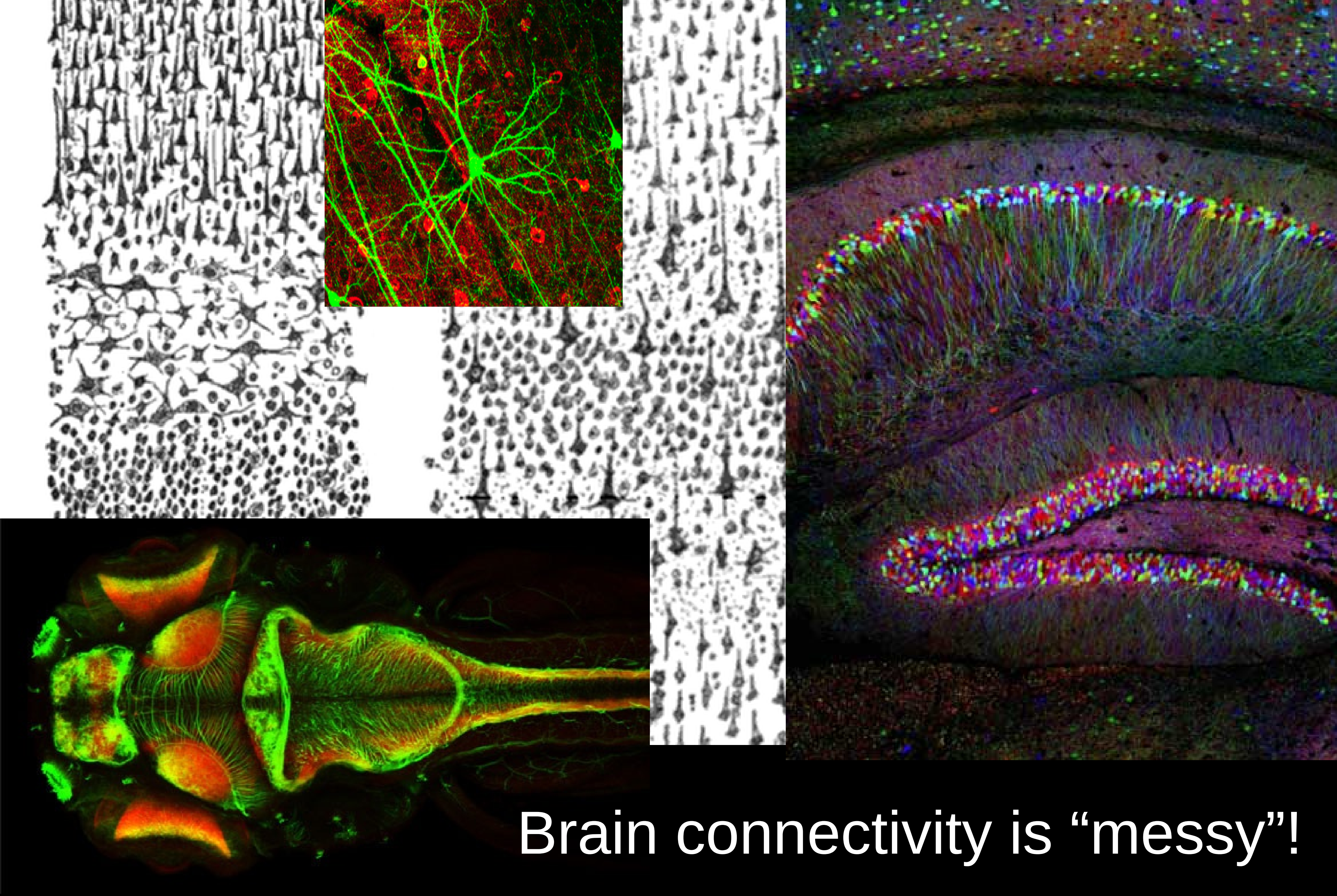
This Brain Is a Mess: Inference, Random Graphs, and Biophysics to Disentangle Neuronal Networks

Kameron Decker Harris

November 30, 2017

Acknowledgements

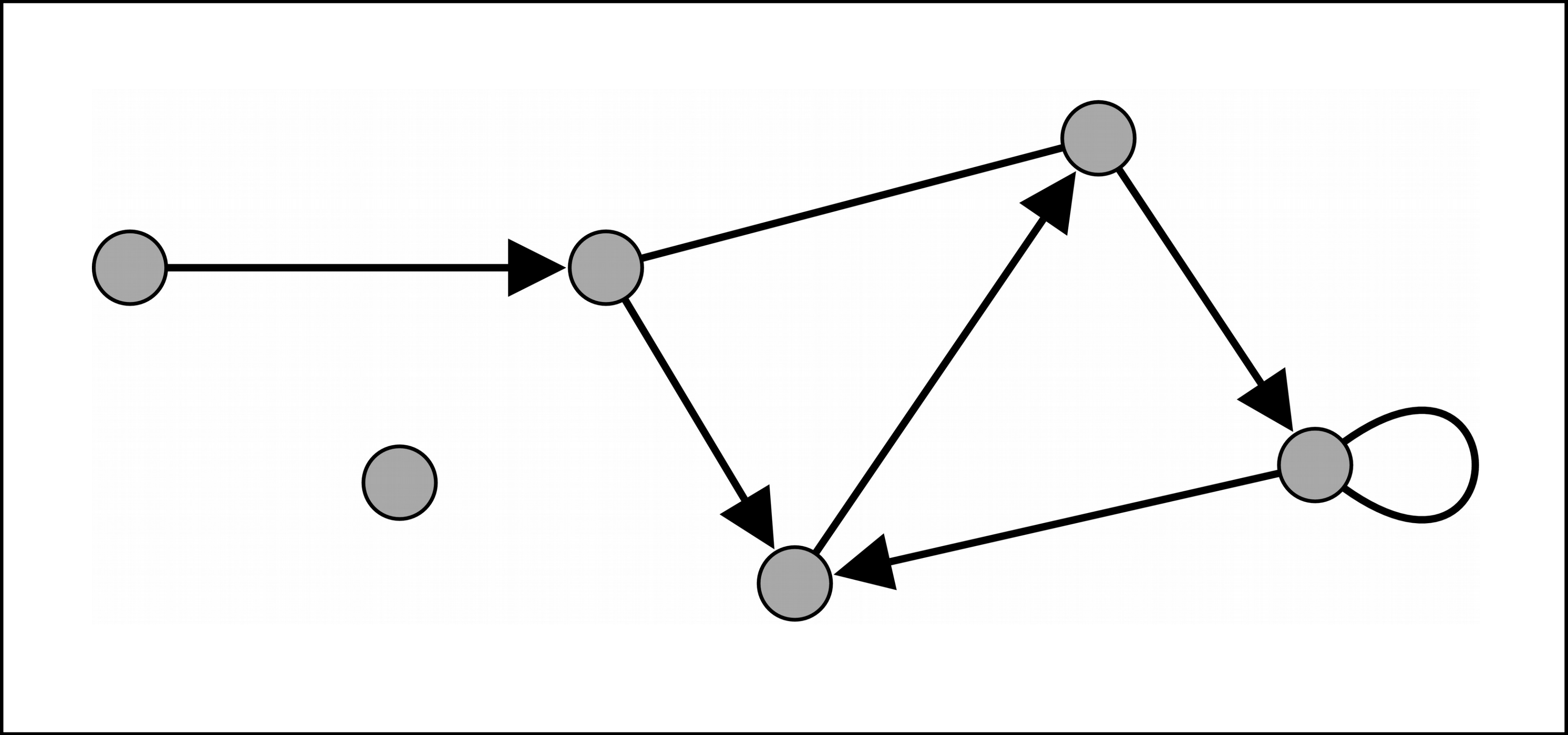
- **Eric Shea-Brown** & team:
  - Josh Mendoza
  - Iris Shi
  - Doris Voina
  - Matt Farrell
  - Ali Weber
  - Kathleen Champion
  - Tim Oleskiw
  - Alex Cayco-Gajic
  - Guillaume Lajoie
  - Yu Hu
  - Braden Brinkman
  - Hannah Choi
  - Merav Stern
  - Gabrielle Gutierrez
  - Joel Zylberberg
- Other folks:
  - Chris Danforth, Peter Dodds (UVM)
  - Ashok Litwin-Kumar, Larry Abbott, Haim Sompolinsky
- Nino Ramirez & the "respirators:"
  - Tatiana Dashevskiy
  - Fred Garcia
  - Aguan Wei
- Stefan Mihalas & Allen Institute "connectors:"
  - Joe Knox
  - Nile Graddis
  - Nick Cain
  - David Feng
  - Lydia Ng
- Ioana Dumitriu & the "graphons:"
  - Gerandy Brito
  - Thanks also to Marina Meilă
- UW AMATH:
  - Keshanie Dissanayake
  - Lauren Lederer
  - Derek Franz
  - Alan Perry
  - Tony Garcia
  - Everyone else!



Brain connectivity is “messy”!

Credits: Lee et al. (2006) cortical pyramidal cell; Santiago Ramon y Cajal; UCL Zebrafish Group; Tamily Weissman, Jean Livet, Ryan Draft (mouse hippocampus)

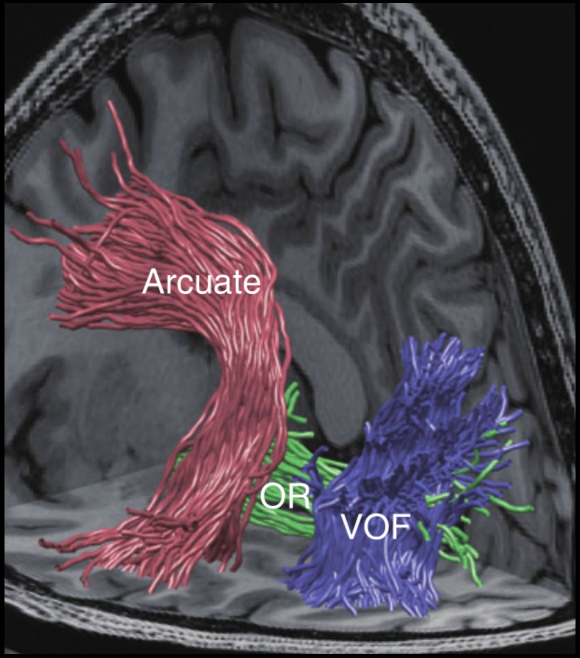
Neuron wiring forms a **network** or **graph**



Structural connectivity data

Structural connectivity data

Diffusion MRI
Macroscopic

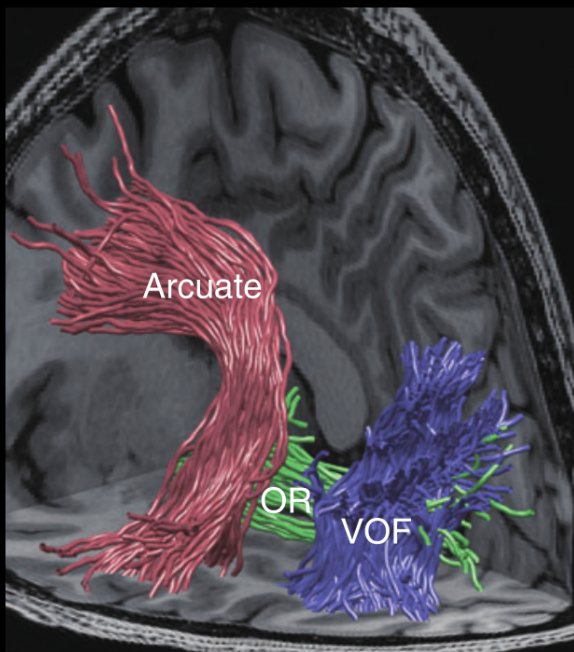


Takemura et al. (2016)

1-3 mm
Undirected
Non-destructive

Structural connectivity data

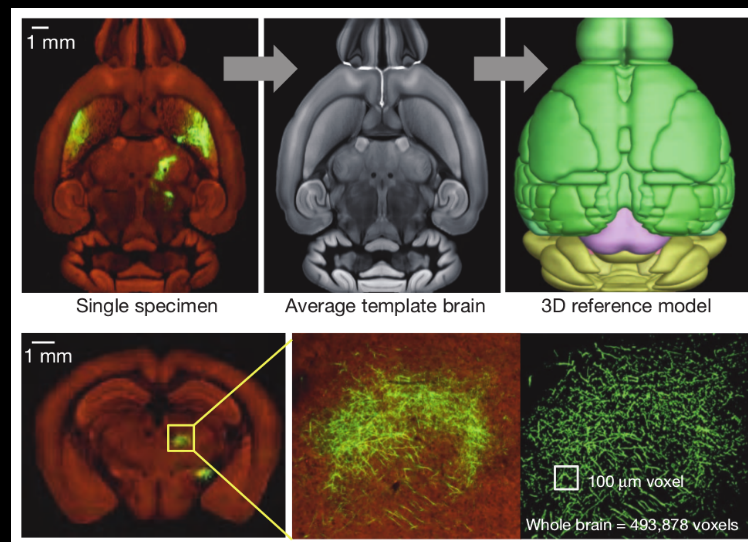
Diffusion MRI
Macroscopic



Takemura et al. (2016)

1-3 mm
Undirected
Non-destructive

Tracing & tomography
Mesoscopic



Oh et al. (2014)

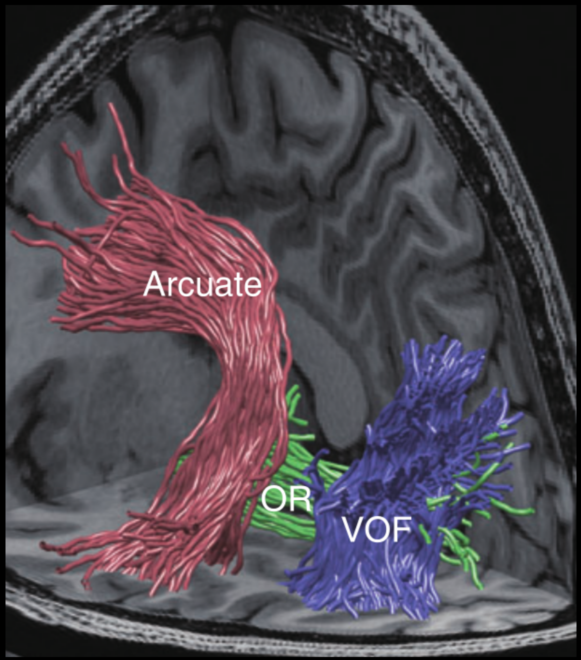
10-100 µm
Directional
100's of neurons

Increasing resolution

All require algorithms!

Structural connectivity data

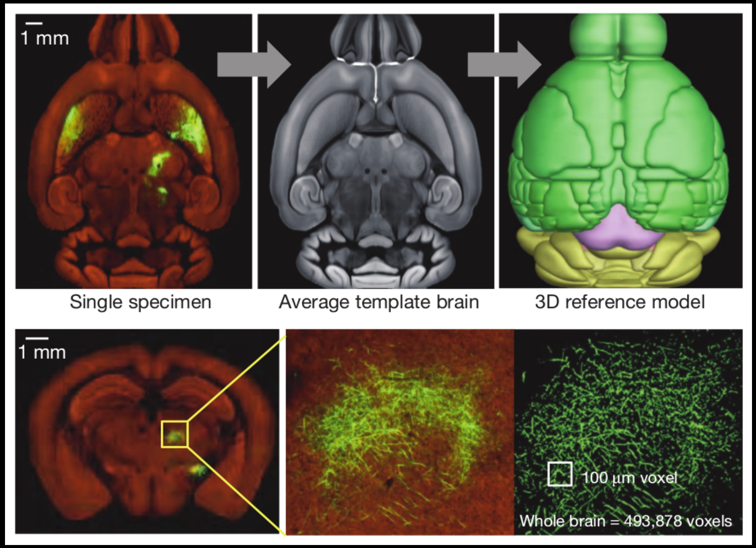
Diffusion MRI
Macroscopic



Takemura et al. (2016)

- 1-3 mm
- Undirected
- Non-destructive

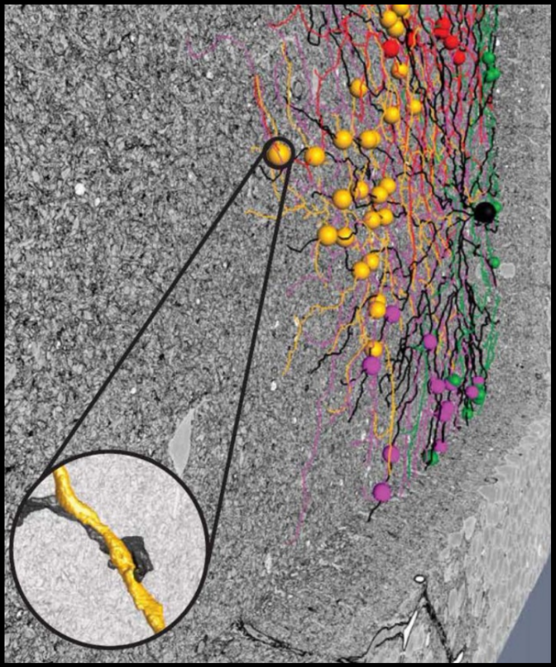
Tracing & tomography
Mesoscopic



Oh et al. (2014)

- 10-100 µm
- Directional
- 100's of neurons

Electron Microscopy
Microscopic



Kleinfeld et al. (2011)

- 10 nm
- Neurons & synapses

Increasing resolution

All require algorithms!

Connectivity questions

Connectivity questions

1) How do we infer mesoscopic connections?

Connectivity questions

1) How do we infer mesoscopic connections?

2) What are good microscopic models?

Connectivity questions

1) How do we infer mesoscopic connections?
2) What are good microscopic models?
3) How does connectivity affect brain dynamics?

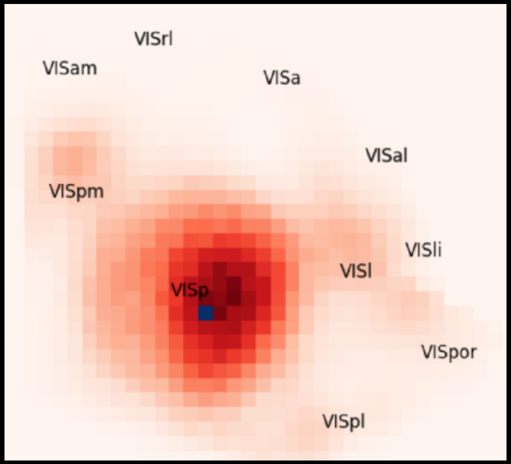
Connectivity questions

1) How do we infer mesoscopic connections?
2) What are good microscopic models?
3) How does connectivity affect brain dynamics?

Machine learning for neuronal network data

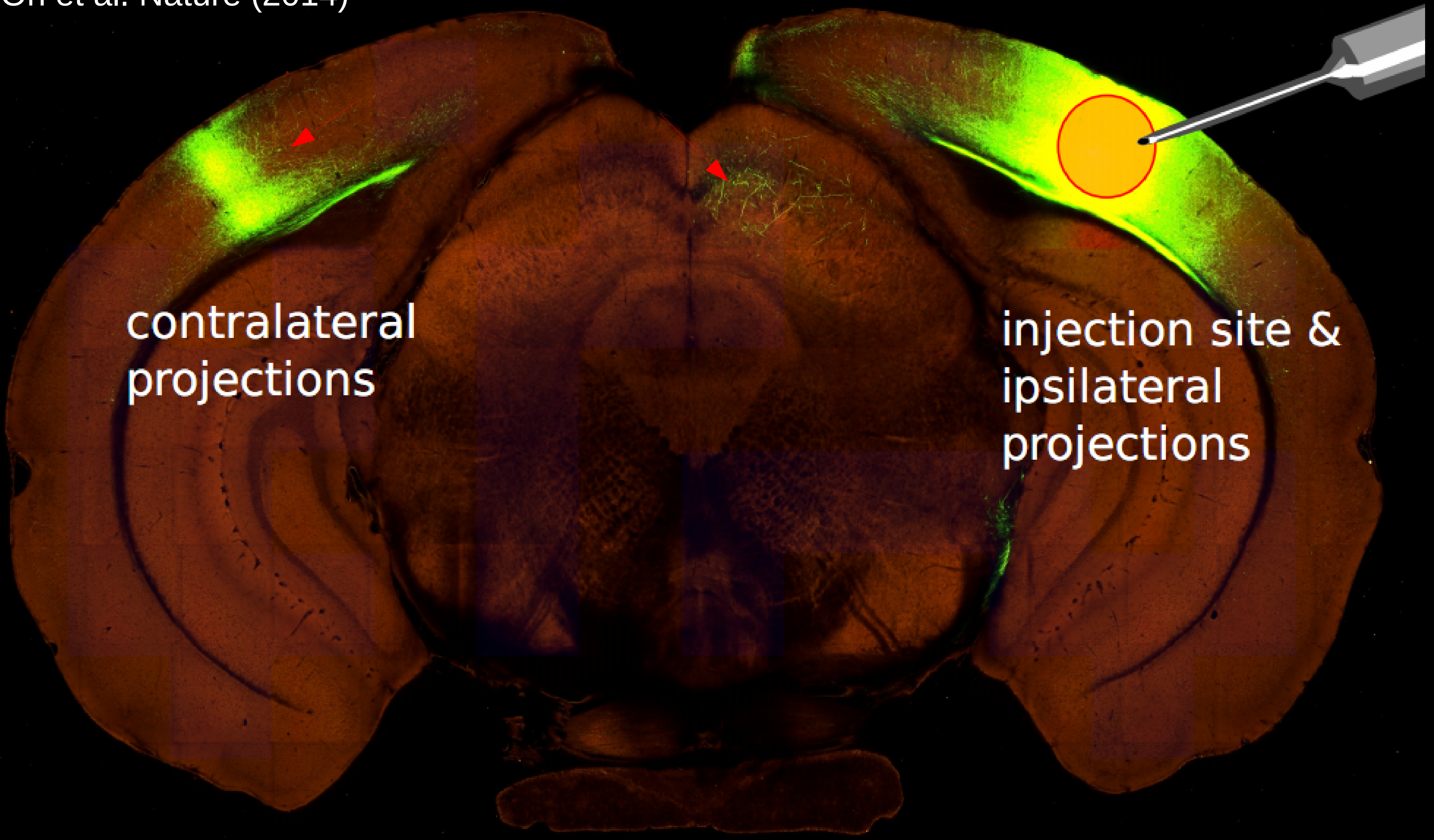
Published as:
Harris, Mihalas, Shea-Brown.
“Nonnegative spline regression of incomplete tracing data reveals high resolution neural connectivity.”
In proceedings of NIPS. 2016.

Ongoing work with Joe Knox and others at Allen Institute

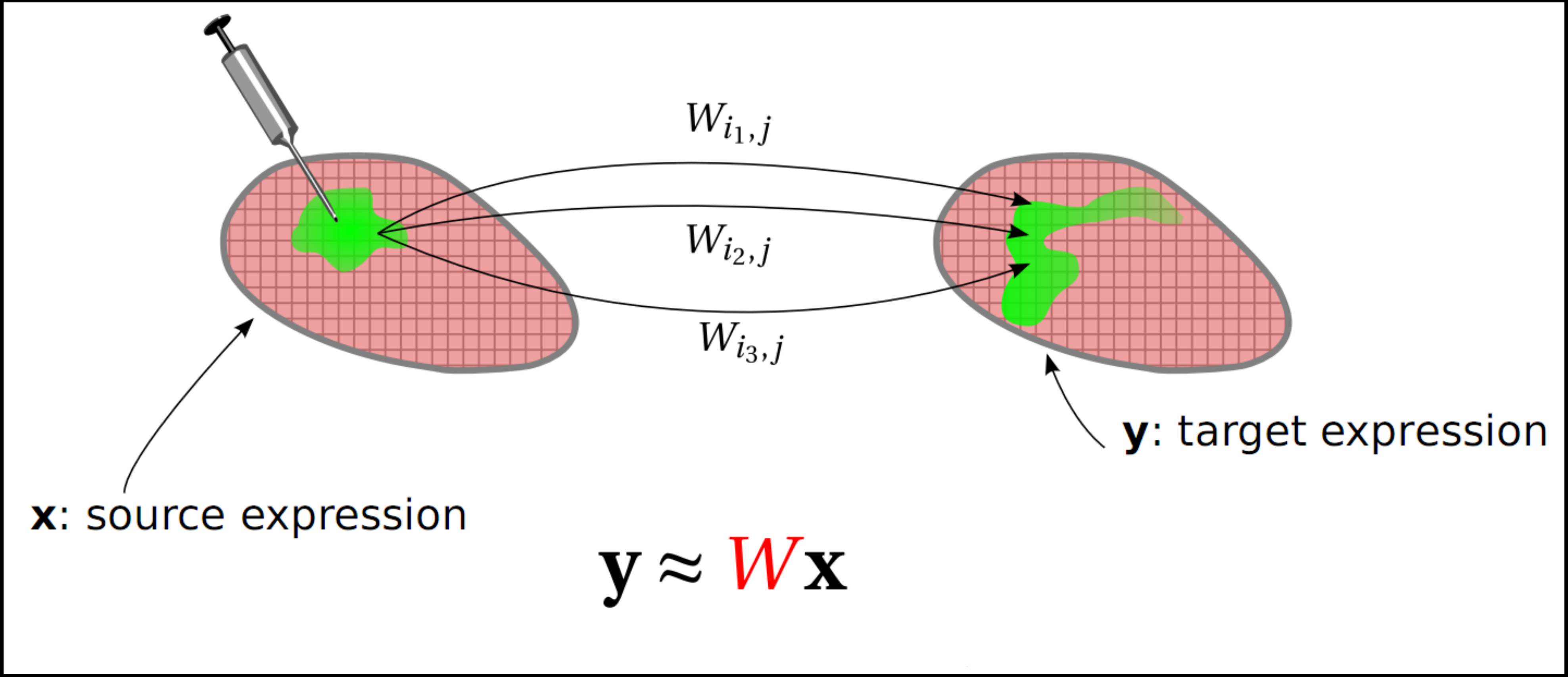


Mesoscale viral tracing experiments
Allen Institute for Brain Science (AIBS)

Oh et al. Nature (2014)



Model connectivity as a matrix



Challenges for inference:

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined

2) Projection strength unknown at injection site

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined

2) Projection strength unknown at injection site

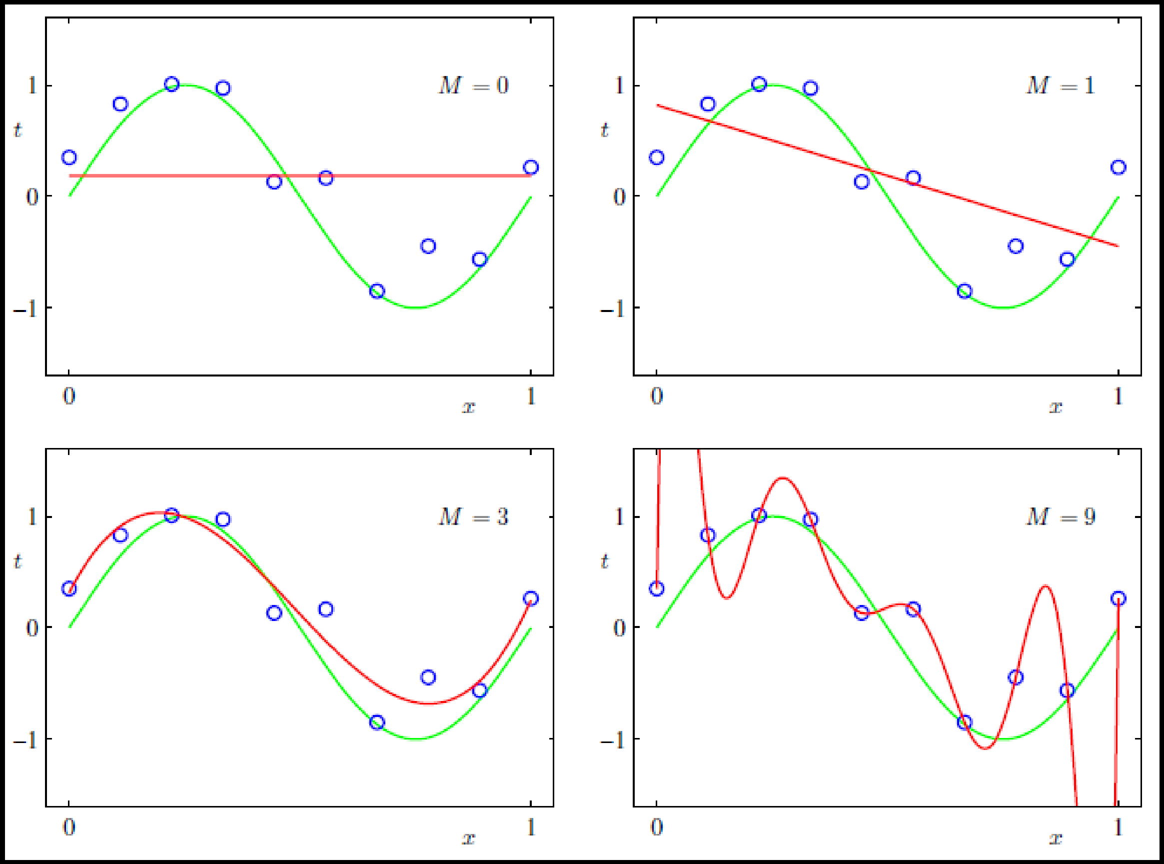
3) Dimensionality of unknown *W*

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined
   - Fill in gaps with smoothing regularizer
2) Projection strength unknown at injection site
3) Dimensionality of unknown *W*

Regularization prevents over-fitting

High bias (underfit)

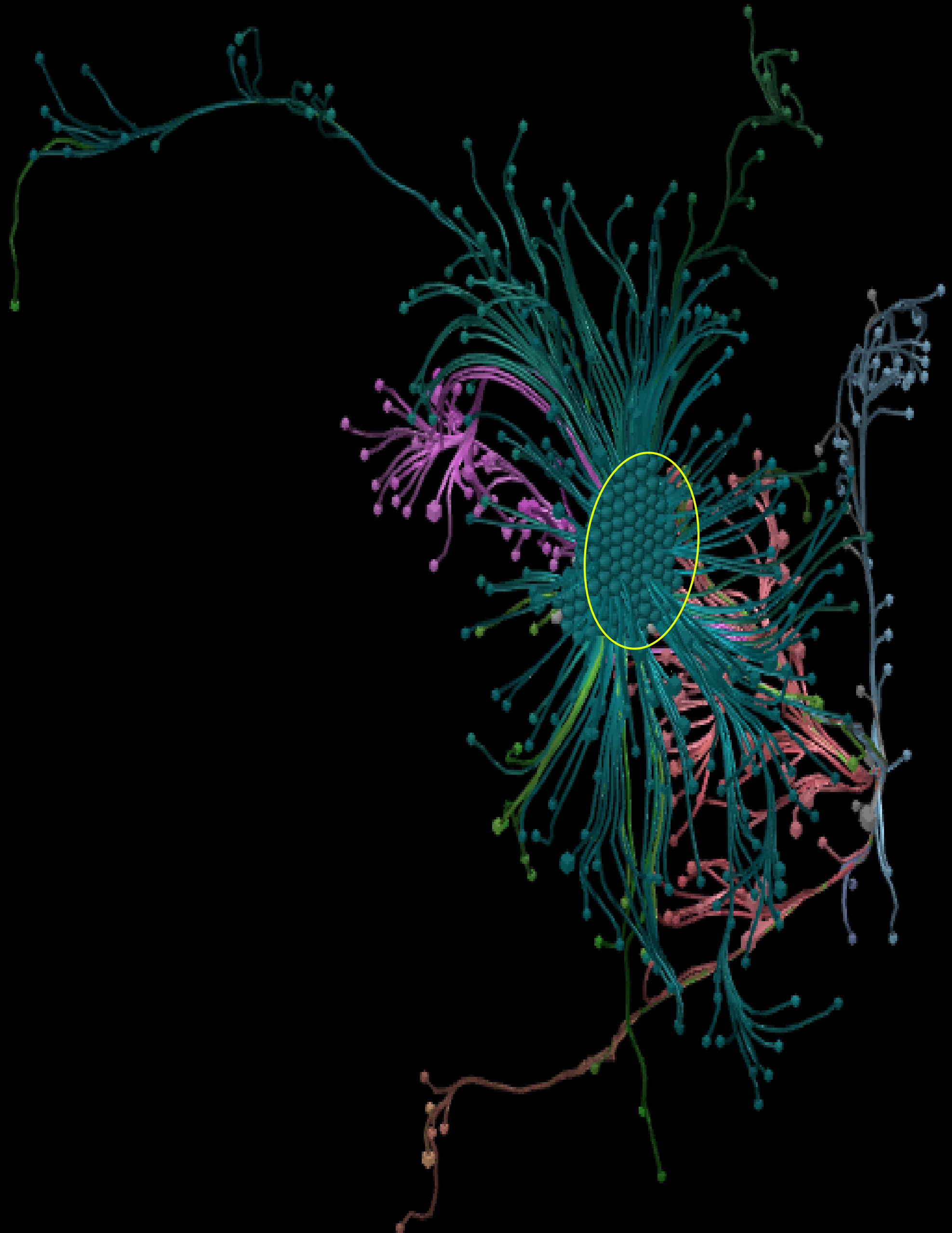


Just right

High variance (overfit)

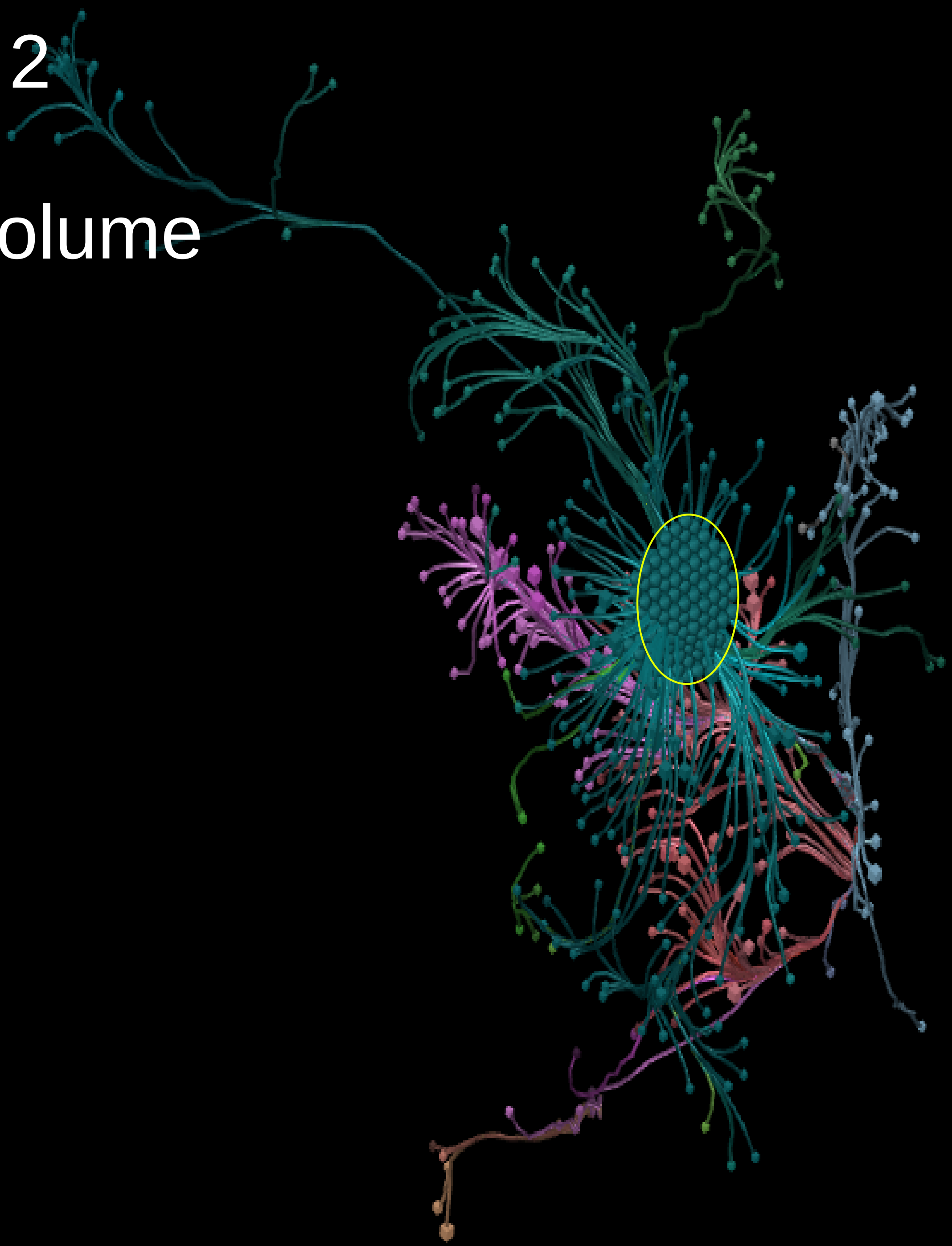
Bishop “Pattern Recognition & Machine Learning”

Injection 1 into VISp

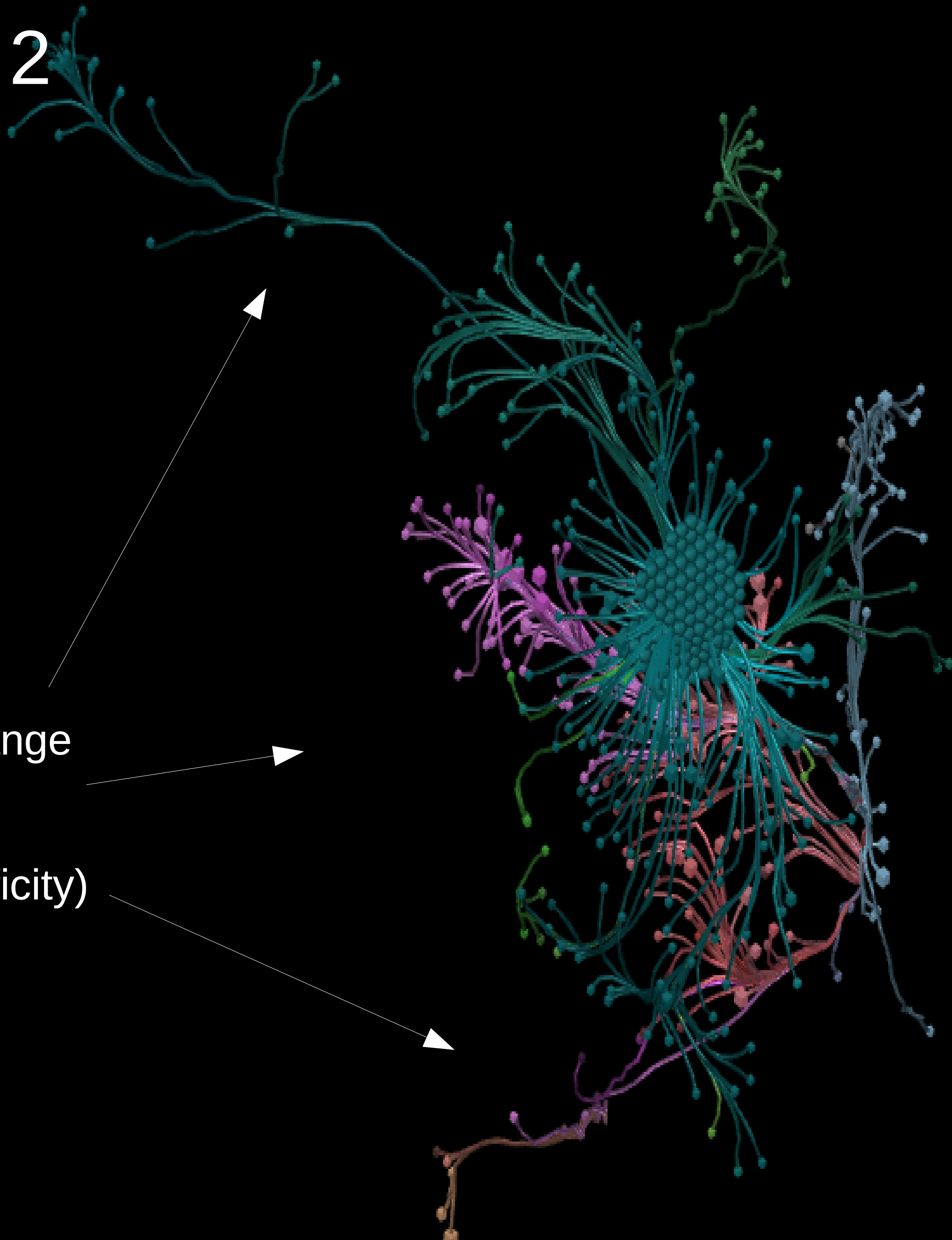


Images made with
AIBS Brain Explorer

Injection 2
Nearby
Similar volume

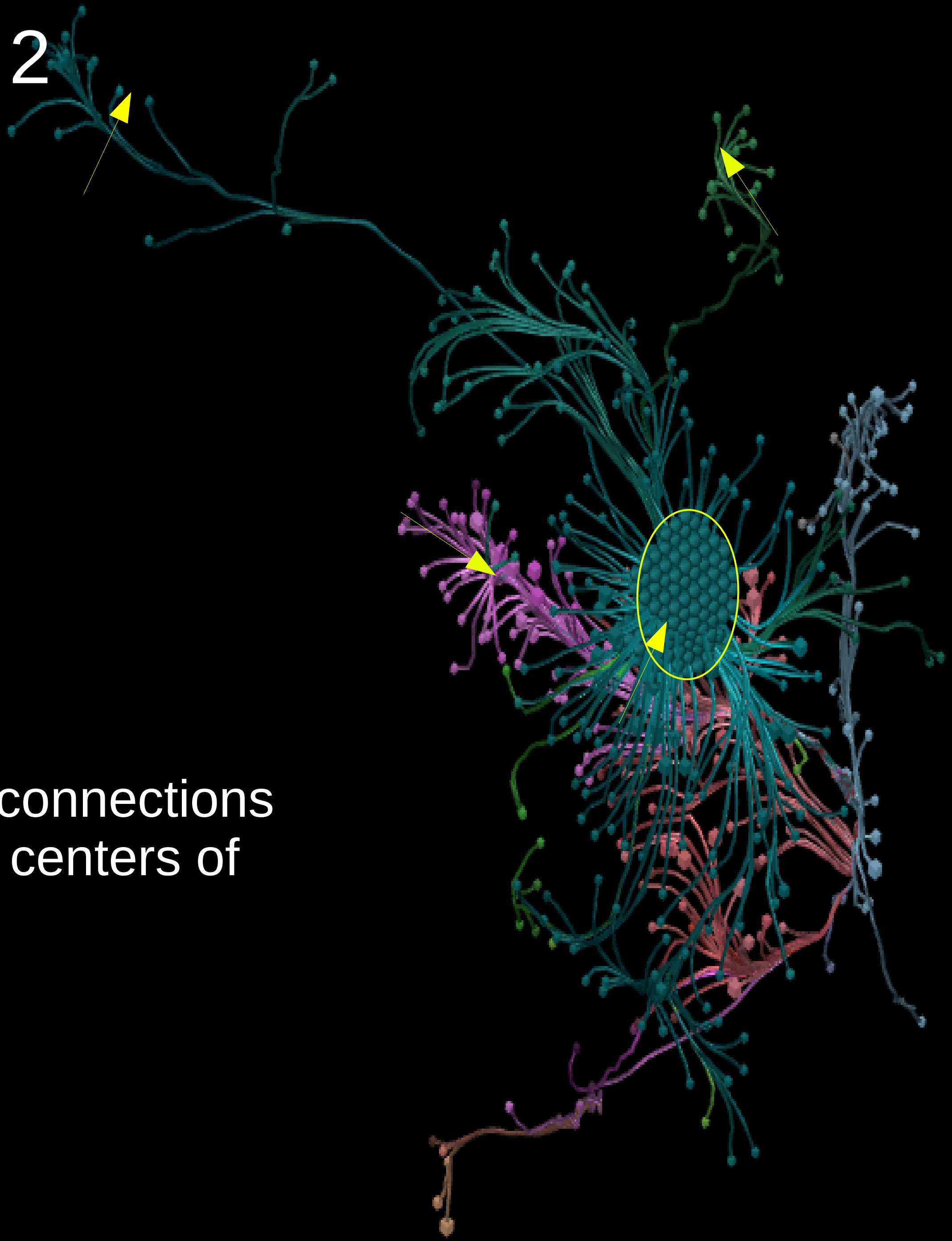


Injection 2



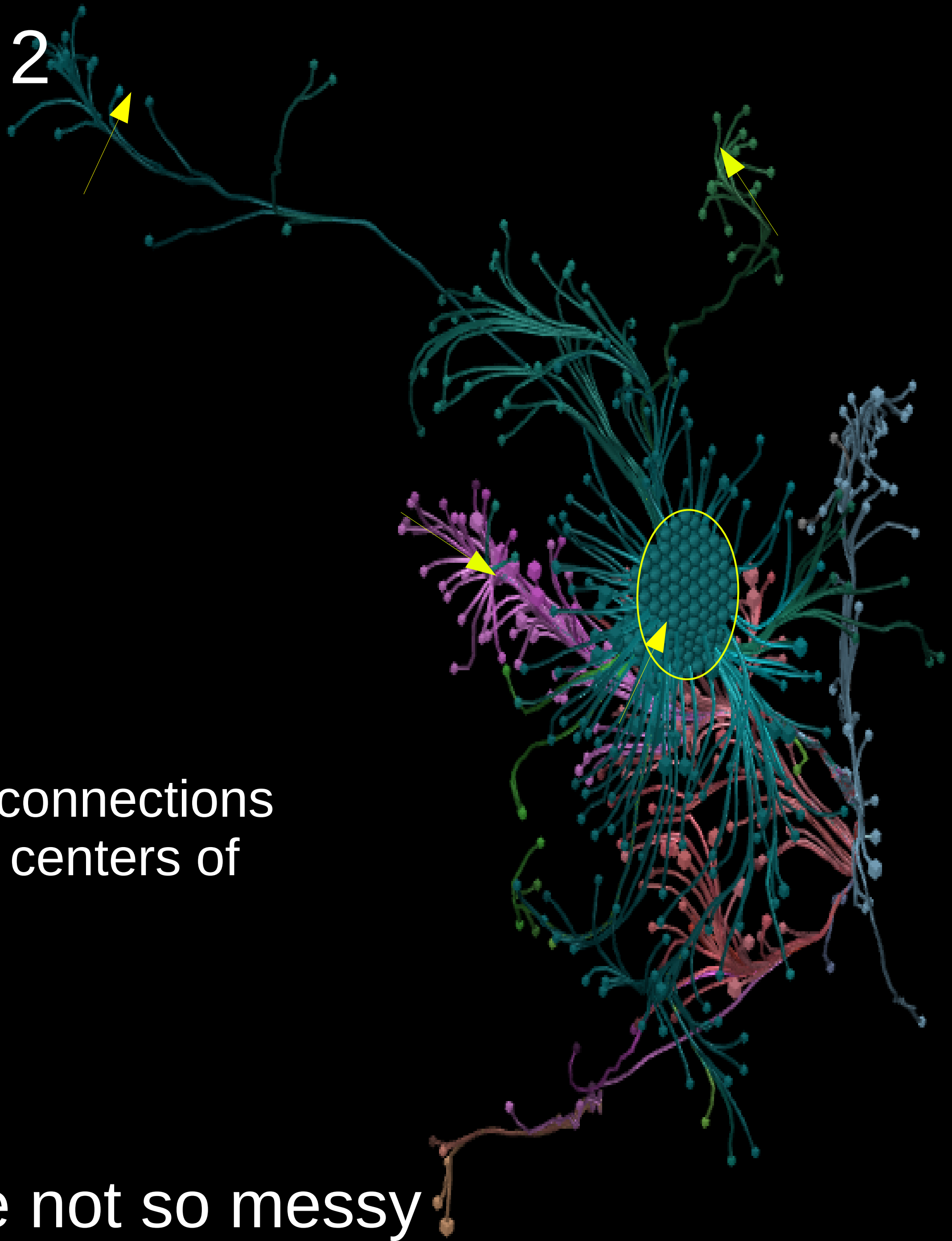
Same long-range clusters of projections (region specificity)

Injection 2



Long-range connections have shifted centers of mass

Injection 2



Long-range connections have shifted centers of mass

Mesoscale not so messy
Smoothness assumption is reasonable

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined

   – Fill in gaps with smoothing regularizer

2) Projection strength unknown at injection site

   – Ignore unknown residuals

3) Dimensionality of unknown *W*

Netflix challenge: matrix completion

Ratings of movies →

Users ↓

		-1		
			1	
1	1	-1	1	-1
1				-1
		-1		

1	1	-1	1	-1
1	1	-1	1	-1
1	1	-1	1	-1
1	1	-1	1	-1
1	1	-1	1	-1

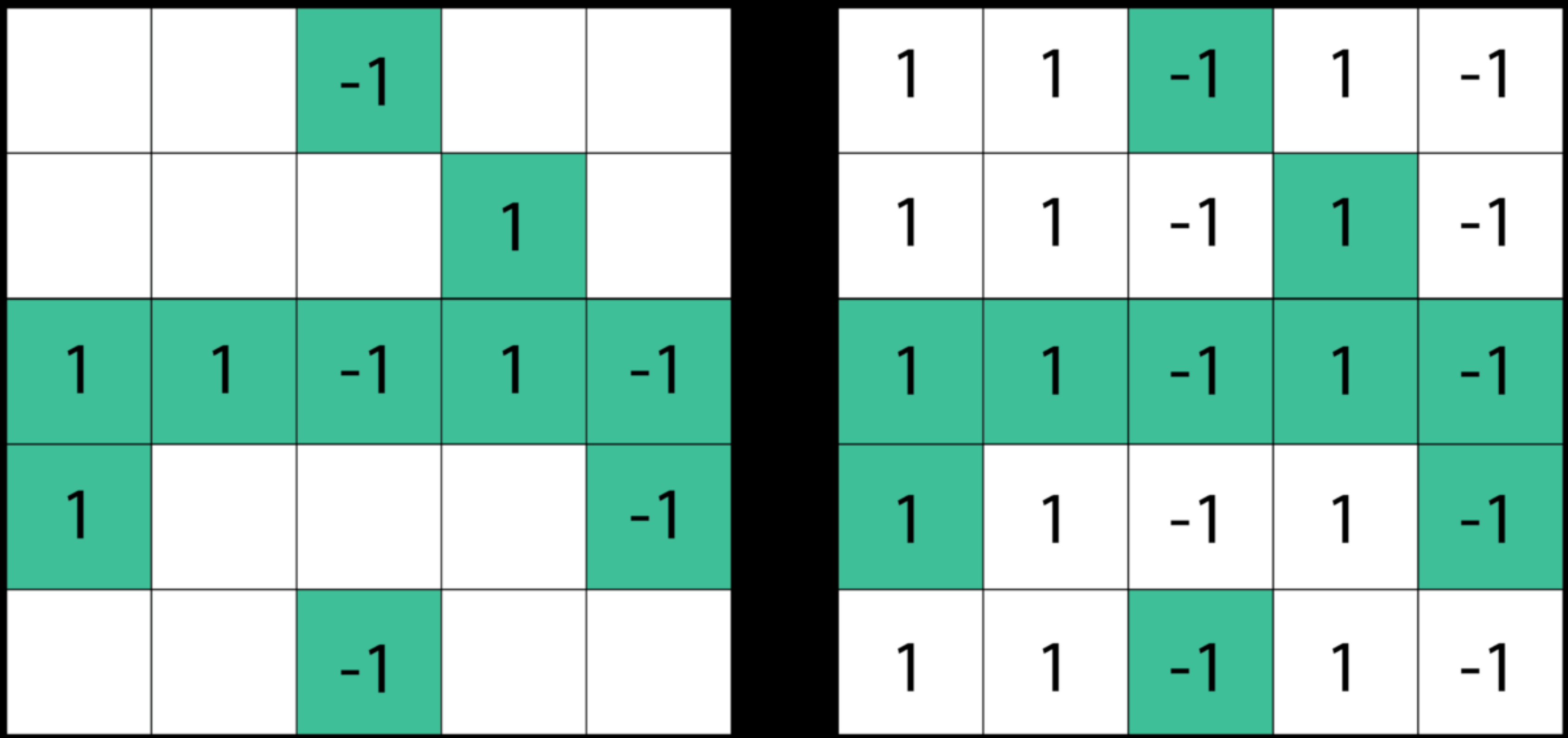
Lepeisi, https://commons.wikimedia.org/w/index.php?curid=45676223

Observation *M* — Full solution *W*, rank 1

Netflix challenge: matrix completion

Ratings of movies

Users



Lepeisi, https://commons.wikimedia.org/w/index.php?curid=45676223

Observation *M*

Full solution *W*, rank 1

$$\min_{W} \underbrace{\|W\|_*}_{\text{Complexity of } W} \text{ where } \underbrace{\boxed{P(W - M)}}_{\text{Match } W \text{ to data } M \text{ where observed}} = 0$$

Challenges for inference:

1) Injection sites do not cover whole brain; model is underdetermined
   - Fill in gaps with smoothing regularizer
2) Projection strength unknown at injection site
   - Ignore unknown residuals
3) Dimensionality of unknown W
   - Make $W = UV$ low rank

Both regularization and compression

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Goodness of fit
(loss)

Roughness penalty
(regularization, prior)

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Squared Frobenius norms = sum of squares of matrix entries
= Gaussian noise model

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Unknown weight matrix

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Injection data

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Projection data

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Deals with holes in data, just like **matrix completion**

Ignores residuals in injection sites

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Controls strength of smoothing

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Laplacian “roughness” of *W*

Can respect region boundaries

6-dimensional!

Spline regression model of connectome

- Find *W* nonnegative that minimizes the expression

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

Problem is convex:

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

We found *W* for mouse visual cortex

- 7497 x 7497 matrix fit with 28 injections
- **Marked improvement** over regional model:

–	Regional model:	48% regional	107% voxel
–	Voxel model:	16% regional	33% voxel

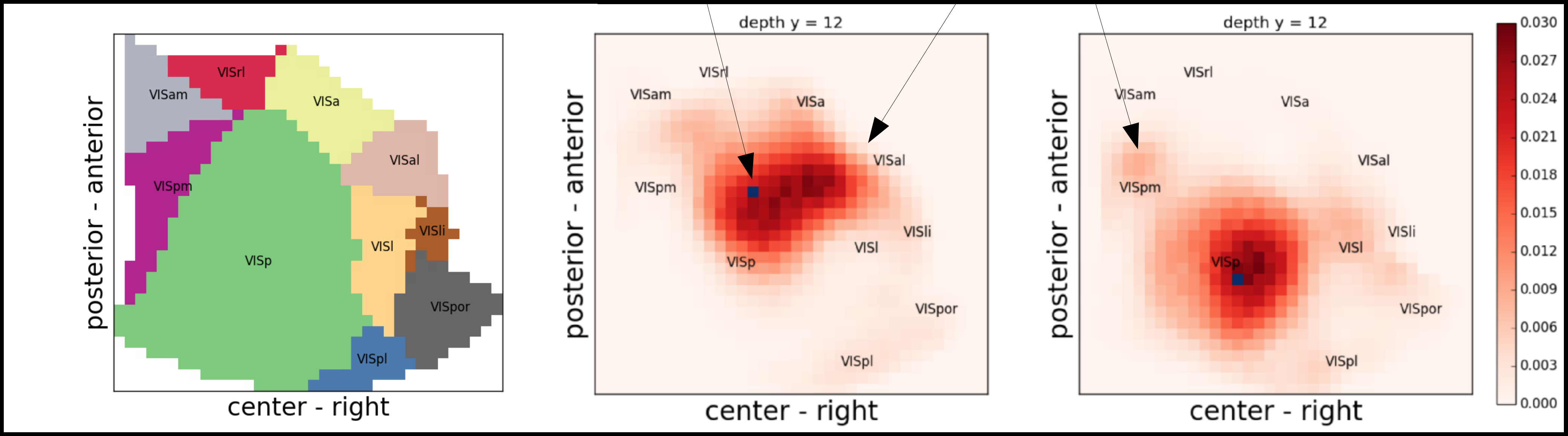
$$\frac{\|Y_{\mathrm{pred}}\|^2}{\frac{1}{2}\|Y_{\mathrm{pred}}\|^2 + \frac{1}{2}\|Y_{\mathrm{true}}\|^2}$$

Applied to visual cortex we see hints of retinotopy

Maps of retinal (visual) space between areas

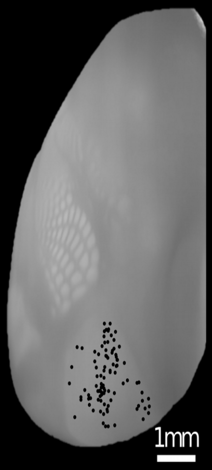
Source voxel

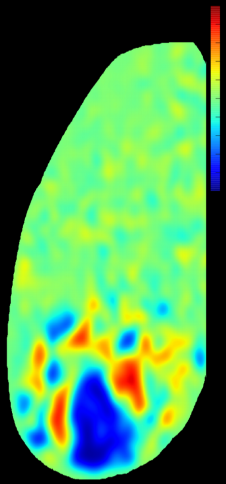
"Blobby" projections move with source



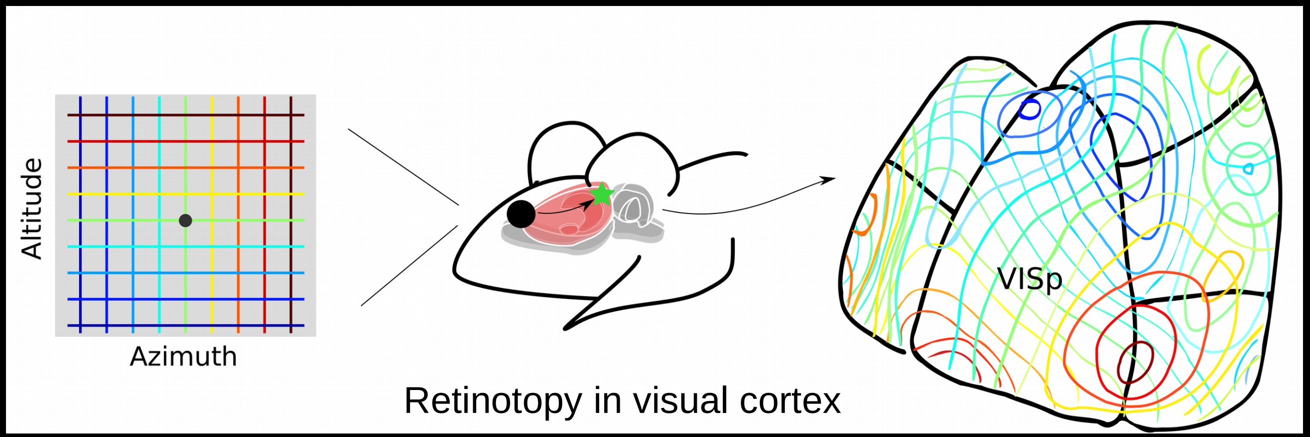
Spatial connectivity opens exciting scientific directions

- Comparable to neuron activity data
  - e.g., Kim et al. Cell Reports (2016), “Crystal Skull”
- Topography between regions (retinotopy, tonotopy, etc.)
- Cell-type specific data: E/I, layers, etc.
- Connectivity-defined regions?





Zhuang, et al. eLife (2017)



Conclusions: mesoscopic inference

Conclusions: mesoscopic inference

- New spatial inference method tailored to data

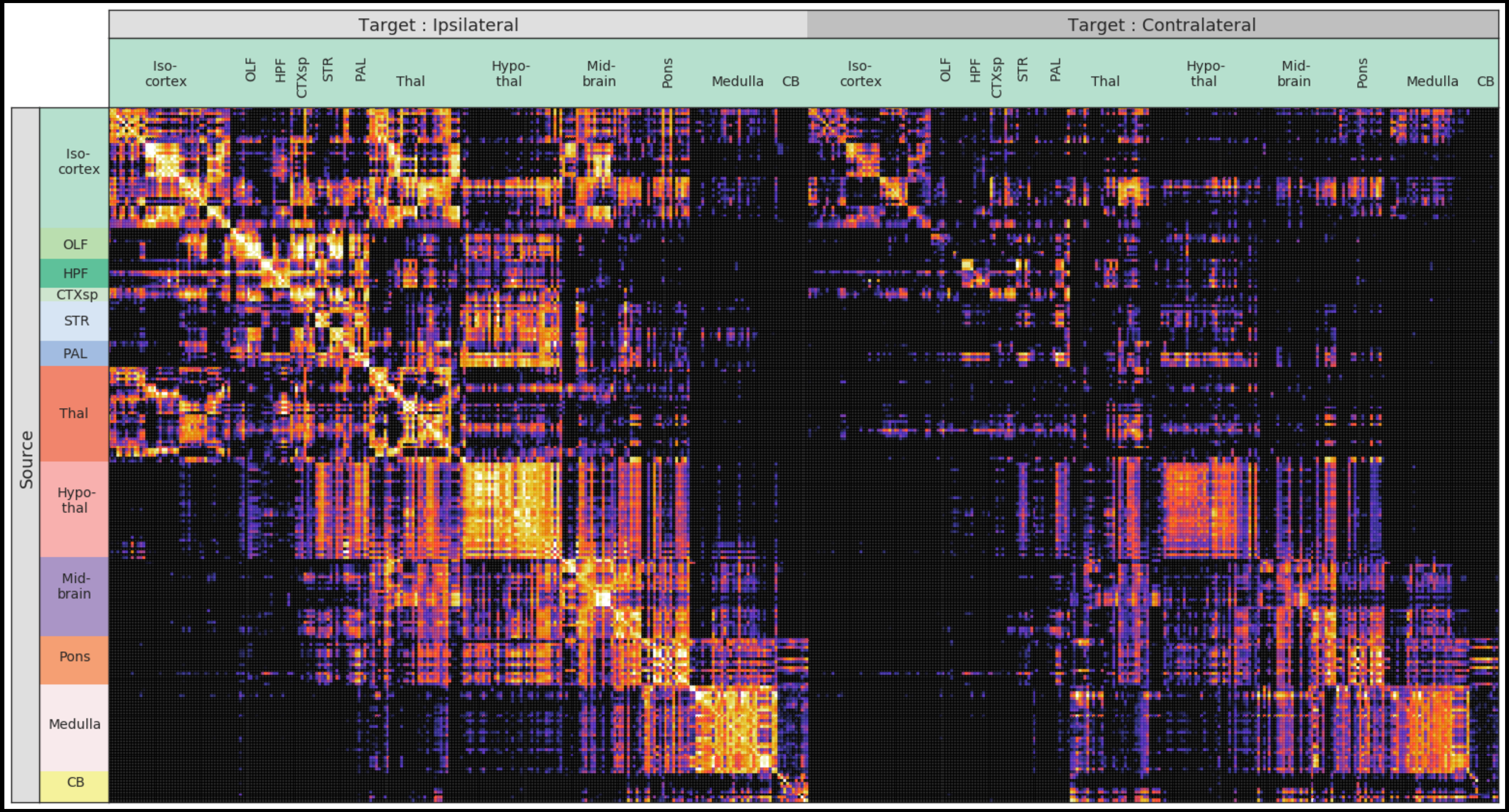
Conclusions: mesoscopic inference

- New spatial inference method tailored to data
  - More predictive than before

Conclusions: mesoscopic inference

- New spatial inference method tailored to data
  - More predictive than before
  - Improves regional models, too!

Joe Knox (AIBS)



Connectivity questions

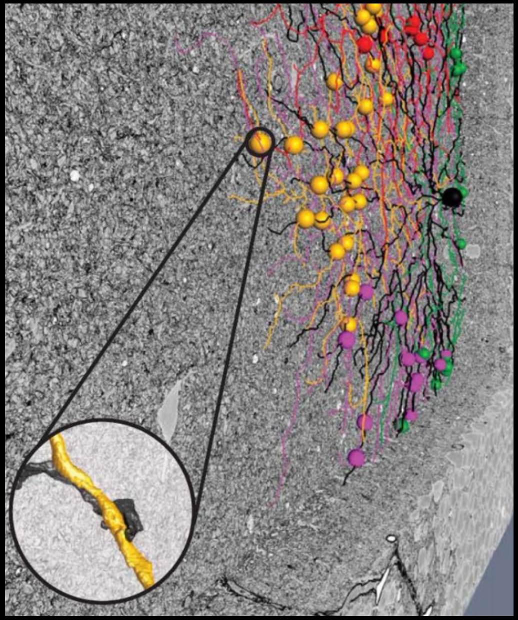
1) How do we infer mesoscopic connections?

2) What are good microscopic models?

3) How does connectivity affect brain dynamics?

Zooming in with random graphs

In preparation:
Brito, Dumitiru, Harris.
“Spectral gap in random bipartite biregular graphs and its applications.”

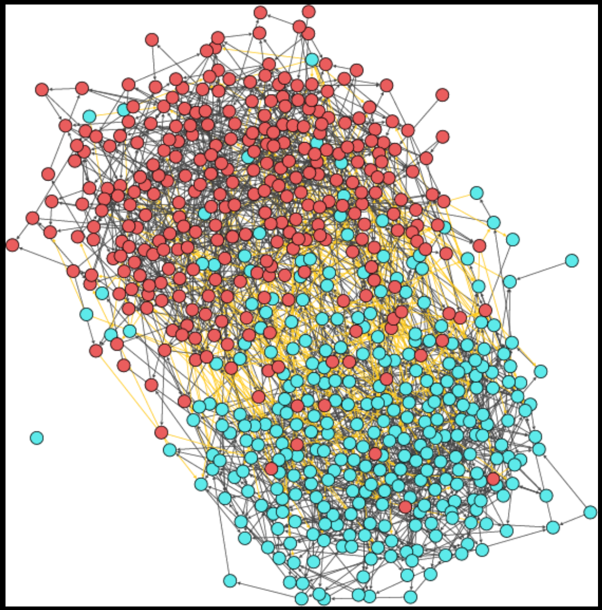


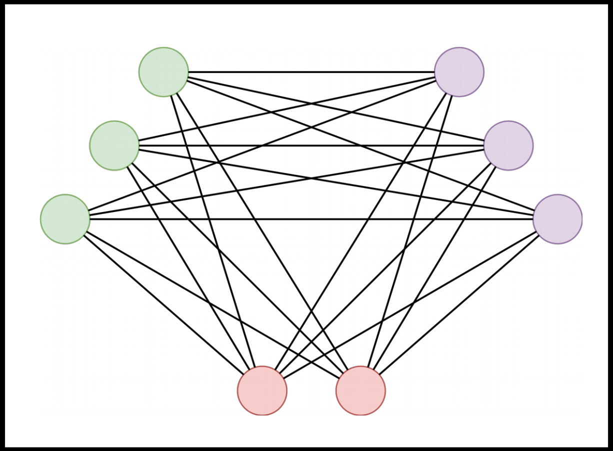
Kleinfeld et al. (2011)

Random graphs can match measureable microscopic features

Joshua Mendoza

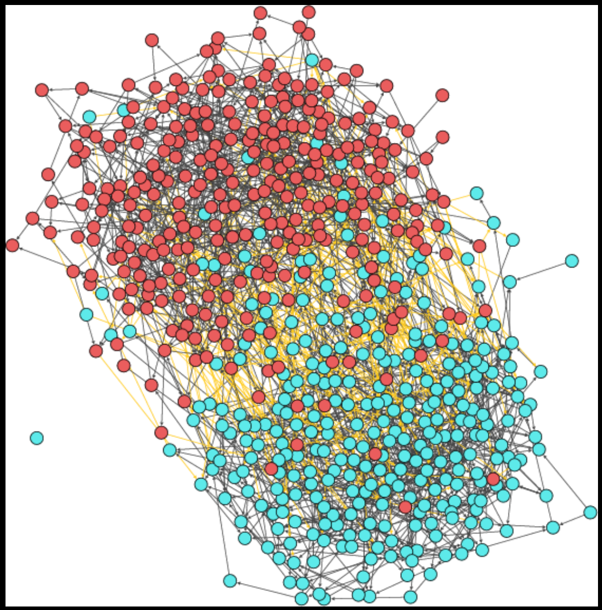
- Example statistics:
  - Average # connections (degree)
  - Number of cycles
  - Other subgraph counts



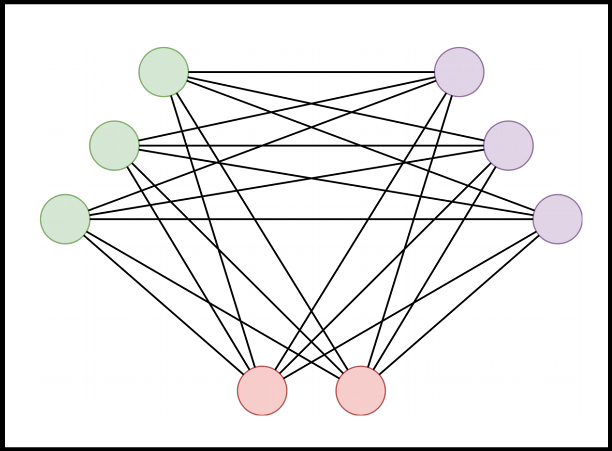


Random graphs can match measureable microscopic features

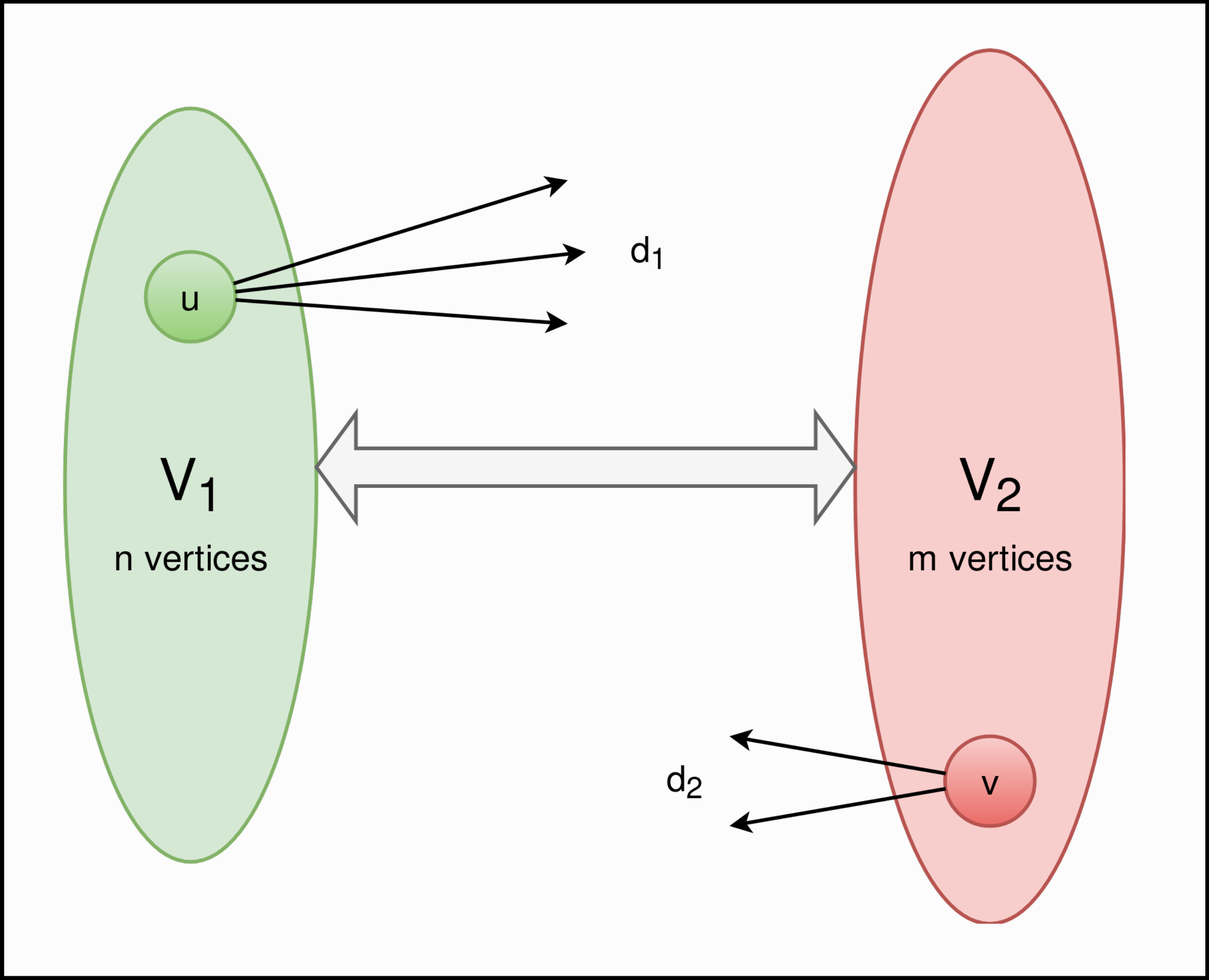
Joshua Mendoza



- Example statistics:
  - Average # connections (degree)
  - Number of cycles
  - Other subgraph counts
- Community structure
  - Block models
  - Multi-partite graphs



Bipartite, biregular random graphs



Fixed d’s mean these graphs are **very sparse**

We found a spectral “gap!”

- $\lambda_1 \gg \lambda_2$ → **expander**

Extends past work for d-regular graphs:

Friedman (2003, 2004)
Alon (1986)
Bordenave (2015)
Angel, Friedman, Hoory (2015)
Marcus, Spielman, Srivastava (2013)

We found a spectral “gap!”

- $\lambda_1 \gg \lambda_2$ → **expander**
- Many applications:
  - Random walks
  - Community detection & spectral clustering
  - Error correcting codes
  - Matrix completion

Extends past work for d-regular graphs:

Friedman (2003, 2004)
Alon (1986)
Bordenave (2015)
Angel, Friedman, Hoory (2015)
Marcus, Spielman, Srivastava (2013)

We found a spectral “gap!”

- $\lambda_1 \gg \lambda_2$ → **expander**
- Many applications:
  - Random walks
  - Community detection & spectral clustering
  - Error correcting codes
  - Matrix completion
- Can measure network parameters in experiments

Extends past work for d-regular graphs:

Friedman (2003, 2004)
Alon (1986)
Bordenave (2015)
Angel, Friedman, Hoory (2015)
Marcus, Spielman, Srivastava (2013)

We found a spectral “gap!”

- $\lambda_1 \gg \lambda_2$ → **expander**
- Many applications:
  - Random walks
  - Community detection & spectral clustering
  - Error correcting codes
  - Matrix completion

★ Can measure network parameters in experiments

Extends past work for d-regular graphs:

Friedman (2003, 2004)
Alon (1986)
Bordenave (2015)
Angel, Friedman, Hoory (2015)
Marcus, Spielman, Srivastava (2013)

Hold that thought!

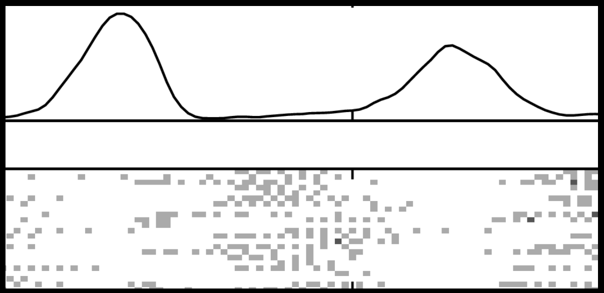
Connectivity questions

1) How do we infer mesoscopic connections?

2) What are good microscopic models?

3) How does connectivity affect brain dynamics?

Effects of sparsity on rhythm generation



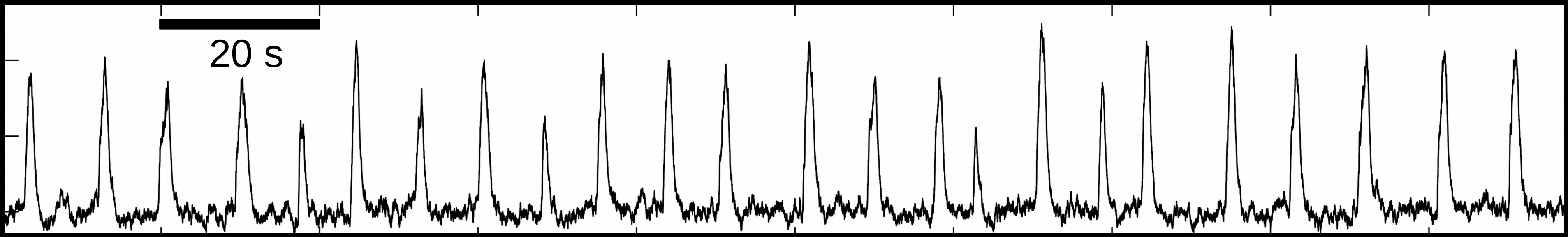
Published as:
Harris, Dashevskiy, Mendoza, Garcia III, Ramirez, Shea-Brown.
“Different roles for inhibition in the rhythm-generating respiratory network.”
J Neurophys 118(4), 2070-2088. 2017.

Litwin-Kumar, Harris, Sompolinsky, Abbott.
“Optimal synaptic connectivity.”
Neuron 93, 1153-1164. 2017.

Sparsity is good for
“classifier” circuits

Breathing arises in the brainstem

- The “pre-Bötzinger Complex”

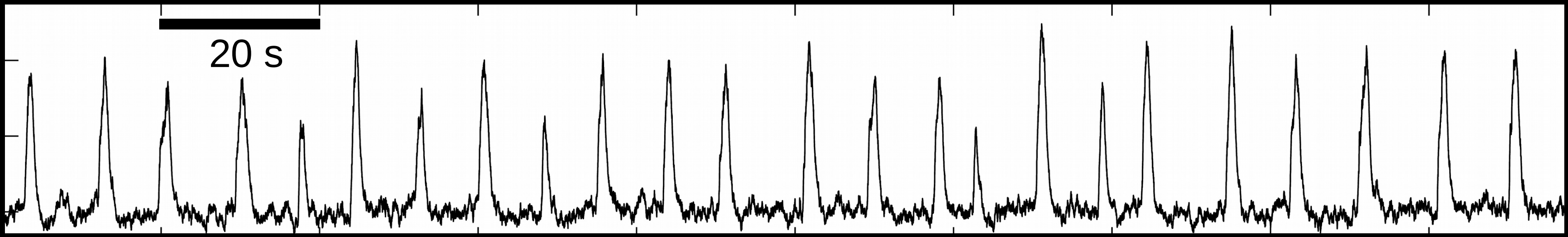


Important related papers:

Smith et al. 1991
Ramirez & Richter 1996
Rekling & Feldman 1998
Feldman et al. 2013

Breathing arises in the brainstem

- The “pre-Bötzinger Complex”
  - Bursting, tonic spiking, and quiescent E / I cells

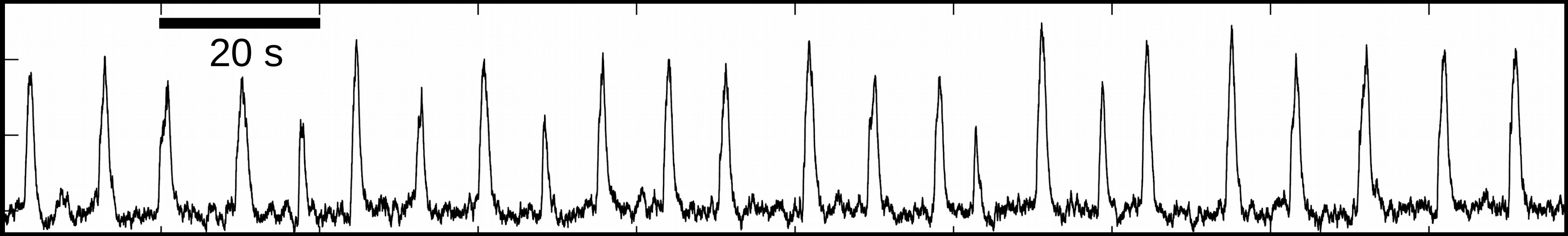


Important related papers:

Smith et al. 1991
Ramirez & Richter 1996
Rekling & Feldman 1998
Feldman et al. 2013

Breathing arises in the brainstem

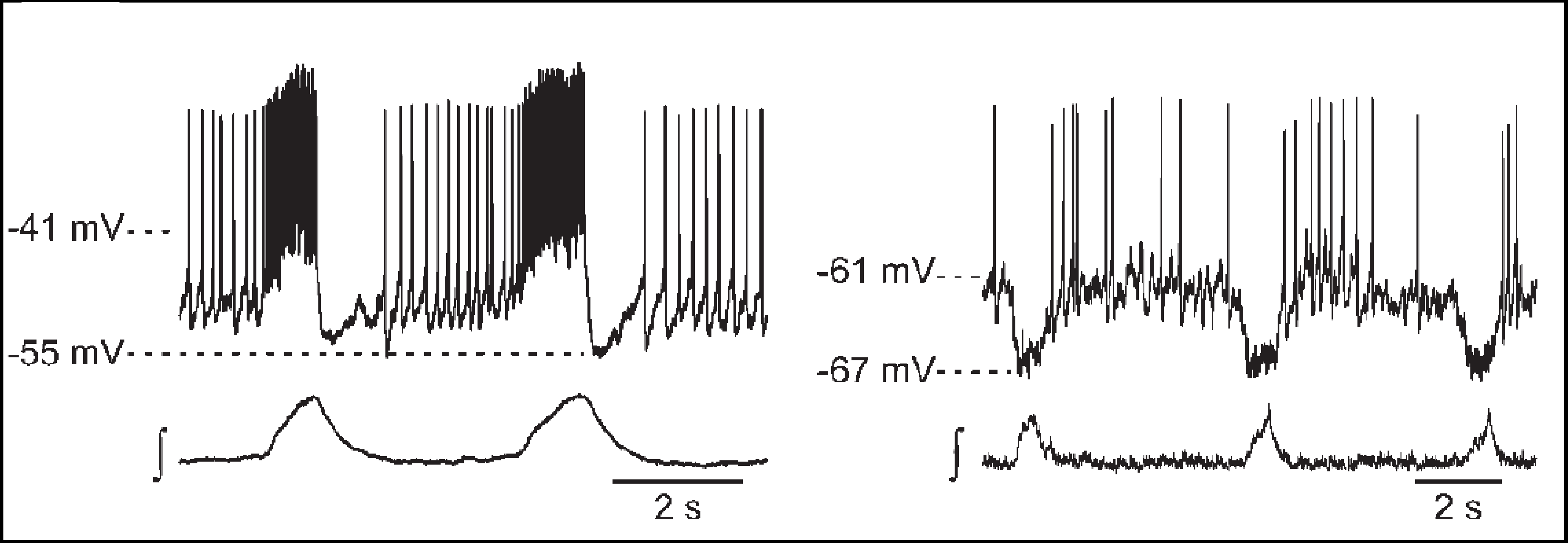
- The “pre-Bötzinger Complex”
  - Bursting, tonic spiking, and quiescent E / I cells
  - Synchronized population bursts via excitation



Important related papers:

Smith et al. 1991
Ramirez & Richter 1996
Rekling & Feldman 1998
Feldman et al. 2013

Why do you get expiratory cells?

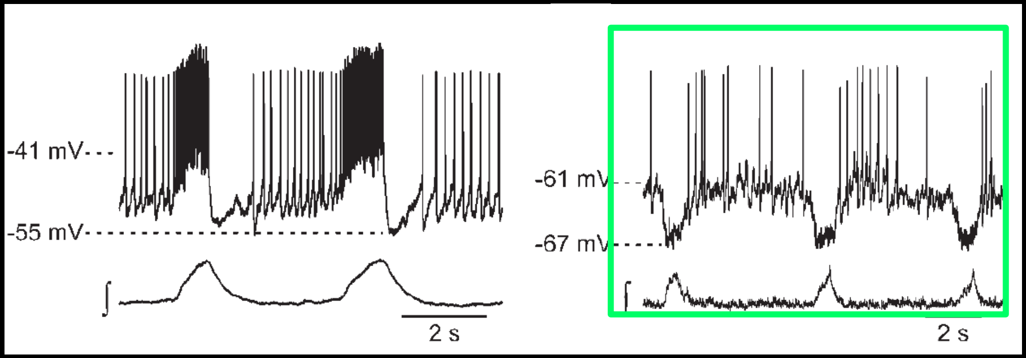


inspiratory

expiratory

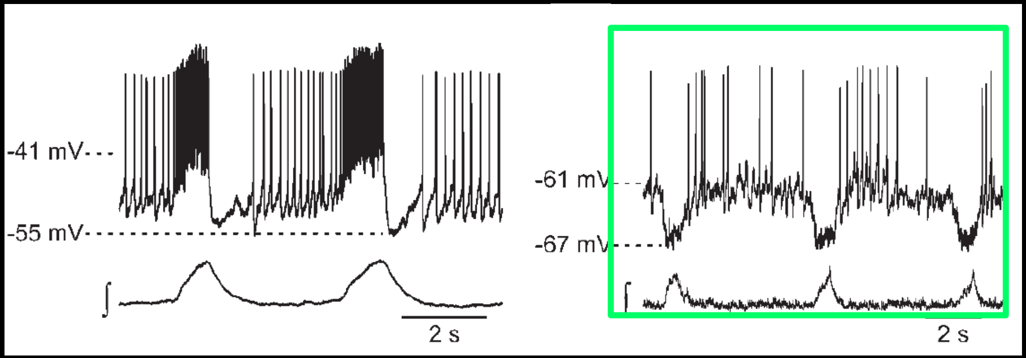
Figure from:
Lieske, Thoby-Brisson, Telgkamp, Ramirez (2000)

Why do you get expiratory cells?

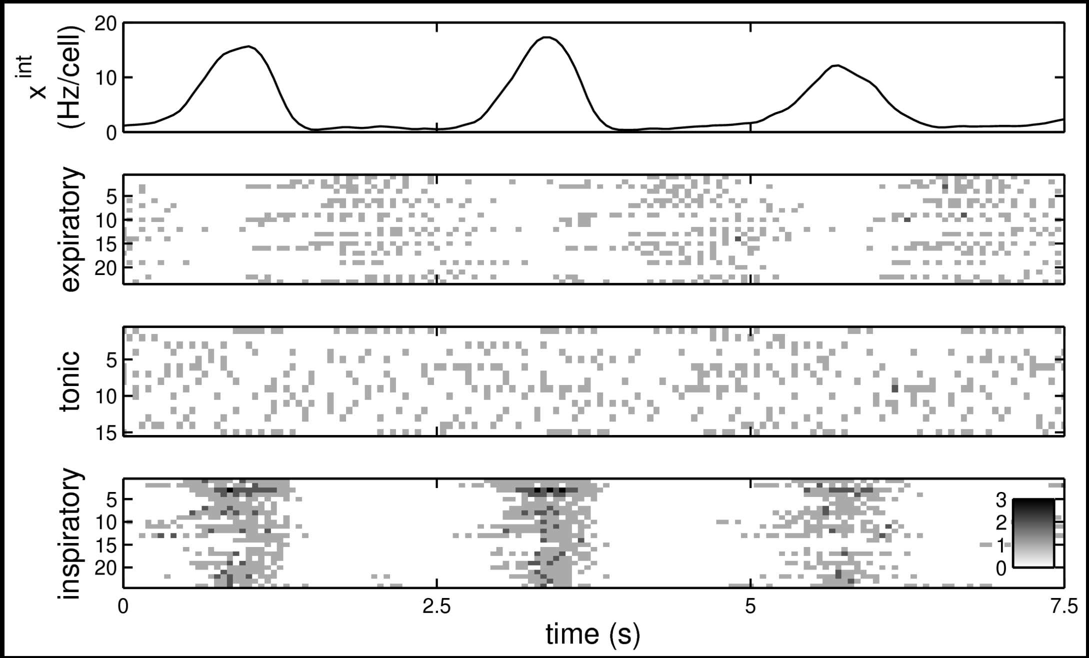


inspiratory cell expiratory

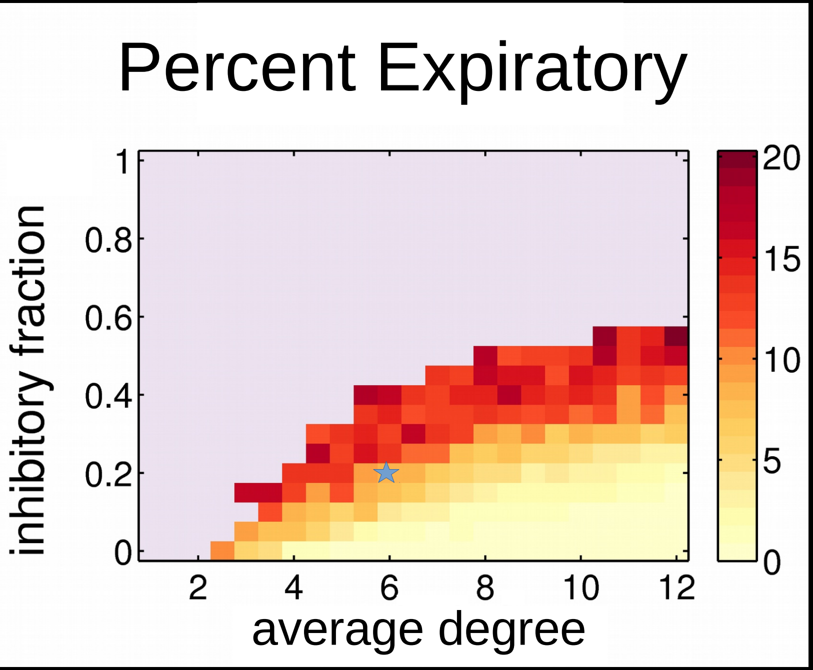
Why do you get expiratory cells?

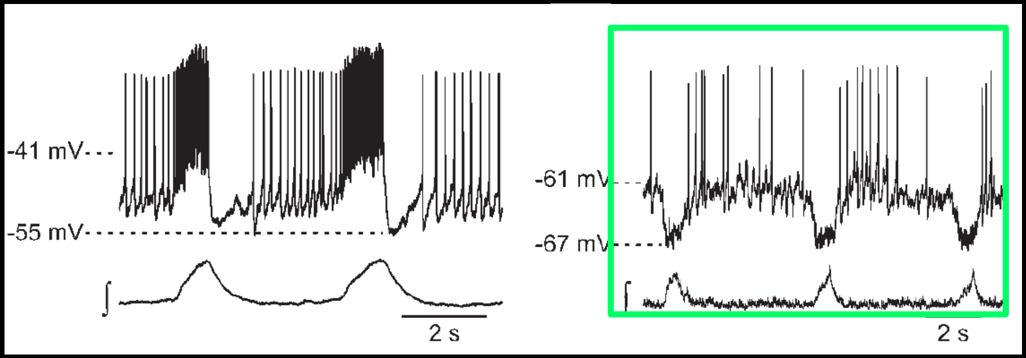


inspiratory cell expiratory

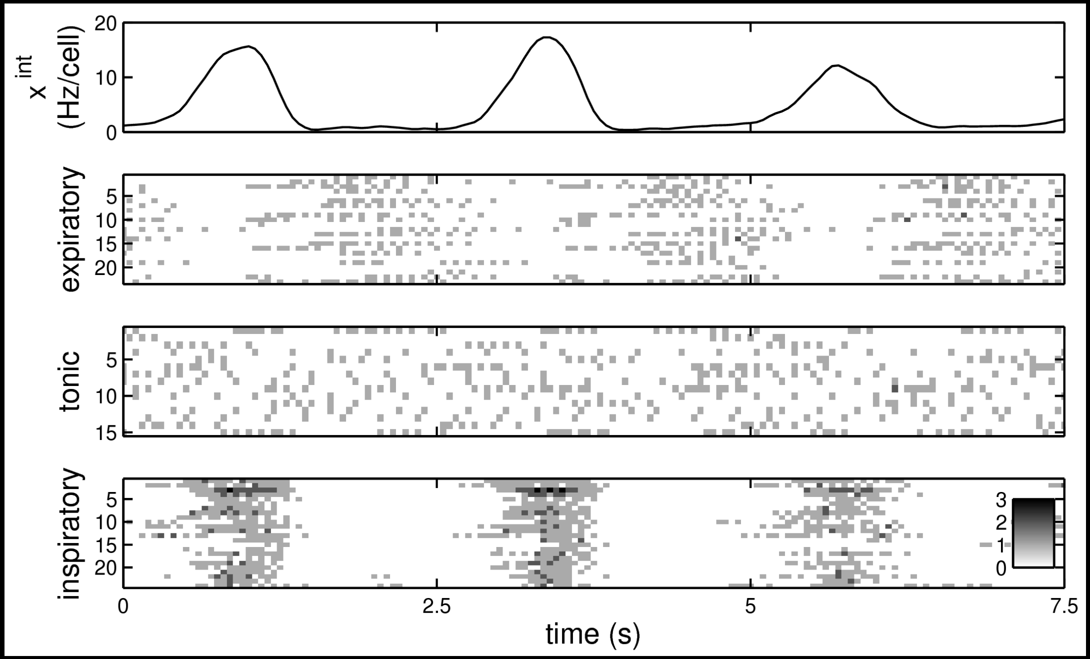


Why do you get expiratory cells?

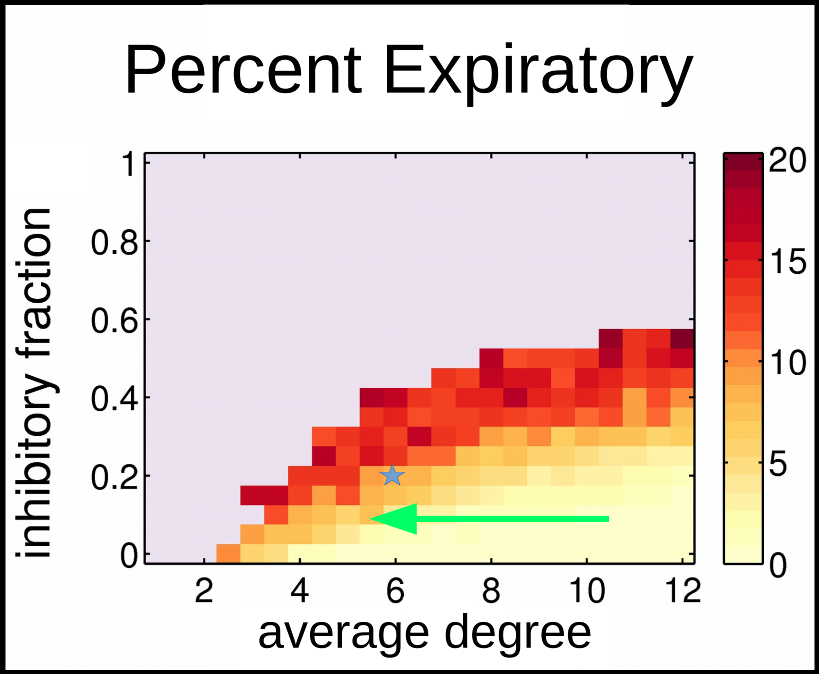


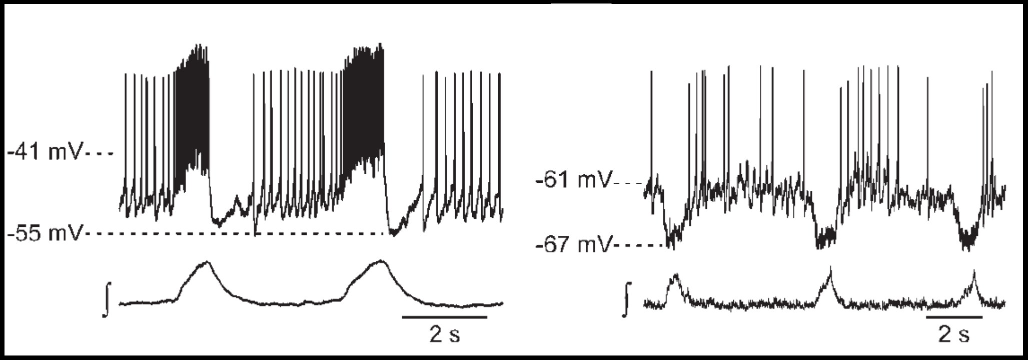


inspiratory cell expiratory

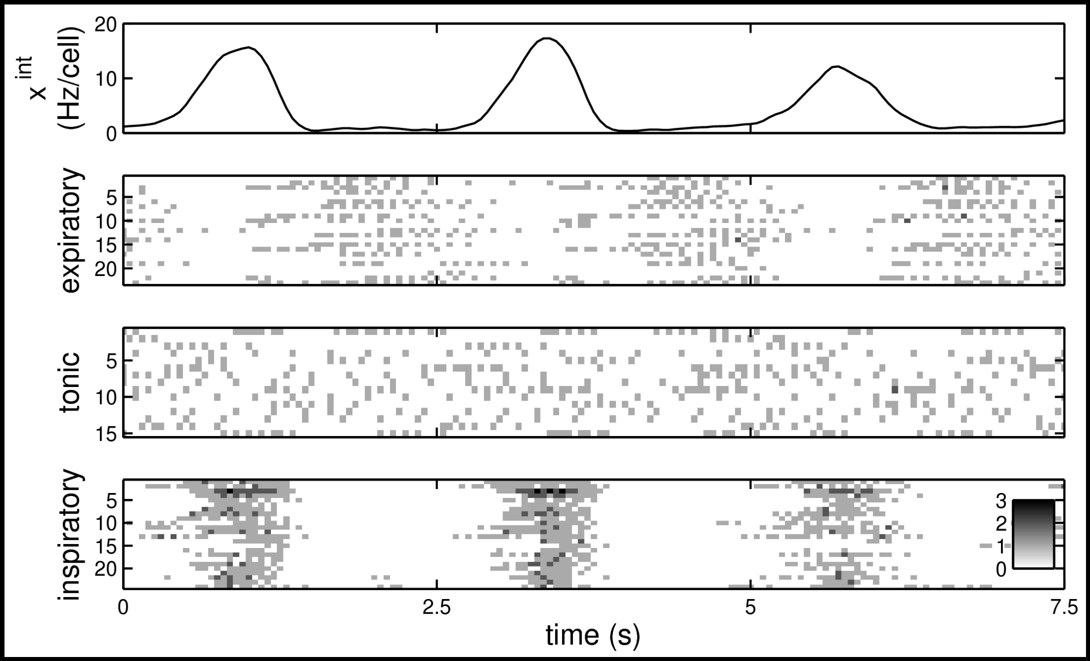


Why do you get expiratory cells?

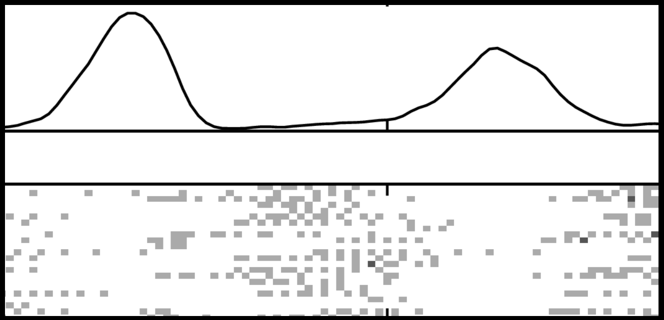




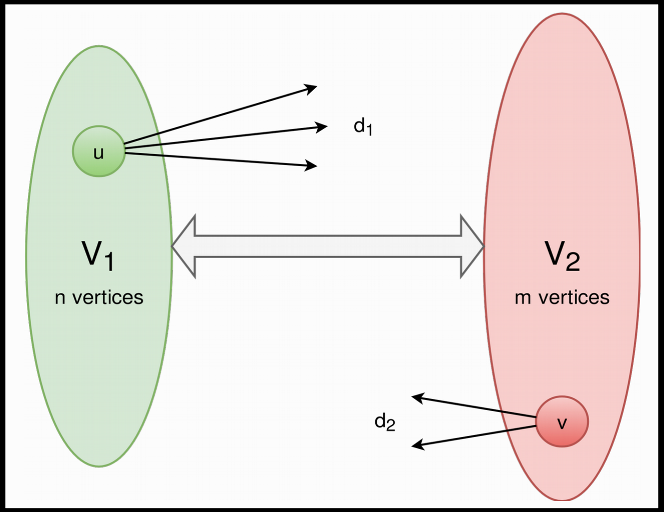
inspiratory cell expiratory



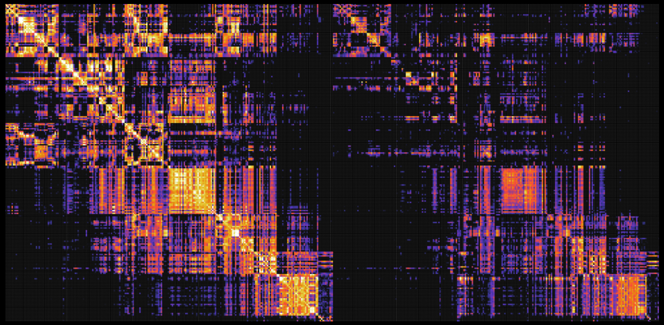
Sparse graph:
some cells randomly
driven into expiratory phase



- Neuronal network dynamics
  - Choose graph class with measurable parameters



- Random graph theory
  - Rich mathematical area
  - Spectra, expansion, & dynamics



- Mesoscopic network inference
  - Methods tailored to new datasets

More acknowledgements



Dave Brown



Stuart Ryan


Jason Griffith


Drew Tabke


Thank you
for listening!
Scott Rinckenberger