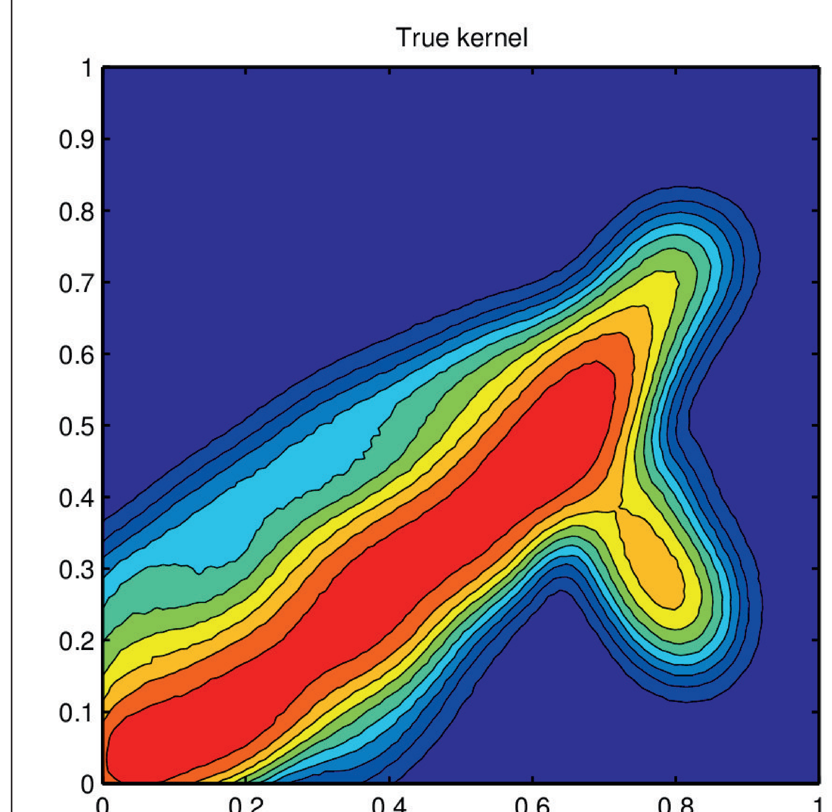
Different norms (L^p, nuclear norm, etc.)

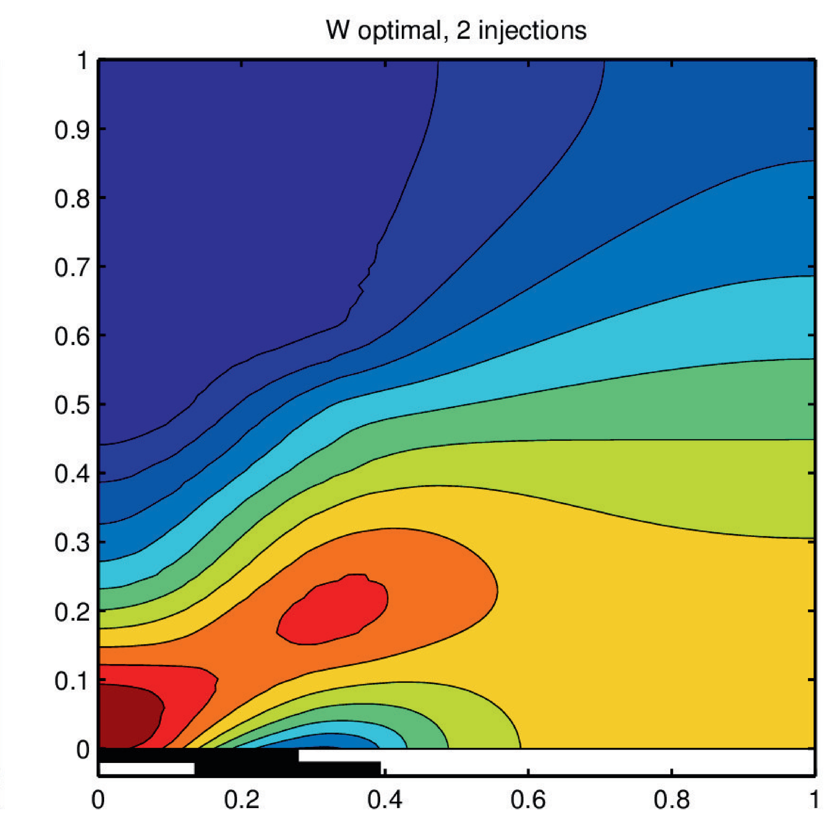
Low rank—express W using the SVD and constrain rank—perhaps a general solution connectivity exhibits symmetries?

Test Cases

Solving for optimal W gives a linear system of equations which can be solved iteratively or as a very large linear system for vec(W)

$$W X X^T + \frac{\lambda}{2}\left(L_y + L_y^T\right) W \left(L_x + L_x^T\right) + \lambda W L_x^T L_x + \lambda L_y^T L_y W - Y X^T = 0$$

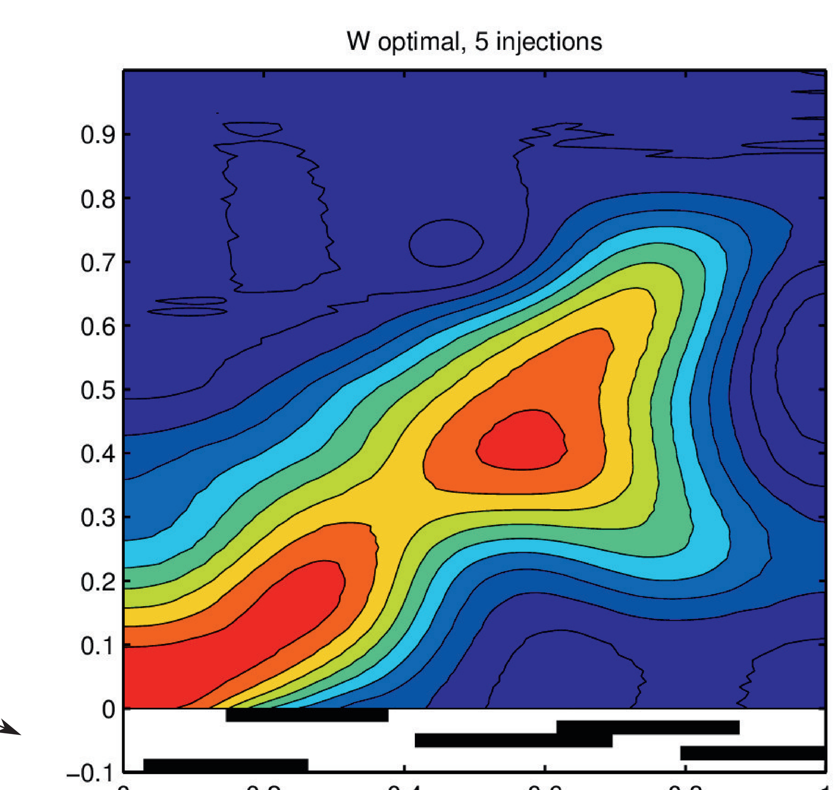




Randomly placed injections within region

Good results with better coverage

Injection locations



Future Work

Prove convergence for data consistent with model

How much injection coverage is enough?

Numeric stability for:
- large # voxels,
- higher dimensionality (3 + 3 = 6 for 3d brain)
- iterative methods

Implement with real mouse data