Kameron Decker Harris' PhD. Research in UW Applied math

Before   After

- Voxel-based mesoscopic connectome inference (today)
- **Respiratory rhythm generation** in the pre-Bötzinger complex and the roles of **network structure** and **inhibition**
  - With Jan-Marino Ramirez, Tatiana Dashevskiy, Alfredo Garcia at CIBR, Seattle Children's Research Inst.
- Random network models with community structure, with Ioana Dumitriu (UW Math)

Voxel is the natural resolution for viral tracing experiments

Voxel is the natural resolution for viral tracing experiments

- CCF data at 10-100 μm, so build voxel-voxel *W*

Voxel is the natural resolution for viral tracing experiments

- CCF data at 10-100 μm, so build voxel-voxel *W*
- Less biased than regional model

Voxel is the natural resolution for viral tracing experiments

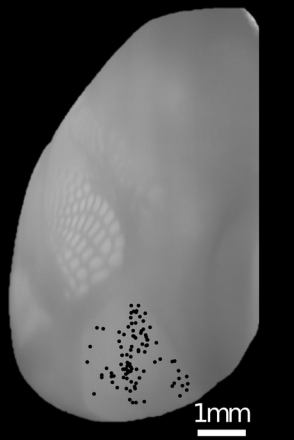
- CCF data at 10-100 μm, so build voxel-voxel *W*
- Less biased than regional model
- Challenges:
  - ~1000 injection experiments
  - 500,000 voxels in whole brain (at 100 μm)... start with visual areas
  - Very high-dimensional, $O(10^{10})$ entries in whole-brain voxel *W*
  - Inference is underdetermined

Voxel is the natural resolution for viral tracing experiments

- CCF data at 10-100 μm, so build voxel-voxel *W*
- Less biased than regional model
- Challenges:
  - ~1000 injection experiments
  - 500,000 voxels in whole brain (at 100 μm)... start with visual areas
  - Very high-dimensional, $O(10^{10})$ entries in whole-brain voxel *W*
  - Inference is underdetermined
- Can we leverage **prior** knowledge?
  - Recent successes in statistics: compressed sensing, LASSO, etc.

Voxel-based connectivity opens up new science

- Higher spatial resolution
- Connectivity-defined region boundaries
- Automatic ID of topography between regions (e.g. retinotopy)
- Combined with *Cre* data, many opportunities for examining layer-specificity, fan-out radii, etc.



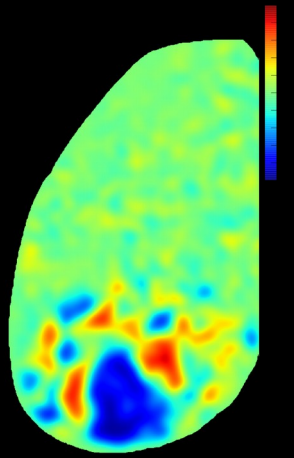
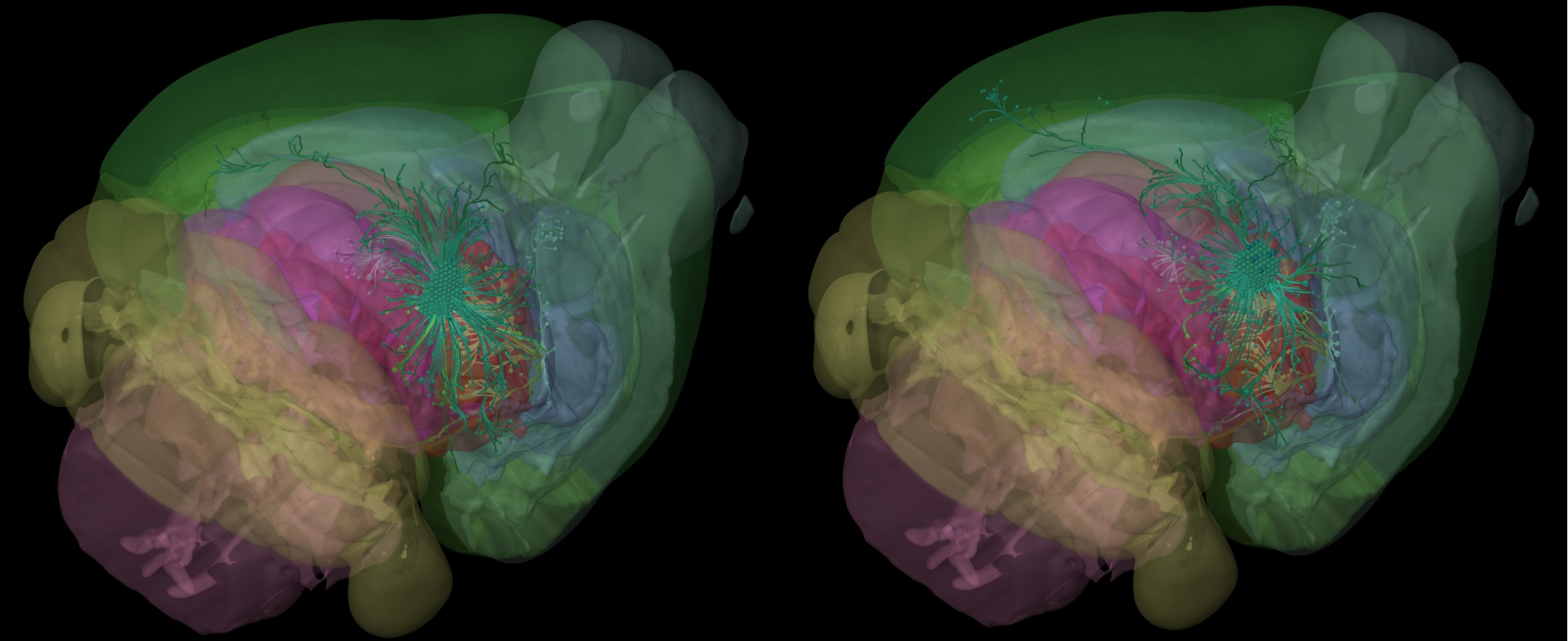


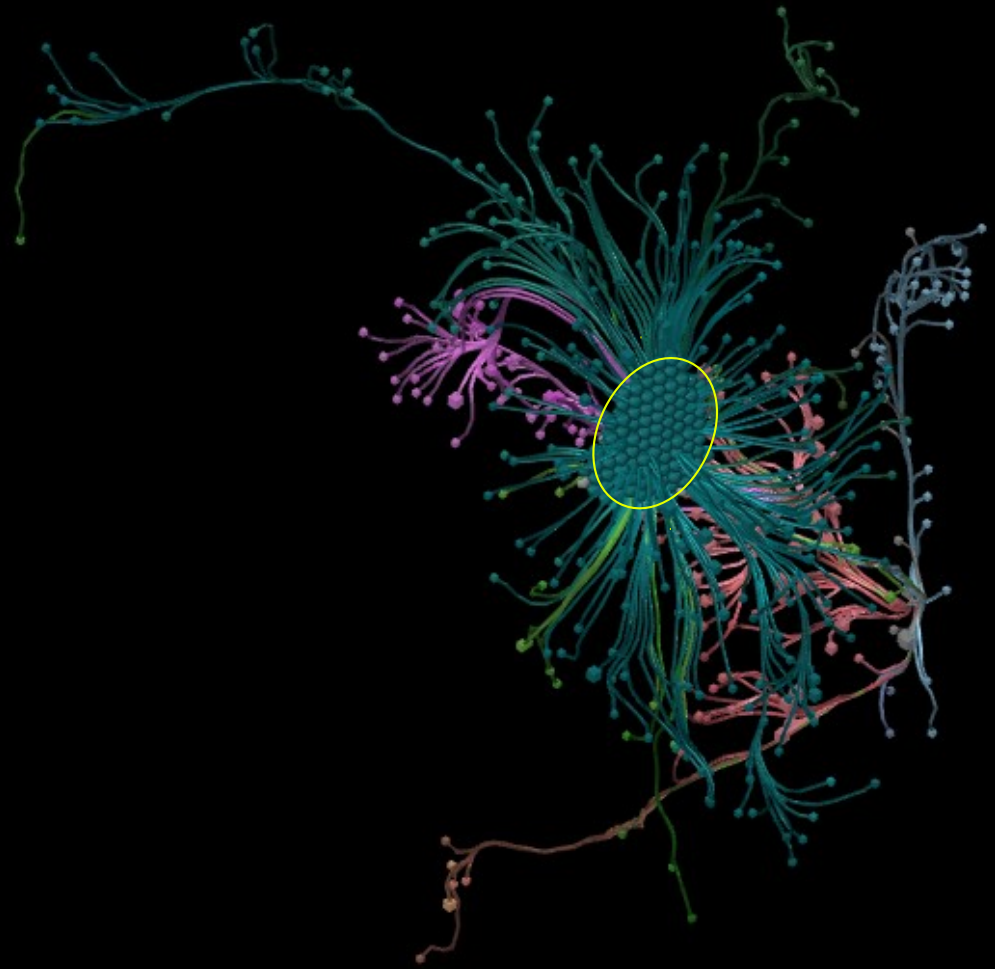
Image from Jack Waters, Jun Zhuang, et al. preprint

Nearby injections project with similar global spatial patterns
Locally, they are shifted in different directions

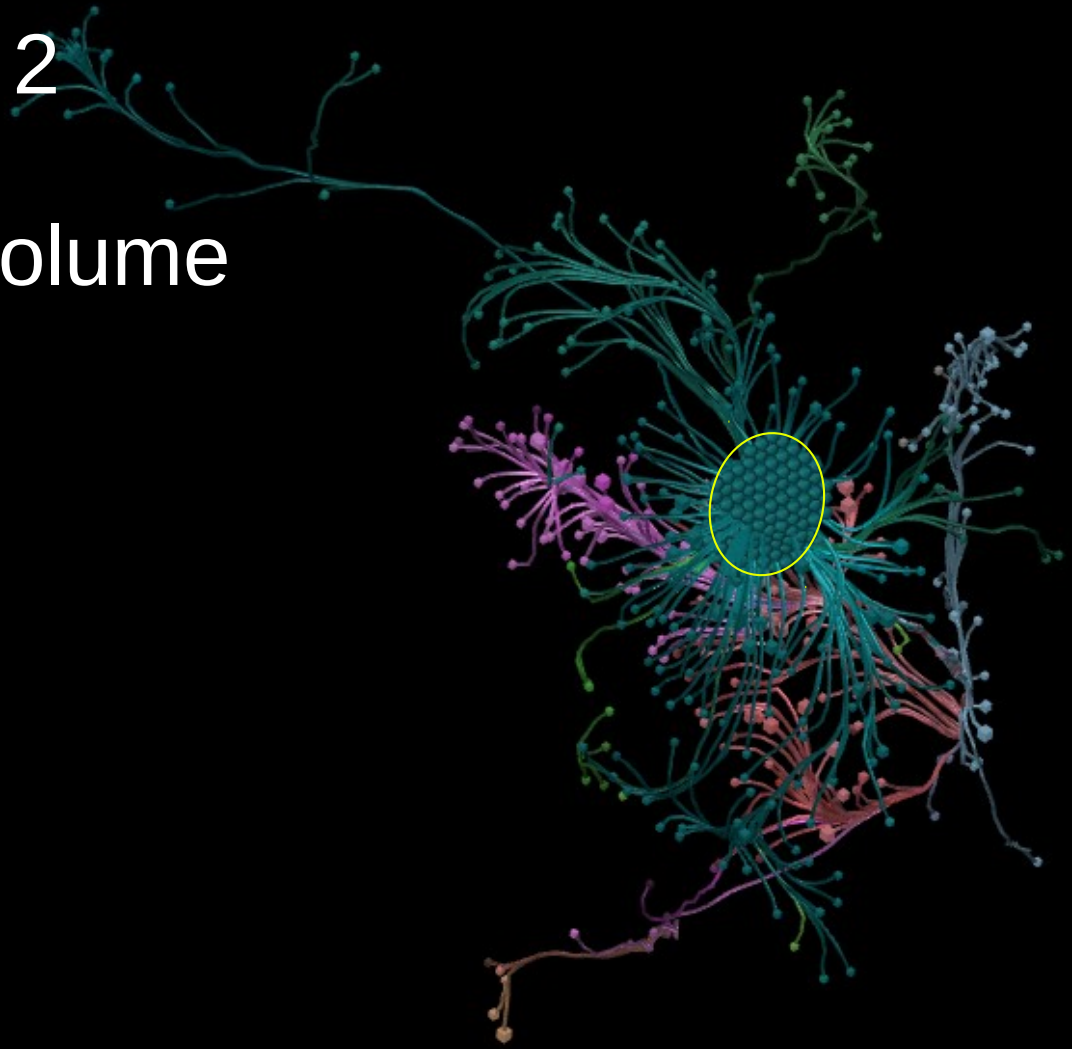
How do we use this knowledge to infer *W*?



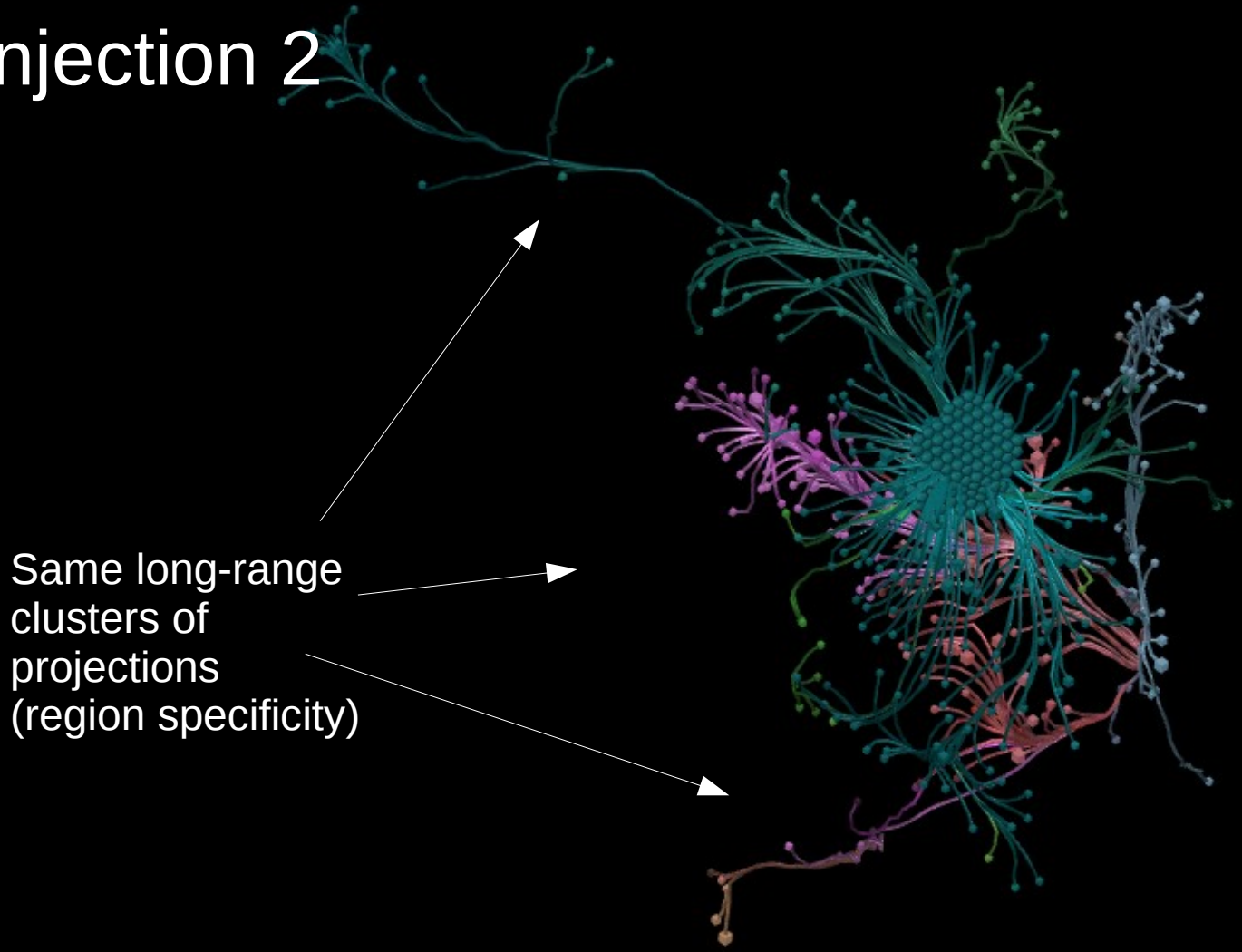
Injection 1 into VISp



Injection 2
Nearby
Similar volume

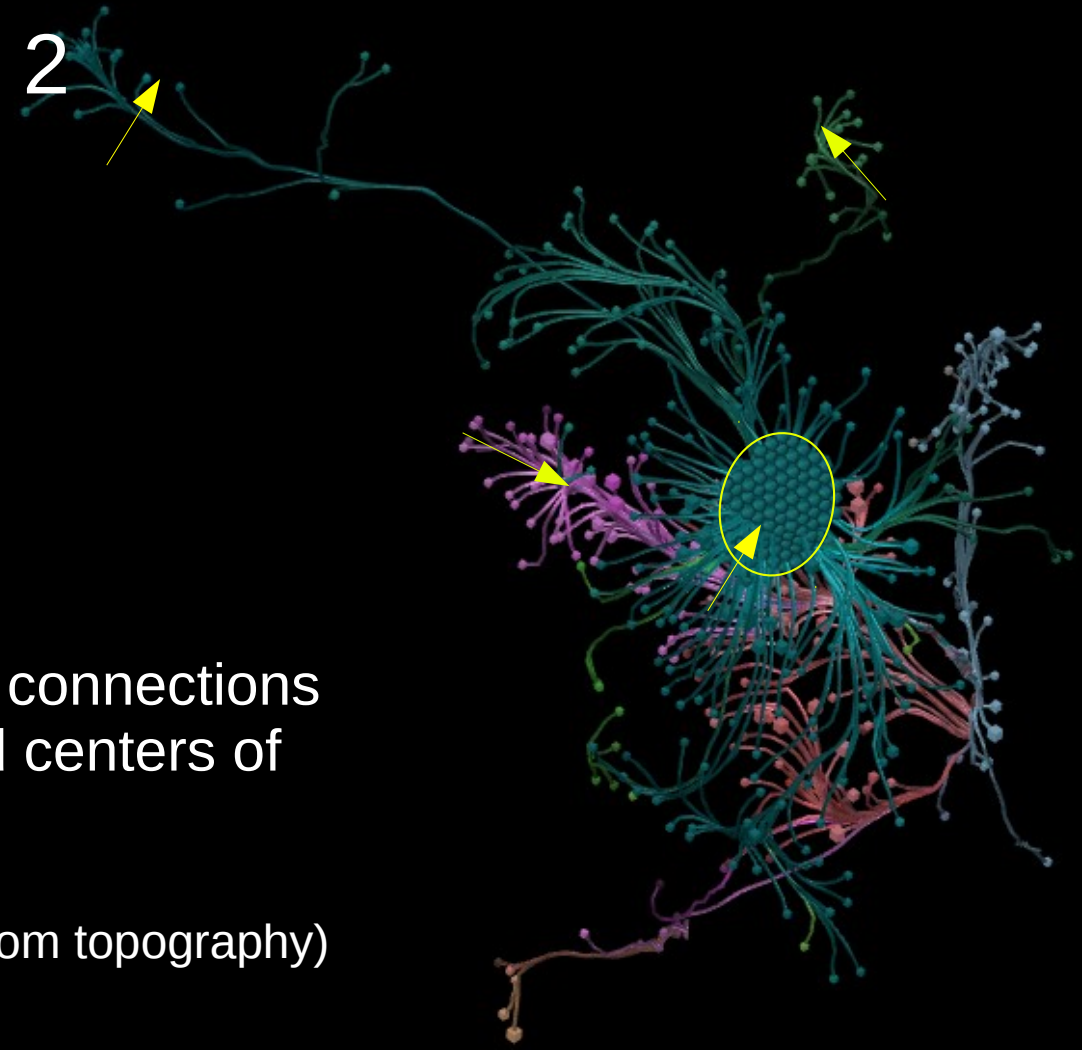


Injection 2



Same long-range clusters of projections (region specificity)

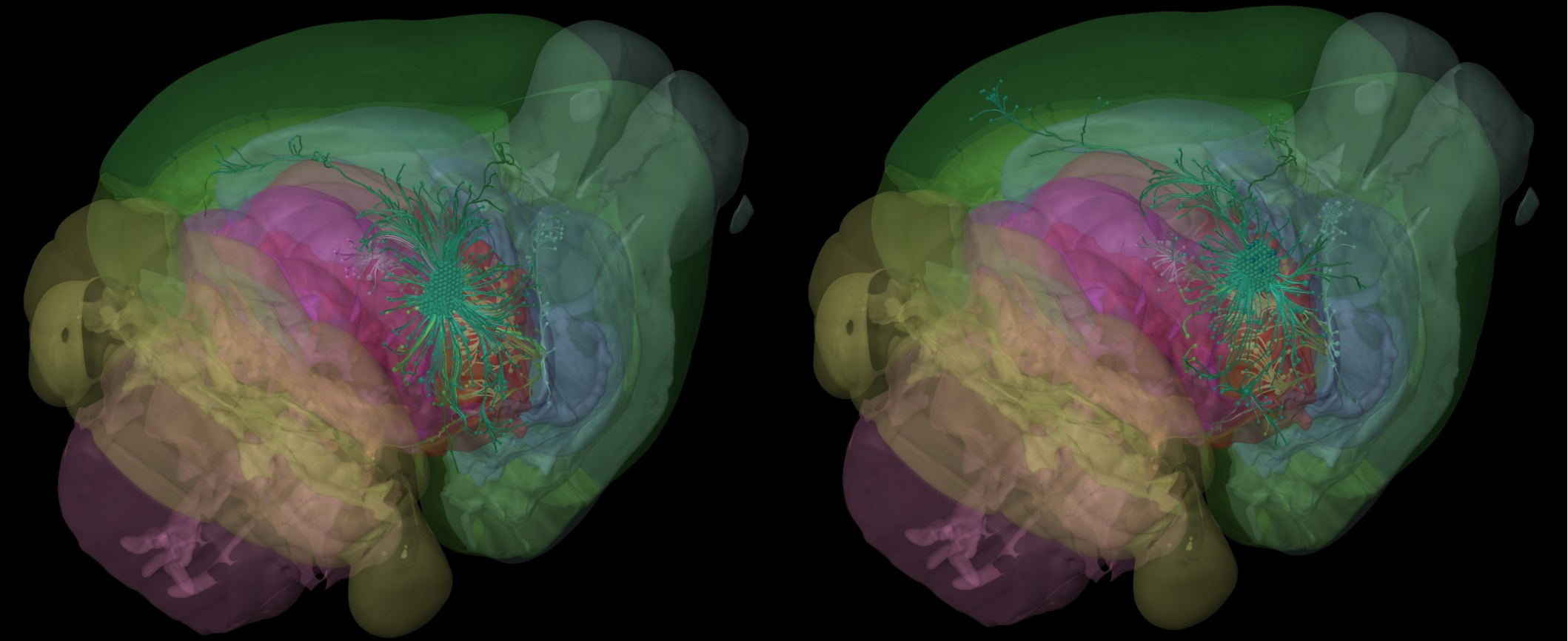
Injection 2



Long-range connections have shifted centers of mass

(could result from topography)

Long-range consistency with short-range differences suggests connectivity varies smoothly in space



Desired *W* is a spatial adjacency matrix

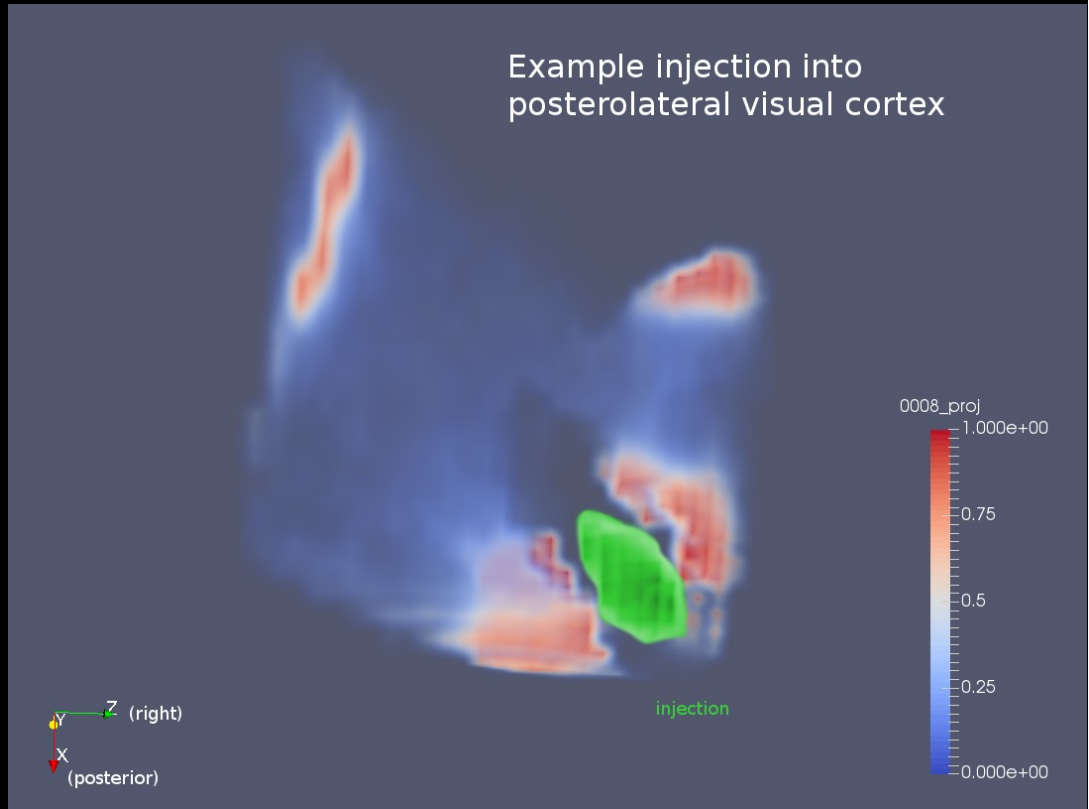
- W_{ij} = projection volume at voxel *j* from 1 unit injection volume in voxel *i*
- *W* is a linear function from *brain* to *brain*:

Input:

Injection volume (an image of a blob in the brain)

Output:

projection volume (another image)



Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\,(XW - Y)\|_F^2 + \lambda \|L\,(W)\,\|_F^2$$

Goodness of fit
(loss)

Roughness penalty
(regularization, prior)

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Squared Frobenius norms: sum of squares of matrix entries

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\,(XW - Y)\|_F^2 + \lambda \|L\,(W)\,\|_F^2$$

Unknown adjacency matrix

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Injection data

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Projection data

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW-Y\right)\|_F^2+\lambda\|L\left(W\right)\|_F^2$$

Deals with holes in data

Mask which zeroes residuals in injection sites

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Hyperparameter controls strength of smoothing

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Roughness operator
(2nd derivative of *W*)

Can respect region boundaries

Similar injections ~ similar projections Implies smooth connectivity

- Smoothness prior enters fitting as regularization, aka penalized regression
- Find *W* nonnegative that minimizes the expression

$$\|P\left(XW - Y\right)\|_F^2 + \lambda\|L\left(W\right)\|_F^2$$

Problem is convex:

unique global solution and **standard methods to find it efficiently**

We solved the problem for visual areas using 27 *wildtype* injections

We solved the problem for visual areas using 27 *wildtype* injections

- 5908 x 5908 matrix

We solved the problem for visual areas using 27 *wildtype* injections

- 5908 x 5908 matrix
- Takes a few hours on typical machine

We solved the problem for visual areas using 27 *wildtype* injections

- 5908 x 5908 matrix
- Takes a few hours on typical machine
- Cross-validation selects $\lambda = 10^4$

We solved the problem for visual areas using 27 *wildtype* injections

- 5908 x 5908 matrix
- Takes a few hours on typical machine
- Cross-validation selects $\lambda = 10^4$
- Cross-val **errors show improvement** over regional model (ipsilateral numbers):
  - Regional model: 44.3% regional 118% voxel
  - Voxel model: 18.8% regional 37% voxel

We solved the problem for visual areas using 27 *wildtype* injections

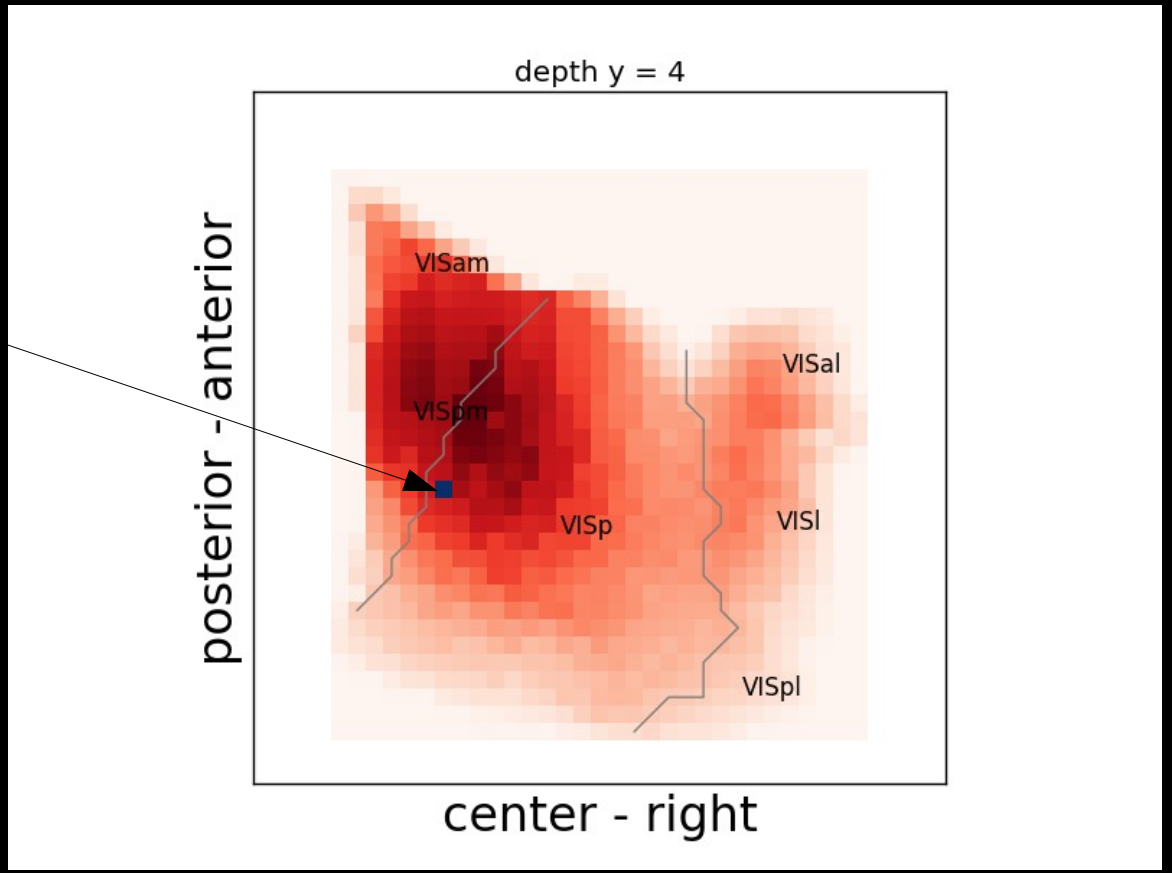
- 5908 x 5908 matrix
- Takes a few hours on typical machine
- Cross-validation selects $\lambda = 10^4$
- Cross-val **errors show improvement** over regional model (ipsilateral numbers):
  - Regional model: 44.3% regional 118% voxel
  - Voxel model: 18.8% regional 37% voxel
  - Roughly 2-3x improvement in predictive power

We solved the problem for visual areas using 27 *wildtype* injections

- 5908 x 5908 matrix
- Takes a few hours on typical machine
- Cross-validation selects $\lambda = 10^4$
- Cross-val **errors show improvement** over regional model (ipsilateral numbers):
  - Regional model: 44.3% regional | 118% voxel
  - Voxel model: 18.8% regional | 37% voxel
  - Roughly 2-3x improvement in predictive power
  - Relative MSE = $$\frac{\|Y_{\text{pred}}\|^2}{\frac{1}{2}\|Y_{\text{pred}}\|^2 + \frac{1}{2}\|Y_{\text{true}}\|^2}$$

Visualizing the matrix *W*

- Visualization of 1 row of *W*, corresponding to blue voxel
- Red shows projection vol
- “Virtual injection experiment”
- 2D, top-down view of 3D image
- Change the seed location to visualize complete connectivity



Sweeping virtual injections reveals overall connectivity patterns

- Show the movie!

My next steps

My next steps

- Flattening into cortical plane

My next steps

- Flattening into cortical plane
- Fan-out & fan-in (asymmetry?)
  - Size of projections from area A to B

My next steps

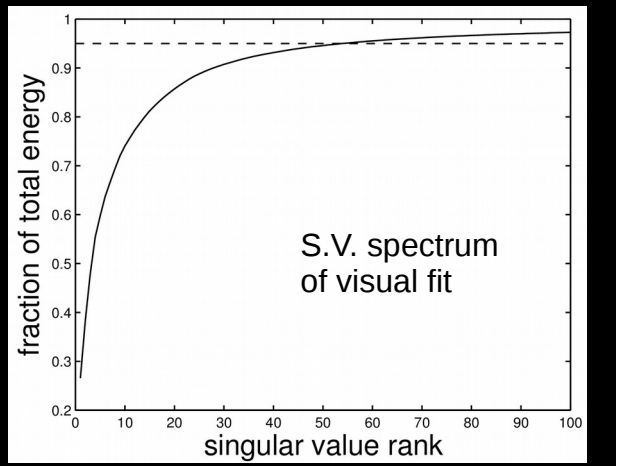
- Flattening into cortical plane
- Fan-out & fan-in (asymmetry?)
  - Size of projections from area A to B
- Retinotopy: have separate functional dataset

My next steps

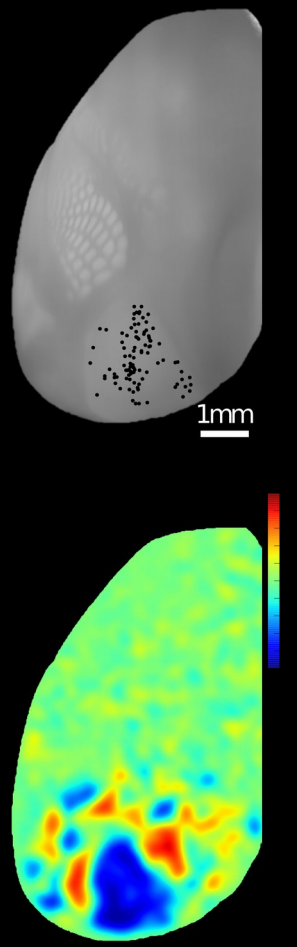
- Flattening into cortical plane
- Fan-out & fan-in (asymmetry?)
  - Size of projections from area A to B
- Retinotopy: have separate functional dataset
- Whole-brain at 100 µm voxel scale **is possible**
  - Huge matrix, but can compress (low rank)

My next steps

- Flattening into cortical plane
- Fan-out & fan-in (asymmetry?)
  - Size of projections from area A to B
- Retinotopy: have separate functional dataset
- Whole-brain at 100 µm voxel scale **is possible**
  - Huge matrix, but can compress (low rank)

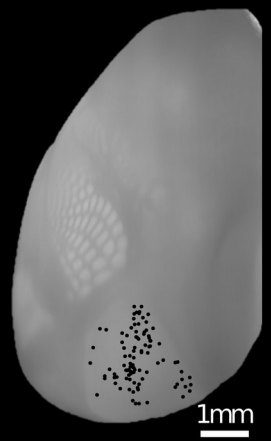


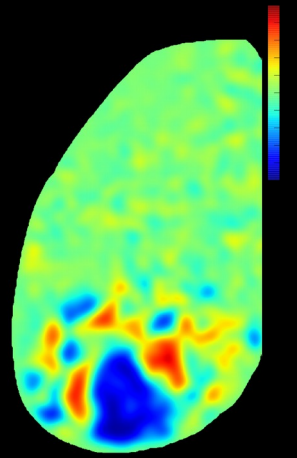
Voxel-based connectivity opens up new science



Voxel-based connectivity opens up new science

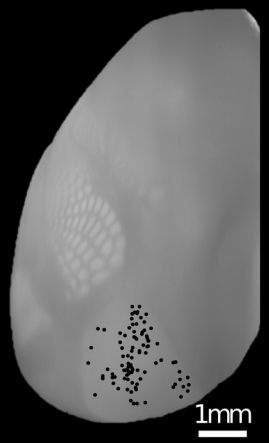
- General mathematical tool denoises and summarizes bulk tracing data

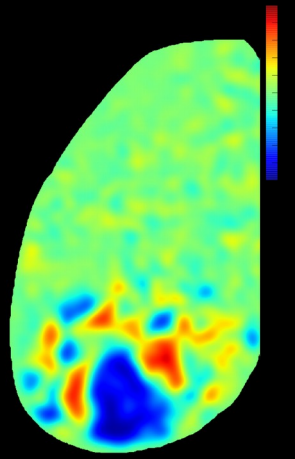




Voxel-based connectivity opens up new science

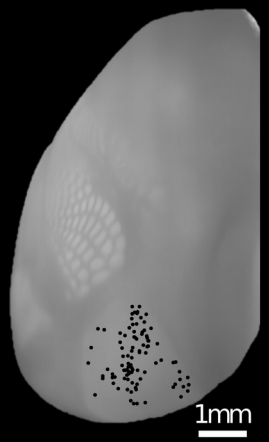
- General mathematical tool denoises and summarizes bulk tracing data
- Higher spatial resolution...
  - Relates to mesoscale functional (activity) data
  - Build better dynamical, computational models (Nick Cain)

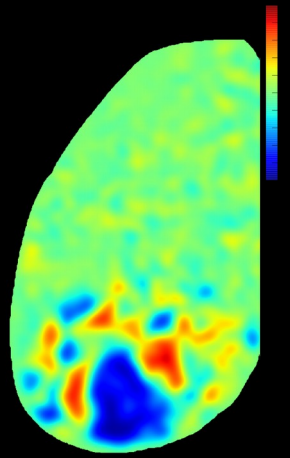




Voxel-based connectivity opens up new science

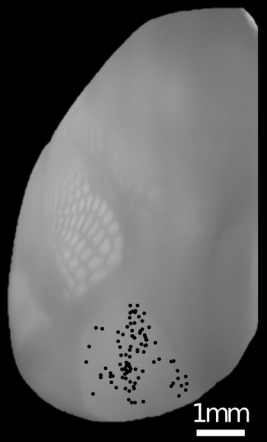
- General mathematical tool denoises and summarizes bulk tracing data
- Higher spatial resolution...
  - Relates to mesoscale functional (activity) data
  - Build better dynamical, computational models (Nick Cain)
- Connectivity-defined region boundaries
  - Factorization of W?

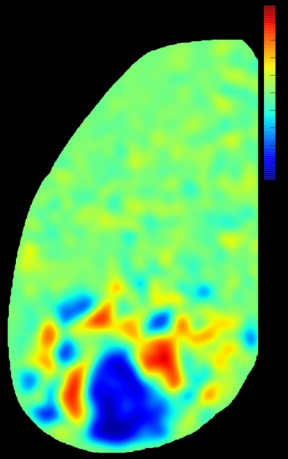




Voxel-based connectivity opens up new science

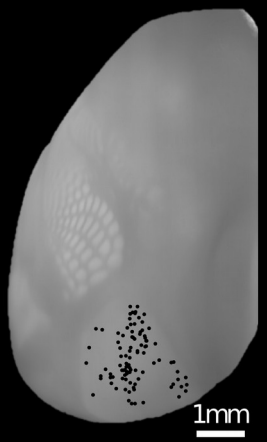
- General mathematical tool denoises and summarizes bulk tracing data
- Higher spatial resolution...
  - Relates to mesoscale functional (activity) data
  - Build better dynamical, computational models (Nick Cain)
- Connectivity-defined region boundaries
  - Factorization of W?
- Automatic ID of topography between regions (e.g. retinotopy)
  - Image from Jack Waters, Jun Zhuang, et al. preprint
  - Retinotopic sign map constructed using nearest-neighbors weighting
  - Many other known 'topies: somatosensory, auditory
  - Are there unknown maps, e.g. between higher areas?

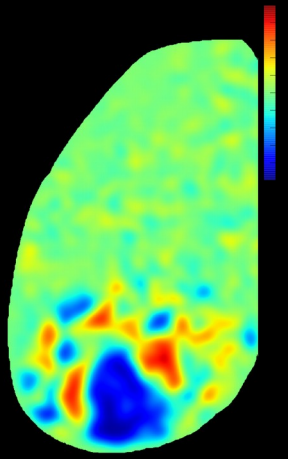




Voxel-based connectivity opens up new science

- General mathematical tool denoises and summarizes bulk tracing data
- Higher spatial resolution...
  - Relates to mesoscale functional (activity) data
  - Build better dynamical, computational models (Nick Cain)
- Connectivity-defined region boundaries
  - Factorization of W?
- Automatic ID of topography between regions (e.g. retinotopy)
  - Image from Jack Waters, Jun Zhuang, et al. preprint
  - Retinotopic sign map constructed using nearest-neighbors weighting
  - Many other known 'topies: somatosensory, auditory
  - Are there unknown maps, e.g. between higher areas?
- Combined with AIBS *Cre* data, can enhance layer-specificity, fan-out radii, etc.





THANK YOU

We wish to thank the Allen Institute for Brain Science founders,
Paul G. Allen and Jody Allen, for their vision, encouragement and support.

Eric Shea-Brown & group at UW
Boeing Fellowship, NSF, Simons Fellowship in Mathematics
Hyak supercomputer system at the University of Washington

ALLENINSTITUTE.ORG
BRAIN-MAP.ORG

ALLEN INSTITUTE for BRAIN SCIENCE

Special shout out! Julie Harris, Jennifer Whitesell, Karla Hirokawa, Stefan Mihalas, Nick Cain, Ram Iyer, Corrine Teeter, Doug Ollerenshaw, David Feng, Lydia Ng, Michael Buice