Construction of a voxel-based mesoscopic mouse connectome

Kameron Decker Harris[1] (kamdh@uw.edu), Julie Harris[2], Hongkui Zeng[2], Stefan Mihalas[2], Eric Shea-Brown[1]

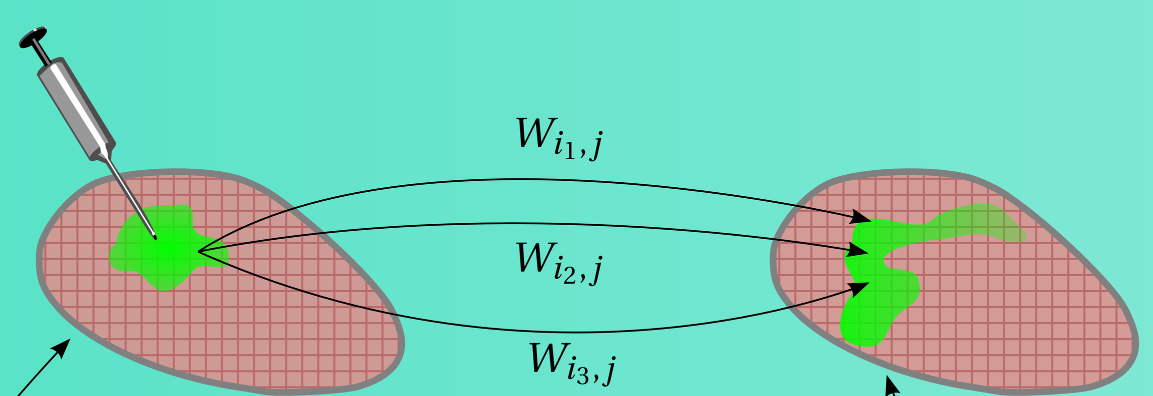
[1]Applied Mathematics, University of Washington, Seattle, WA USA; [2]Allen Institute for Brain Science, Seattle, WA USA

Motivation

Improve the resolution of the weight matrix to voxel scale

Broadly, understand interplay of brain **structure** and **information representation** (coding). Examine functional correlations such as spatial maps in relation to structural connectivity.

Tracing experiments

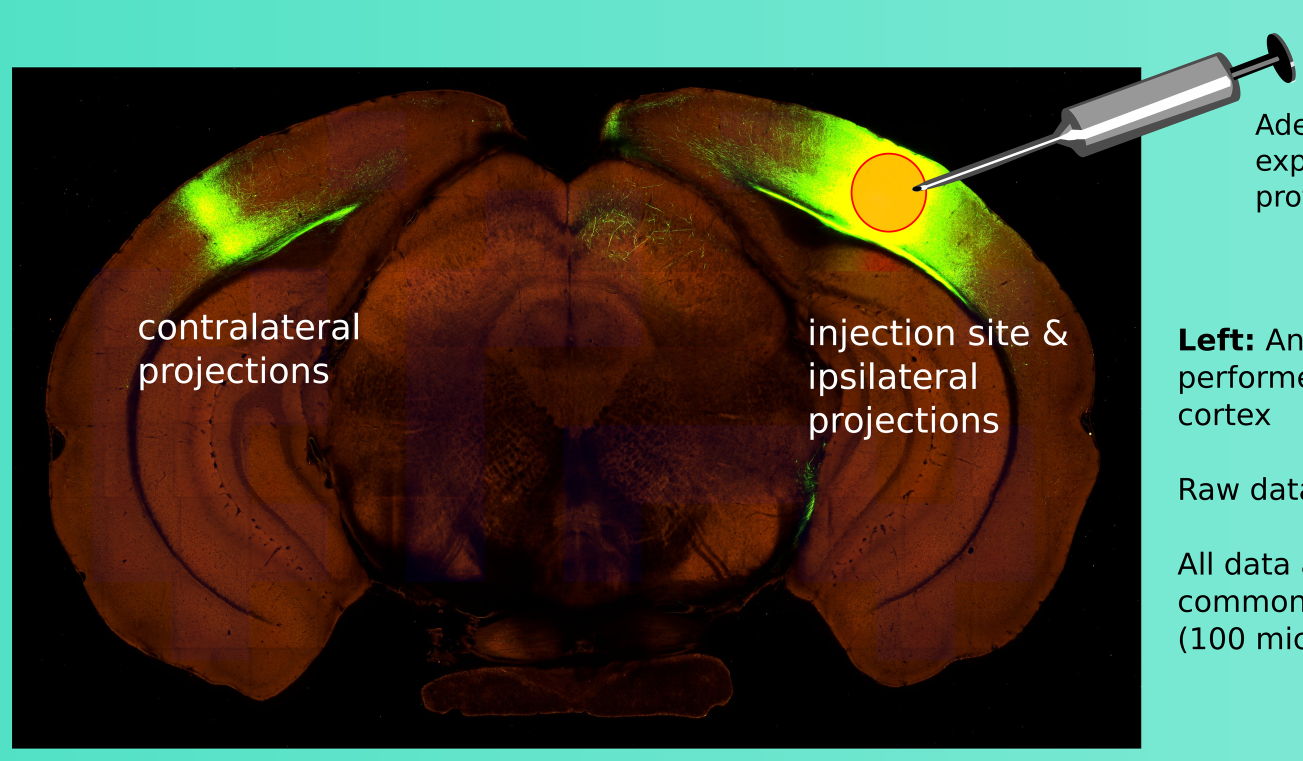


x: source expression (n_x x 1), n_x is # voxels in source regions

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

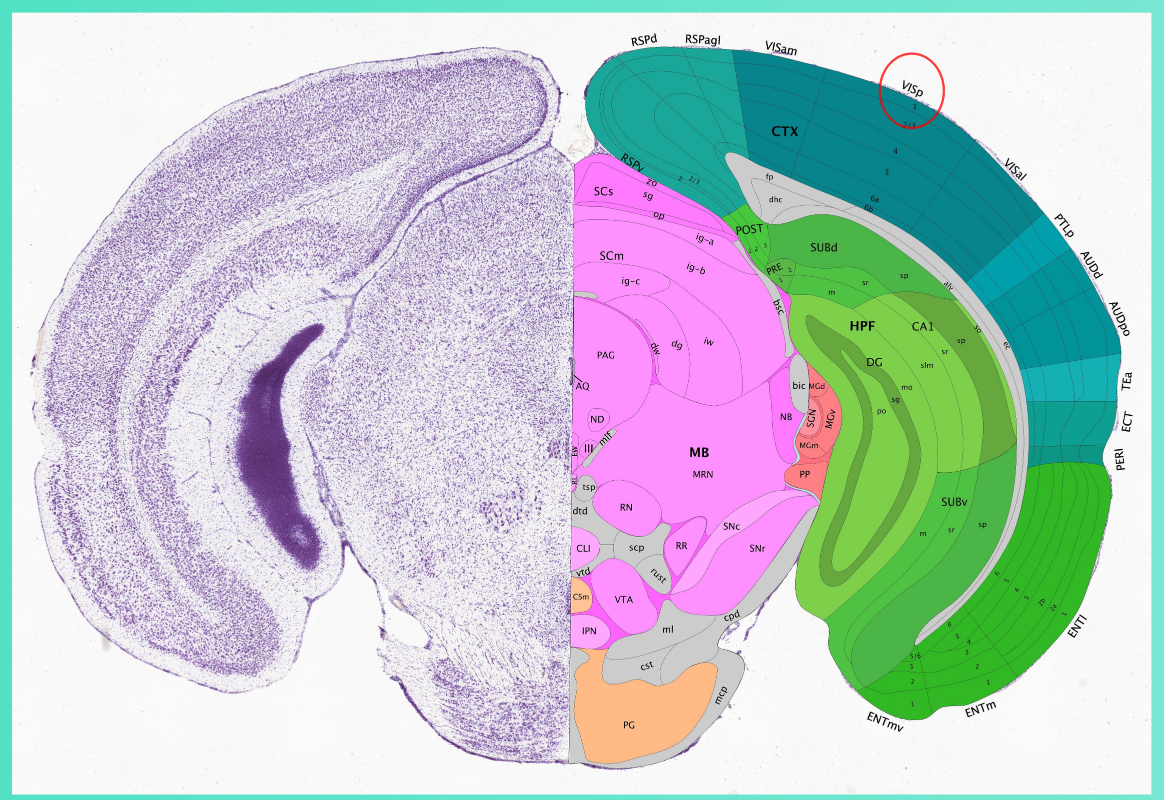


Adeno-associated virus expressing green fluorescent protein

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

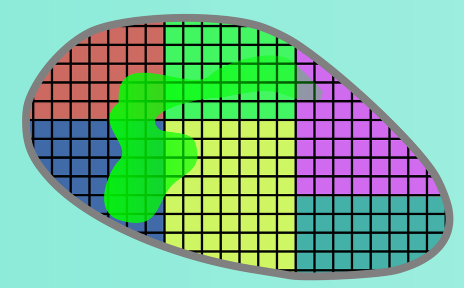
1) Mesoscale: 100-1000 neurons/ voxel, averages over neurons. Each injection covers 30-500 voxels, 240 avg.
2) Still, projections are identifiable at voxel scale and all regions are targeted by at least 1 injection.
3) Connectome fitting is very underconstrained: 5 x 10^5 voxels and only ~1000 injections.

Above images: Allen Institute for Brain Science

Acknowledgements: ETSB and KDH acknowledge support from NSF Grant #1122106 and a Simons Fellowship in Mathematics. KDH was supported by a Boeing fellowship and the Big Data for Genomics and Neuroscience training grant (UW/NIH). We wish to thank the Allen Institute founders, Paul G. Allen and Jody Allen, for their vision, encouragement and support. Thanks also to the computational neuroscience community at UW and Joel Zylberberg for suggestions and discussions. This work was facilitated though the use of advanced computational, storage, and networking infrastructure provided by the Hyak supercomputer system at the University of Washington.

Previous work: regional model

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



colors indicate regions

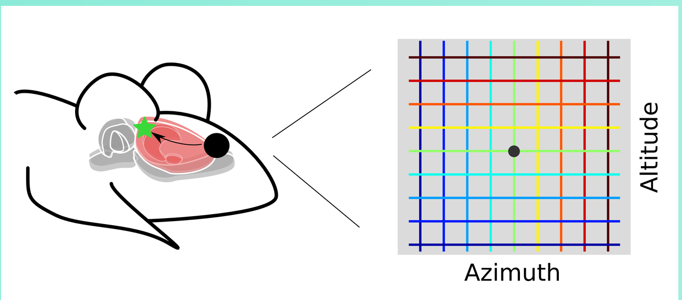
Fit the weight matrix $W^{(r)}$ via non-negative least squares

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

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

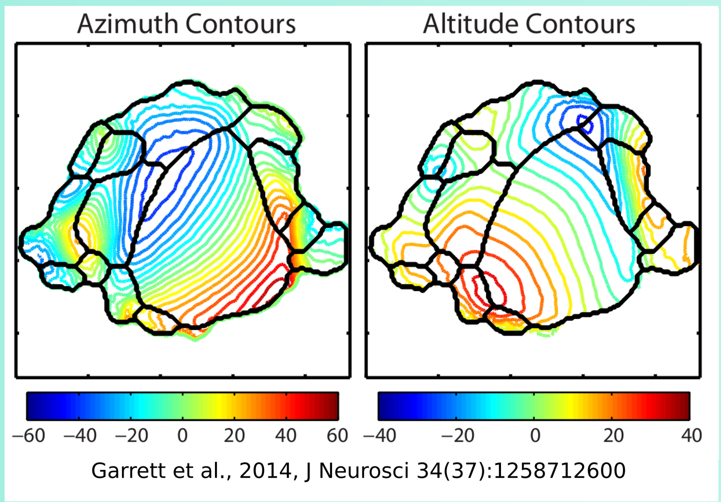
This is the same as choosing a voxel scale W where W_{ij} is constrained to be constant for all voxels *i* in region A and *j* in region B, for all regions A and B

Voxel model strategy: assume smoothness



What the mouse sees

... and it's cortical representation

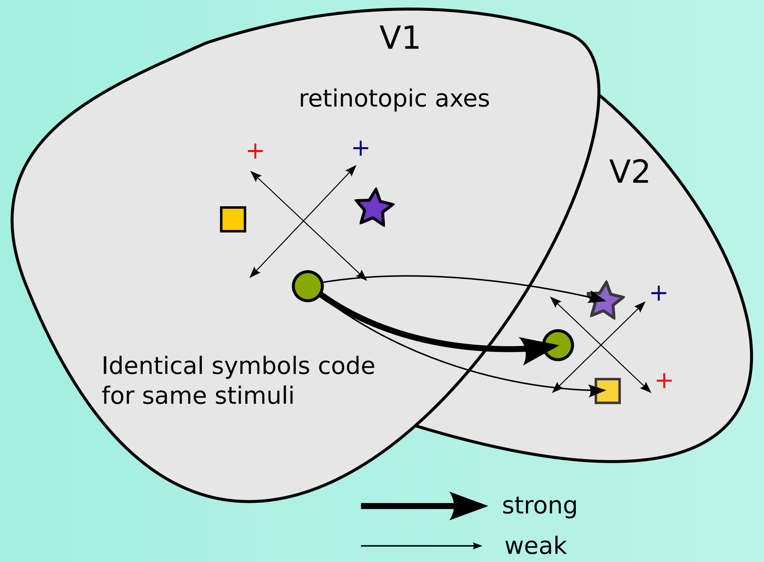


Retinotopy (map representation of visual field) in primary visual cortex is maintained from V1 into deeper areas analagous to V2, etc.

Hypothesis:

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

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:

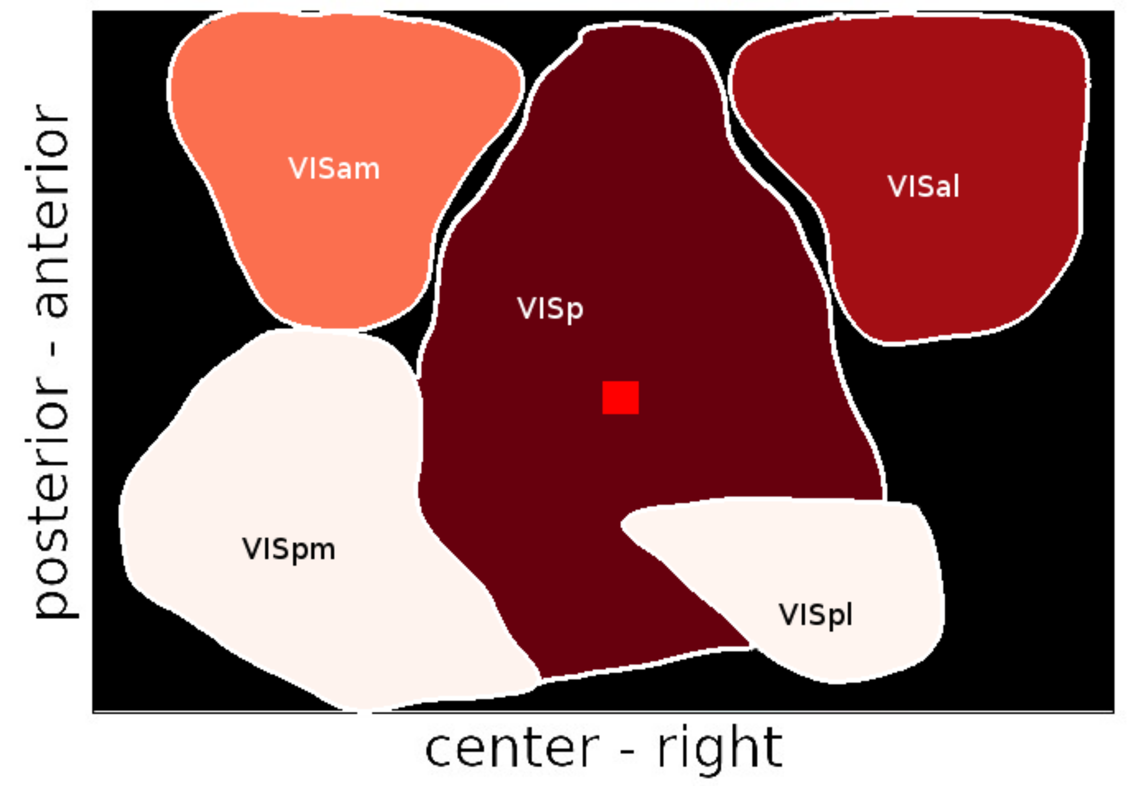
$$\min_{W \succeq 0} \underbrace{\left\| Y - WX \right\|_F^2}_{\text{Goodness of fit (loss) term}} + \lambda \underbrace{\left\| W L_x^T + L_y W \right\|_F^2}_{\text{Smoothness (regularization) term}}$$

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

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

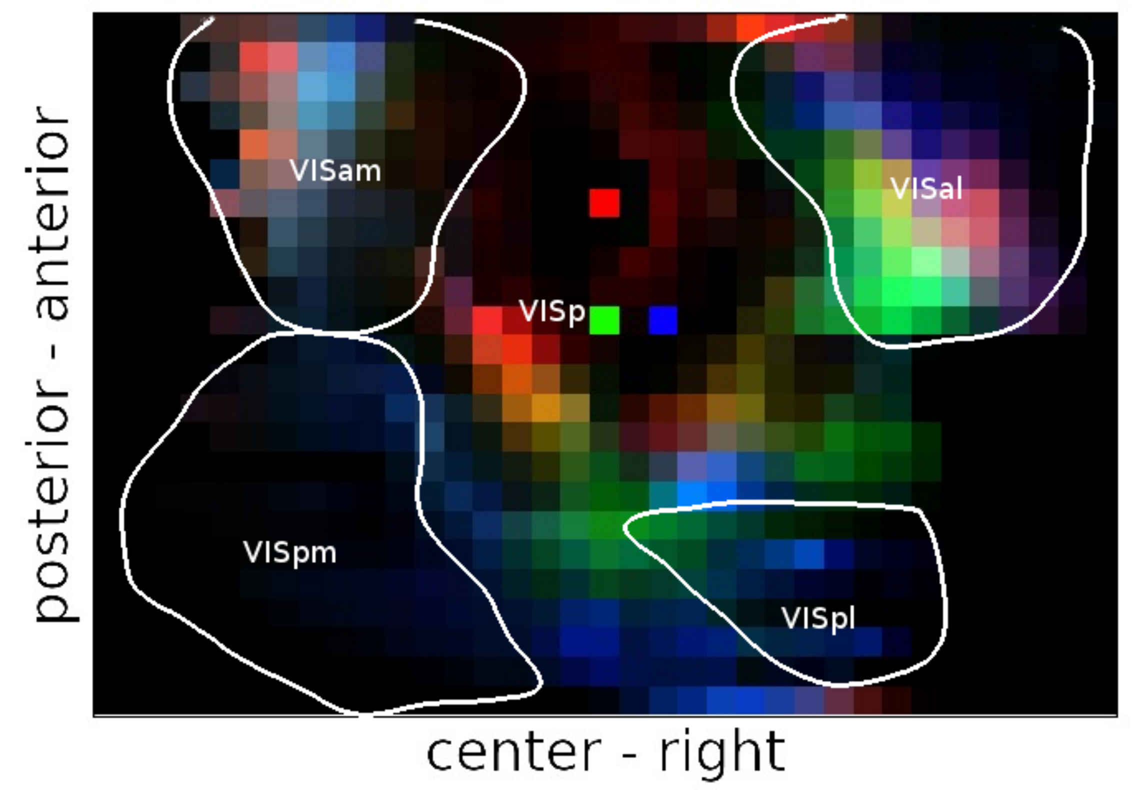
Voxel approach begins to reveal spatial connectivity maps

Regional



Any seed voxel in the region has same effect, one injection in VISp

Voxel-based



Three virtual injections (red, green, blue) yield different projections

Voxel approach yields more predictive connectivities

Regional model

	regional error	voxel error
ipsi:	23%	47%
contra:	83%	87%

Voxel model

	regional error	voxel error
ipsi:	**12%**	**32%**
contra:	**61%**	**75%**

Cross-validated mean square errors relative to $||y^{\text{pred}}||^2 + ||y^{\text{true}}||^2$

To compute **regional error** for the voxel model, we integrate predicted expression over regions:

$y^{\text{pred},r}_i = \int_{\text{region } i} y^{\text{pred}}$

then compute the error $||y^{\text{pred},r} - y^{\text{true},r}||^2$ in "regional space".

To compute **voxel error** for the regional model, we set all voxels in a region equal to the same value:

$y^{\text{pred}}_i = y^{\text{pred},R}_{\text{region } j} / |\text{ region } j\,|$

for all voxels i in region j. Then the error is computed in "voxel space".

Challenges and future work

- Compare *Cre* cell type-specific connectivity
- Compare spatial maps of retinotopy to connectivity
- Fit entire mouse brain, requires massive parallelization