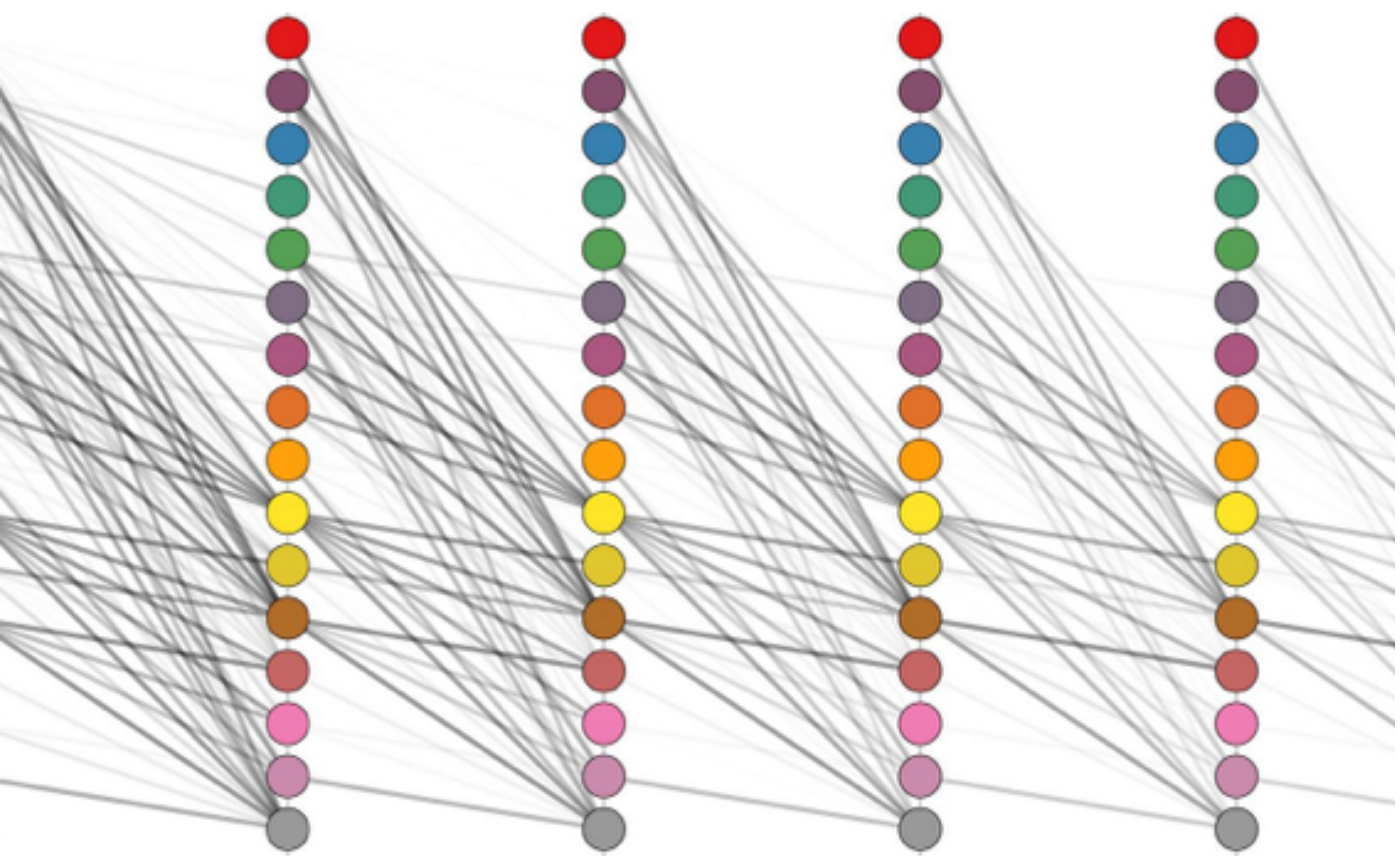
Building models for understanding stuff

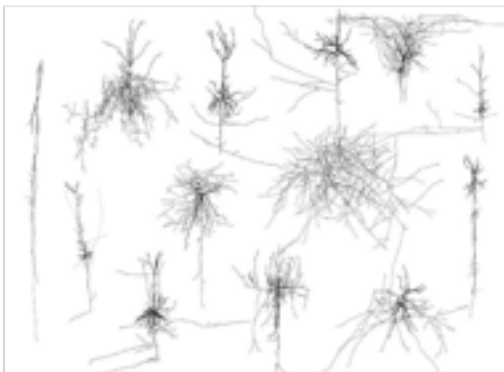


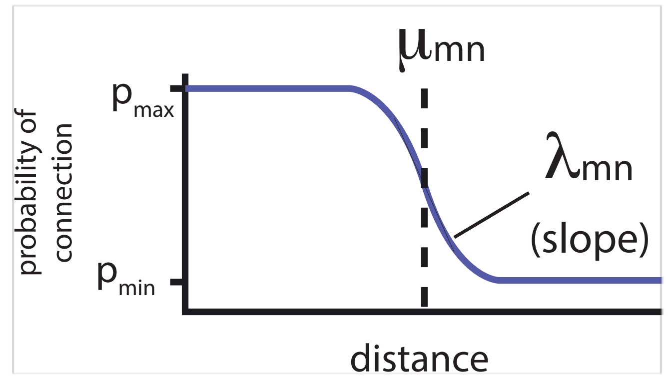
Eric Jonas
UC Berkeley AMP Lab, EECS
@stochastician

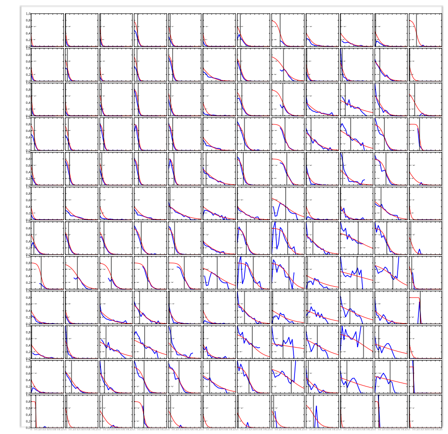
Konrad Kording
Northwestern, @KordingLab

Srini Turaga
HHMI Janelia

Overview







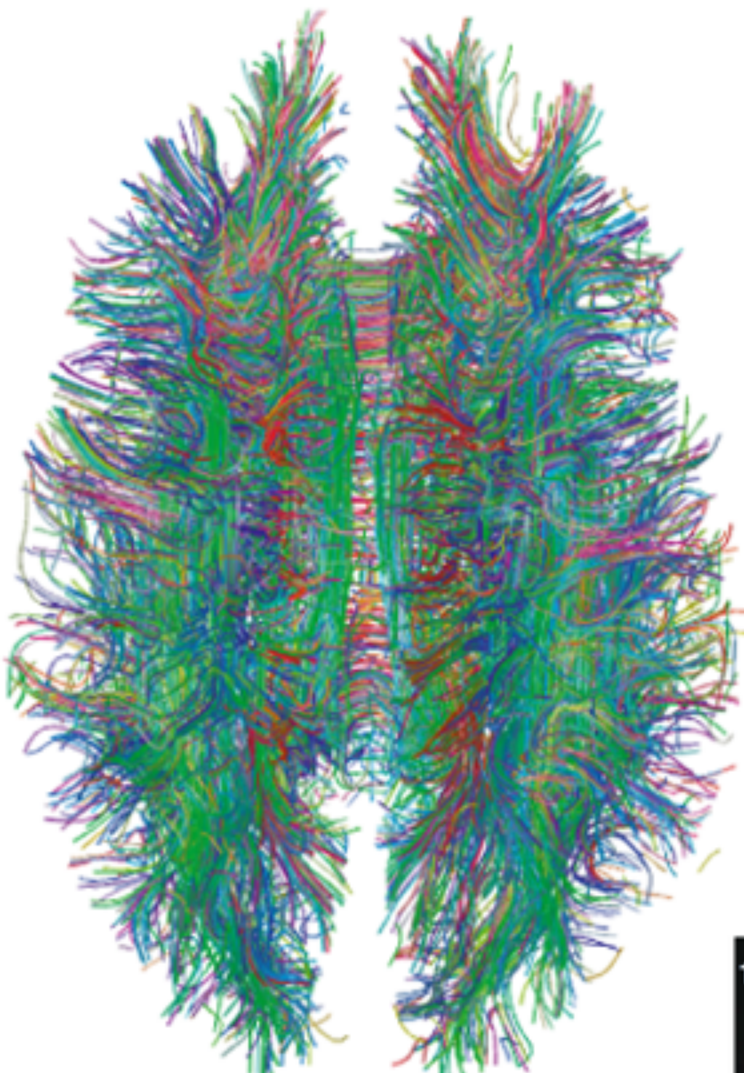
eLIFE
elifesciences.org
TOOLS AND RESOURCES

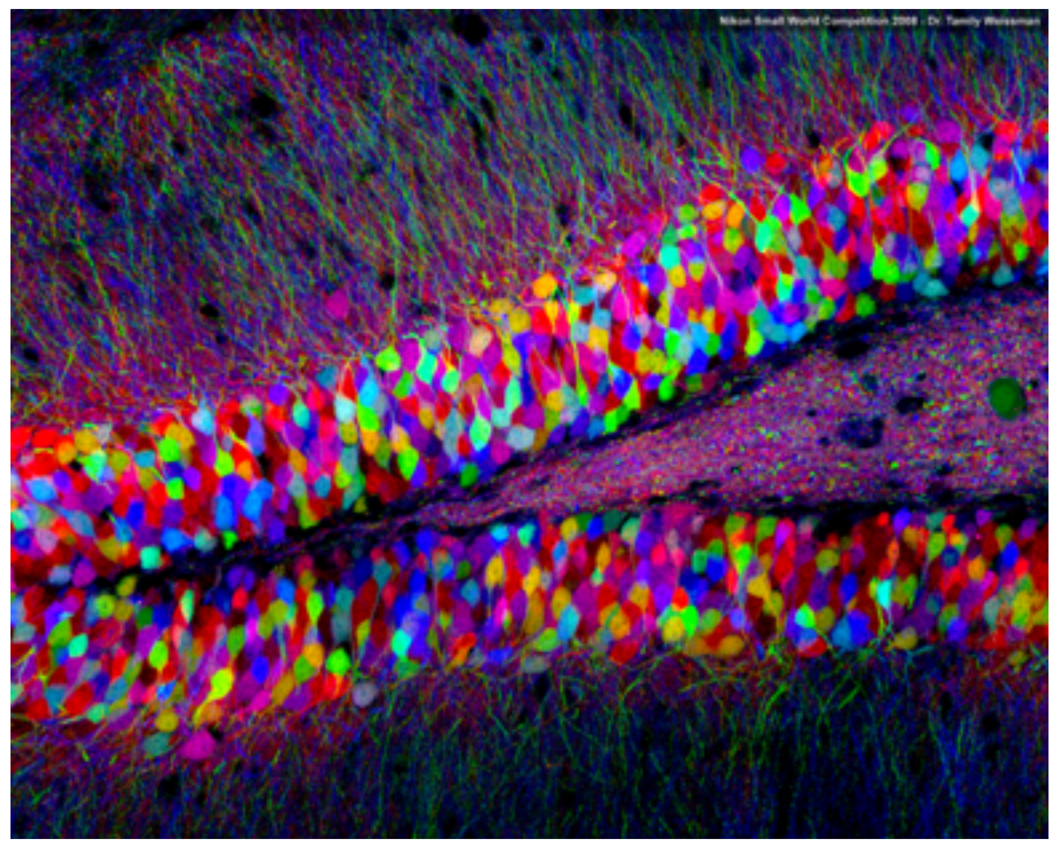
Automatic discovery of cell types and microcircuitry from neural connectomics

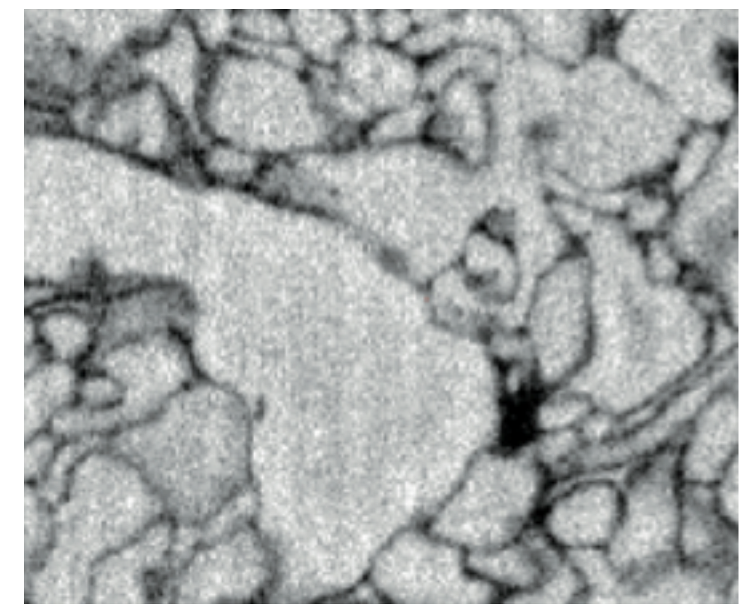
Eric Jonas[1*], Konrad Kording[2,3,4]

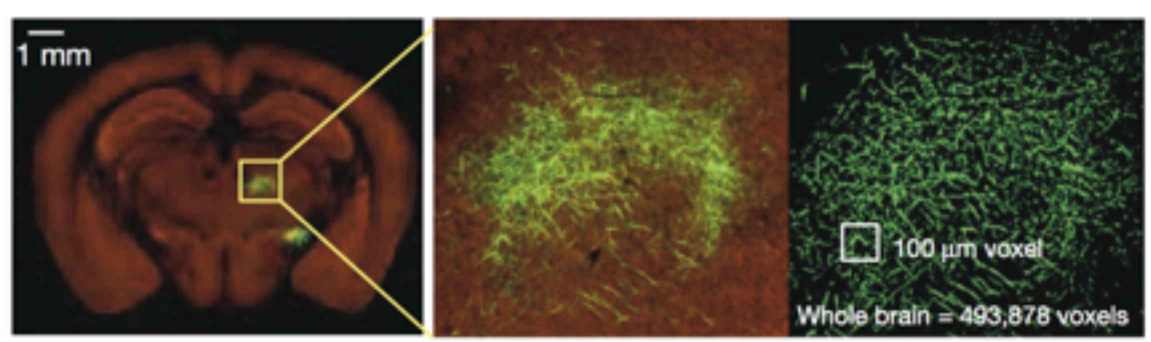
[1]Department of Electrical Engineering and Computer Science, University of California, Berkeley, Berkeley, United States; [2]Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, United States; [3]Department of Physical Medicine and Rehabilitation, Rehabilitation Institute of Chicago, Chicago, United States; [4]Department of Physiology, Northwestern University, Chicago, United States

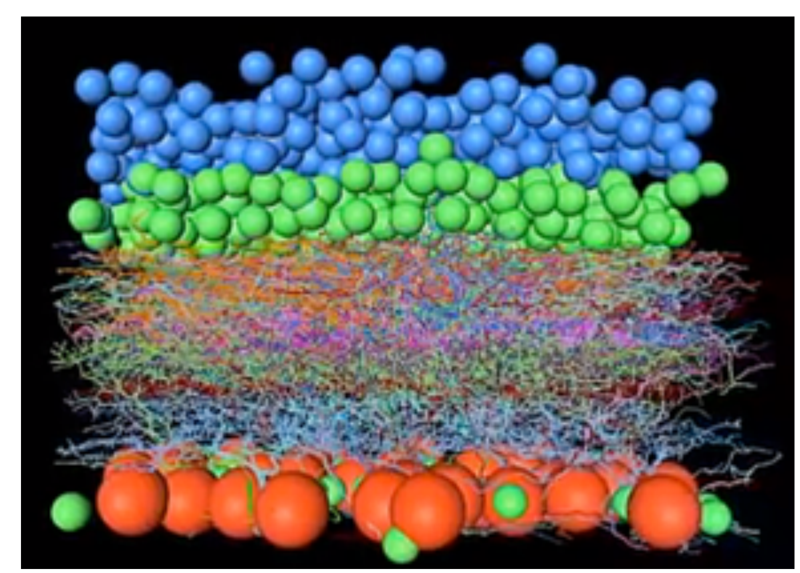
First we need a schematic



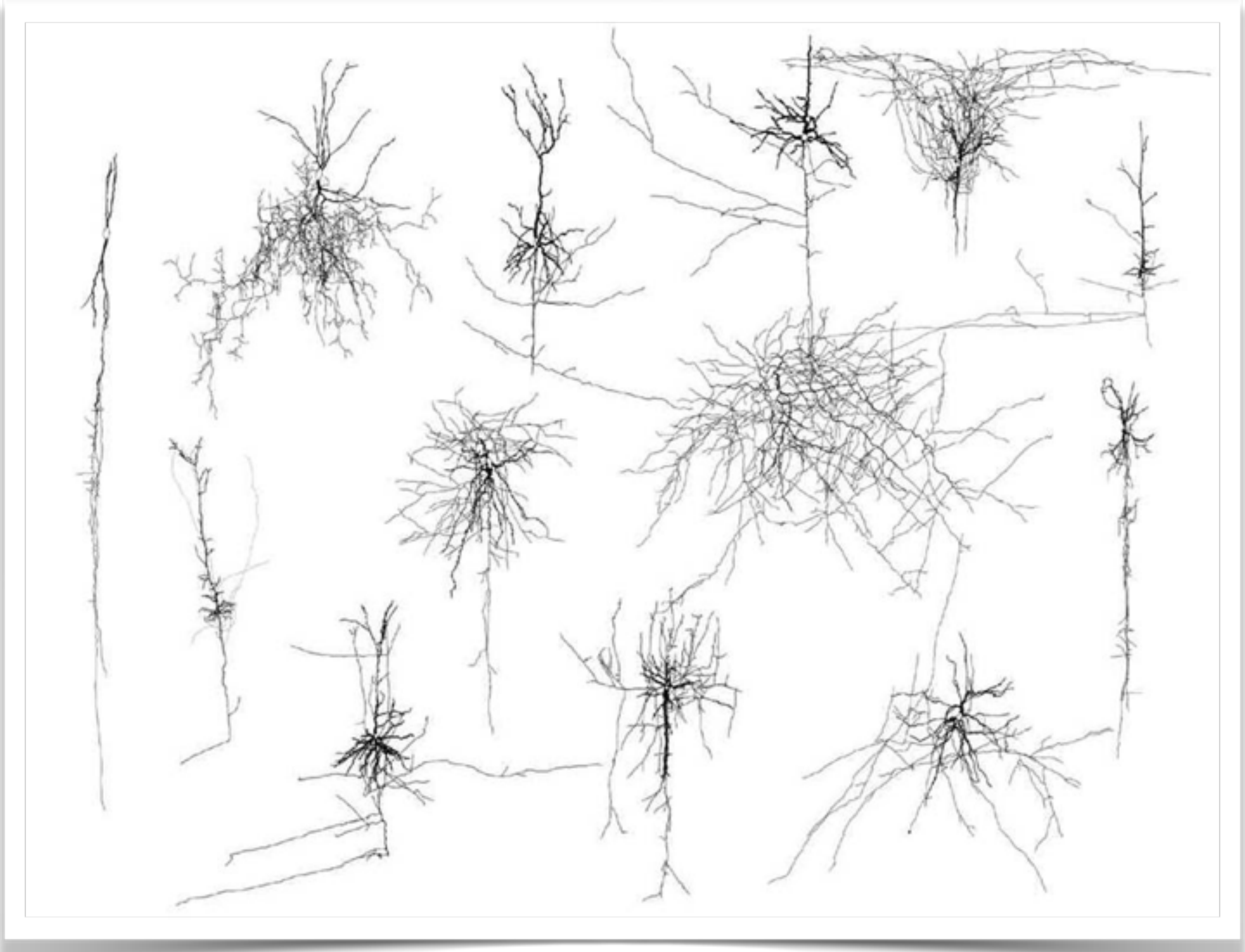






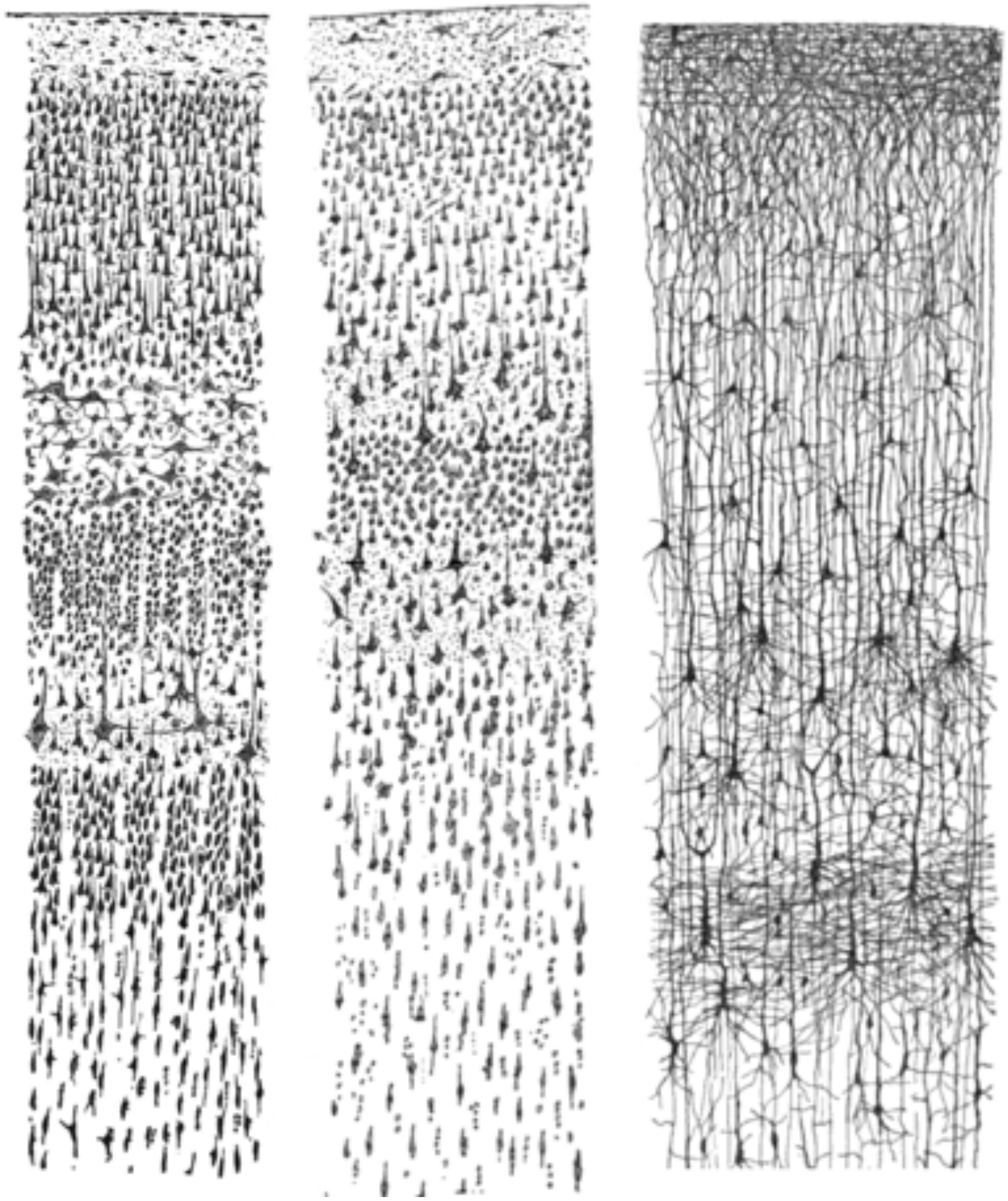


Someday this will be Big Data



The Motivation

Microcircuitry for Computation



visual cortex adult | motor cortex adult | “cortex” infant

Santiago Ramon y Cajal, taken from the book "Comparative study of the sensory areas of the human cortex", pages 314, 361, and 363

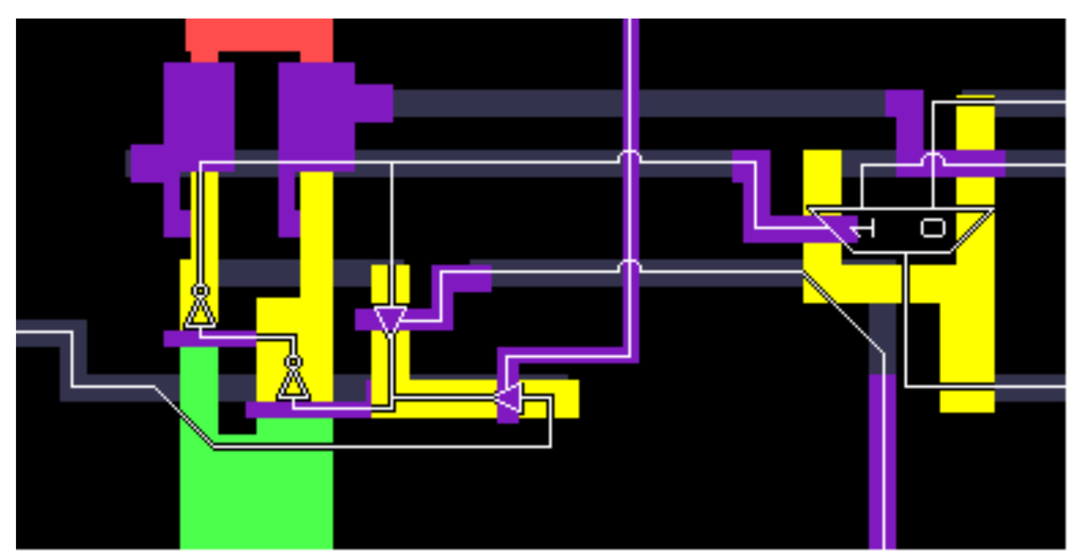
MODALITY AND TOPOGRAPHIC PROPERTIES OF SINGLE NEURONS OF CAT'S SOMATIC SENSORY CORTEX[1]

VERNON B. MOUNTCASTLE
Department of Physiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

(Received for publication November 5, 1956)

INTRODUCTION

THE PRESENT PAPER describes some observations upon the modality and topographical attributes of single neurons of the first somatic sensory area of the cat's cerebral cortex, the analogue of the cortex of the postcentral gyrus in the primate brain. These data, together with others upon the response latencies of the cells of different layers of the cortex to peripheral stimuli, support an hypothesis of the functional organization of this cortical area. This is that the neurons which lie in narrow vertical columns, or cylinders, extending from layer II through layer VI make up an elementary unit of organization, for they are activated by stimulation of the same single class of peripheral receptors, from almost identical peripheral receptive fields, at latencies which are not significantly different for the cells of the various layers. It is emphasized that this pattern of organization obtains only for the early repetitive responses of cortical neurons to brief peripheral stimuli.

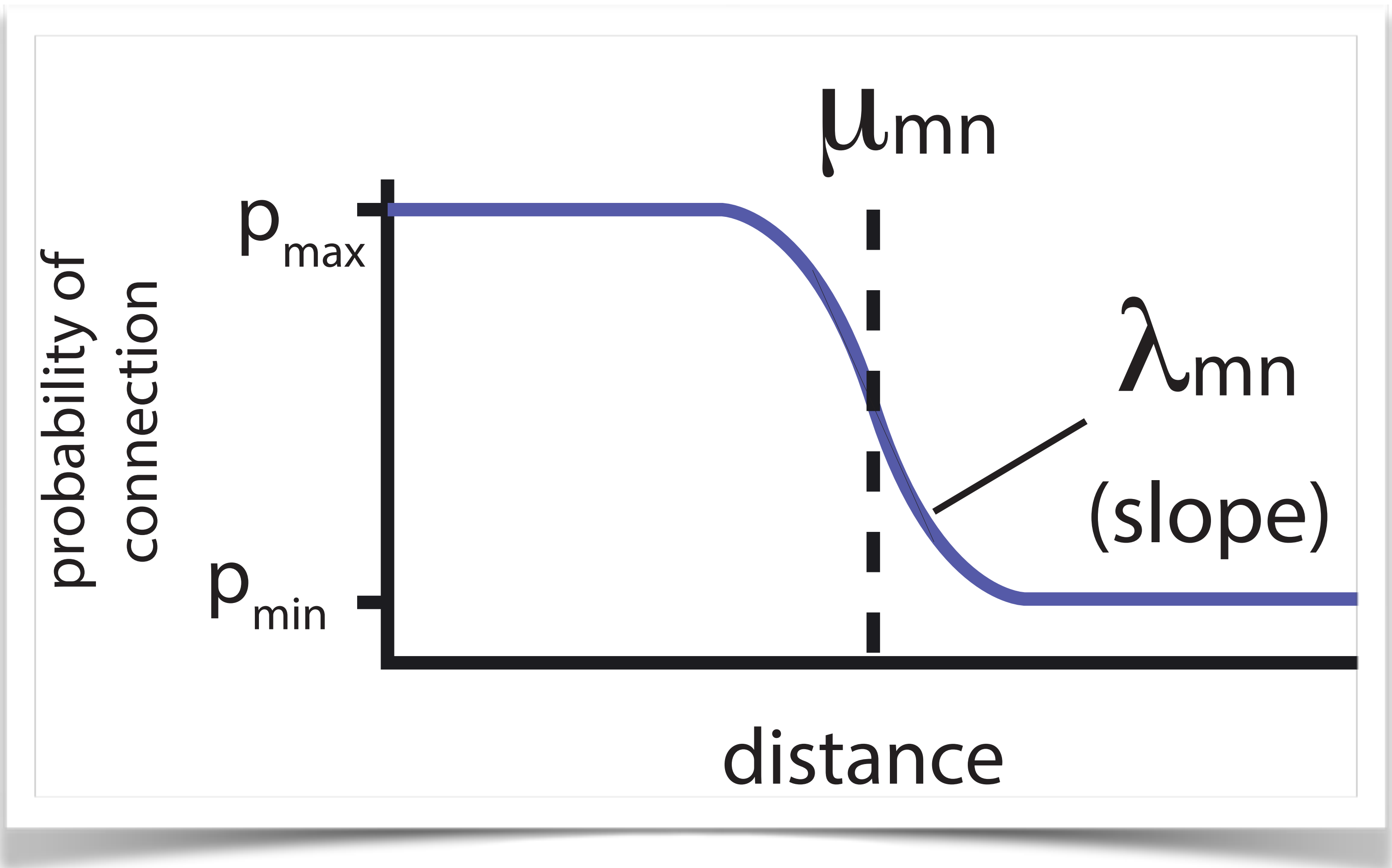


clocked register (asic)

Why?

- What is a type?
- Doesn’t genetics make this all obsolete ?
- Computational Neuroanatomy

type matrix row/column	depth/width ID	Volgyi, B., S. Chheda, et al. (2009). J. Comp. Neurol. 512(5): 664-687.	MacNeil, M. A., J. K. Heussy, et al. (1999). J. comp. neurol. 413(2): 305-326.	cetainty of correspondence	Common name	Other references
1	gc10-40	G11		medium		
2	gc14-30					
3	gc15-42	G7		medium		
4	gc21-69	G4		low		
5	gc35-41	G4		low		
6	gc37-46	G5		medium		Sivyer, B., S. Venkataramani, et al. (2011). J. Comp. Neurol. 519(16): 3128-3138.
7	gc31-56	G8,13		high	local motion detector , local edge detector, "W3"	Kim, I. J., Y. Zhang, et al. (2010). J. Neurosci. 30(4): 1452-1462. Zhang, Y., I. J. Kim, et al. (2012). PNAS 109(36): E2391-2398.
8	gc36-51	G12		medium		
9	gc44-52	G17		high	On-Off direction selective ganglion cell	
10	gc30-63	G4,5,9, and/or 14		low		
11	gc47-57	G14		medium		
12	gc76-86	G1,2, and/or 10		low		
13	ac11-68					
14	ac13-32		Narrow S1	low		
15	ac17-30		Flat bistratified	medium		


μmn
pmax
pmin
probability of connection
λmn
(slope)
distance

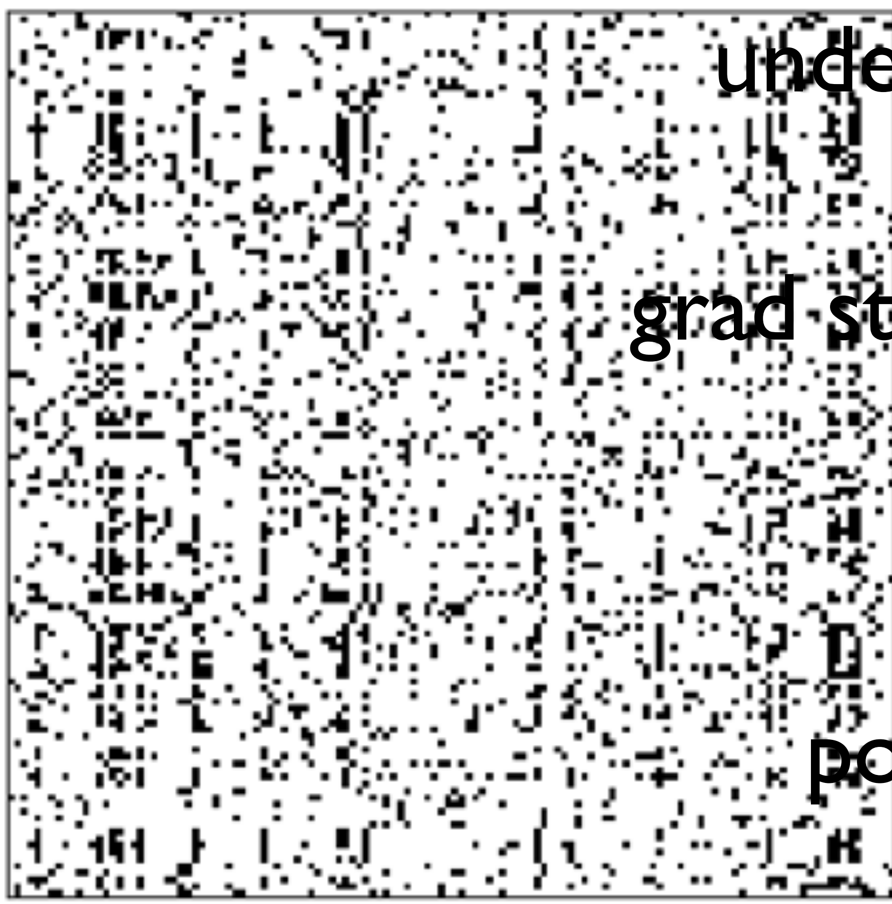
The model

What is our prior

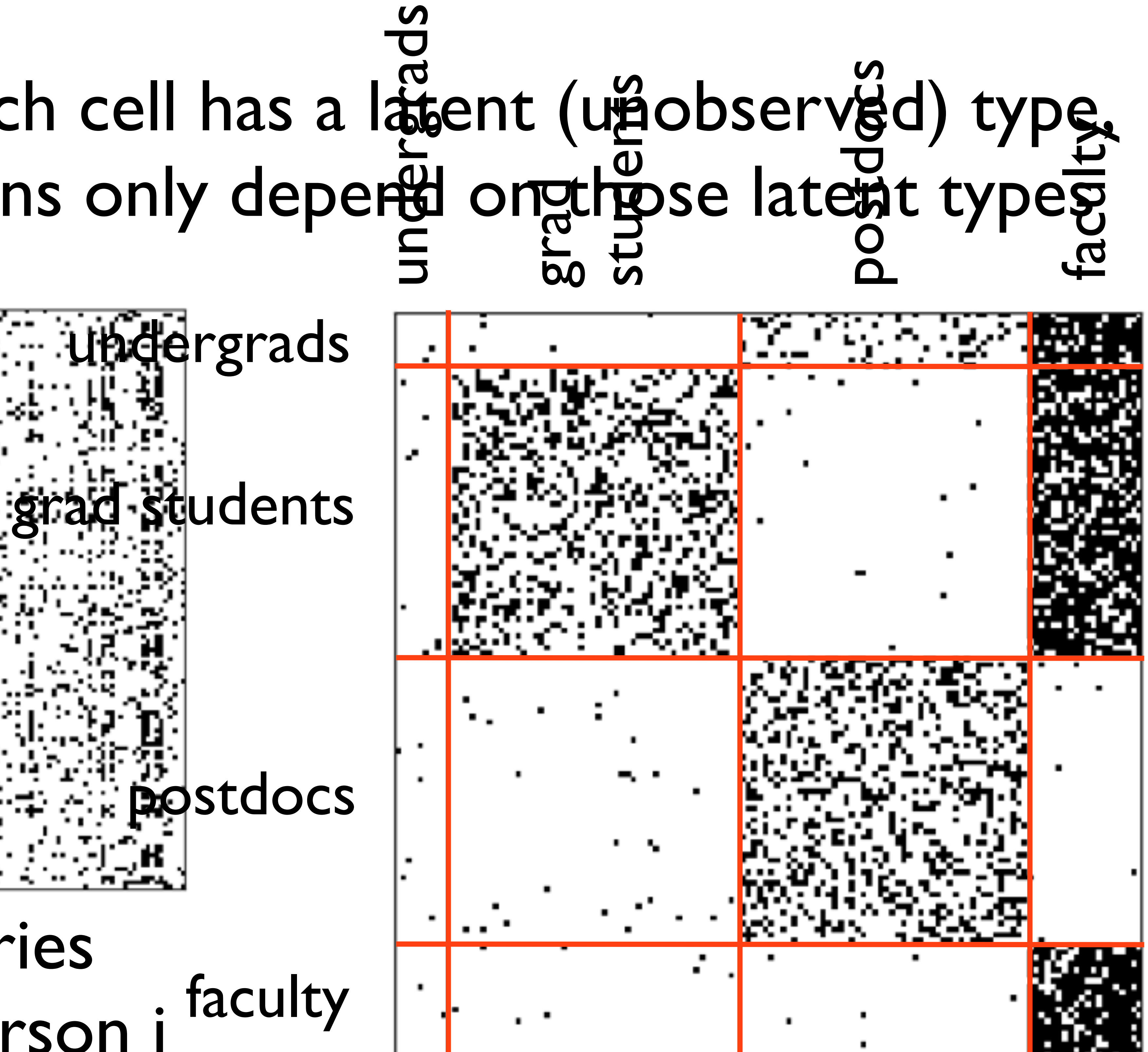
- Cells have types
- Types connect with types
- *Distance matters*

Stochastic Block Model Review

Simple idea: each cell has a latent (unobserved) type, and connections only depend on those latent types.



person i tries to talk to person j



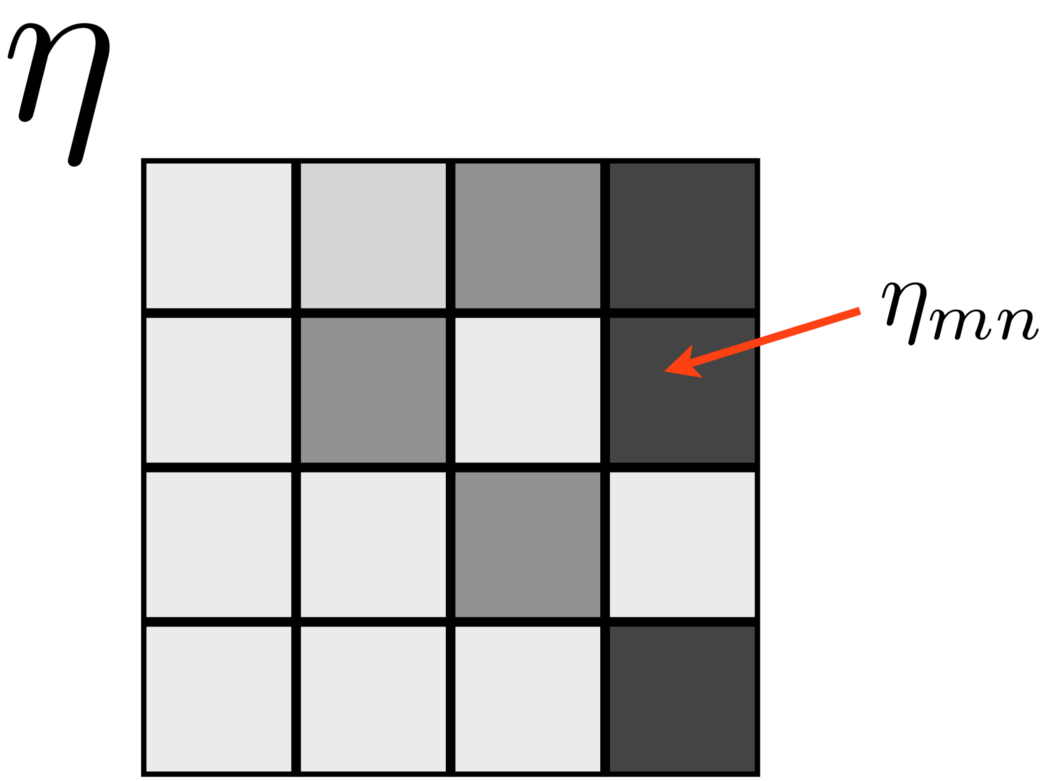
Formally

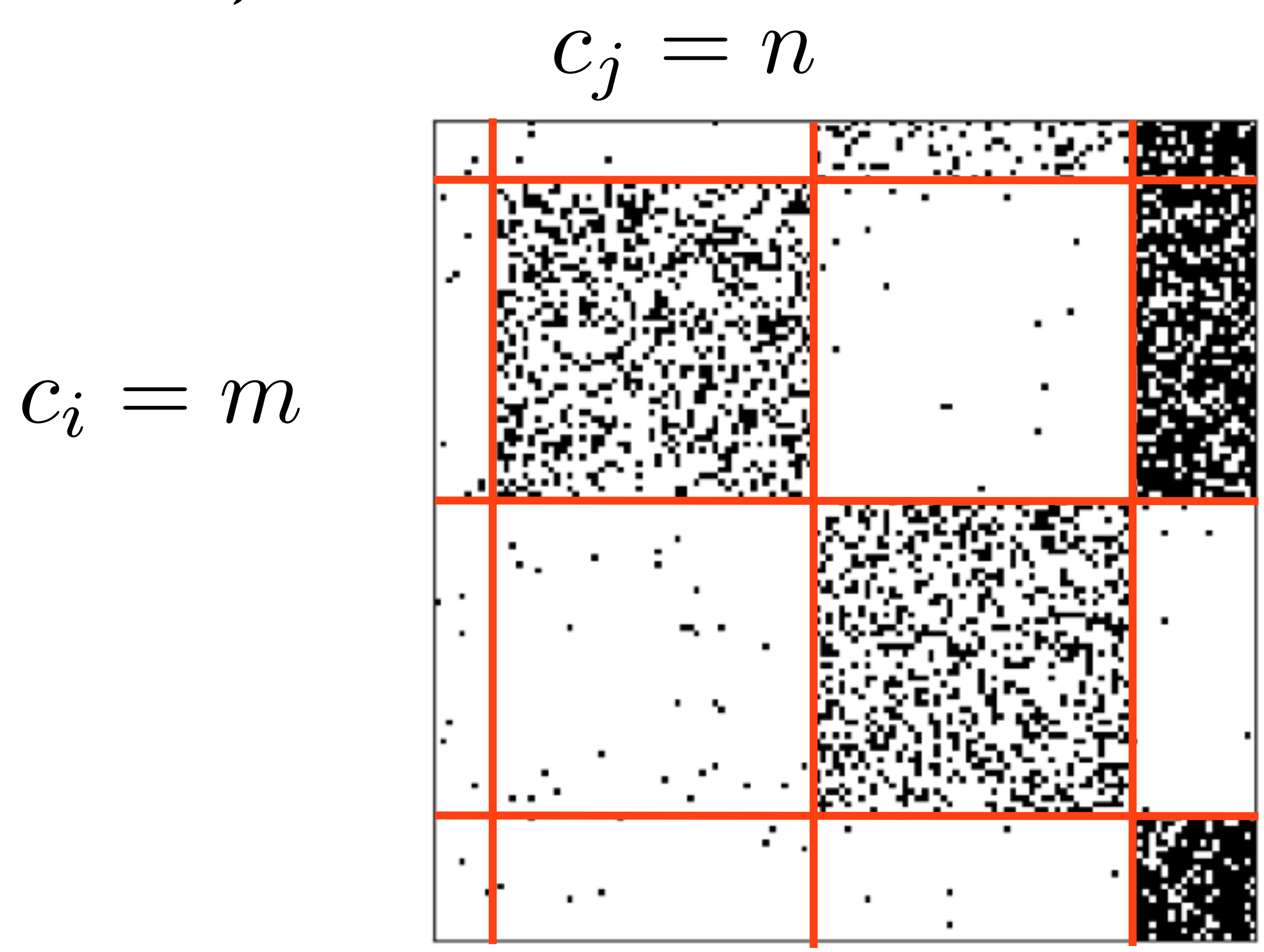
K Number of latent types

$c_i = k$ assignment vector

θ global params

η_{mn} latent params for class m, n





$$R(i, j) = P(\eta_{c_i c_j} | \theta)$$

Infinite Extension

We can add a nonparmatric prior on the number of latent classes

c_i cell i assigned to type k

c_{-i} assignment of all other cells

m_k # of cells in type k

α concentration parameter

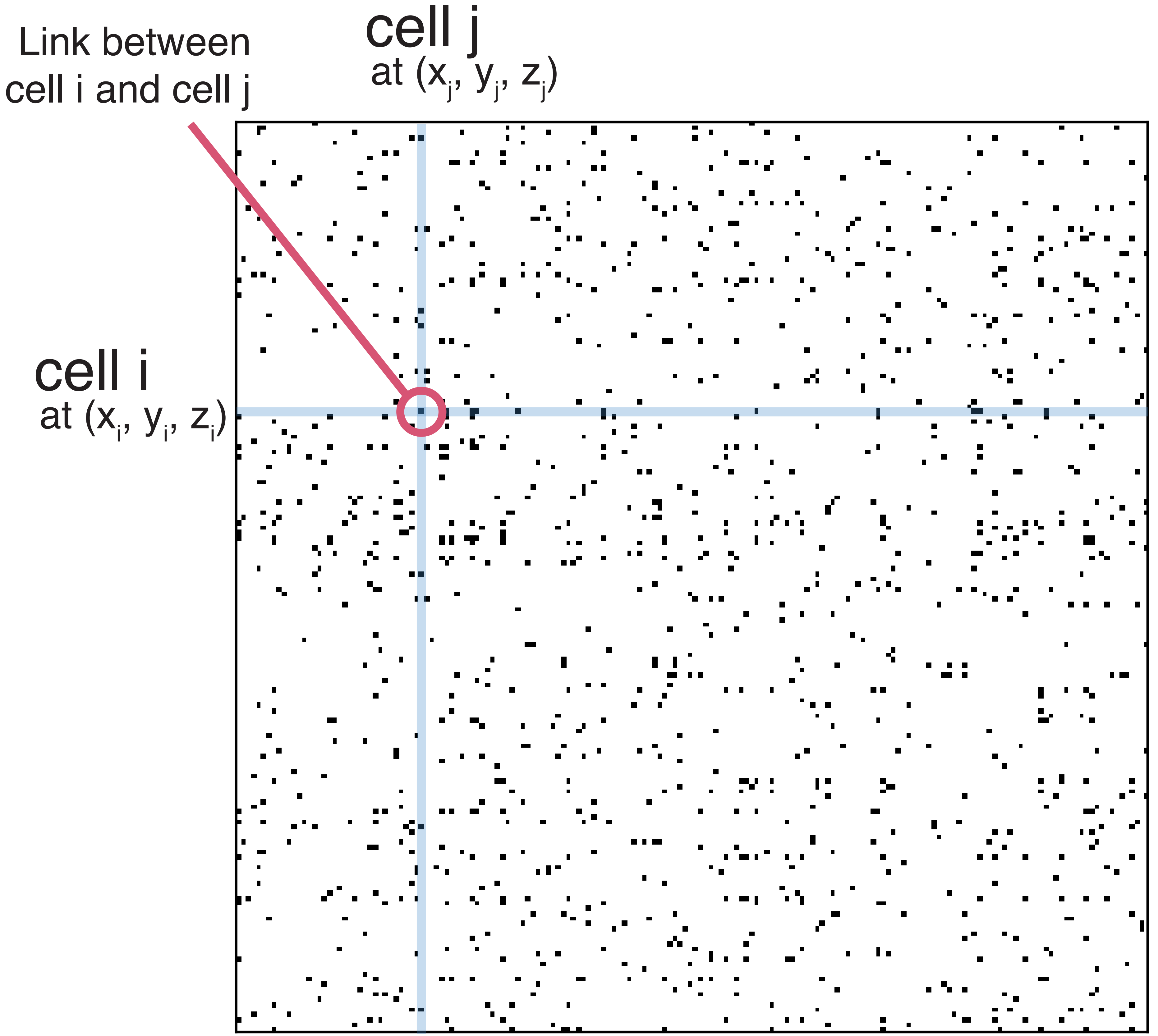
$$P(c_i = k | c_{-i}) = \frac{m_k}{N + \alpha}$$

$$P(c_i = k' | c_{-i}) = \frac{\alpha}{N + \alpha}$$

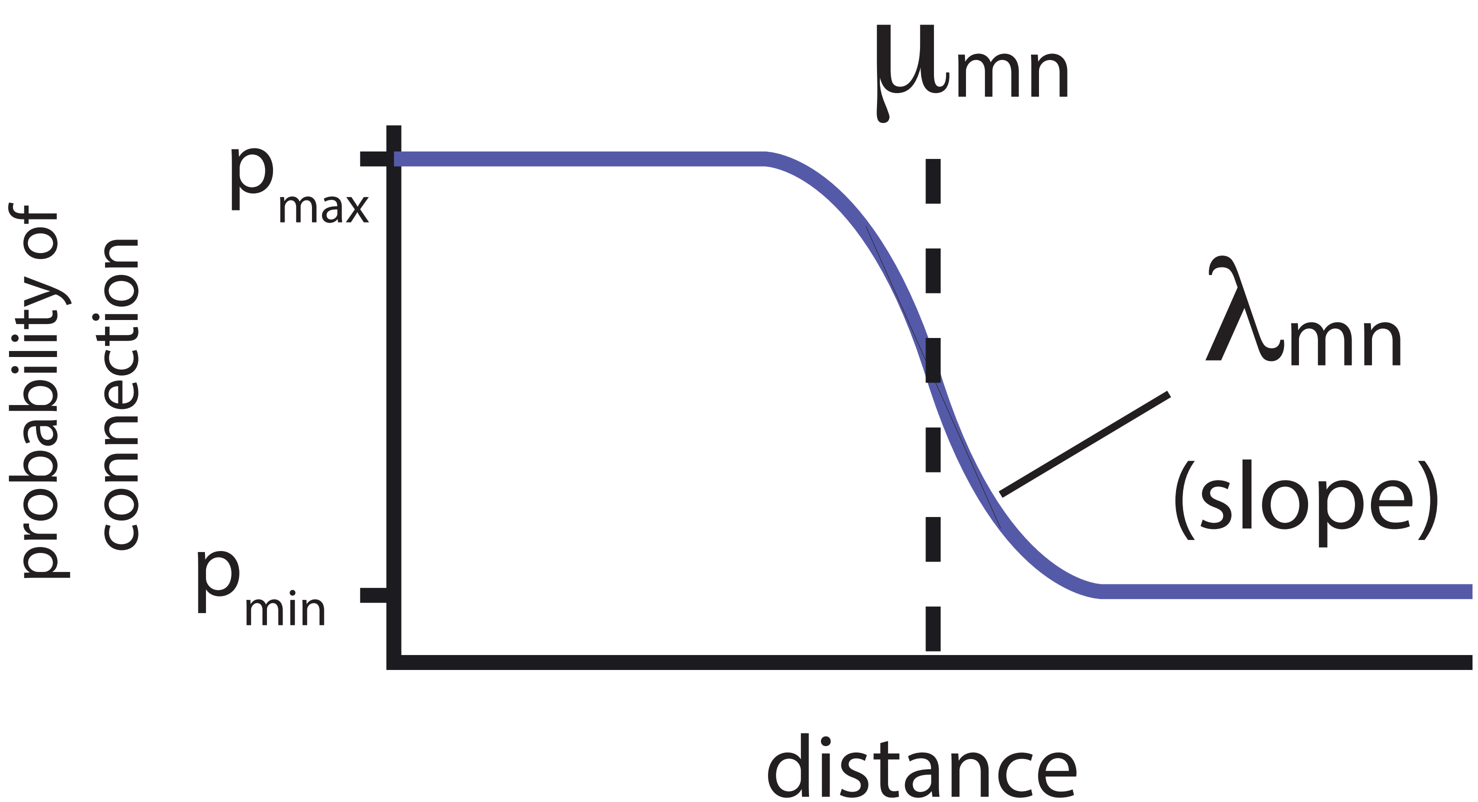
Kemp, C., Tenenbaum, J. & Griths, T. *Learning systems of concepts with an infinite relational model* in Twenty-first National Conference on Artificial Intelligence (AAAI-06) (2006)

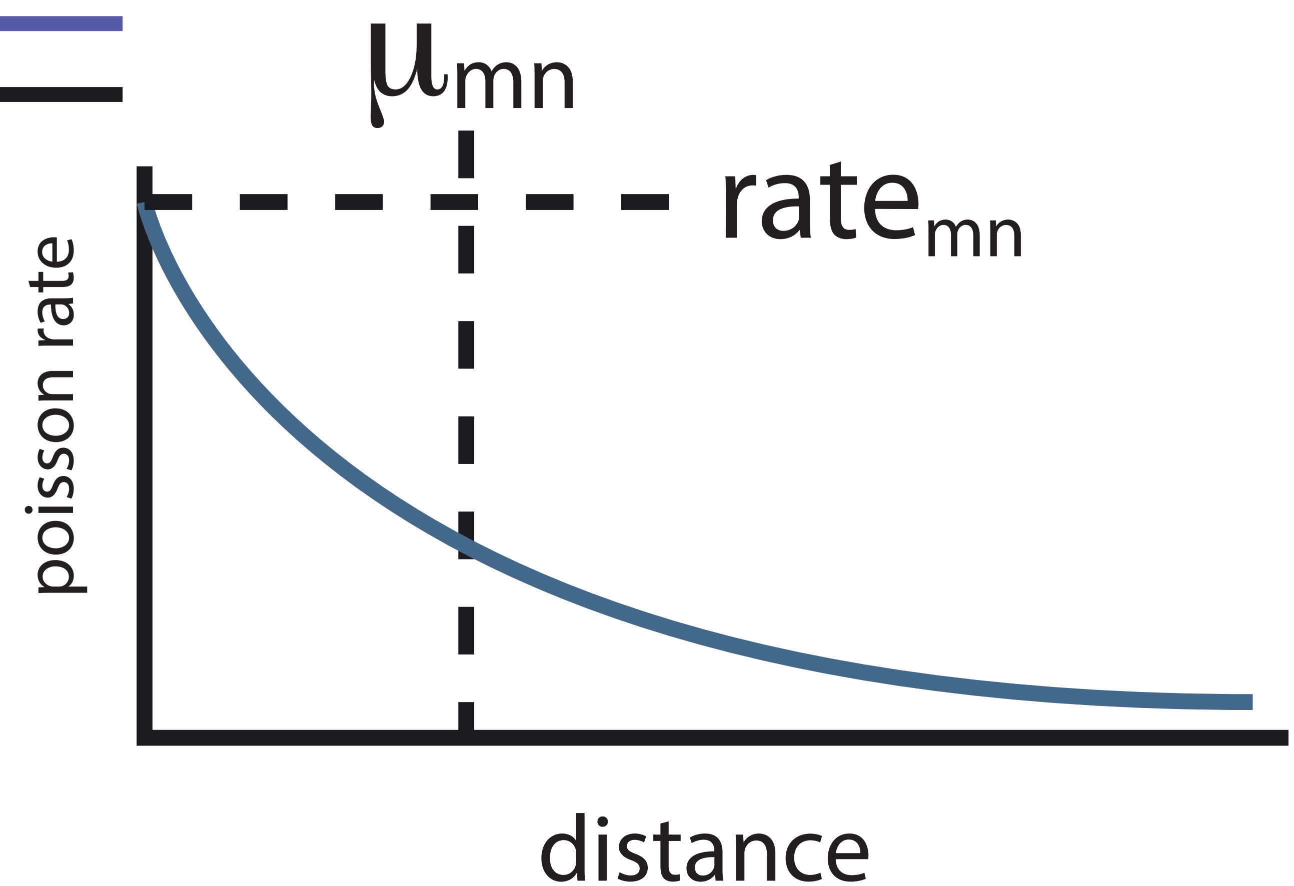
Xu, Z., Tresp, V., Yu, K. & Kriegel, H.-p. *Infinite Hidden Relational Models* in Proceedings of the Twenty-Second Conference on Uncertainty in Artificial Intelligence (2006)

Adding distance

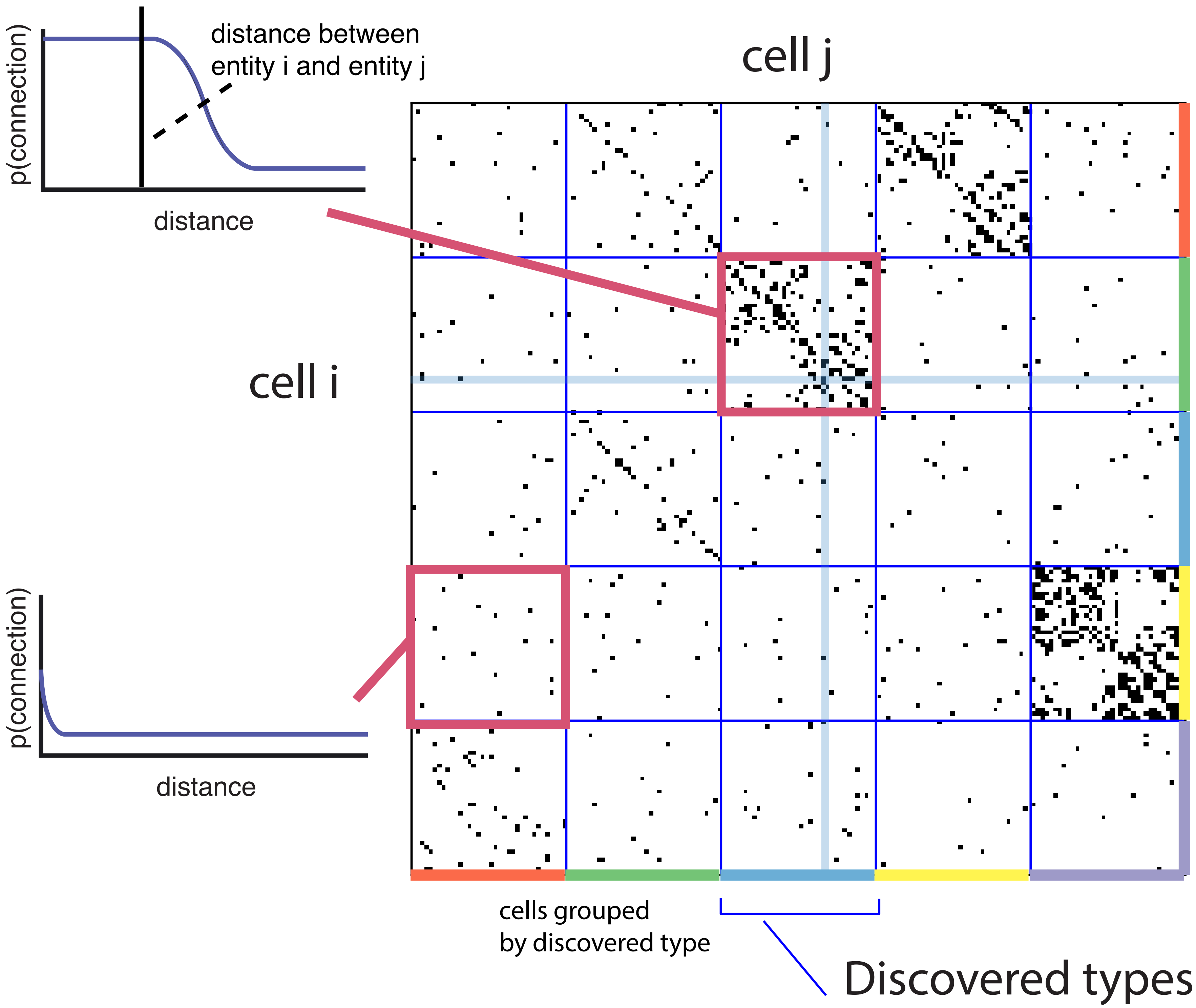


Distance-dependent link functions



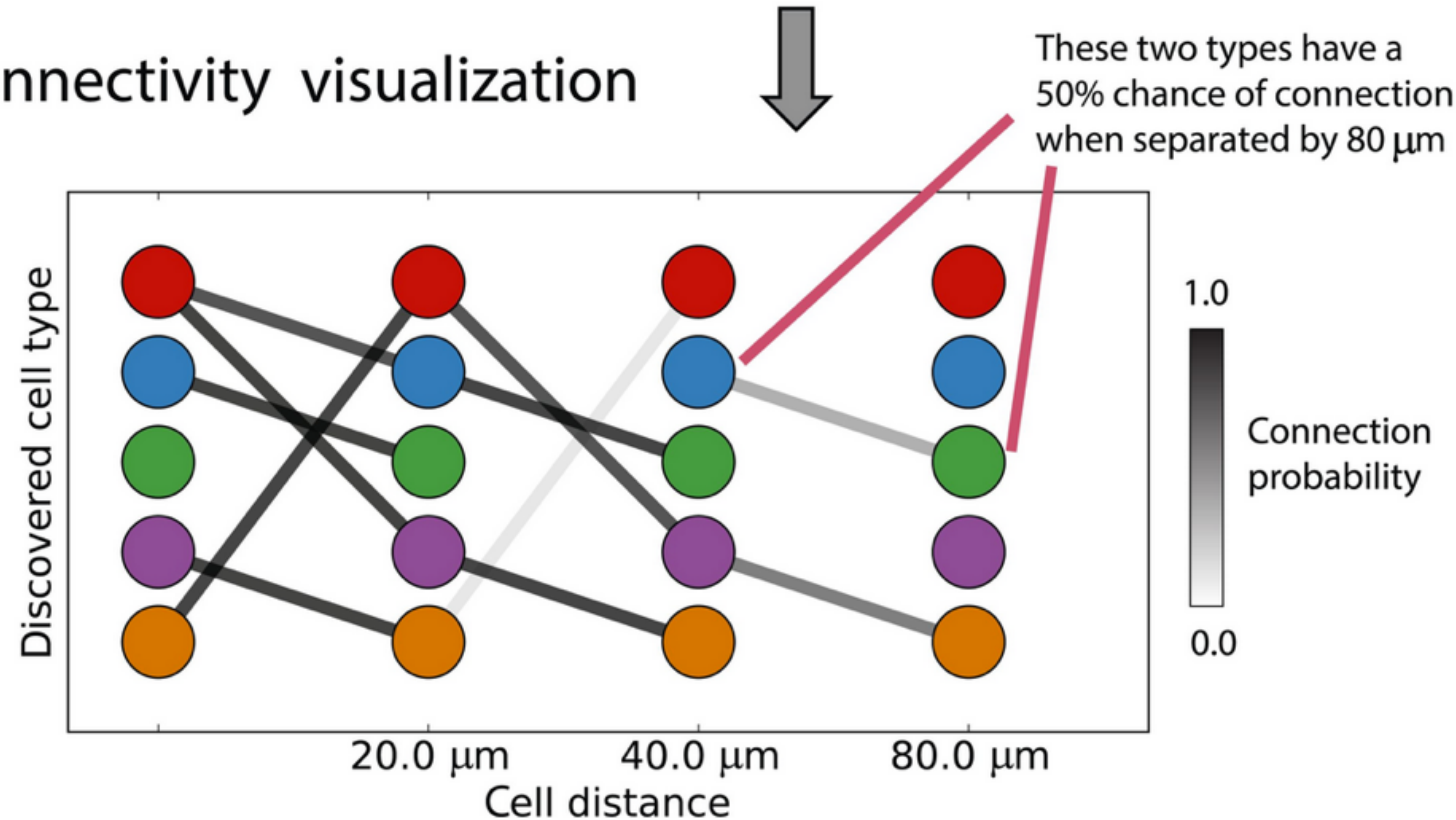


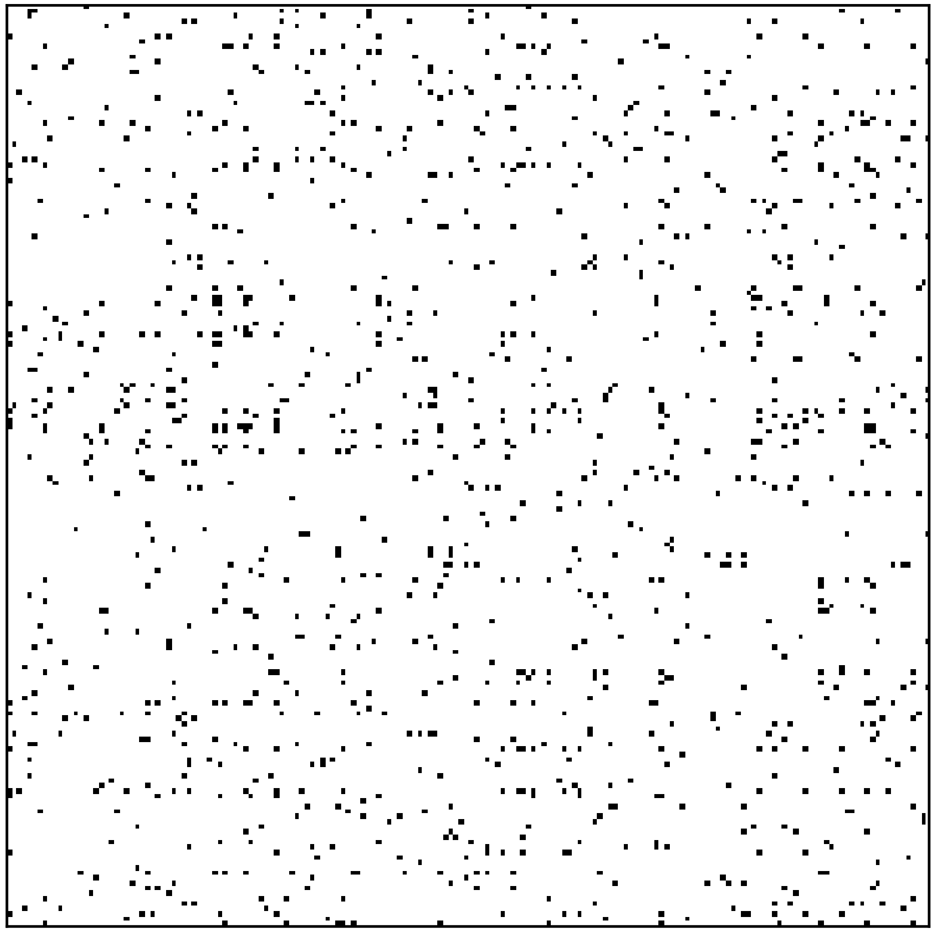
Recovered Latent Structure



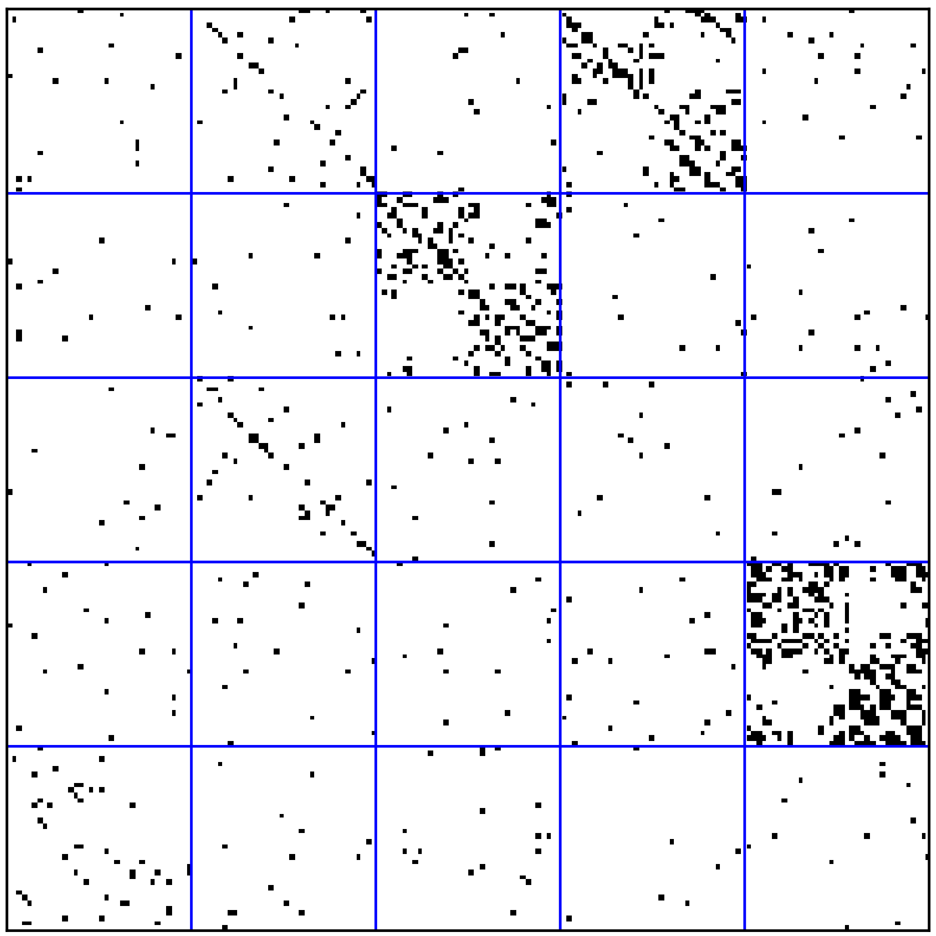
Connectivity visualization

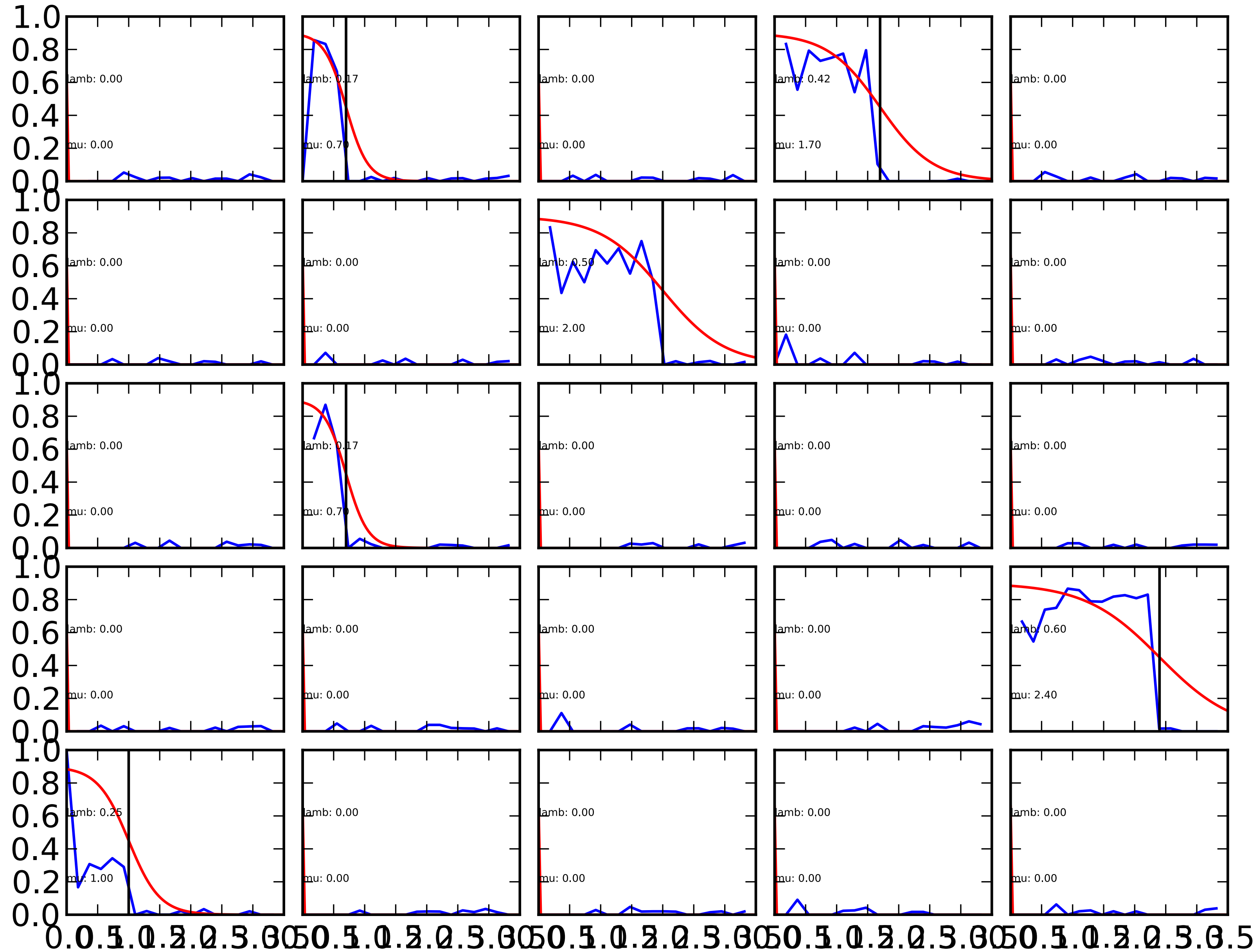
K





Synthetic Example





Inference

$$p(\vec{c}, \eta, \theta | R) \propto \prod_{i,j} p(R(i,j) | f(d(i,j) | \eta_{c_i c_j}), \theta)$$

$$\cdot \prod_{m,n} p(\eta_{mn} | \theta) \cdot p(\theta)$$

$$\cdot \, p(\vec{c} | \alpha) p(\alpha)$$

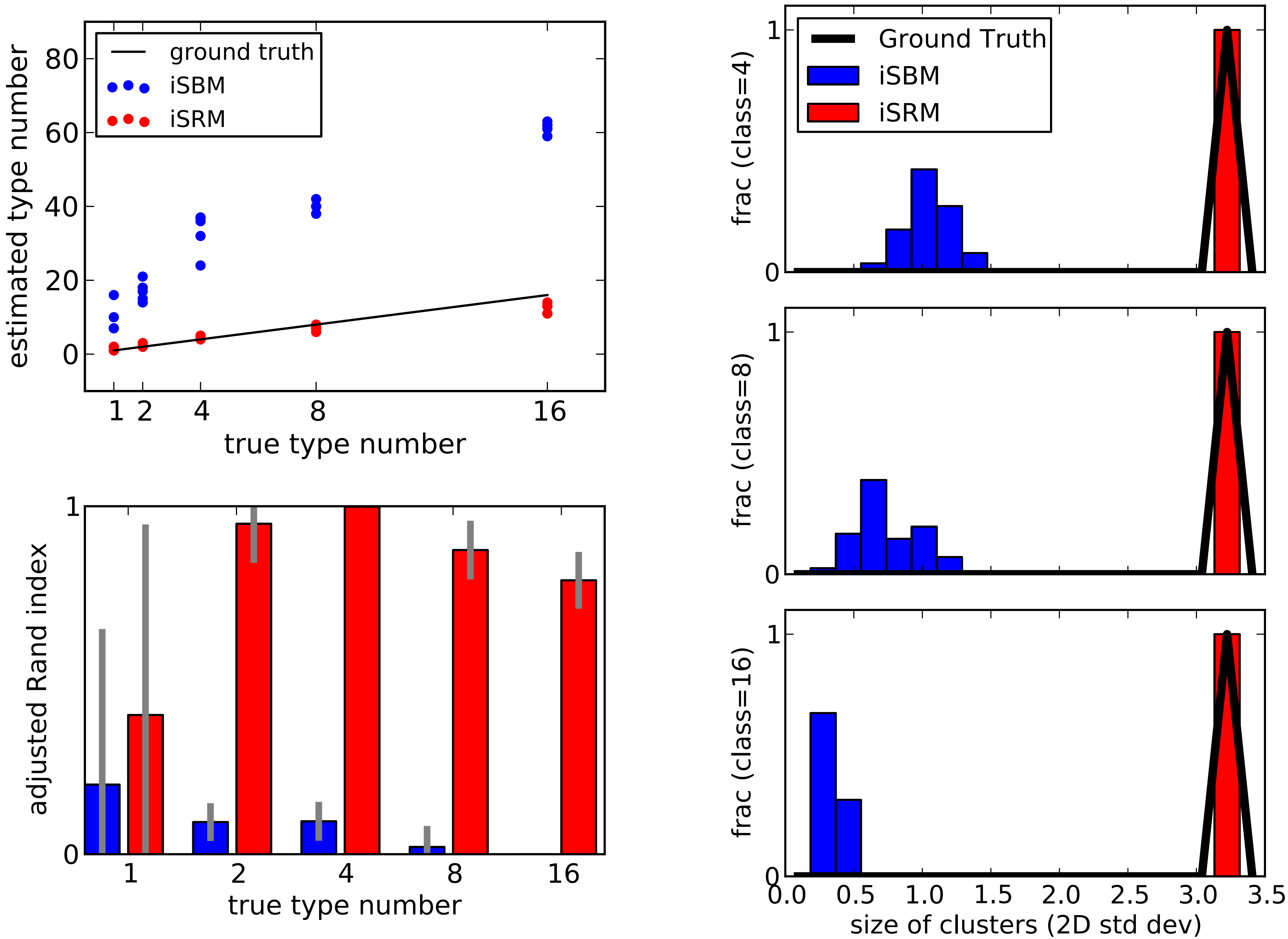
MCMC to the rescue!

Auxiliary Variable-augmented Gibbs for assignment

Slice sampling for per-component params

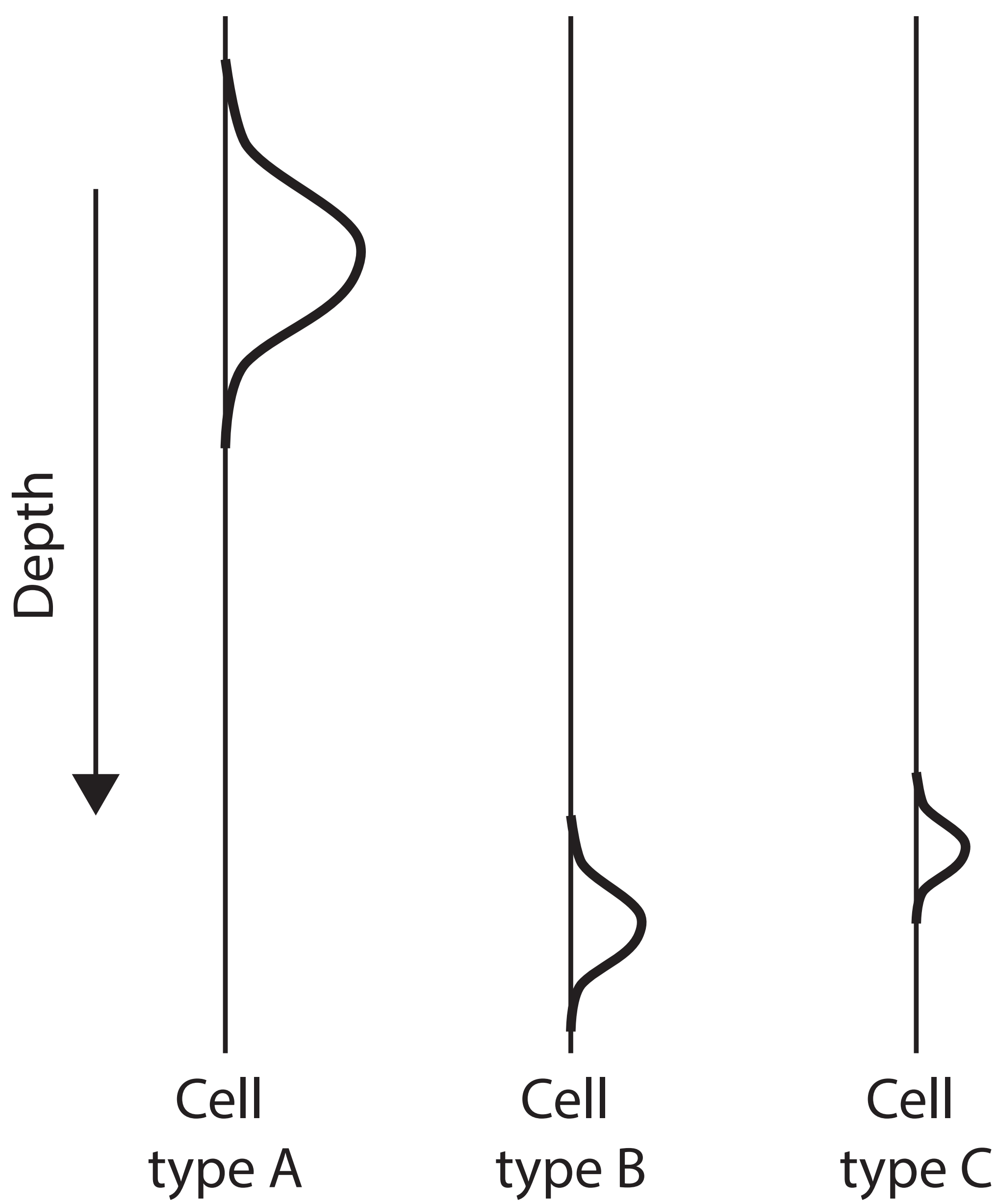
Gridded hyperparameter inference

Synthetic Data

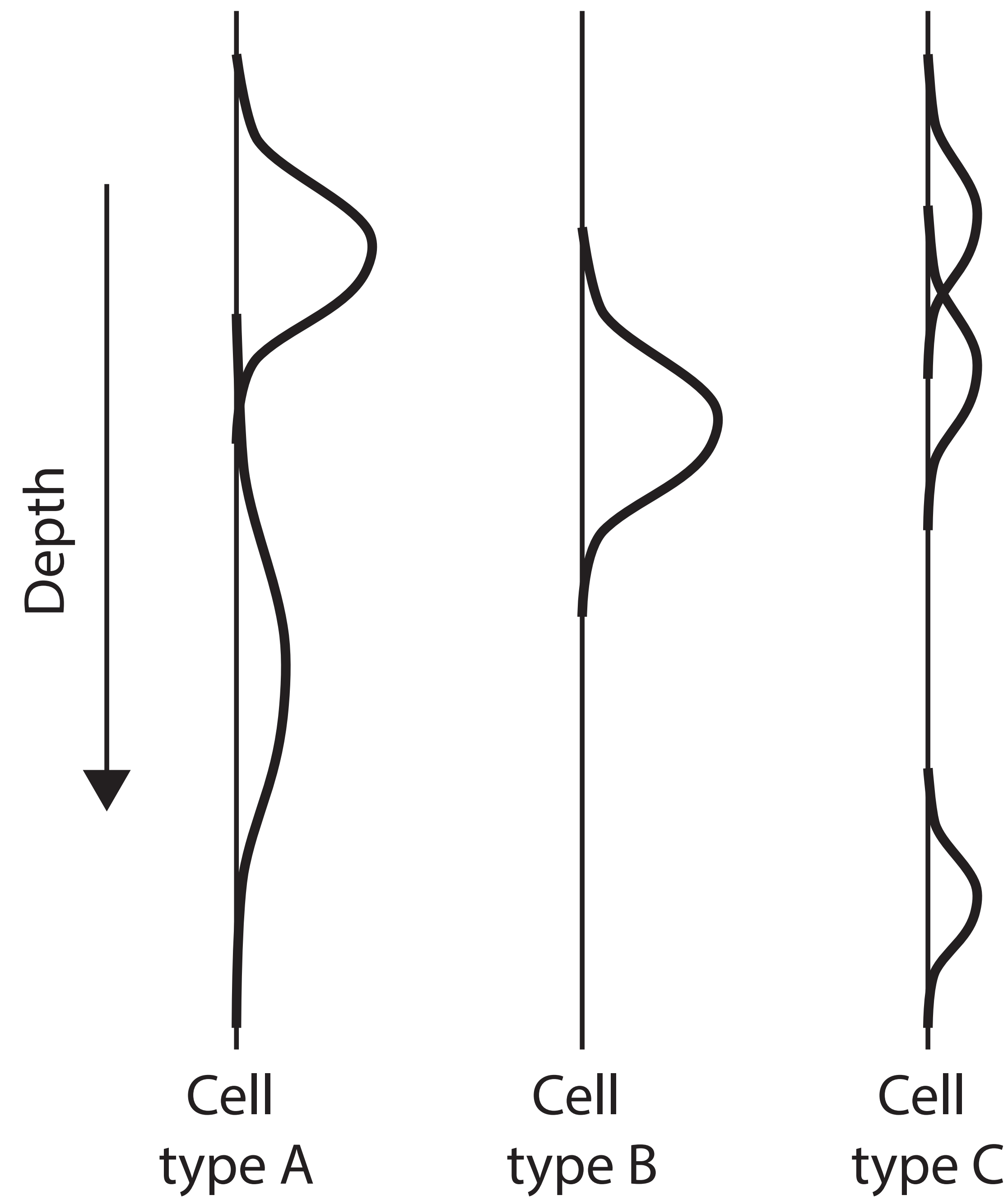


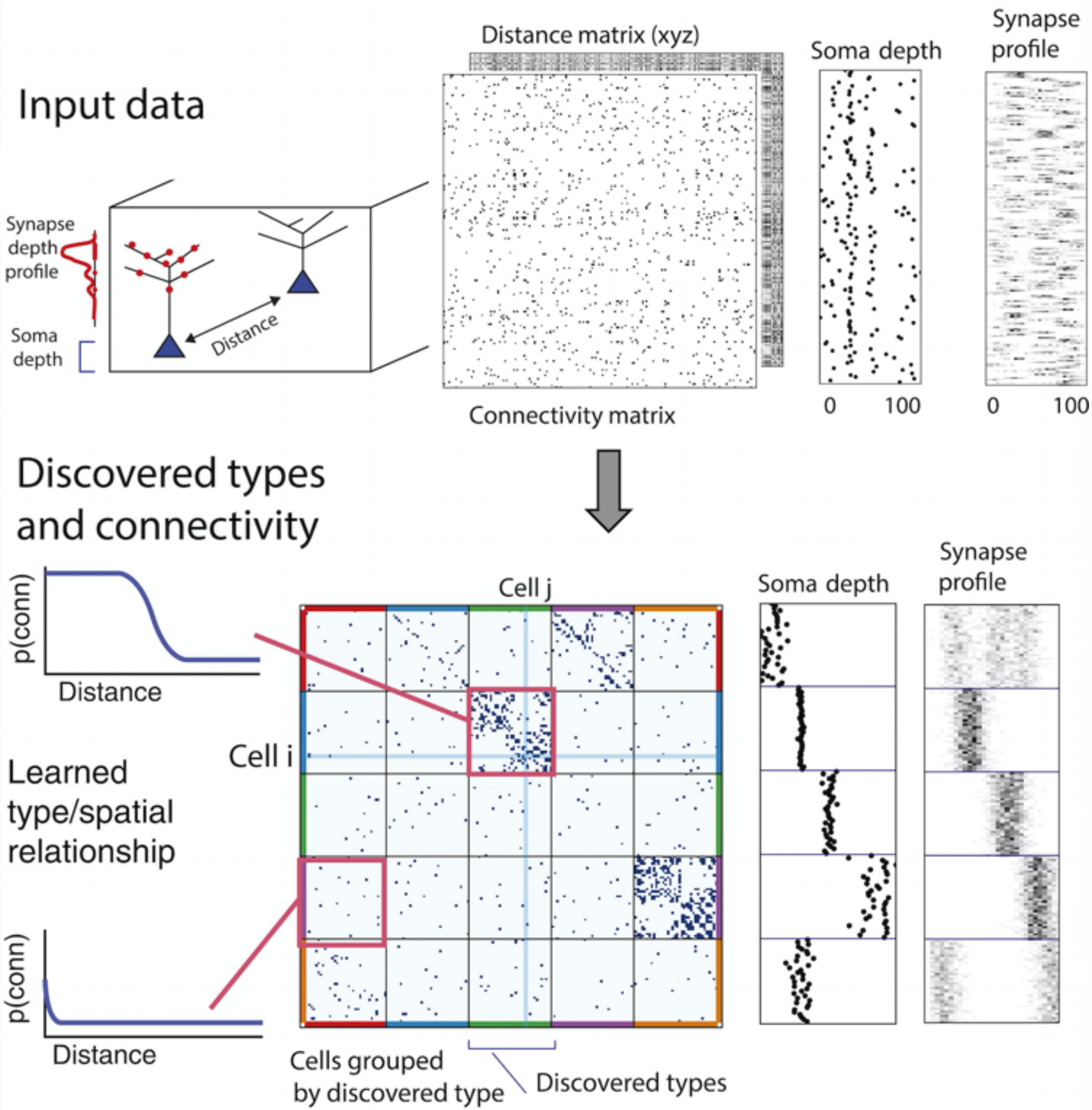
Extensions to model

Soma Depth



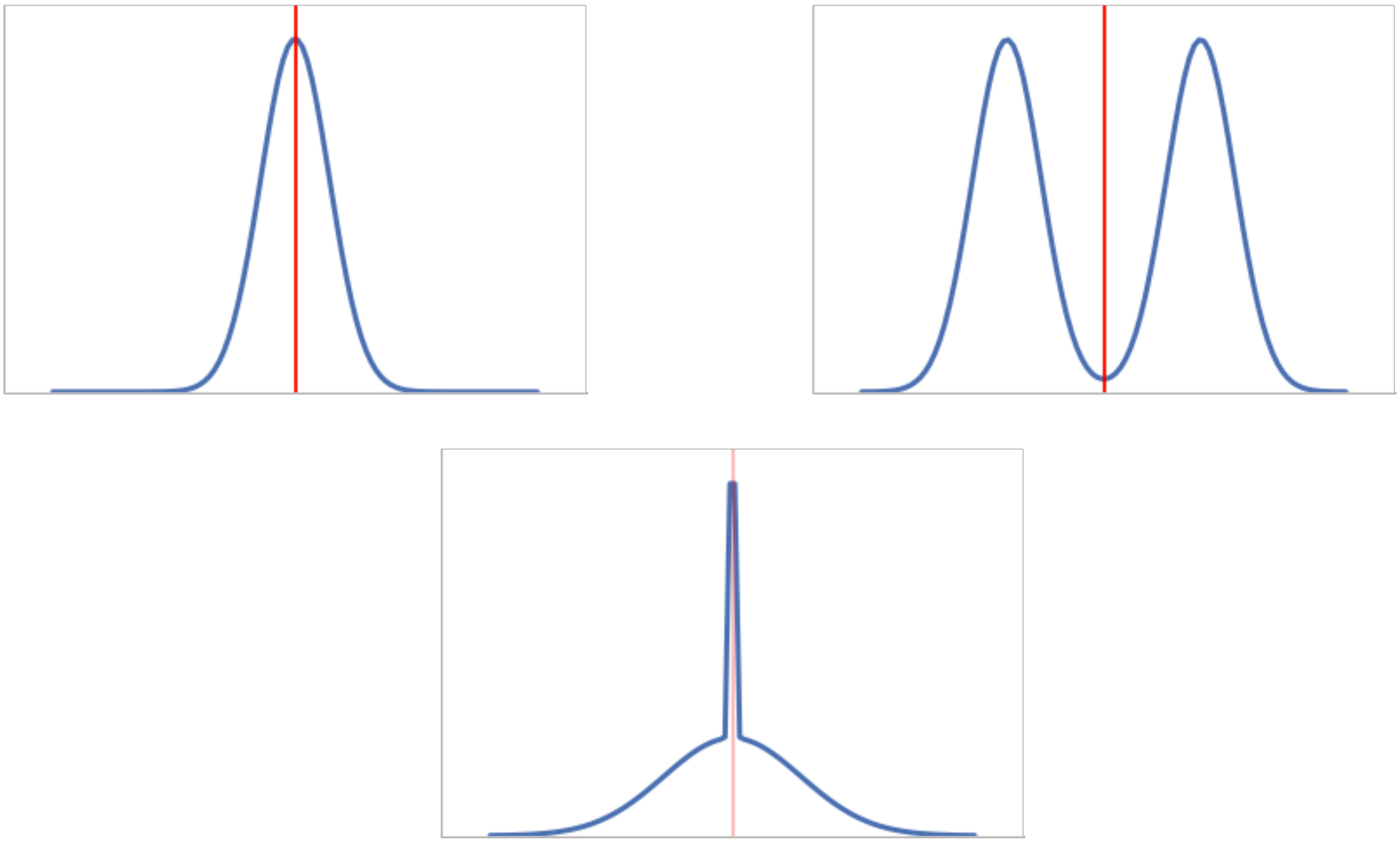
Synapse Depth Profile




Input data
Distance matrix (xyz)
Soma depth
Synapse profile
Synapse depth profile
Soma depth
Distance
Connectivity matrix
0
100
0
100
Discovered types and connectivity
p(conn)
Distance
Cell j
Cell i
Soma depth
Synapse profile
Learned type/spatial relationship
p(conn)
Distance
Cells grouped by discovered type
Discovered types

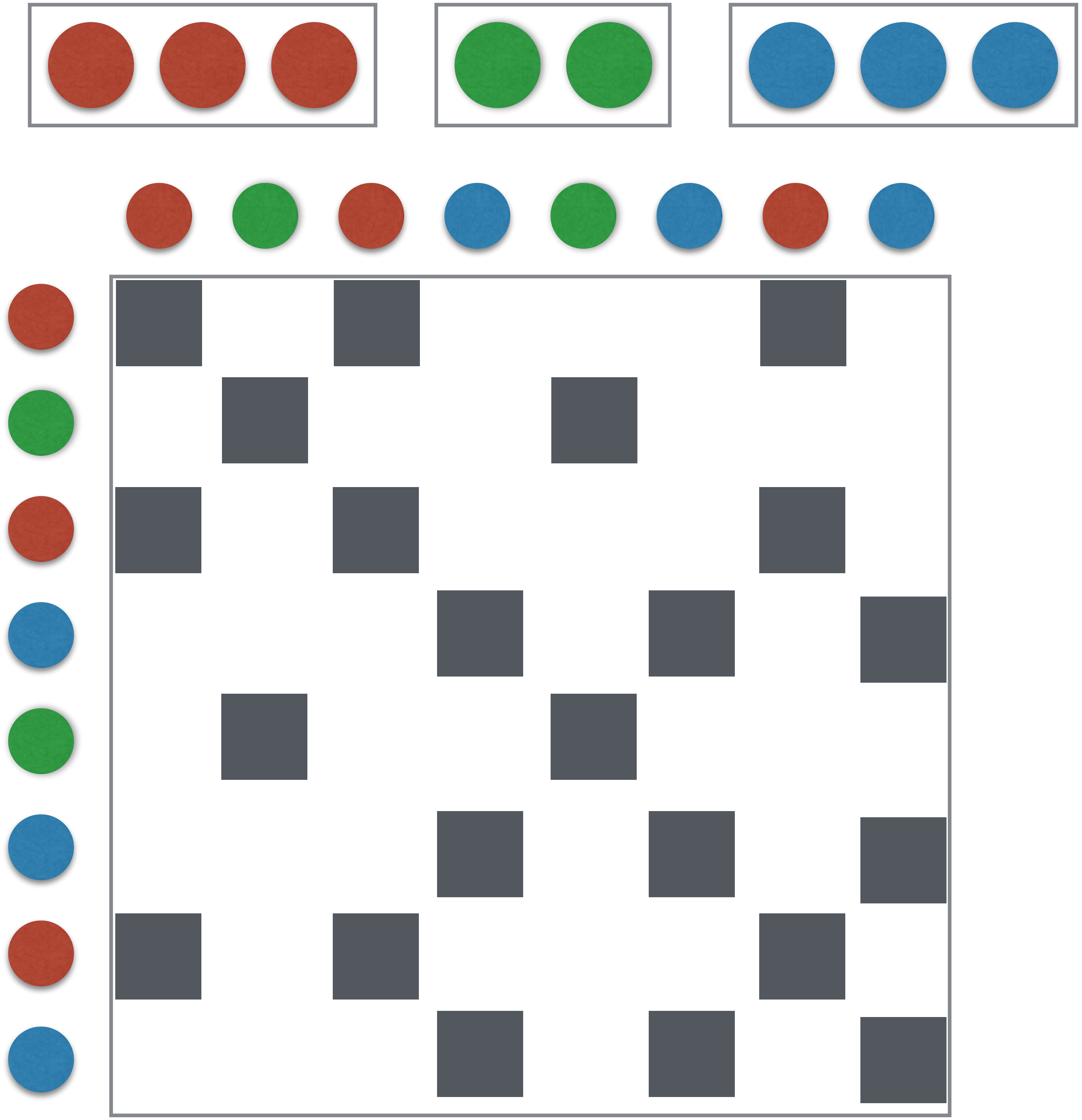
MAP vs Posterior

Do you believe your model?



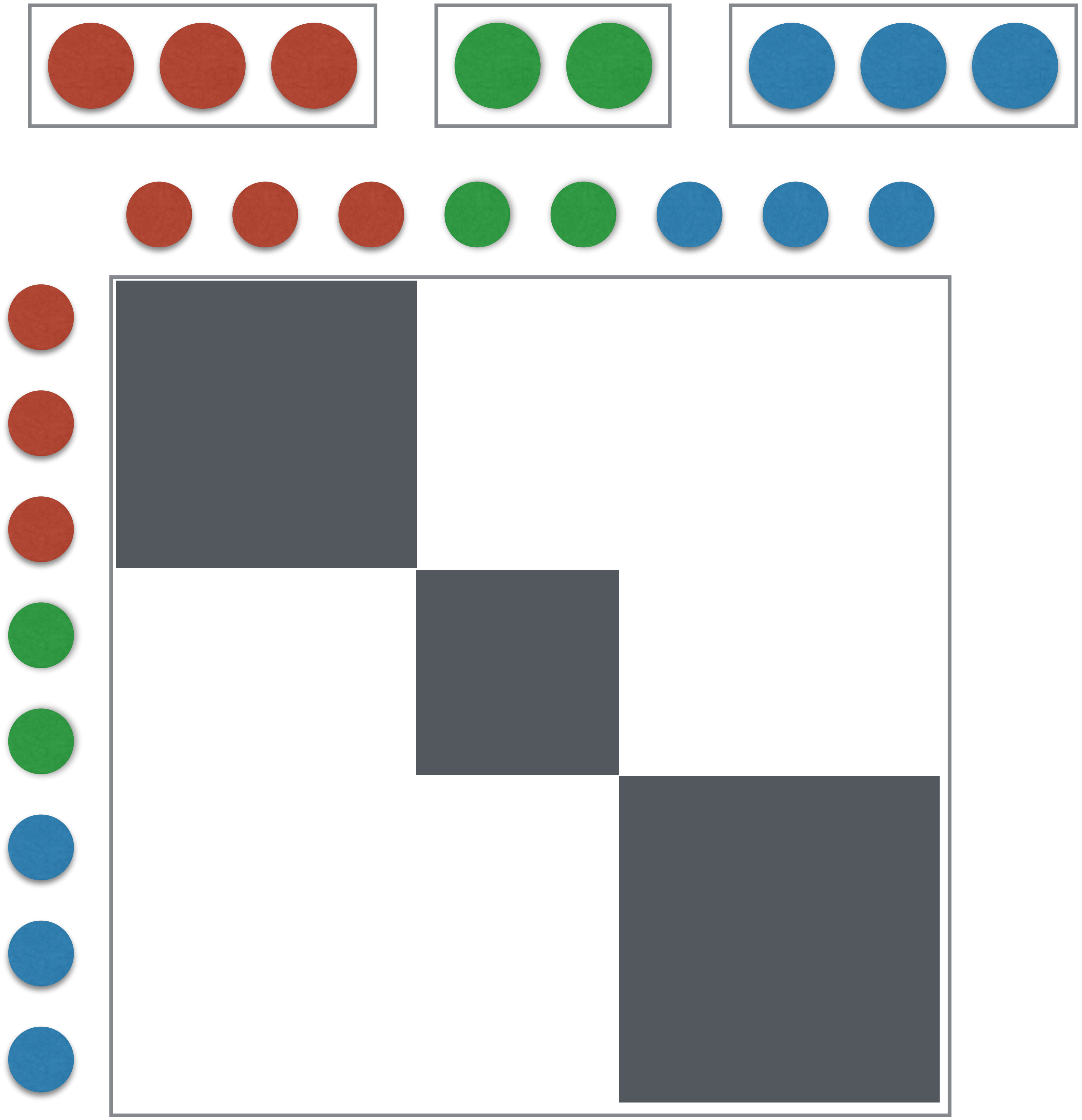
Visualizing Clustering Certainty

Truth:

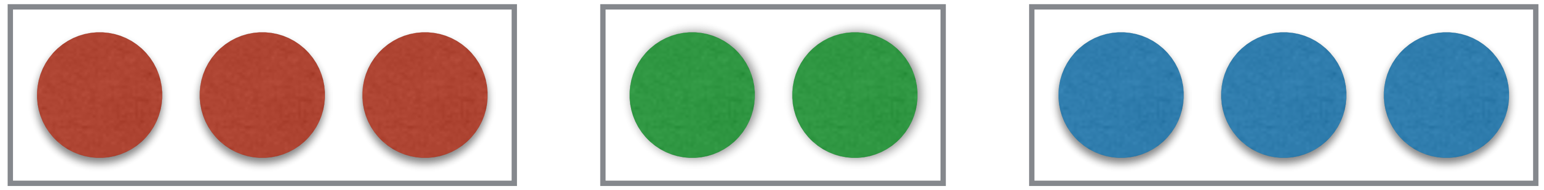


Visualizing Clustering Certainty

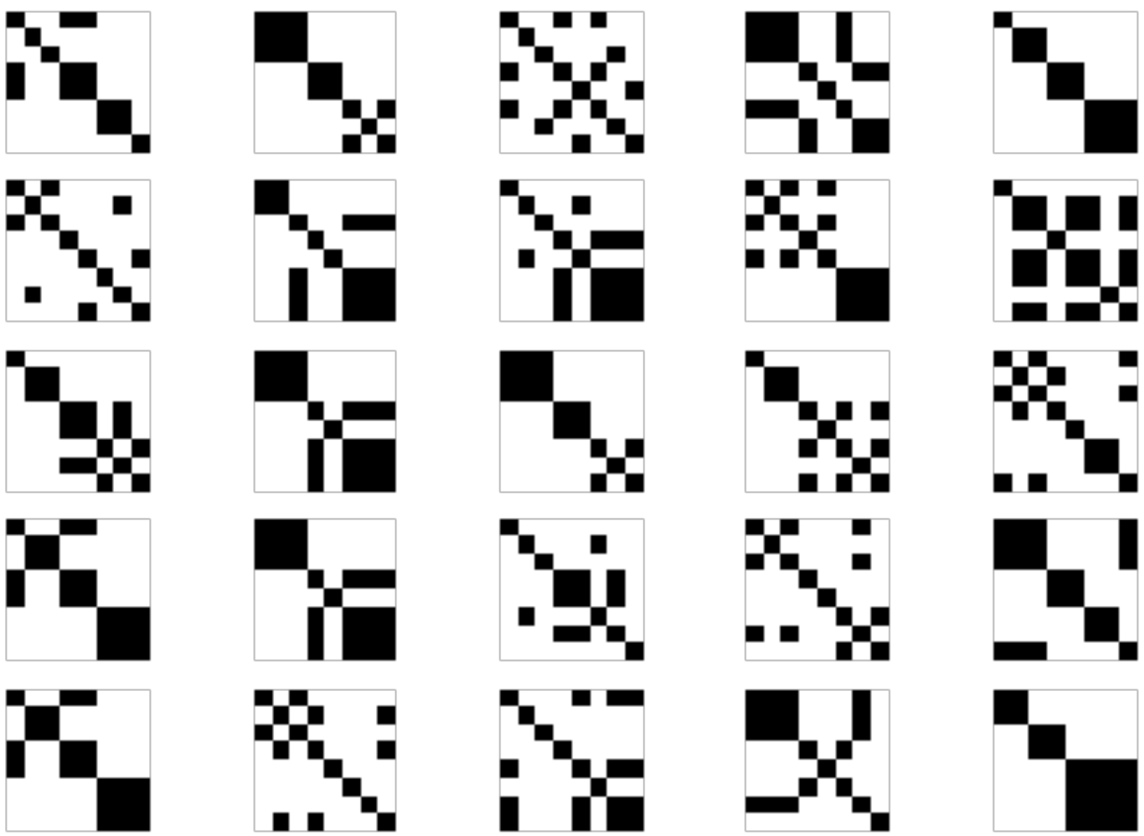
Truth:

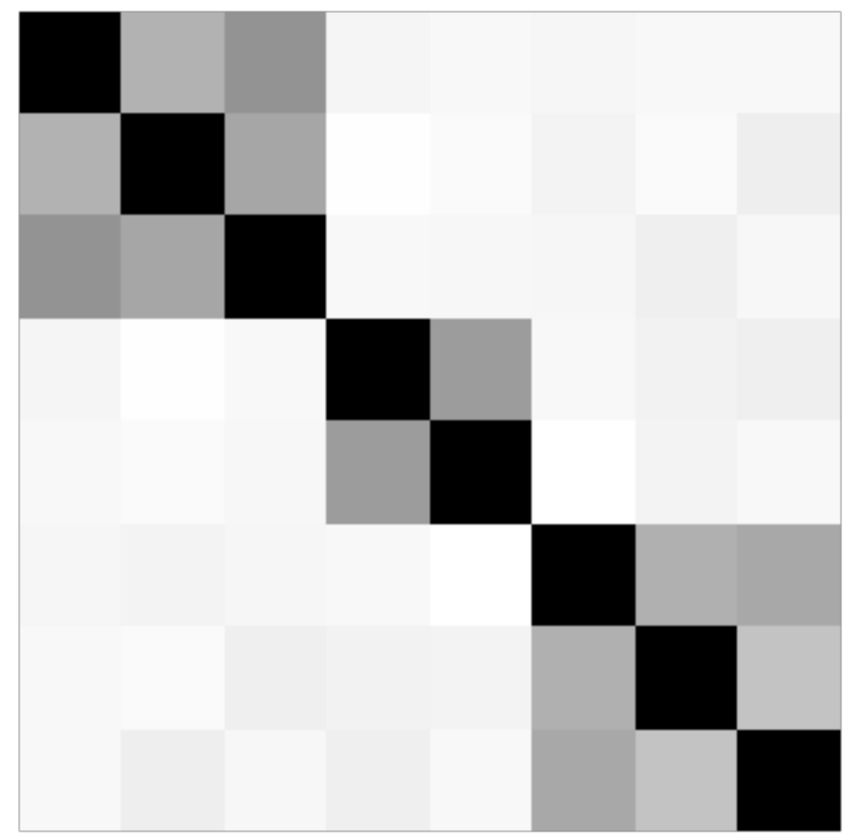


Visualizing Clustering Certainty

Truth: 

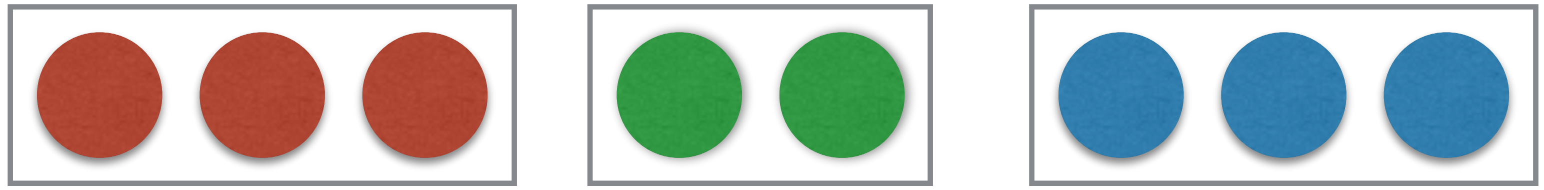
sample ~ p(cluster | data)



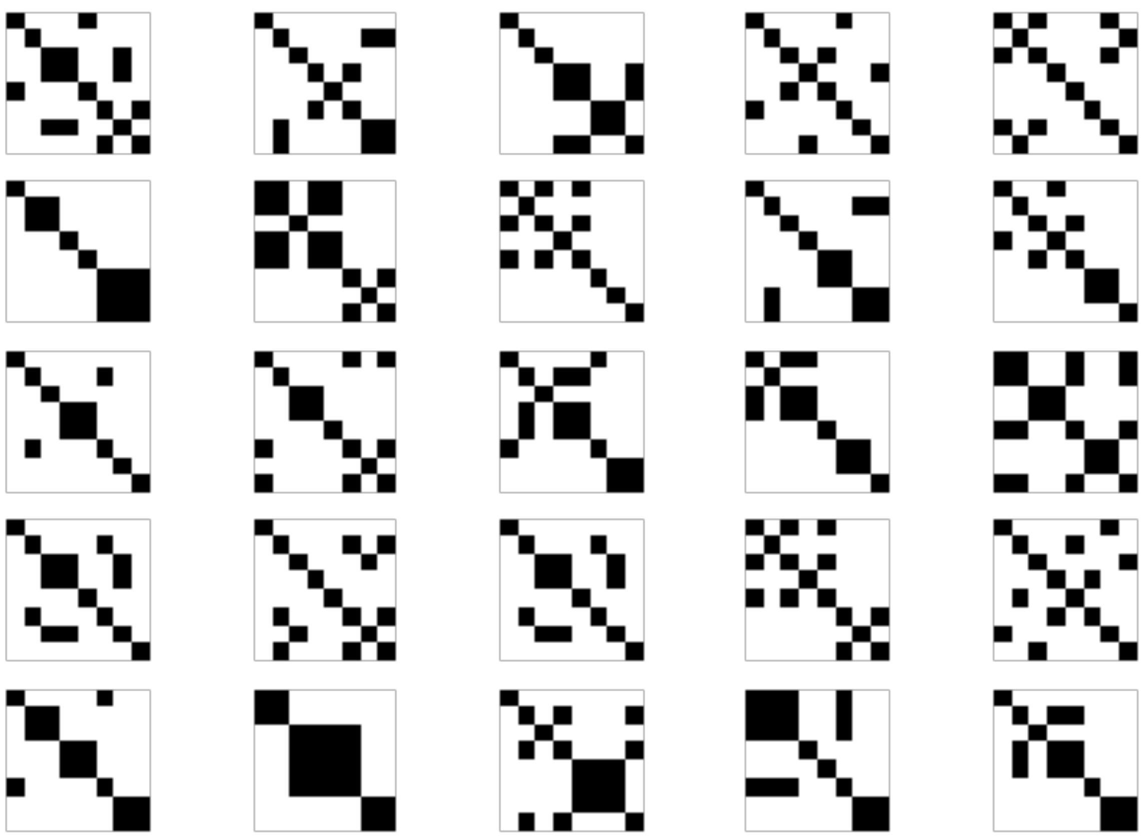


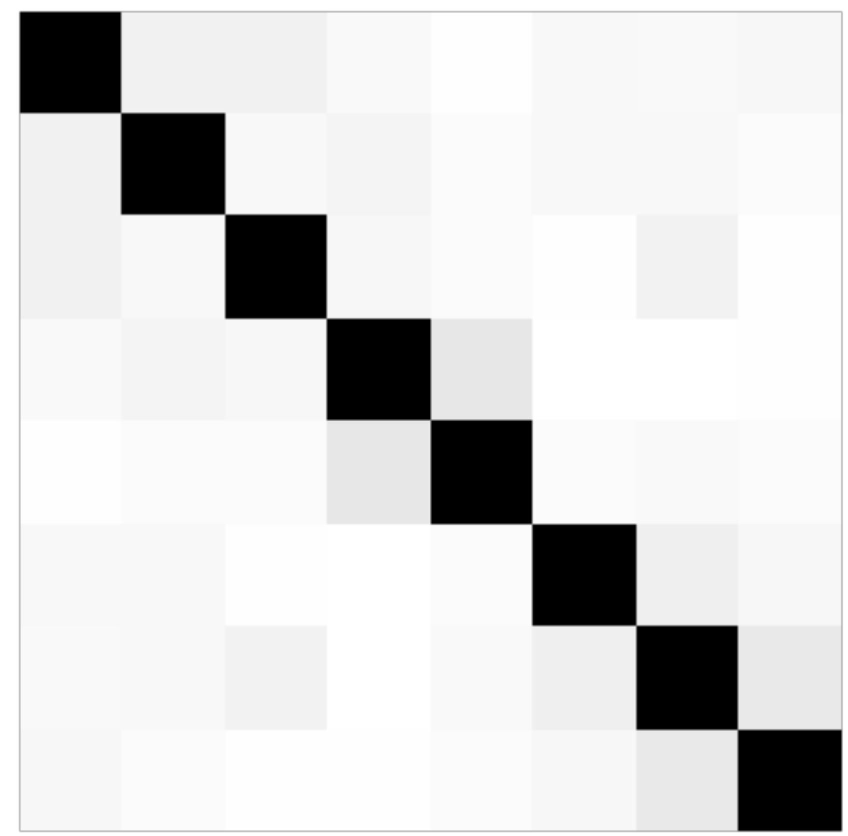
noise = 0.4

Visualizing Clustering Certainty

Truth: 

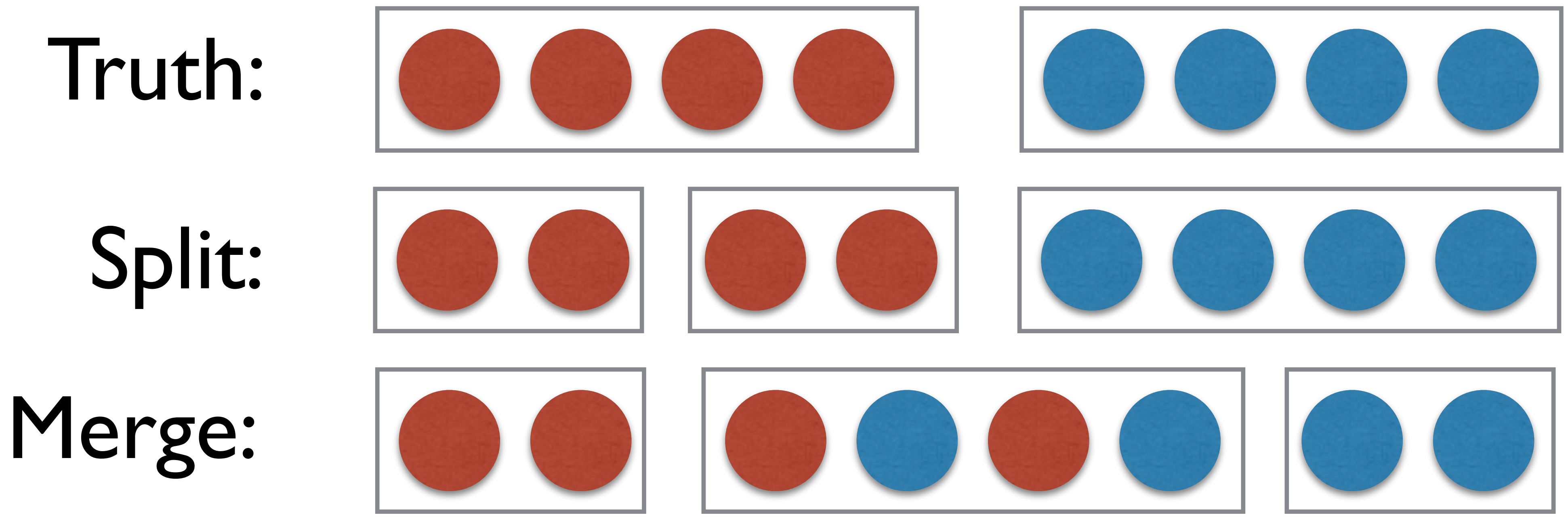
sample ~ p(cluster | data)

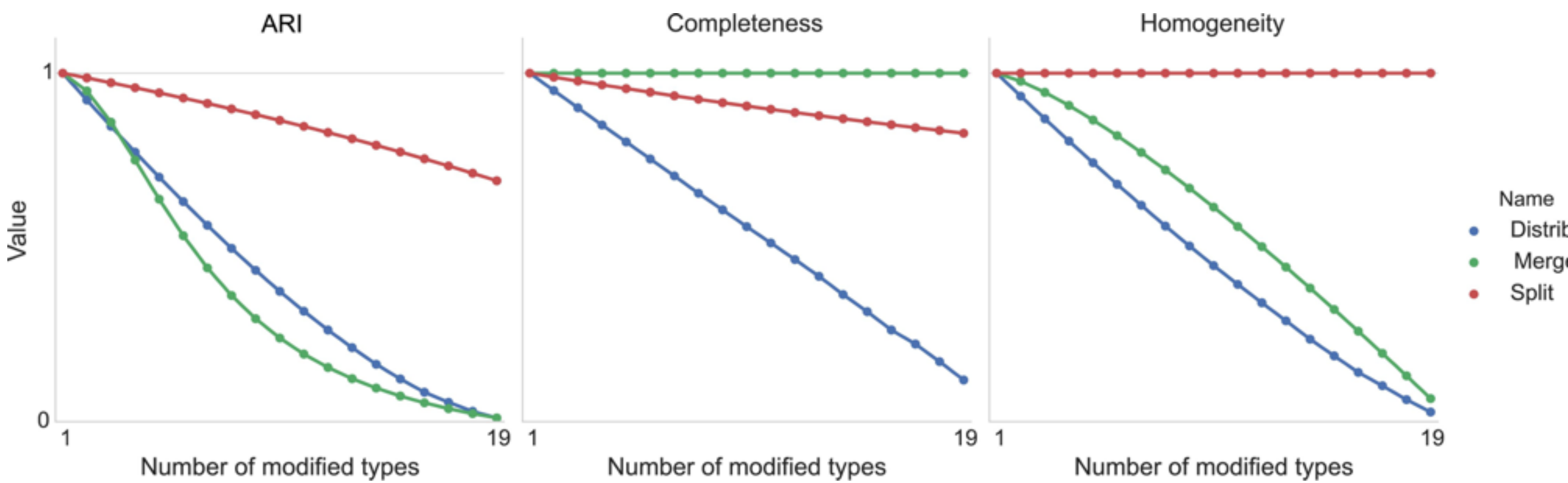


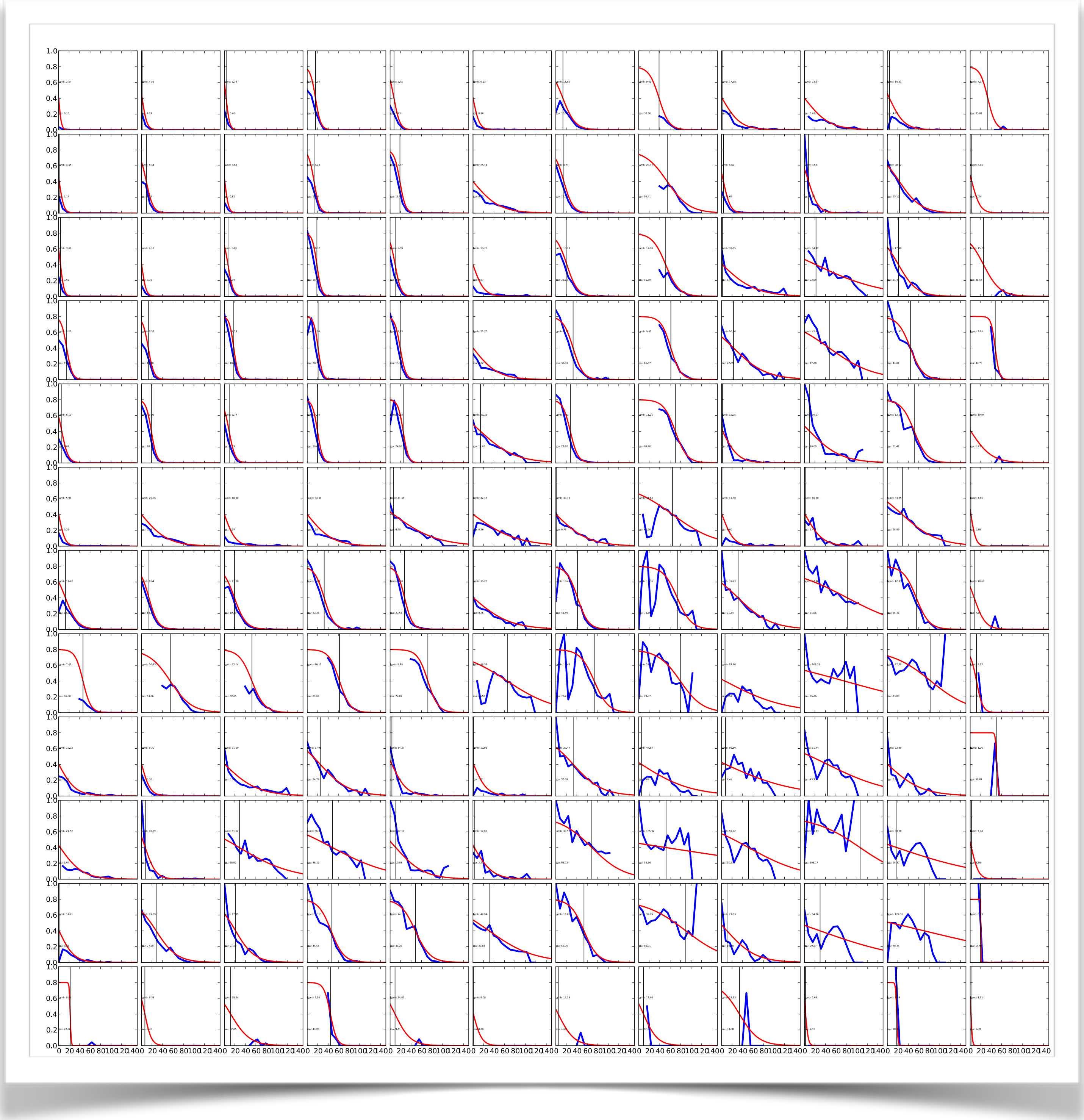


noise = 0.7

Clustering Metrics







The Data

ARTICLE

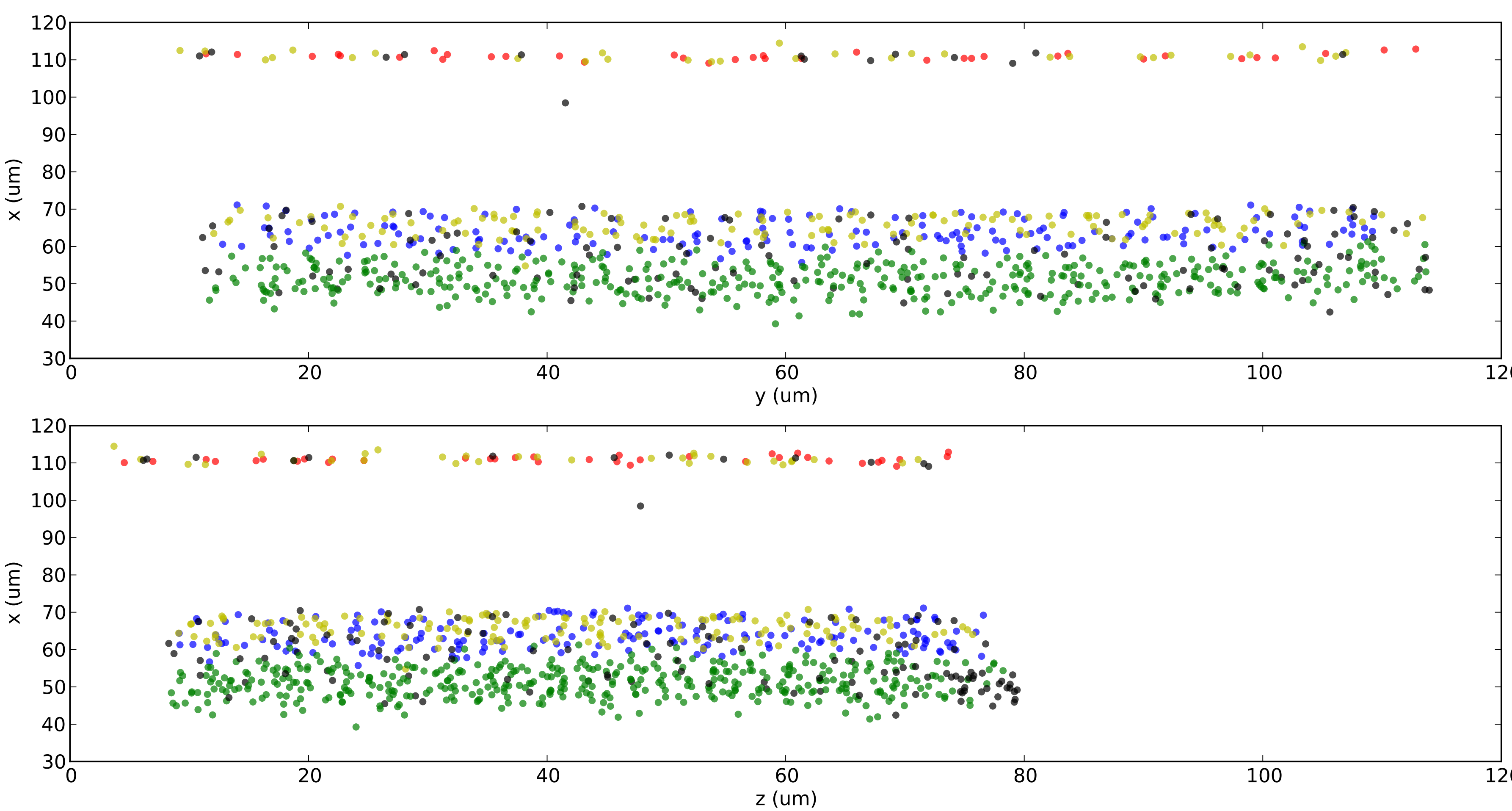
doi:10.1038/nature12346

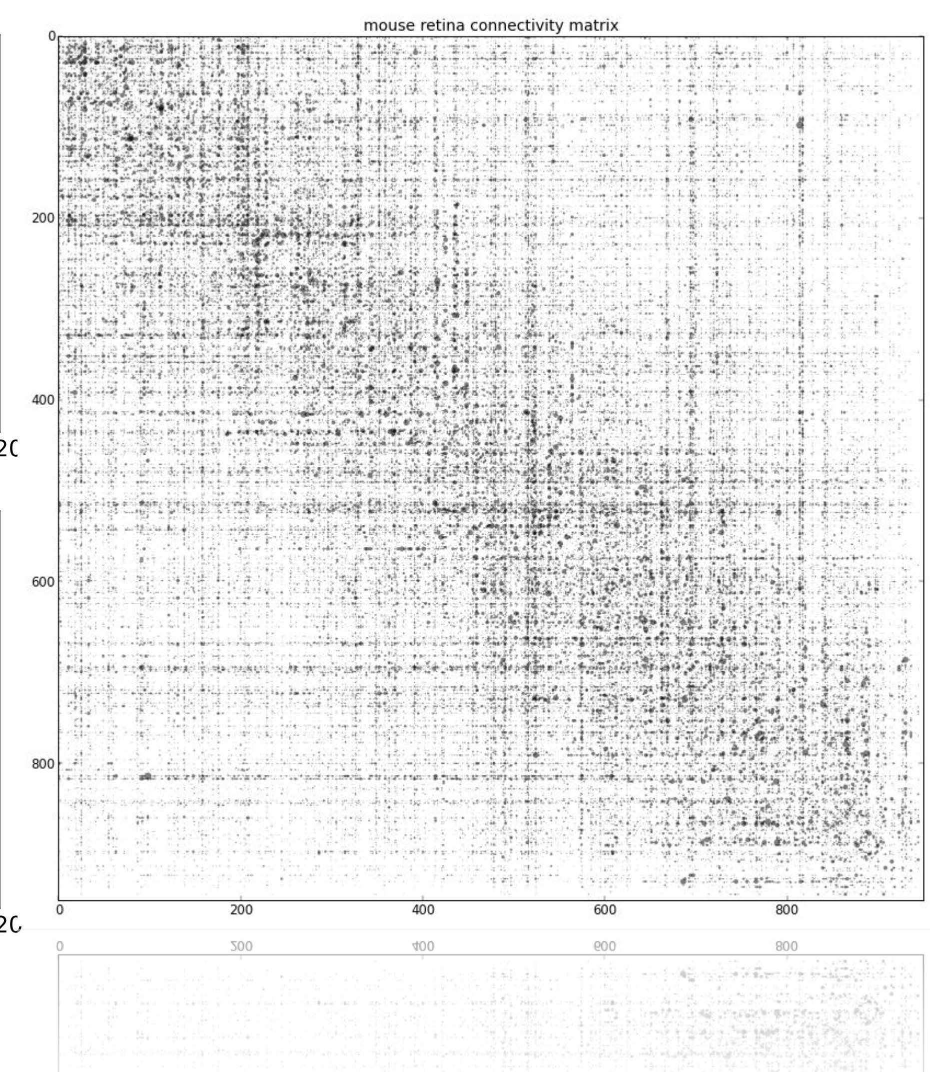
Connectomic reconstruction of the inner plexiform layer in the mouse retina

Moritz Helmstaedter[1]†, Kevin L. Briggman[1]†, Srinivas C. Turaga[2]†, Viren Jain[2]†, H. Sebastian Seung[2] & Winfried Denk[1]

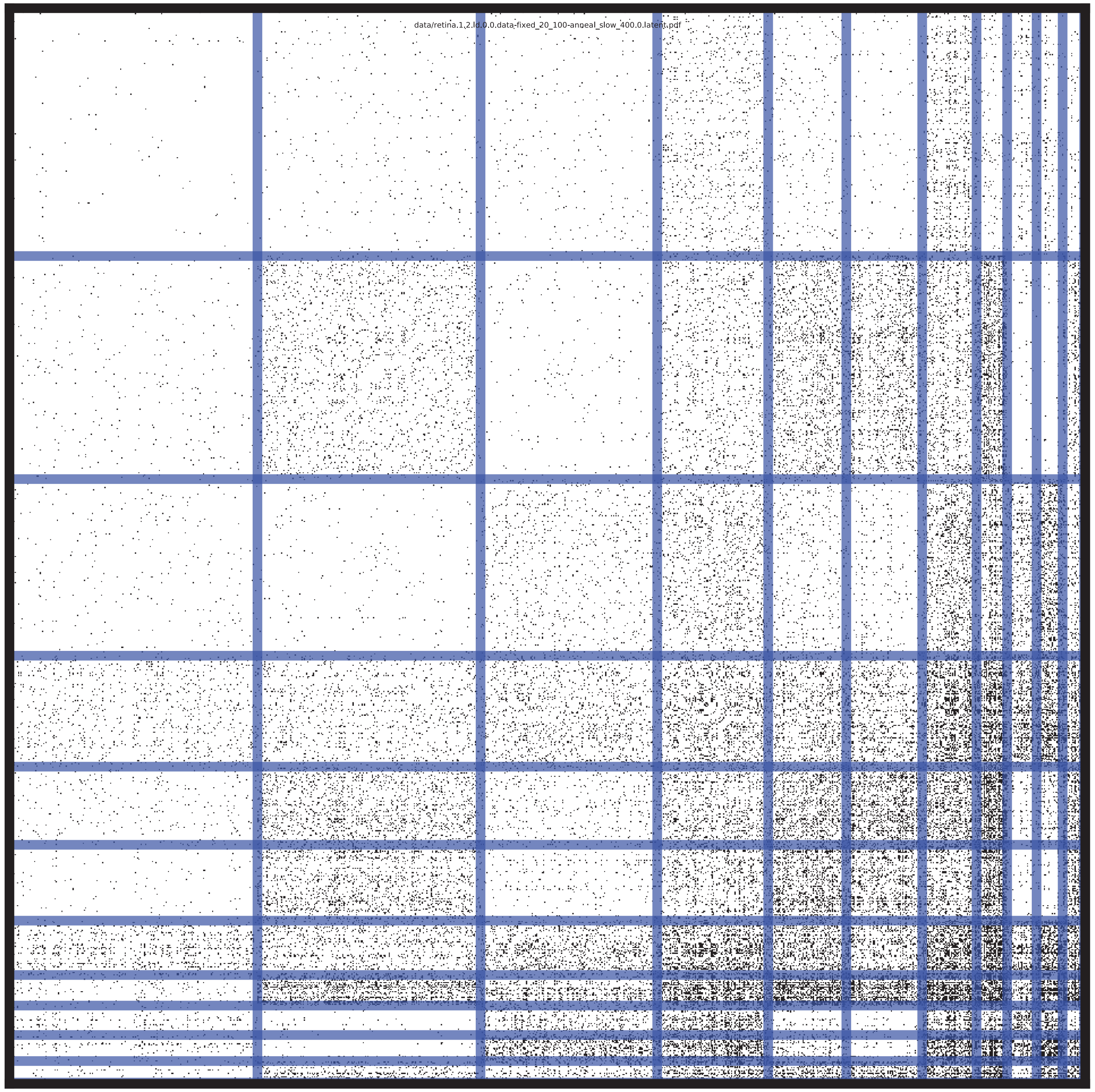
Comprehensive high-resolution structural maps are central to functional exploration and understanding in biology. For the nervous system, in which high resolution and large spatial extent are both needed, such maps are scarce as they challenge data acquisition and analysis capabilities. Here we present for the mouse inner plexiform layer—the main computational neuropil region in the mammalian retina—the dense reconstruction of 950 neurons and their mutual contacts. This was achieved by applying a combination of crowd-sourced manual annotation and machine-learning-based volume segmentation to serial block-face electron microscopy data. We characterize a new type of retinal bipolar interneuron and show that we can subdivide a known type based on connectivity. Circuit motifs that emerge from our data indicate a functional mechanism for a known cellular response in a ganglion cell that detects localized motion, and predict that another ganglion cell is motion sensitive.

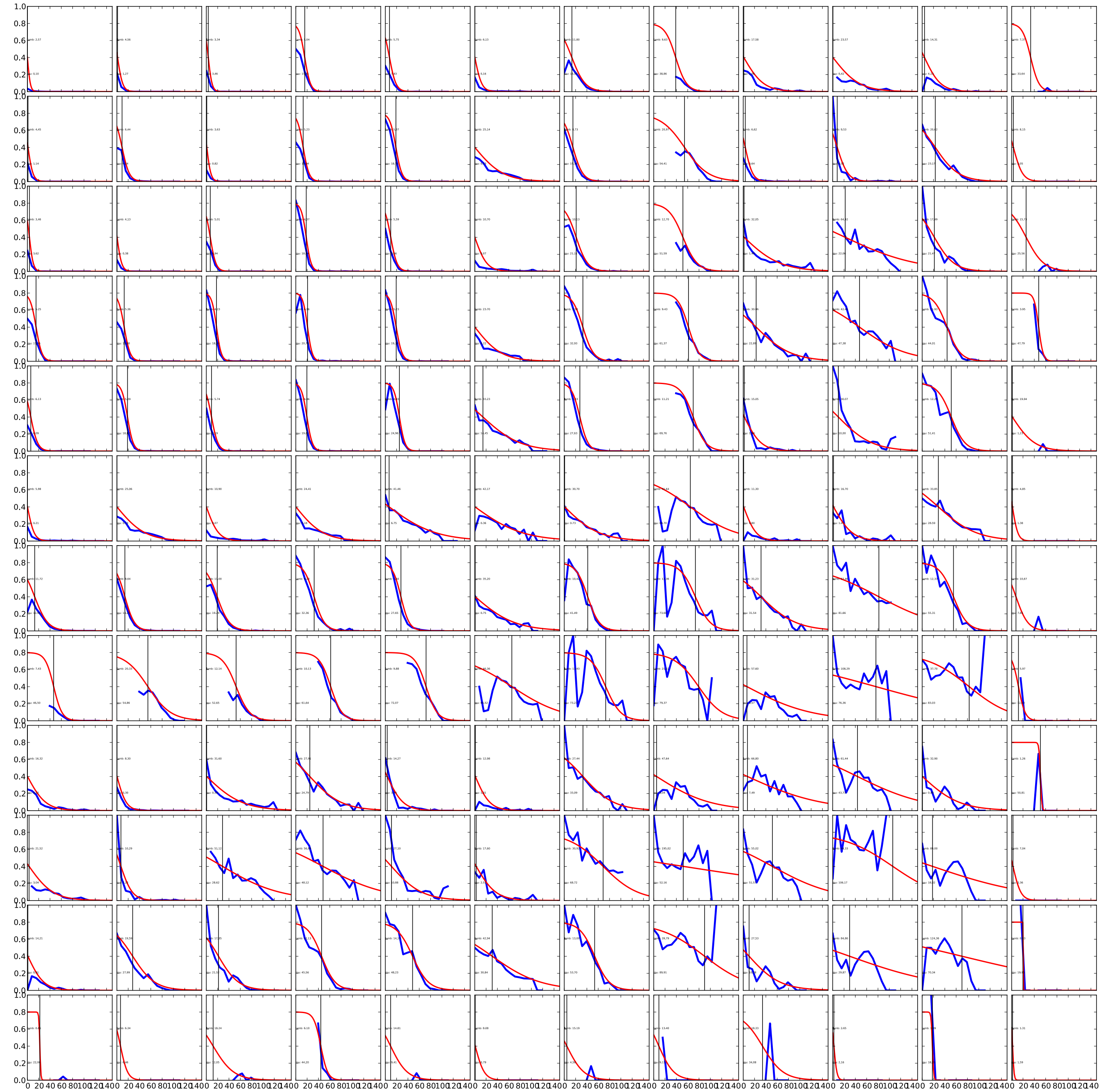
950 cells (ish)
“contactome”
Didn’t release soma positions
types (5/”80”)



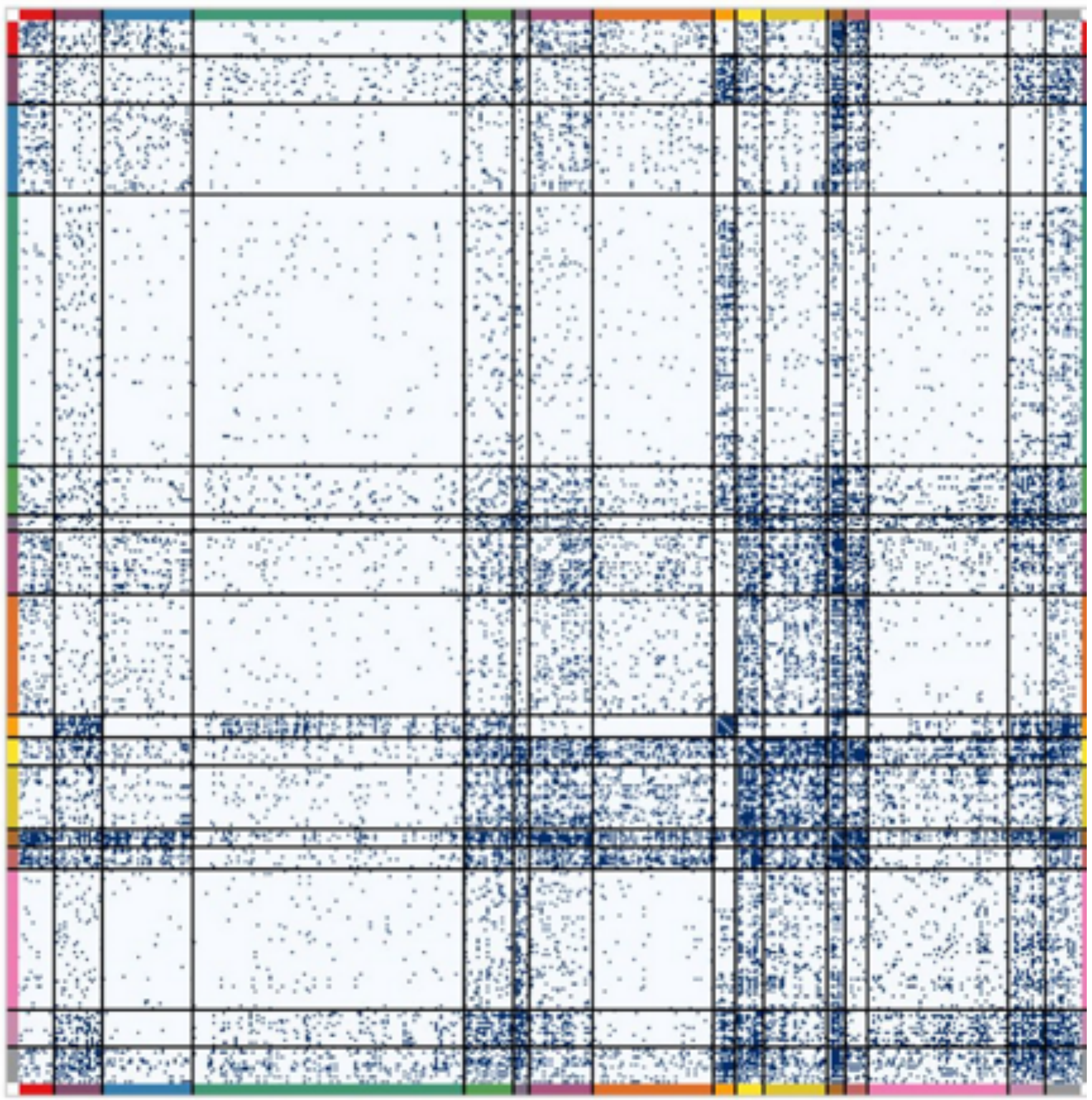


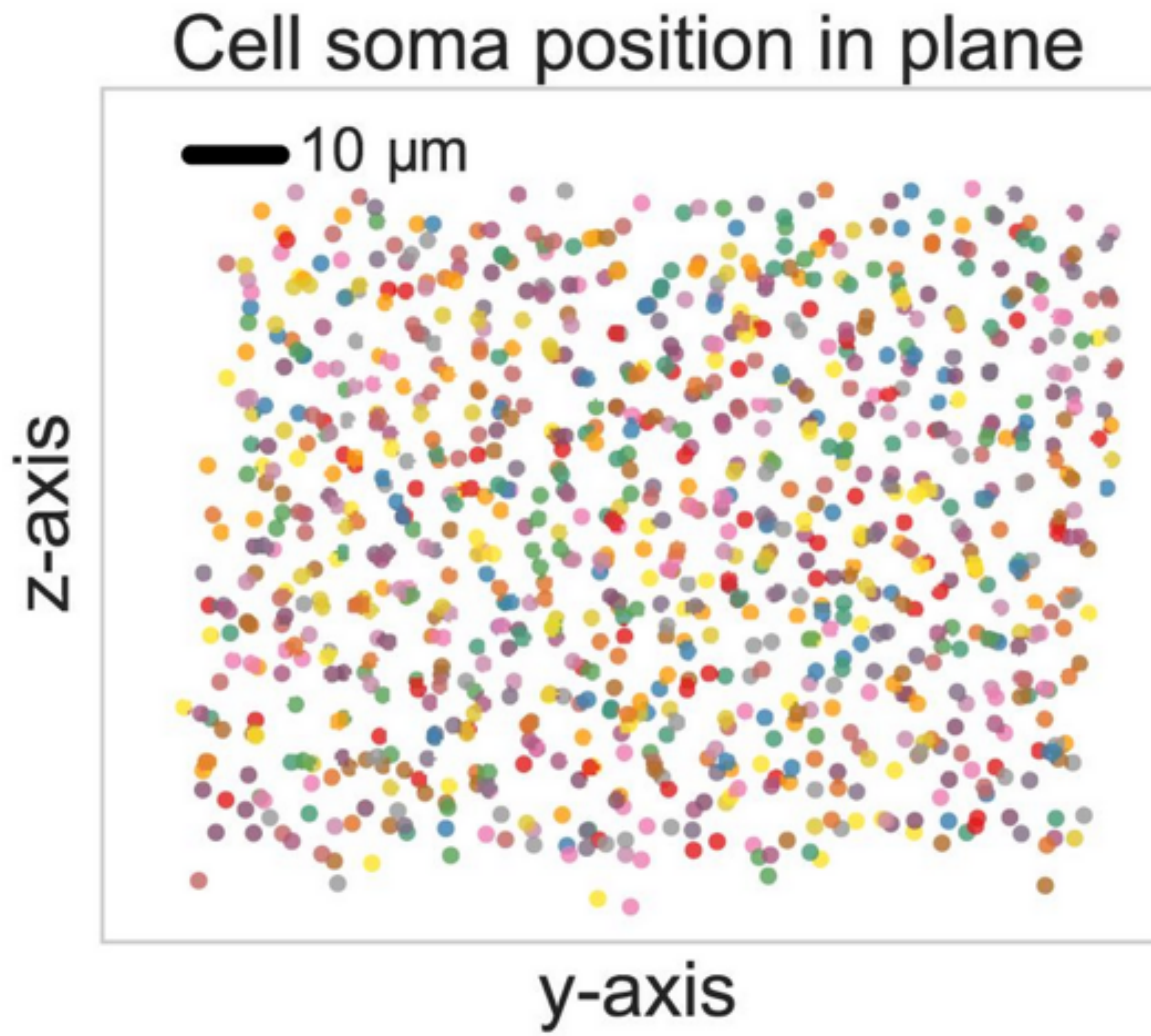
MAP Estimate



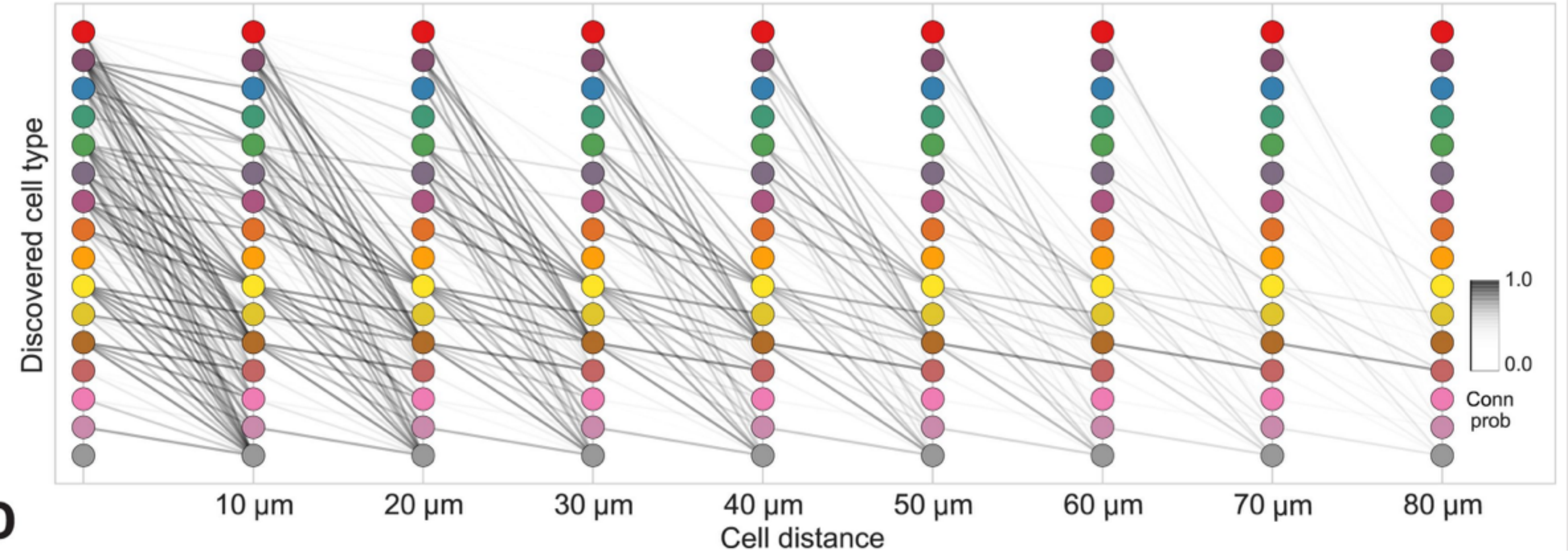


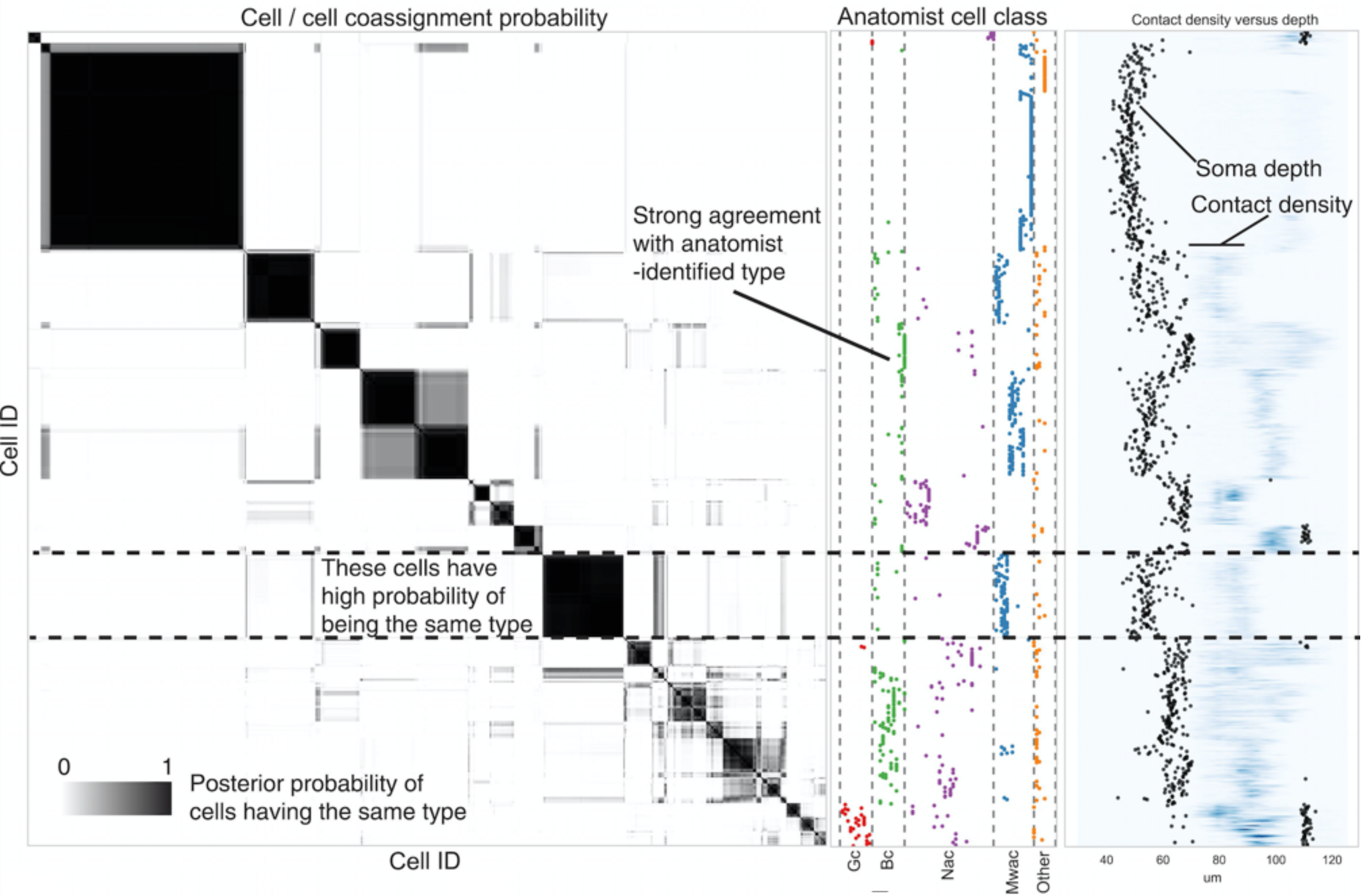
Spatial Extent



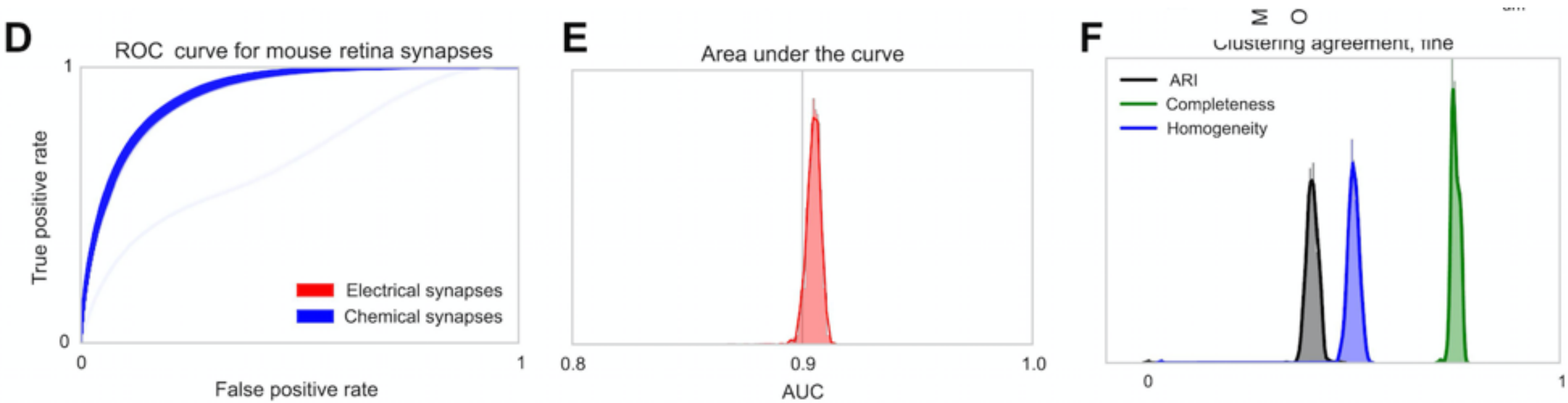


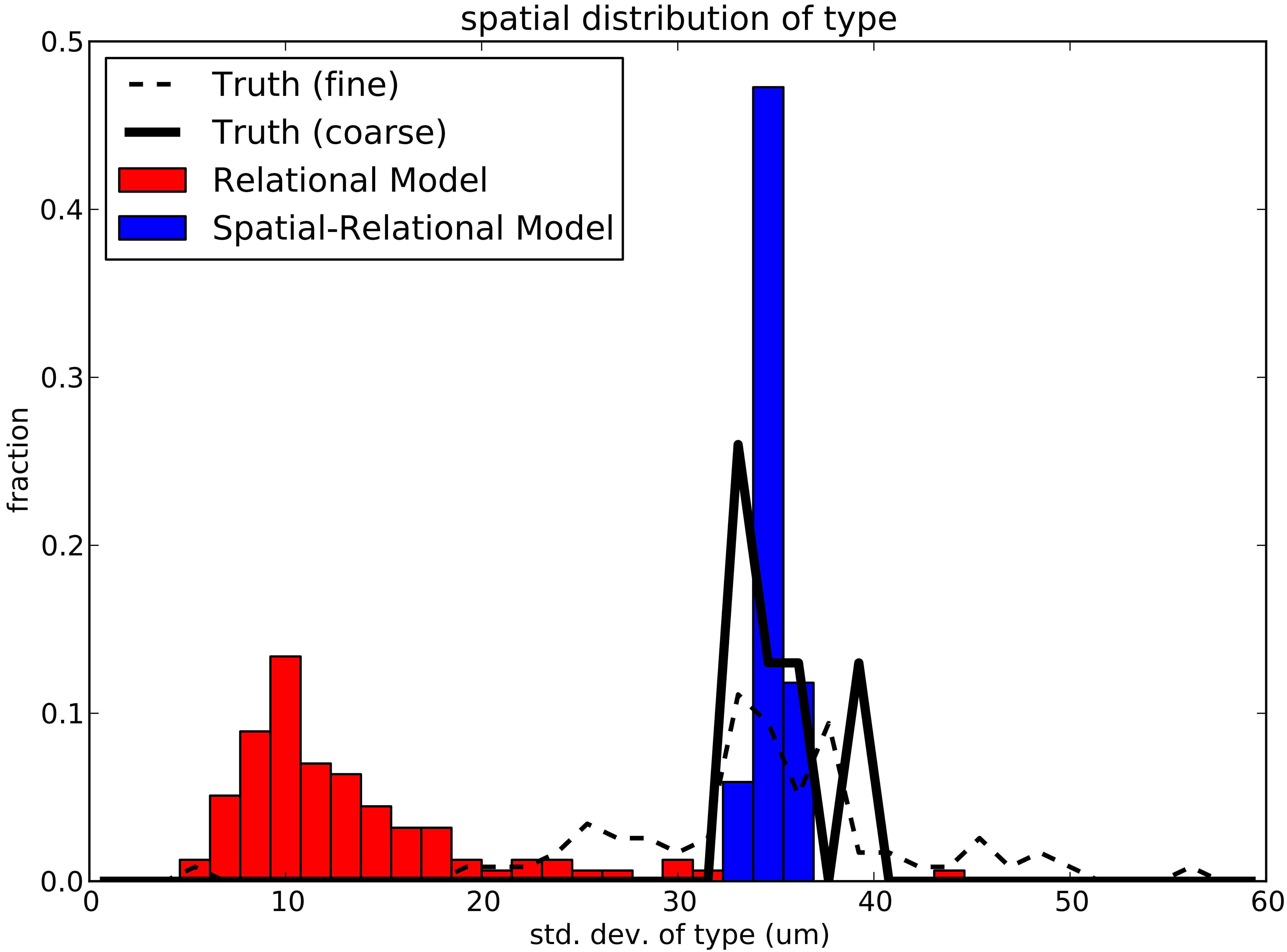
Recovered Connectivity




Cell / cell coassignment probability
Anatomist cell class
Contact density versus depth
Strong agreement with anatomist -identified type
Soma depth
Contact density
These cells have high probability of being the same type
0
1
Posterior probability of cells having the same type
Cell ID
Cell ID
Gc
Bc
Nac
Mwac
Other
40
60
80
100
120
um

Clustering performance




spatial distribution of type
Truth (fine)
Truth (coarse)
Relational Model
Spatial-Relational Model
fraction
0.0
0.1
0.2
0.3
0.4
0.5
0
10
20
30
40
50
60
std. dev. of type (um)

Phil. Trans. R. Soc. Lond. B **314**, 1–340 (1986) [1]
Printed in Great Britain

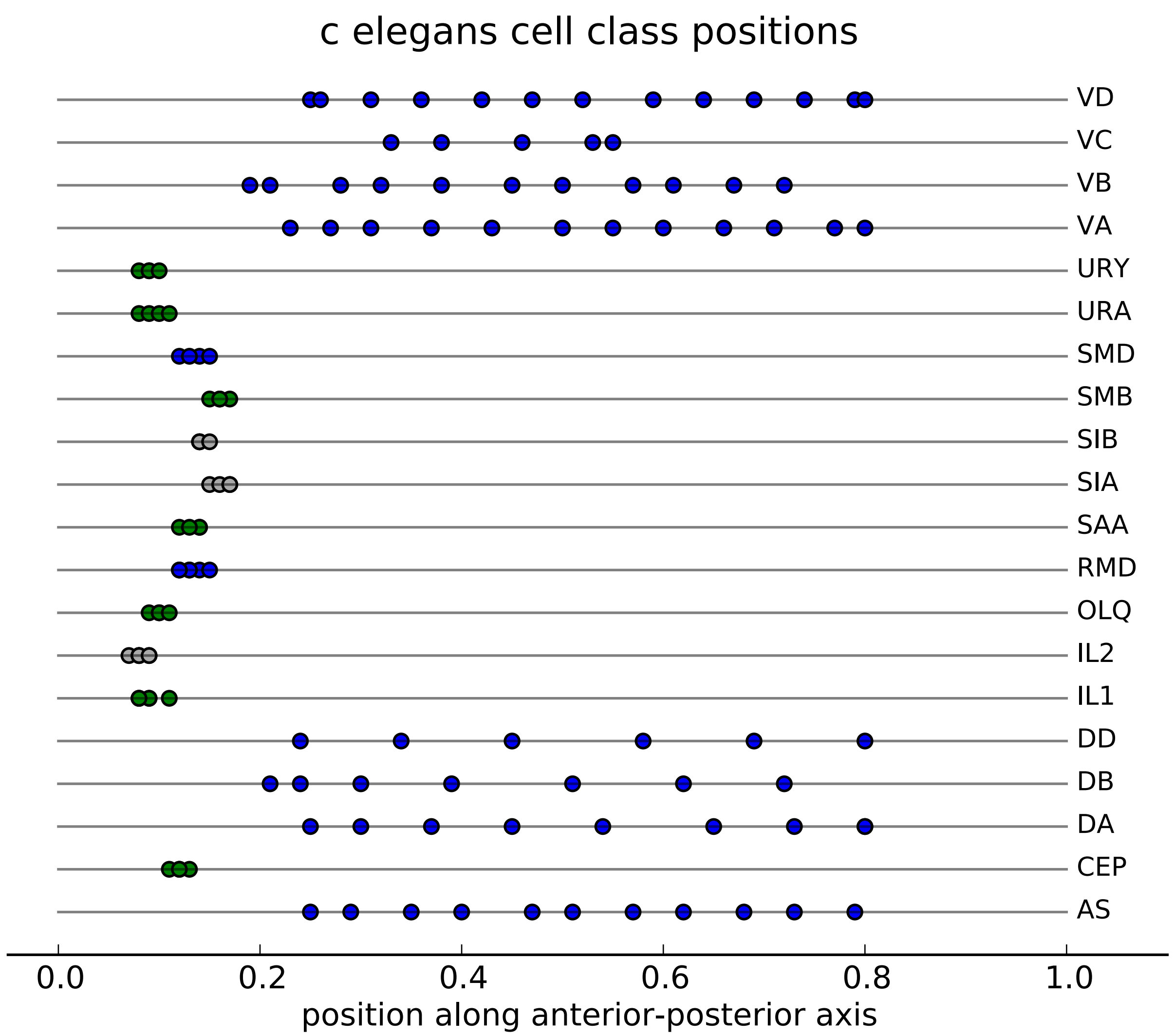
THE STRUCTURE OF THE NERVOUS SYSTEM OF THE NEMATODE *CAENORHABDITIS ELEGANS*

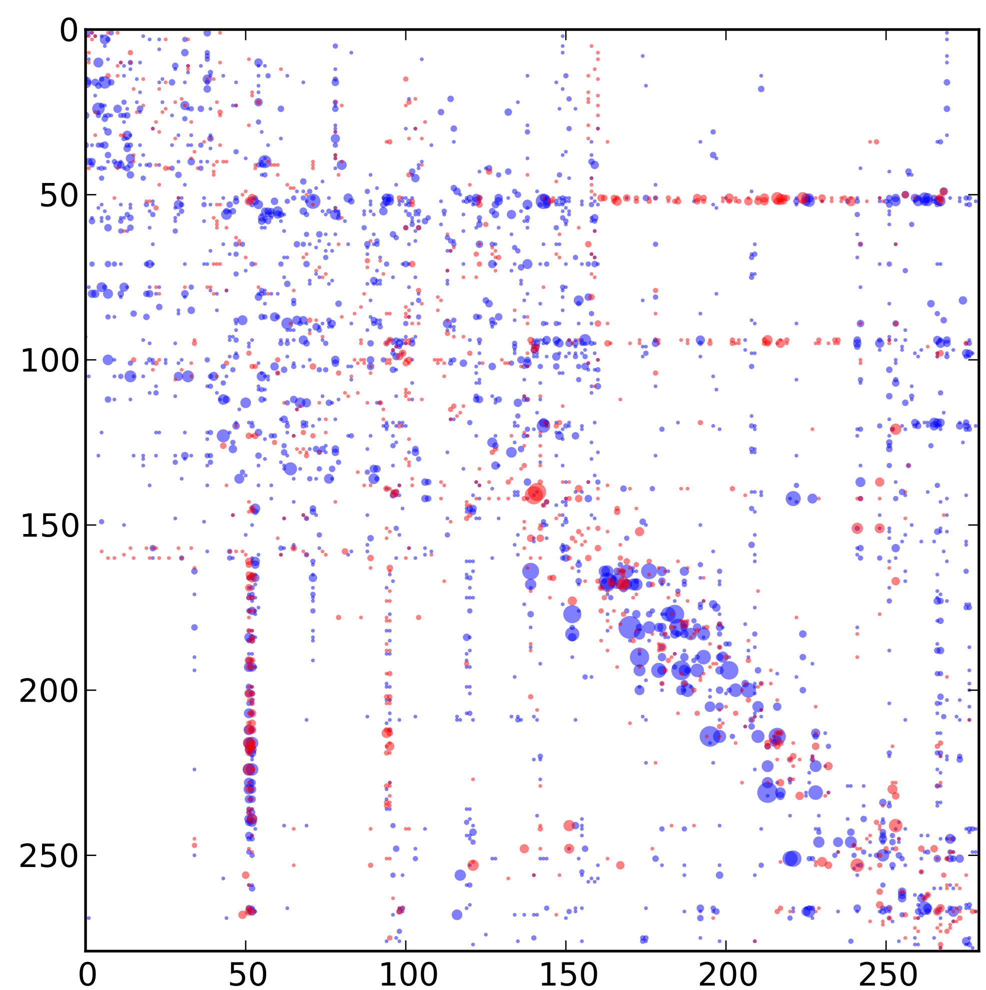
By J. G. WHITE, E. SOUTHGATE, J. N. THOMSON AND S. BRENNER, F.R.S.

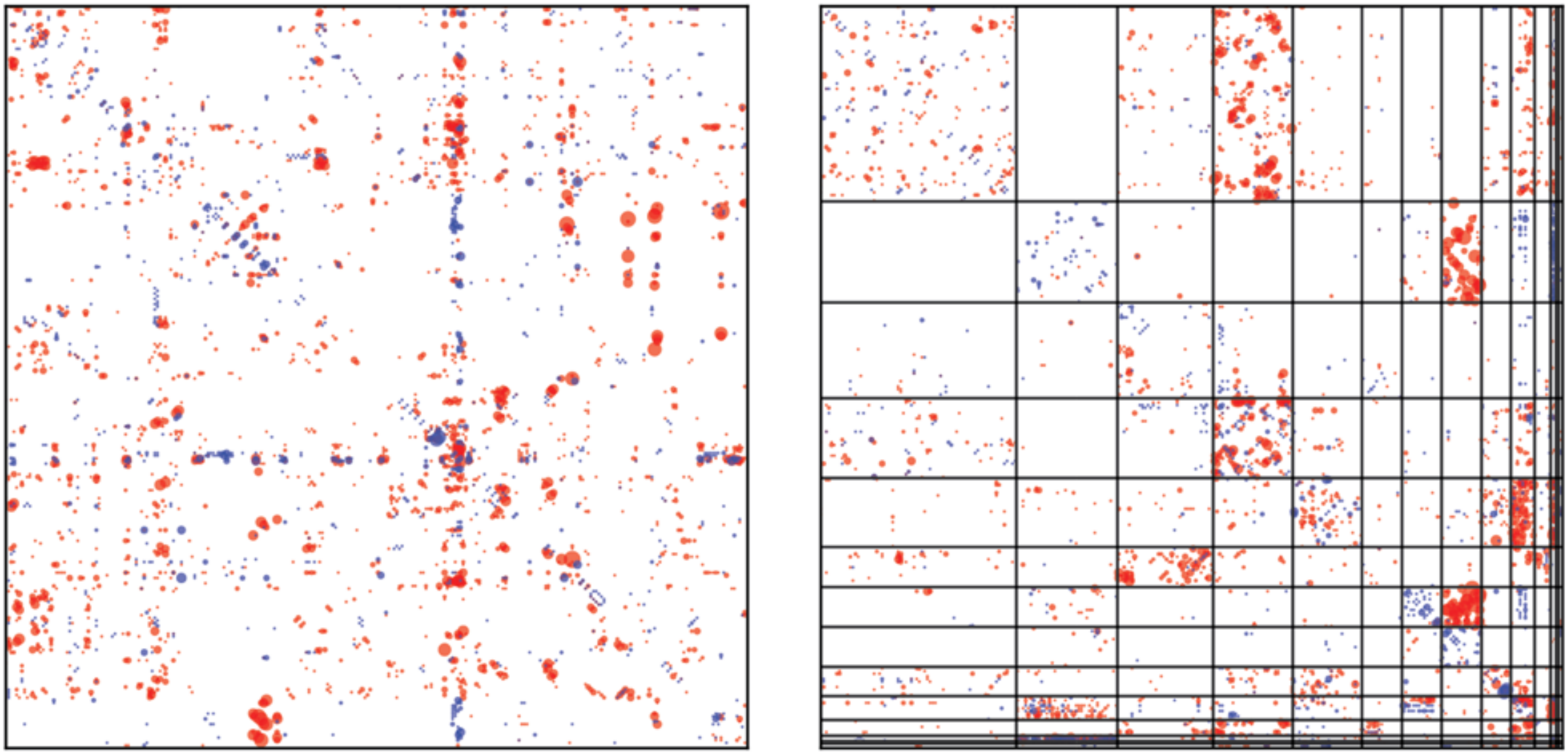
Laboratory of Molecular Biology, Medical Research Council Centre, Hills Road, Cambridge CB2 2QH, U.K.

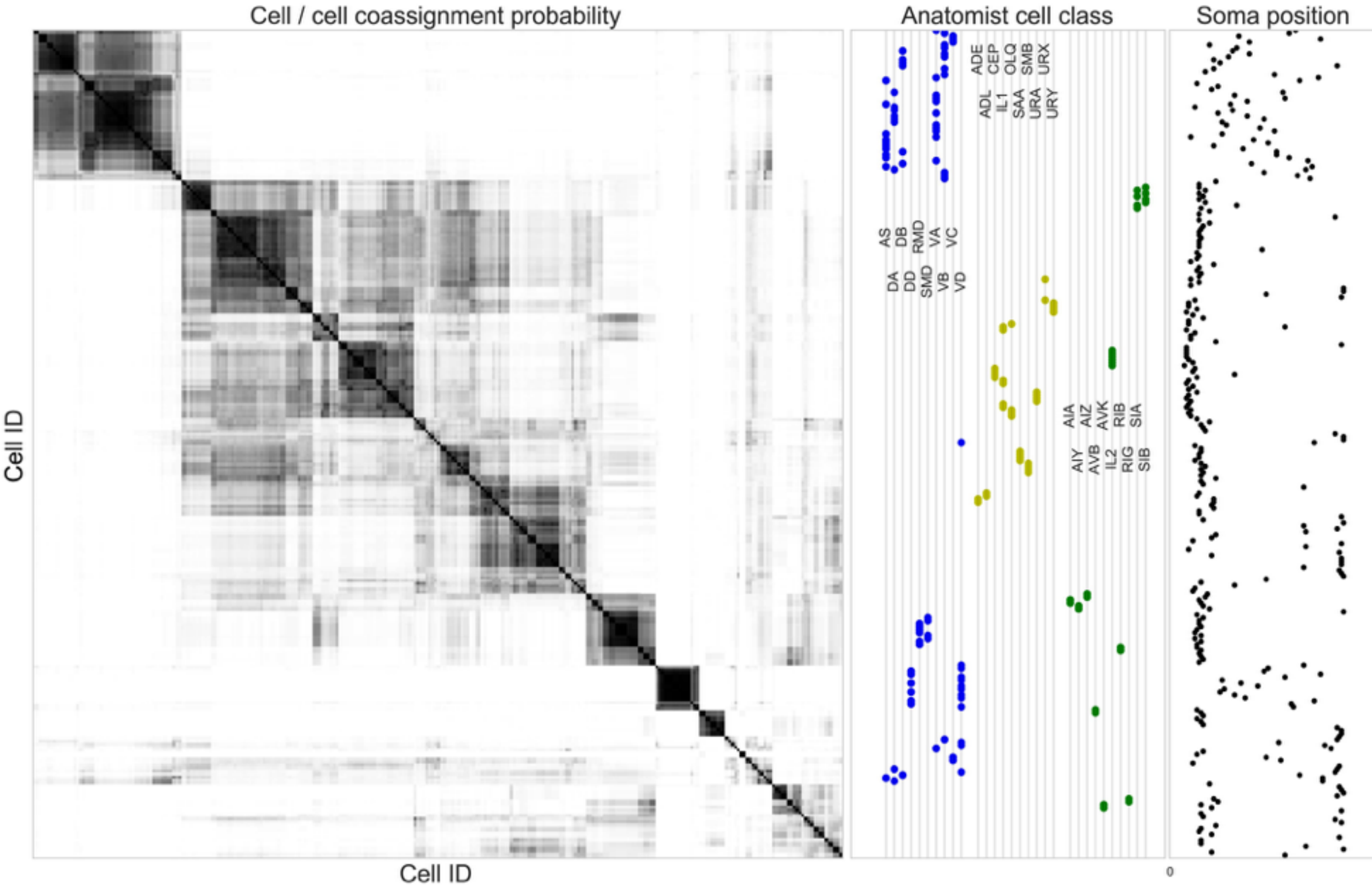
(*Received 9 August 1984 – Revised 12 November 1984*)

279 non-pharyngeal cells
6393 chem. synapses
890 elec. synapses

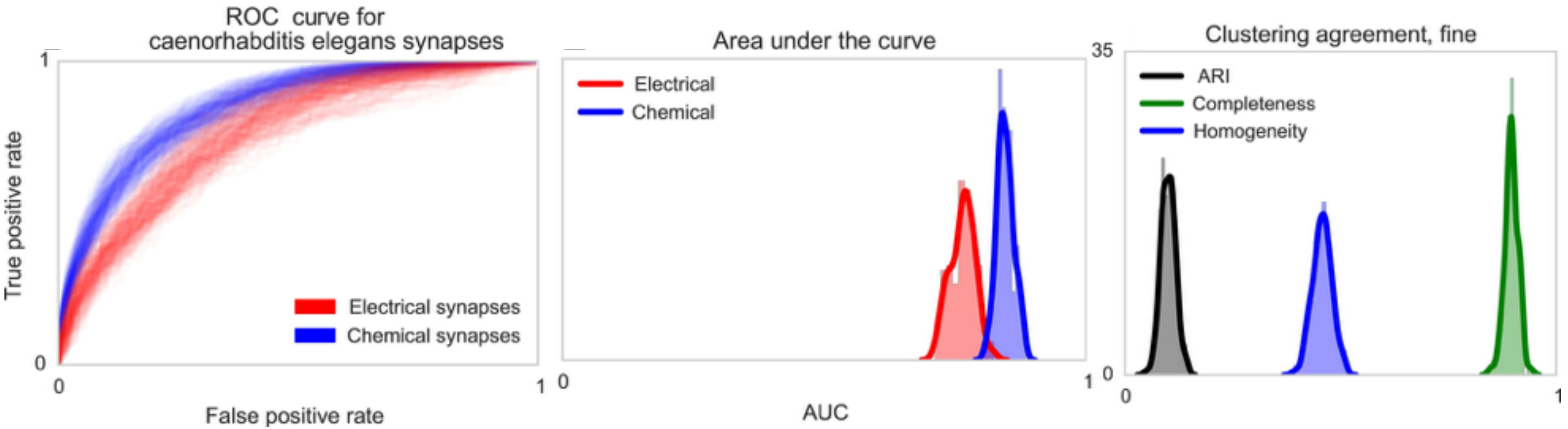







Cell / cell coassignment probability
Anatomist cell class
Soma position
Cell ID
Cell ID
AS DB RMD VA VC
DA DD SMD VB VD
ADE CEP OLQ SMB URX
ADL IL1 SAA URA URY
AIA AIZ AVK RIB SIA
AIY AVB IL2 RIG SIB
0
1

Clustering Accuracy



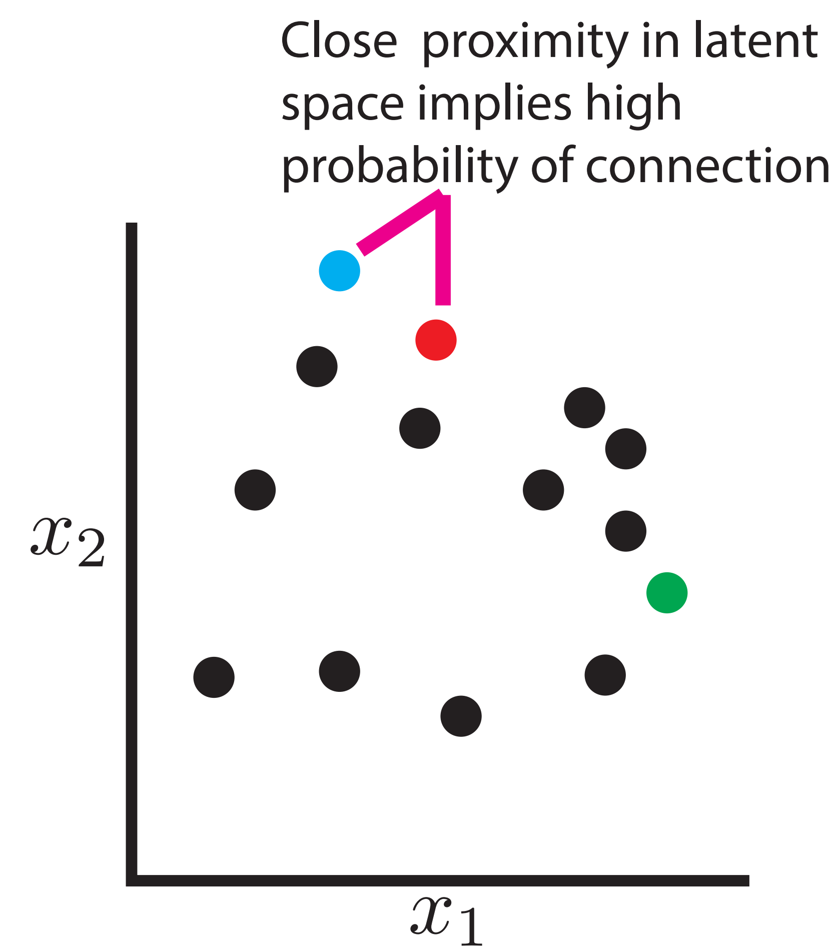
From discrete to continuous type

(warning: preliminary, possibly a bad idea)

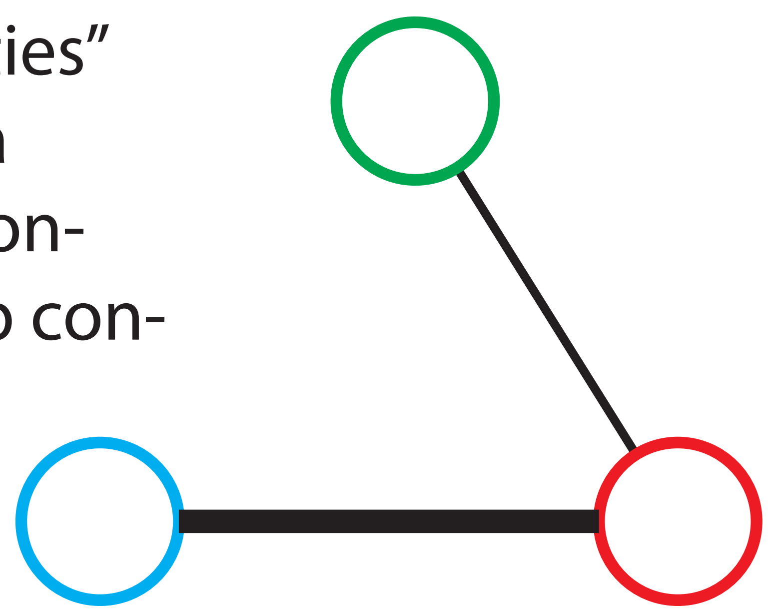
Latent Space Models

Classic latent space models [2] assume that the probability of a connection between two cells as a function of their position in a continuous latent space.

$$p(R_{ij}) = f(||\mathbf{x}_i - \mathbf{x}_j||^2) \quad \mathbf{x}_i \in \mathbb{R}^d$$



Great for modeling "communities" where you have groups with a large number of intra-group connections but fewer inter-group connections.



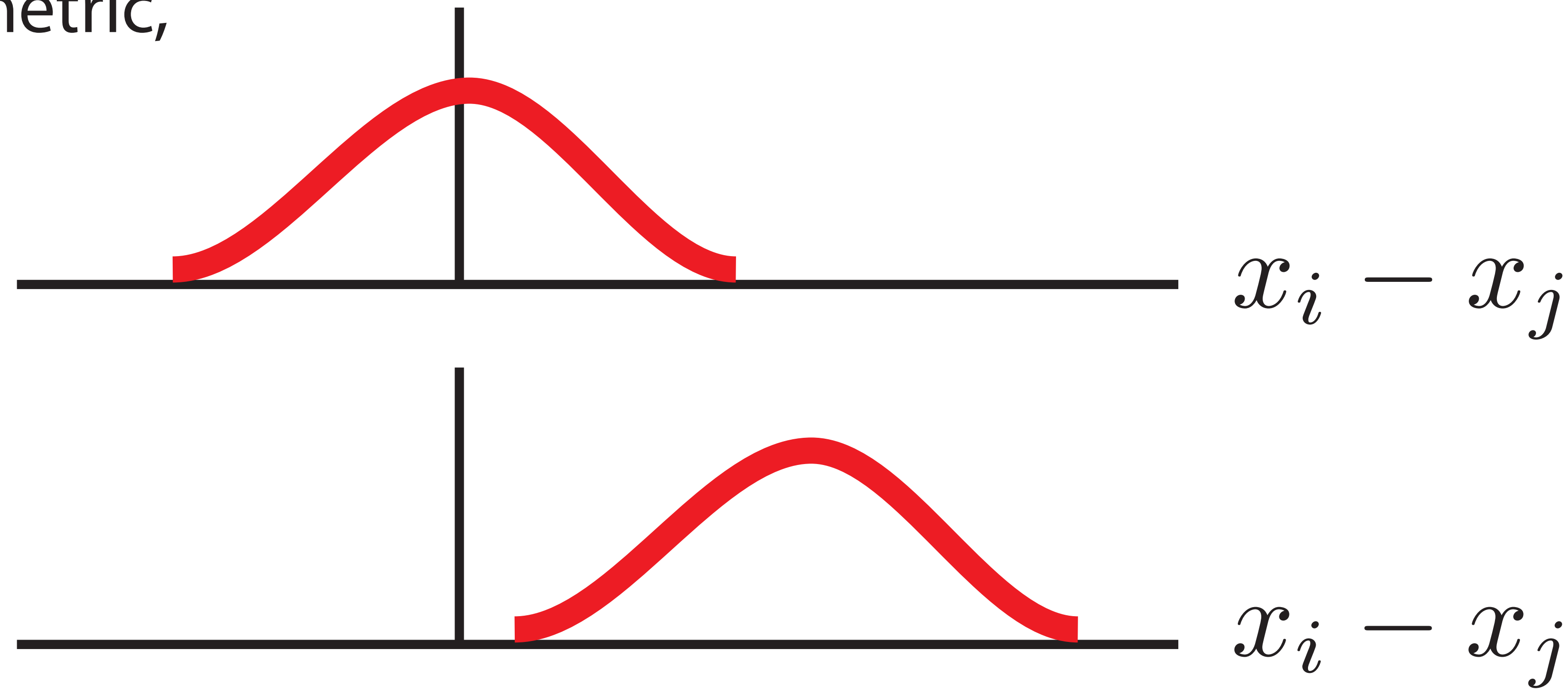
Hoff, P. D., Raftery, A. E., & Handcock, M. S. (2002). **Latent Space Approaches to Social Network Analysis.** Journal of the American Statistical Association, 97(460), 1090–1098. doi:10.1198/016214502388618906

Adding Kernels

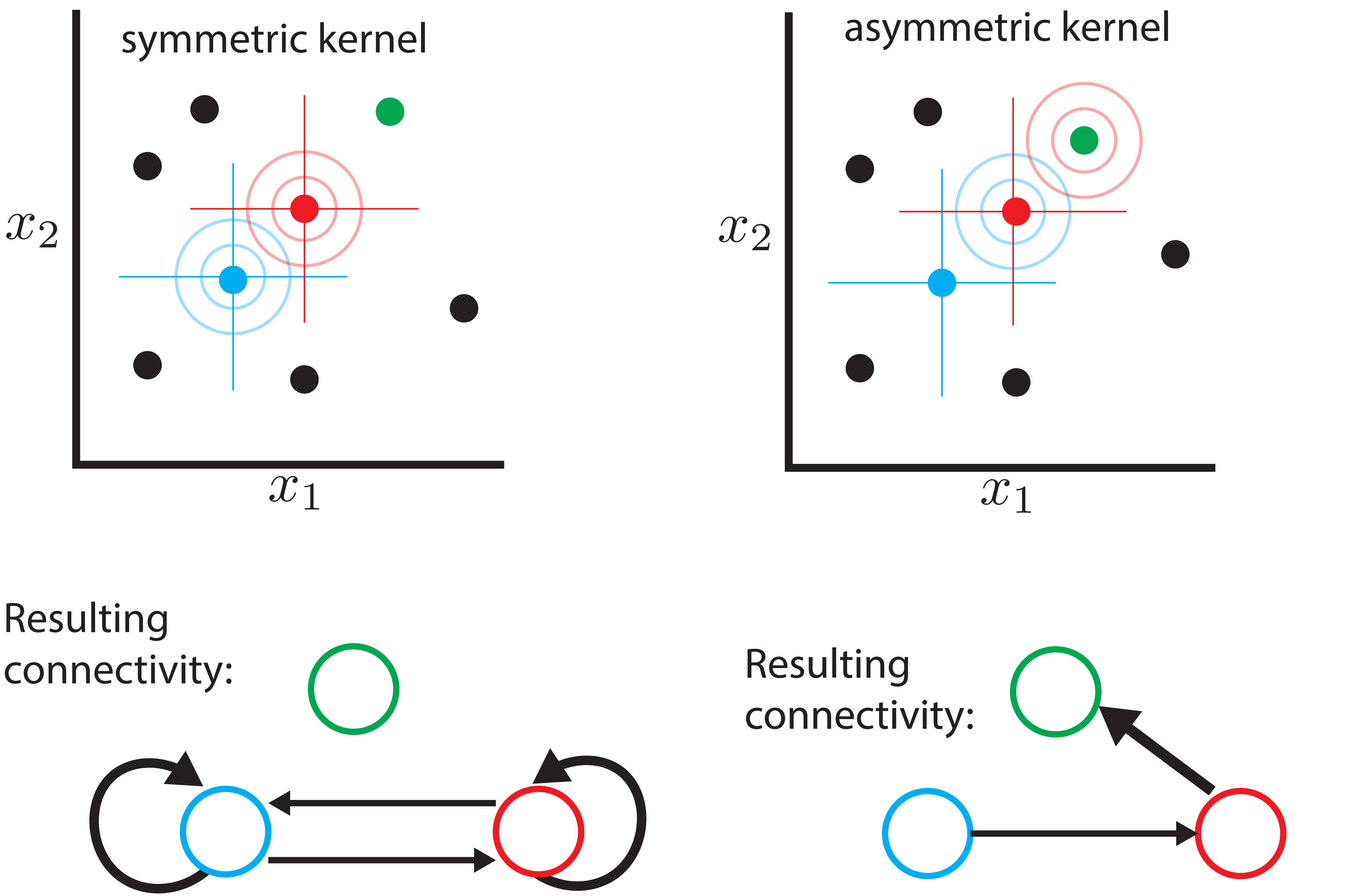
We can replace the Euclidean distance in a latent space model with an arbitrary kernel function.

$$R_{ij} \propto \kappa(\mathbf{x}_i, \mathbf{x}_j) \qquad \mathbf{x}_i \in \mathbb{R}^d$$

Kernel functions can be asymmetric, non-monotonic, non-isotropic



Asymmetric Kernels

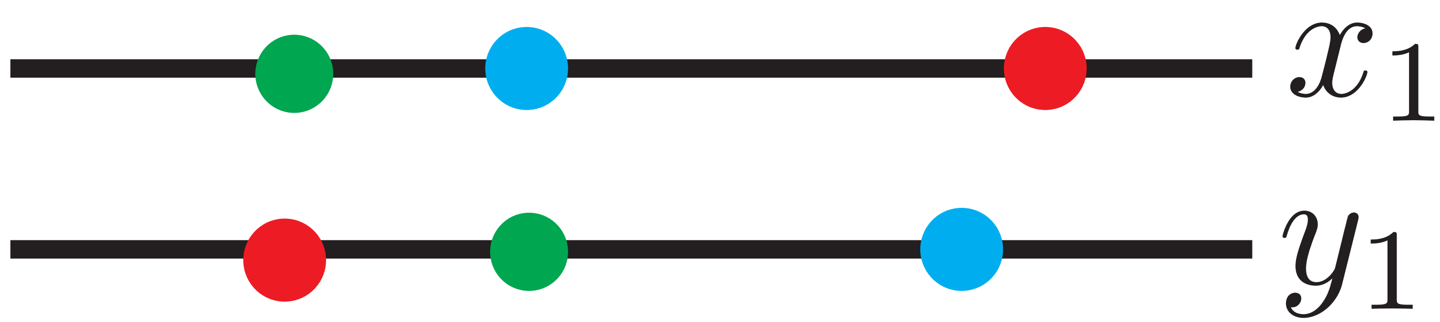


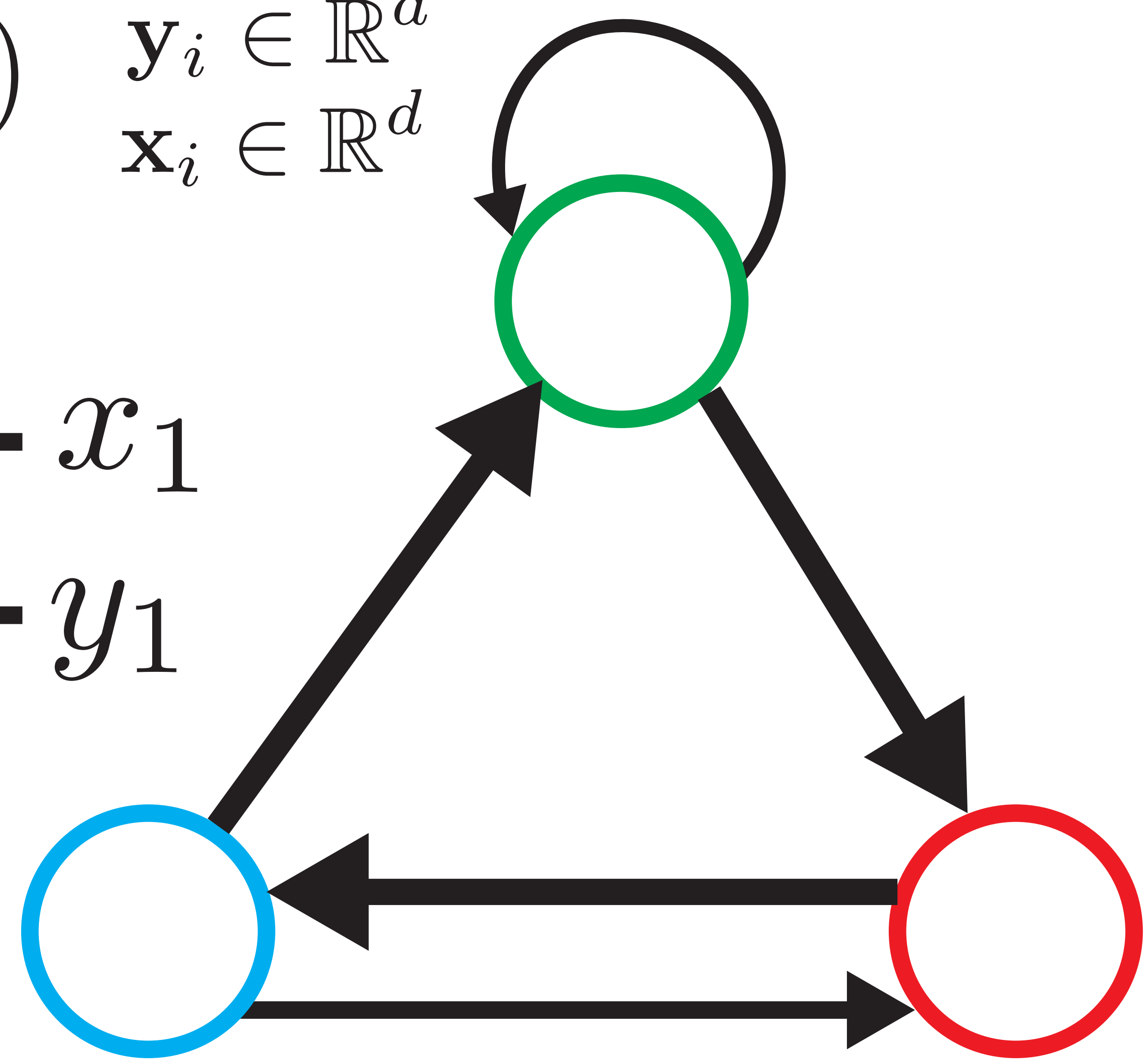
Two-space kernels

Instead of single unified latent space,
split space into pre and post-synaptic spaces

$$p(R_{ij}) = k(\mathbf{x}_i, \mathbf{y}_j)$$

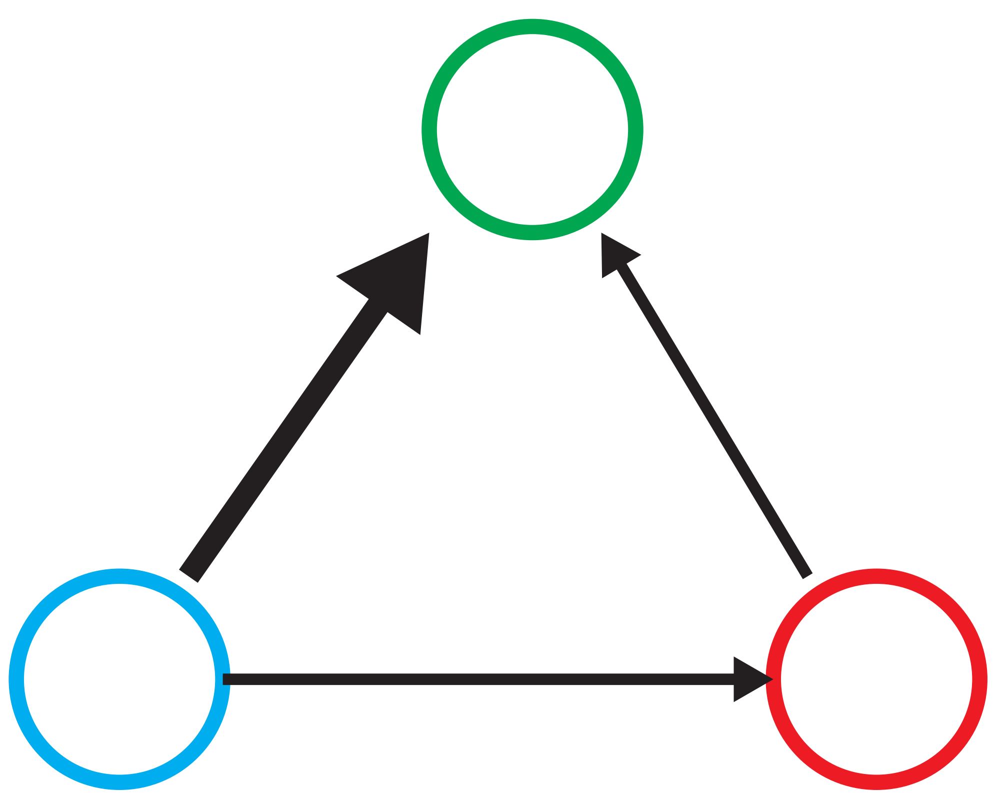
$\mathbf{y}_i \in \mathbb{R}^d$
$\mathbf{x}_i \in \mathbb{R}^d$





Ranking Loss

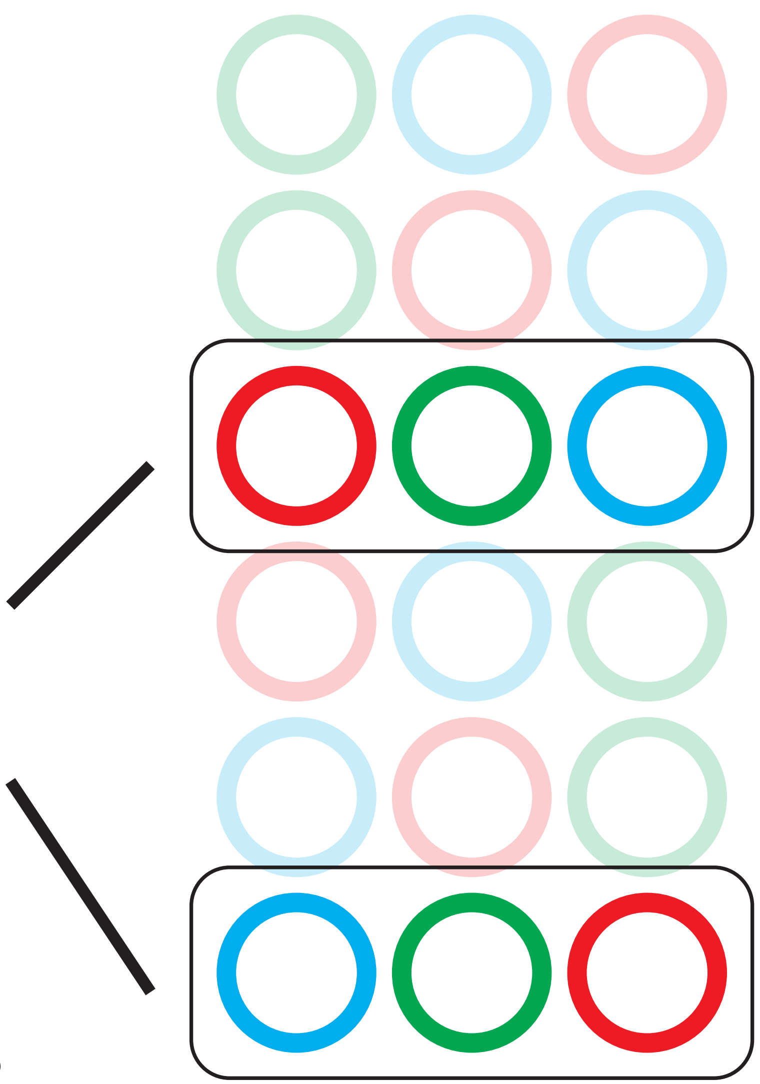
$$p_{ijk} \propto \frac{\kappa(\mathbf{x}_i, \mathbf{x}_j)}{\kappa(\mathbf{x}_i, \mathbf{x}_j) + \kappa(\mathbf{x}_i, \mathbf{x}_k)}$$



Triplet is observed when:

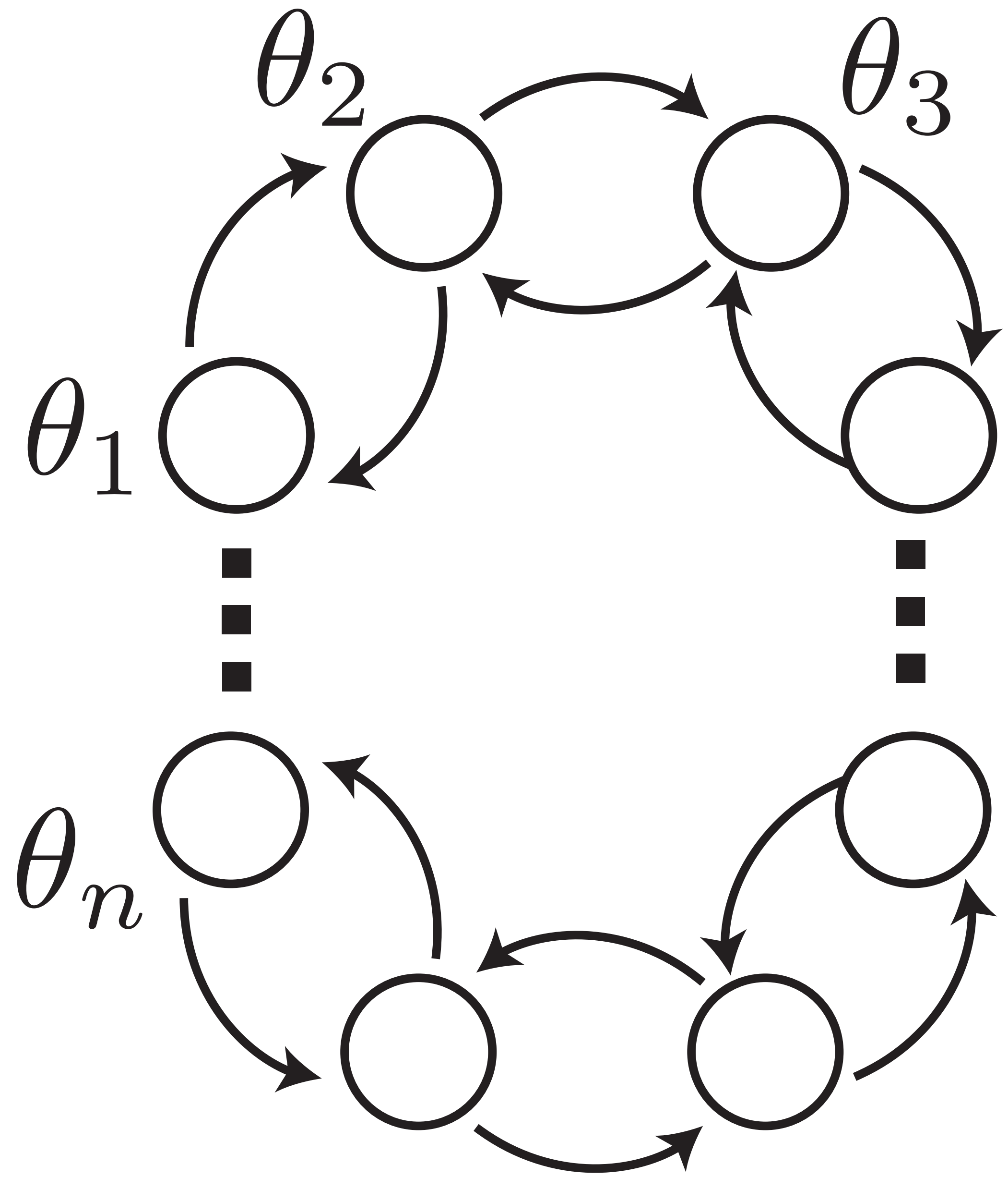
$$R_{ij} > R_{ik}$$

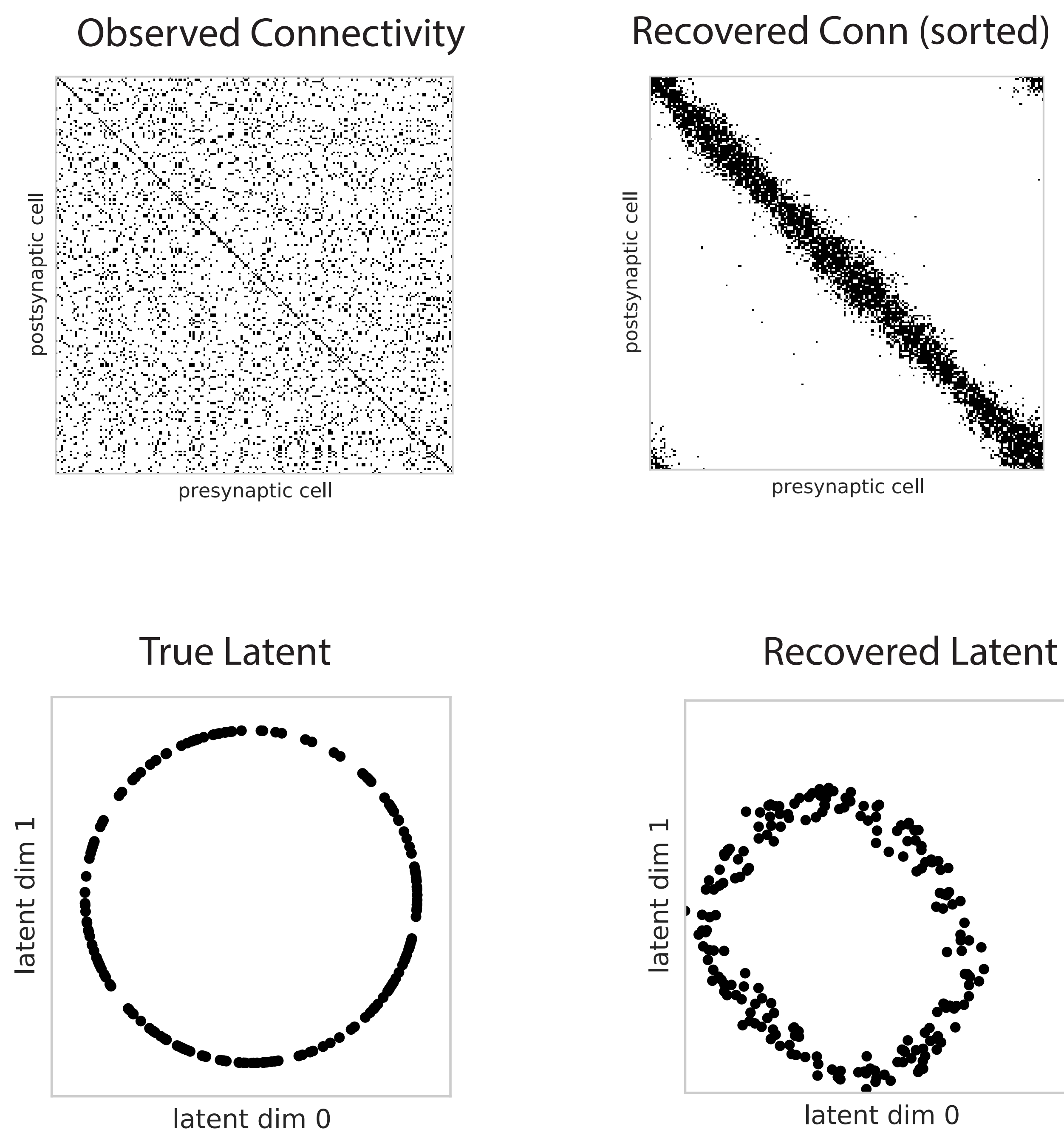
$i \quad j \quad k$



possible triplets for this graph

Symmetric Ring

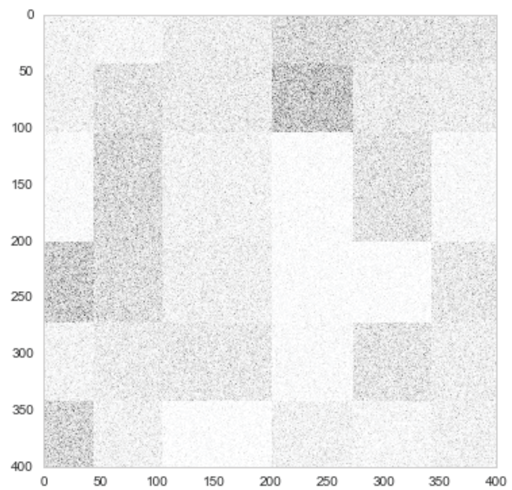




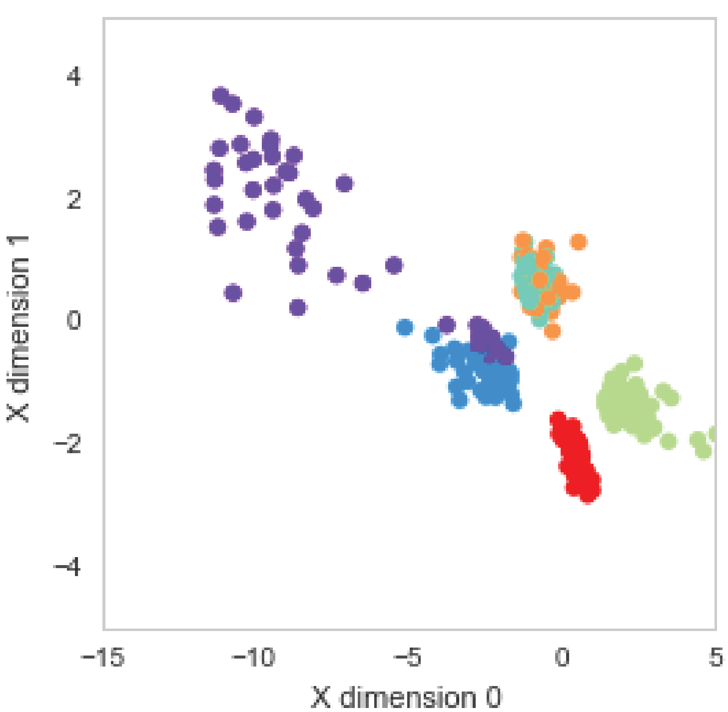
Ben-Yishai, R., Bar-Or, R. L., & Sompolinsky, H. (1995). **Theory of orientation tuning in visual cortex.** Proceedings of the National Academy of Sciences of the United States of America, 92(9), 3844–3848. doi:10.1073/pnas.92.9.3844

Asymmetric Block Model

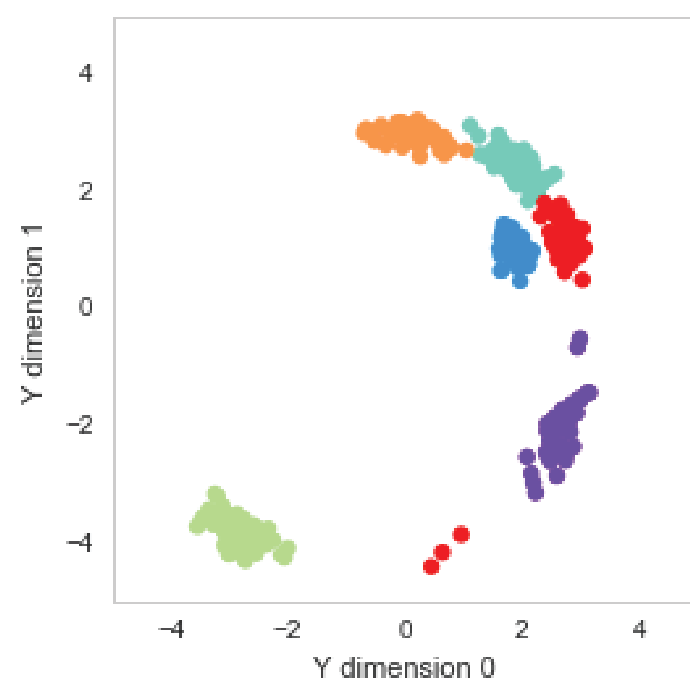
Recovered Conn (sorted)



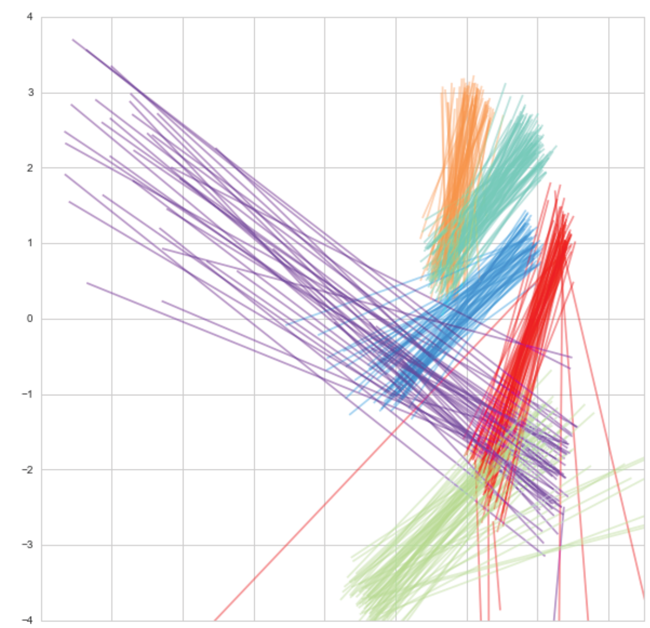
Recovered Latent Space X



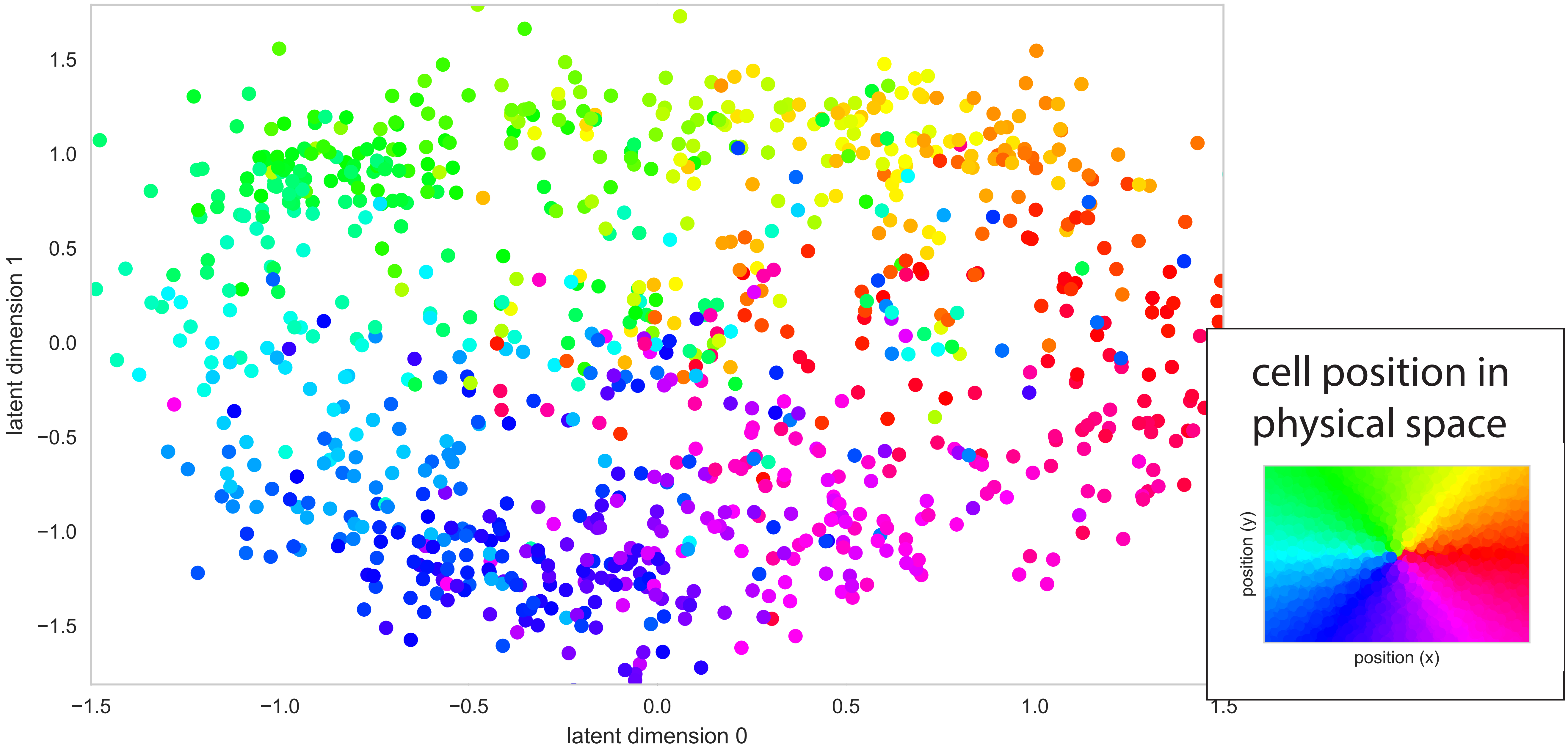
Recovered Latent Space Y



XY Connection

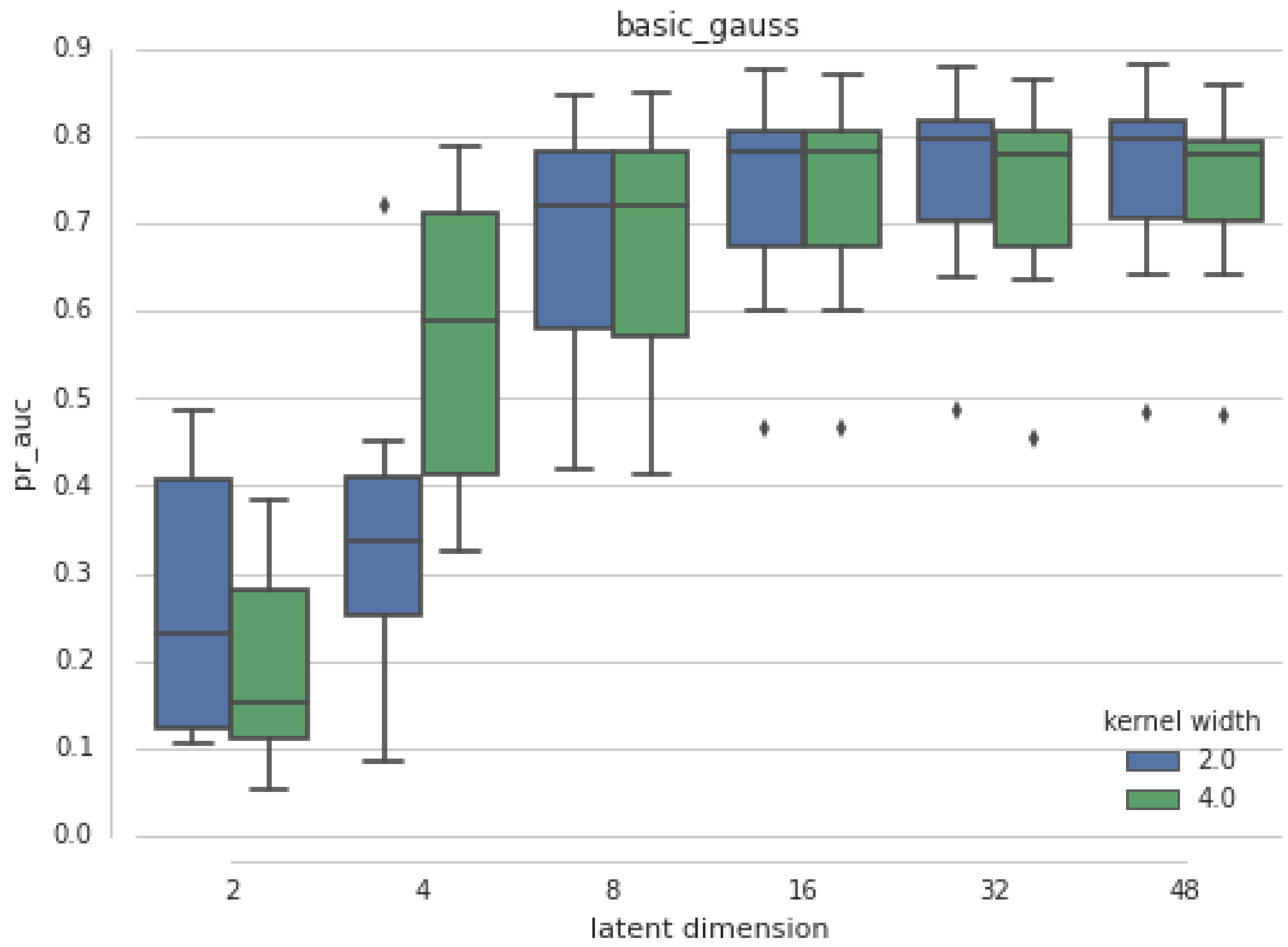


Mouse Retina



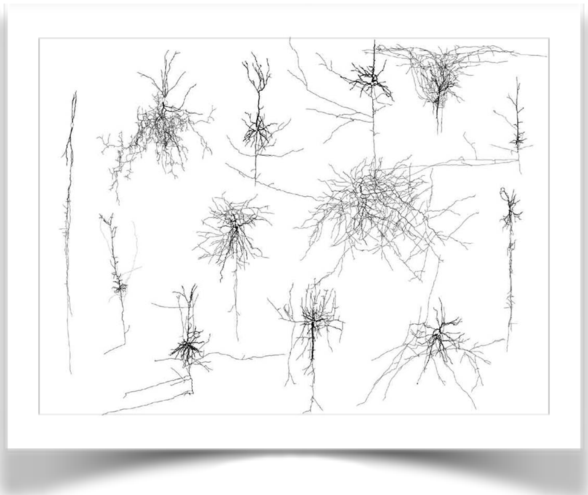
We fit a D =8 latent kernel single-space model to the mouse retina connectome with a symmetric rational quadratic kernel. The first two dimensions recover the intralaminar spatial organization of cells in the retina.

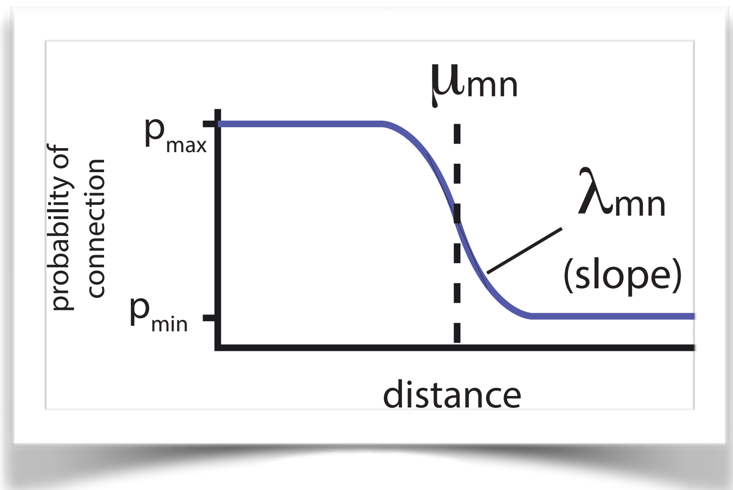
Model Fit

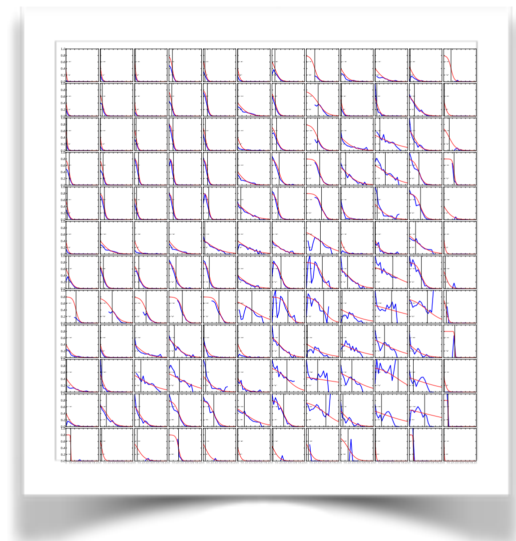


We can hold out connections from the training set and predict the missing connections and compute the area under the resulting precision-recall curve to assess model fit.

Conclusion



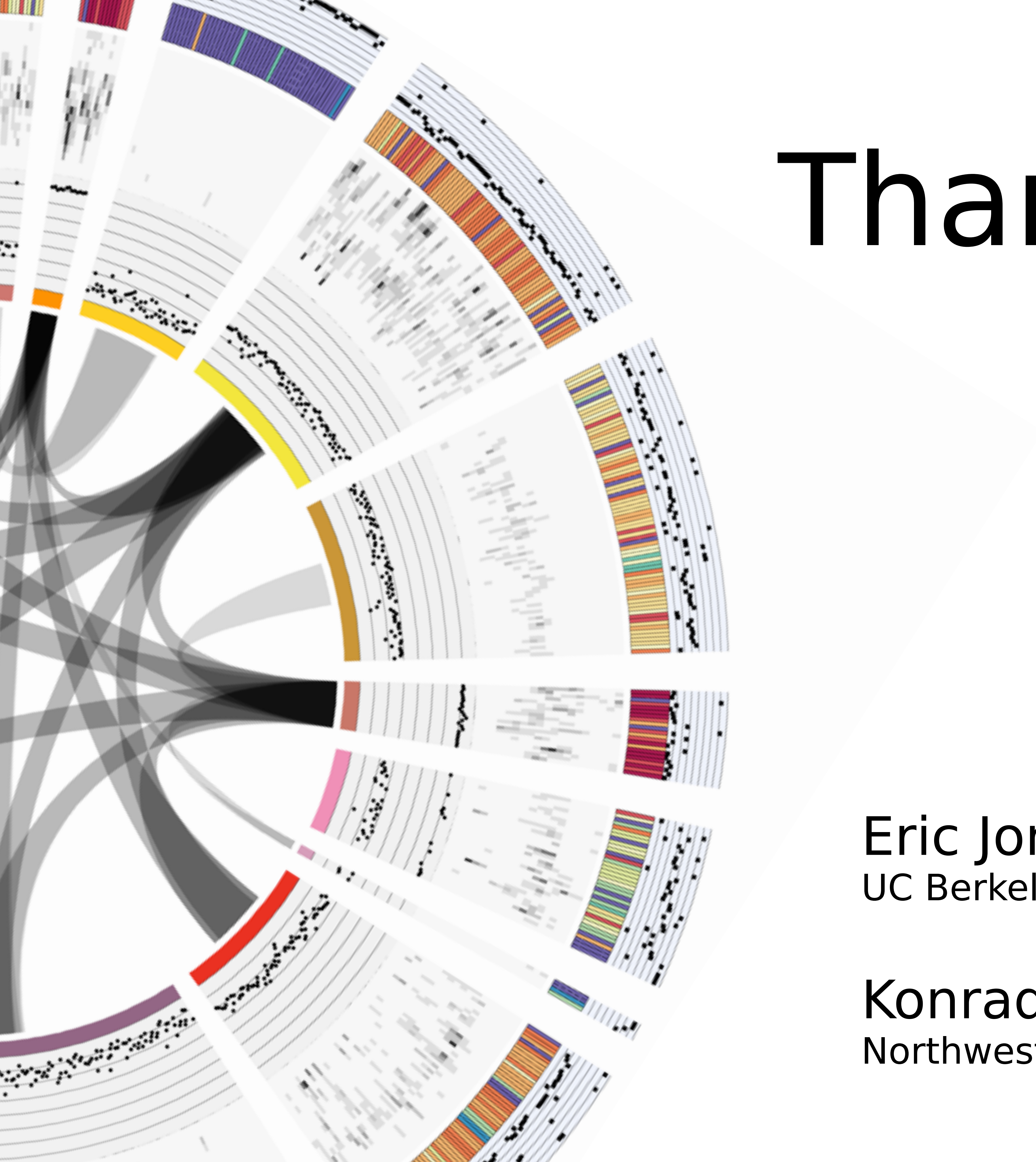




- Other aspects that define a cell type [morphology]
- Different likelihood functions
- Faster inference (spectral methods?)
- Probabilistic framework natural extension

Next questions

- What model most-accurately predicts connectivity in various types of systems?
- Hierarchical extensions?
- Scale?
- Model comparison ?



Thanks

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Konrad Kording
Northwestern, @KordingLab