Course Website

- Everything is hosted on github:
  - https://github.com/AllenBrainAtlas/friday-harbor
  - python library, slides, useful links (wiki)

ALLEN INSTITUTE *for* BRAIN SCIENCE
Fueling Discovery

Linear model of the mouse mesoscale connectome

August 25, 2014

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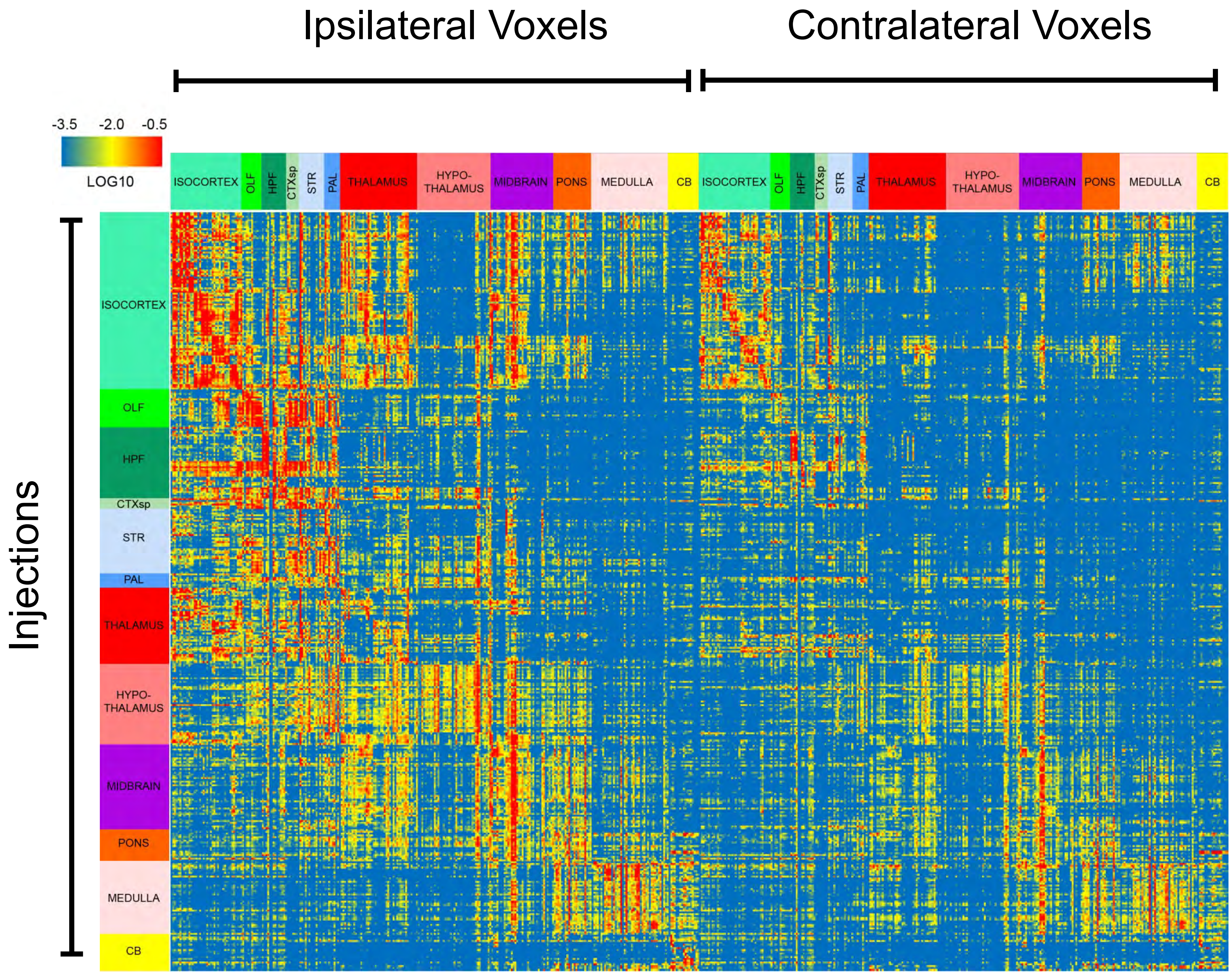
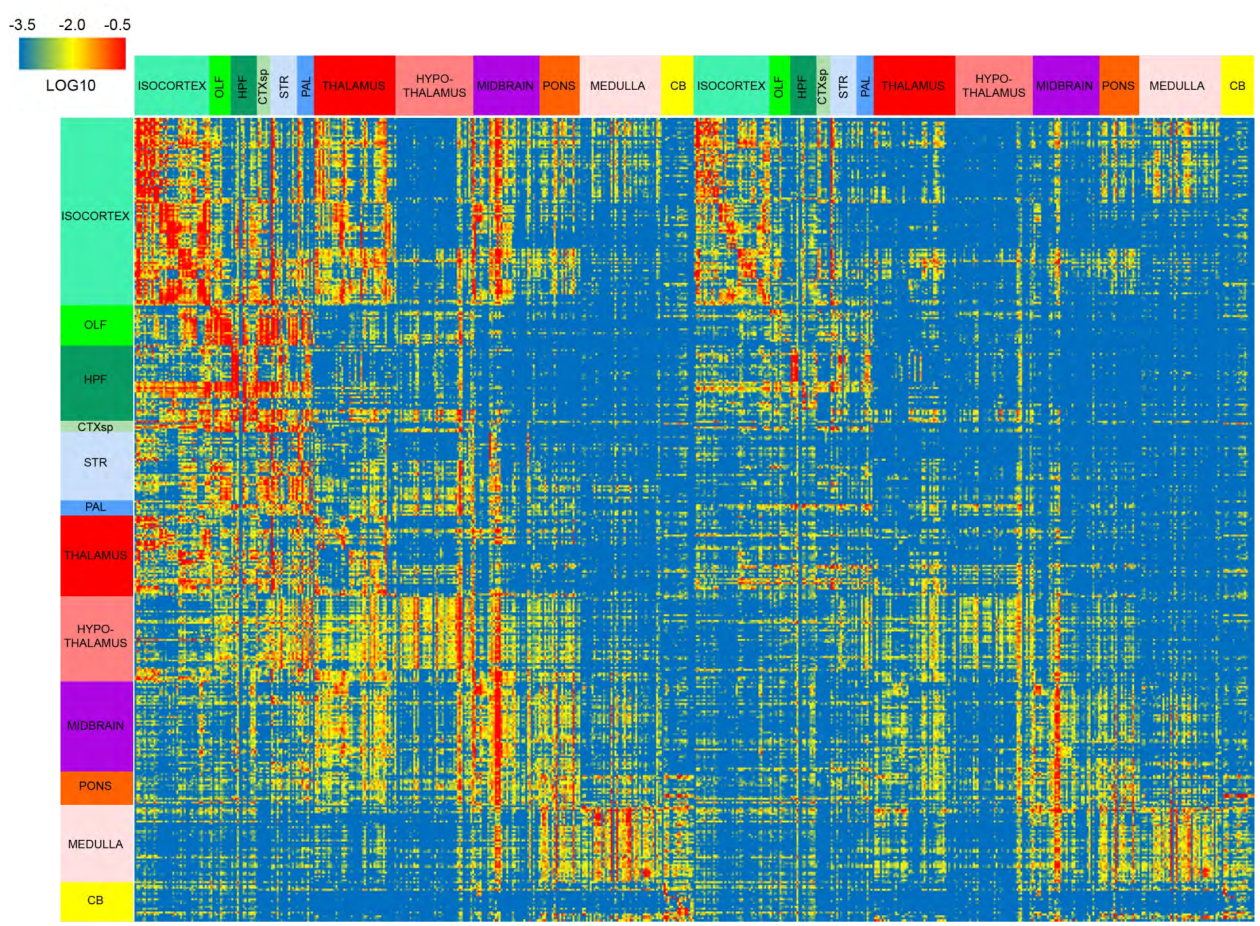
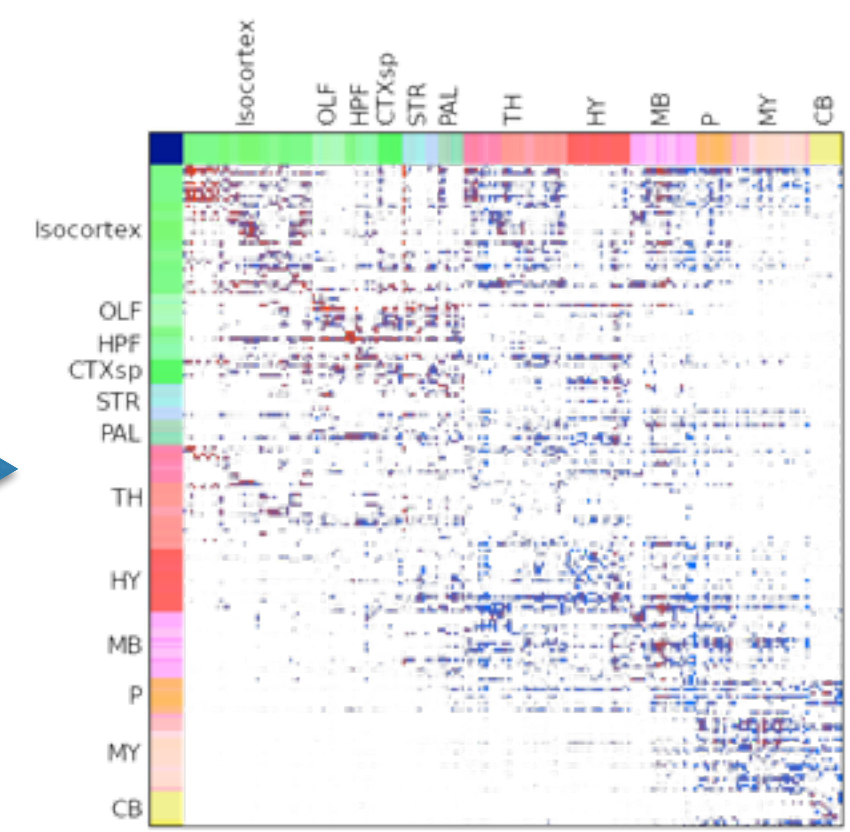
Voxelized Raw Data



Goal: Create a graph

- Not an adjacency matrix
- A mathematical model can help formulate one
- Then we can do network analysis/graph theory, etc.

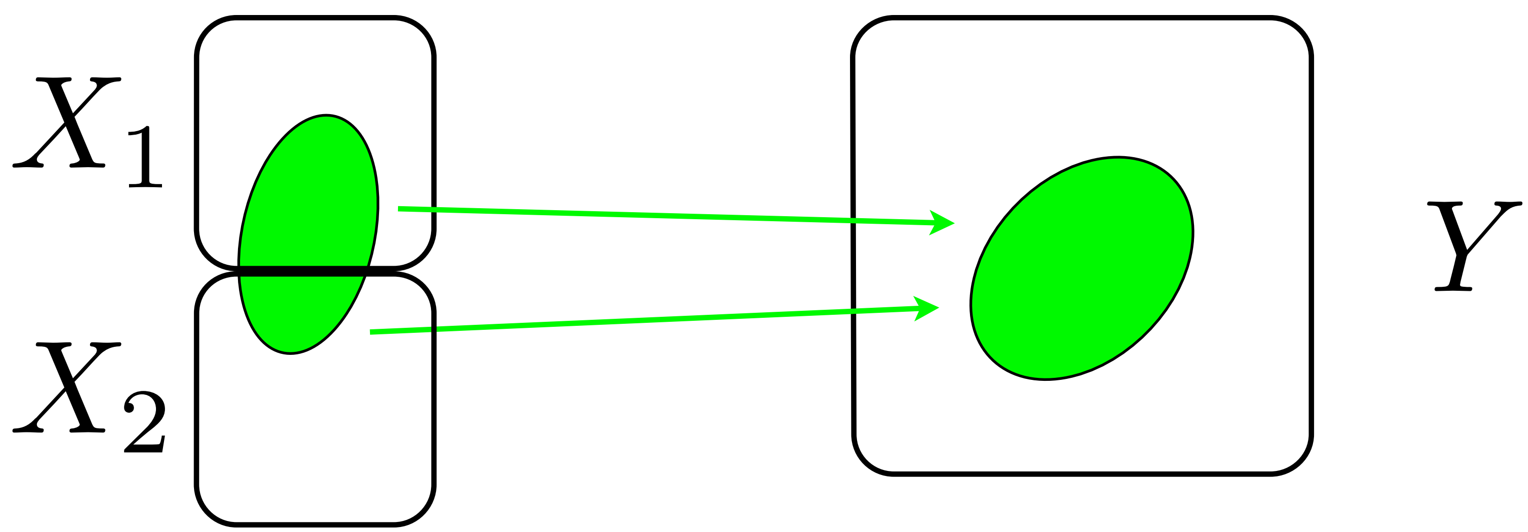




Linear Model

Problem: No experiment is perfect:

- Regions are not totally infected

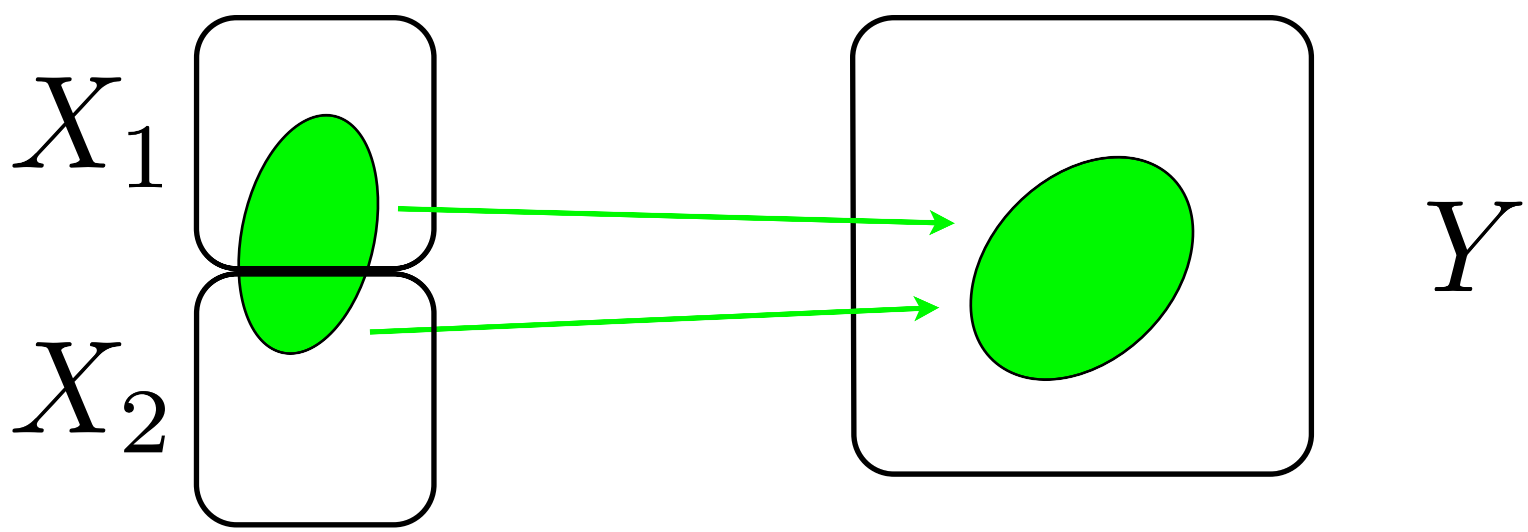


X, Y : Regions from Allen Reference Atlas

Linear Model

Problem: No experiment is perfect:

- Regions are not totally infected
- Leakage into other regions

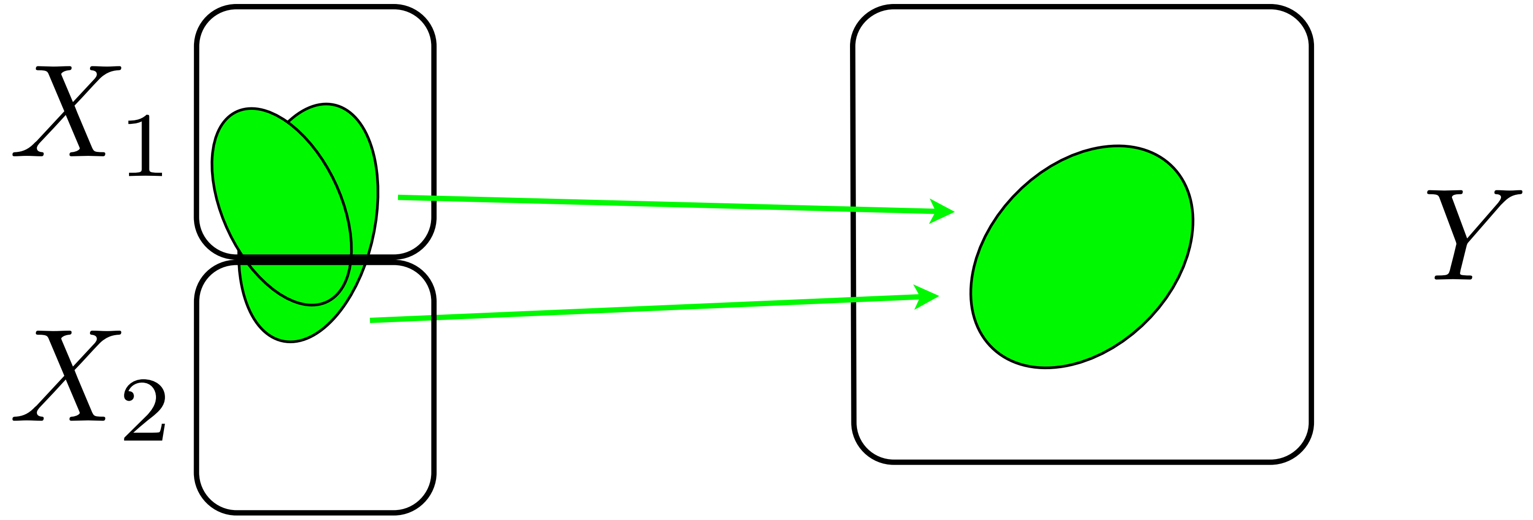


X, Y : Regions from Allen Reference Atlas

Linear Model

Problem: No experiment is perfect:

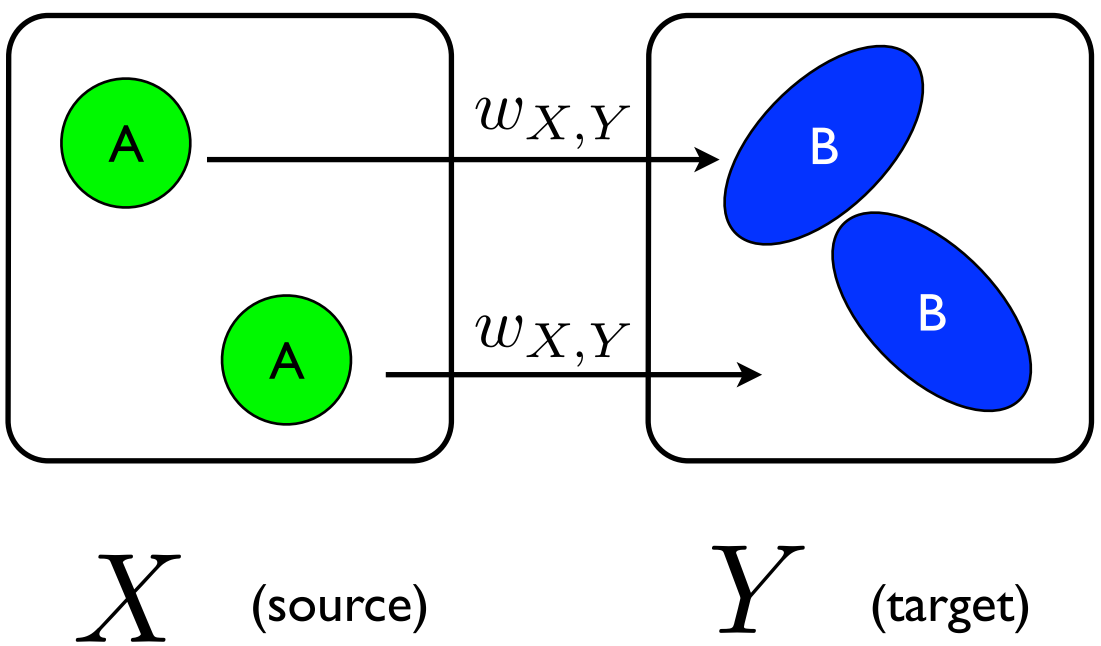
- Regions are not totally infected
- Leakage into other regions
- Variability in repeated injections



X, Y : Regions from Allen Reference Atlas

Linear Model

Assuming two critical approximations:



Homogeneity

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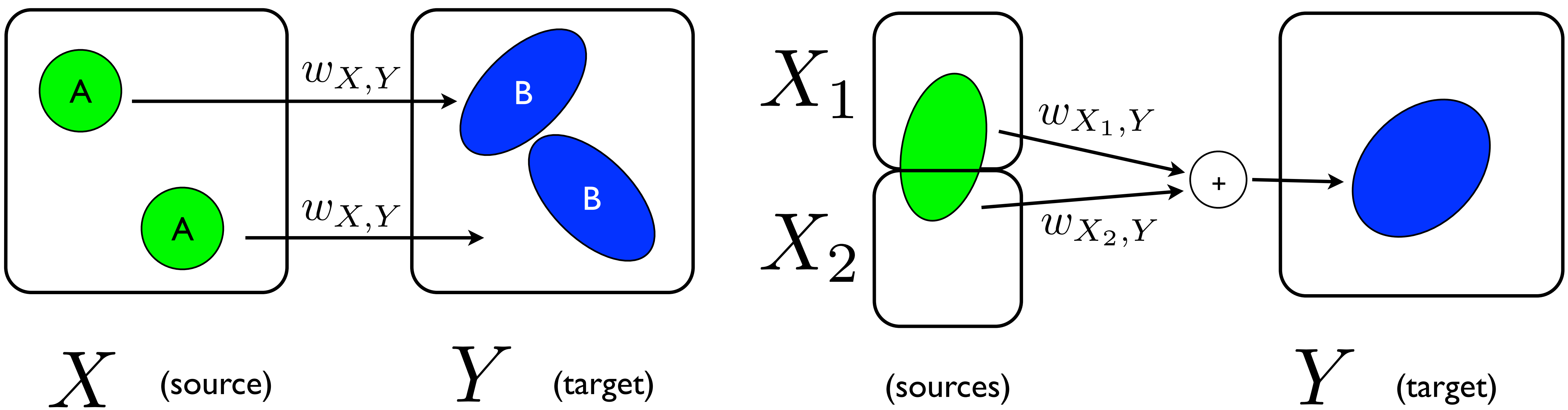
Linear Model

Assuming two critical approximations:



Homogeneity

Additivity

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Linear Model

$$\min_{w_{X,Y}\geq 0} \sum_{i=1}^{|S_E|} \left| \sum_{X \in S_X} w_{X,Y} PD(X \cap E_i; i) - PD(Y; i) \right|$$

X, Y : Regions from Allen Reference Atlas

i : Experiment subscript

PD : Integrated Projection Density
(number of segmented pixels in a structure)

$w_{X,Y}$: Normalized connection strength between X and Y

$$PD(X; i) = \int_X PD_i(v) dv$$

Linear Model

$$\min_{w_{X,Y}\geq 0} \sum_{i=1}^{|S_E|} \left| \sum_{X \in S_X} w_{X,Y} PD(X \cap E_i; i) - PD(Y; i) \right|$$

- Non-negative Least Squares Optimization across all available experiments

- Minimizing error between sources activated by the experiment and a target by fitting connectivity weights

Linear Model

$$\boxed{\min_{w_{X,Y} \geq 0}} \sum_{i=1}^{|S_E|} \left| \sum_{X \in S_X} w_{X,Y} PD(X \cap E_i; i) - PD(Y; i) \right|$$

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Linear Model

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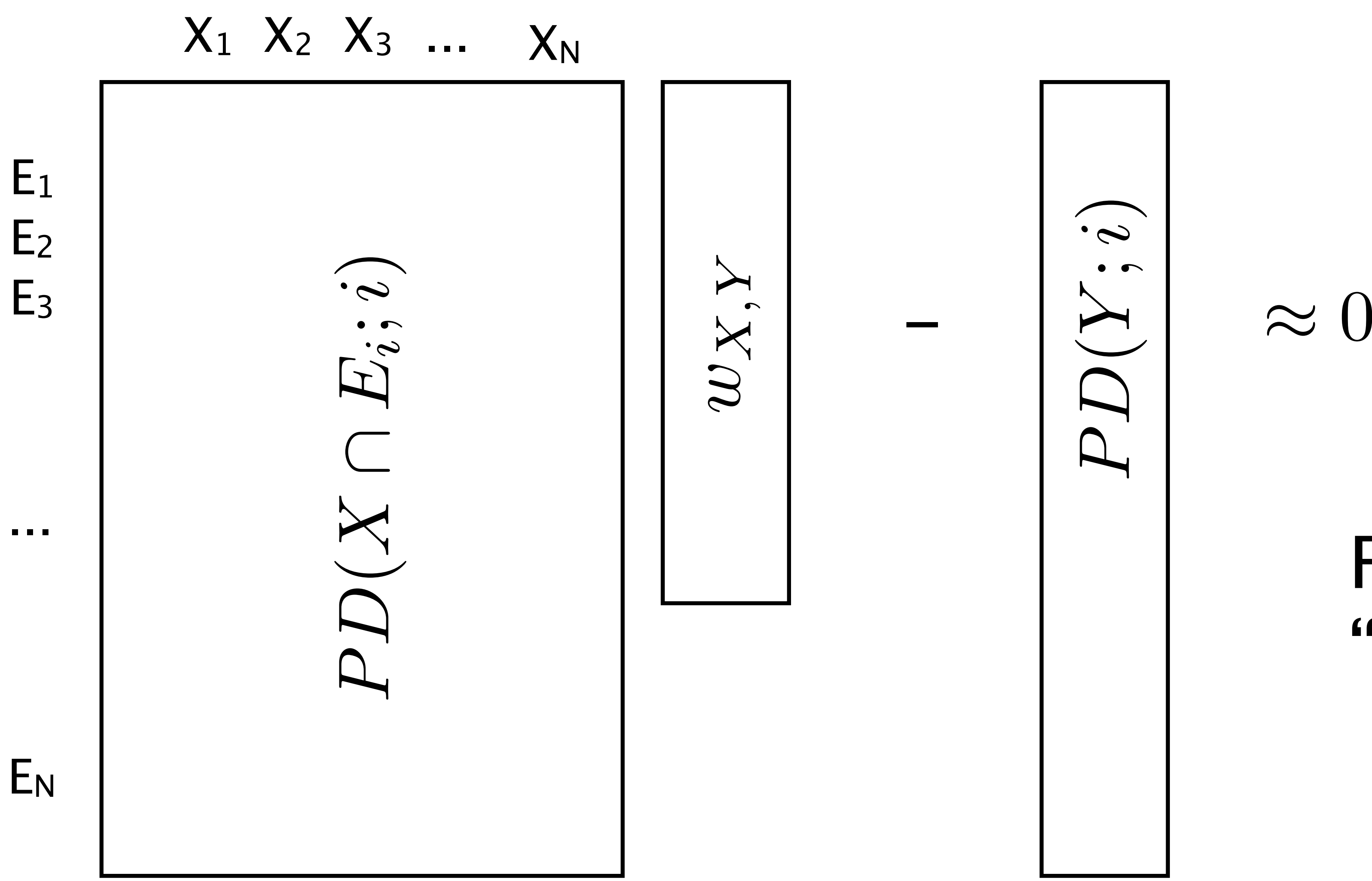
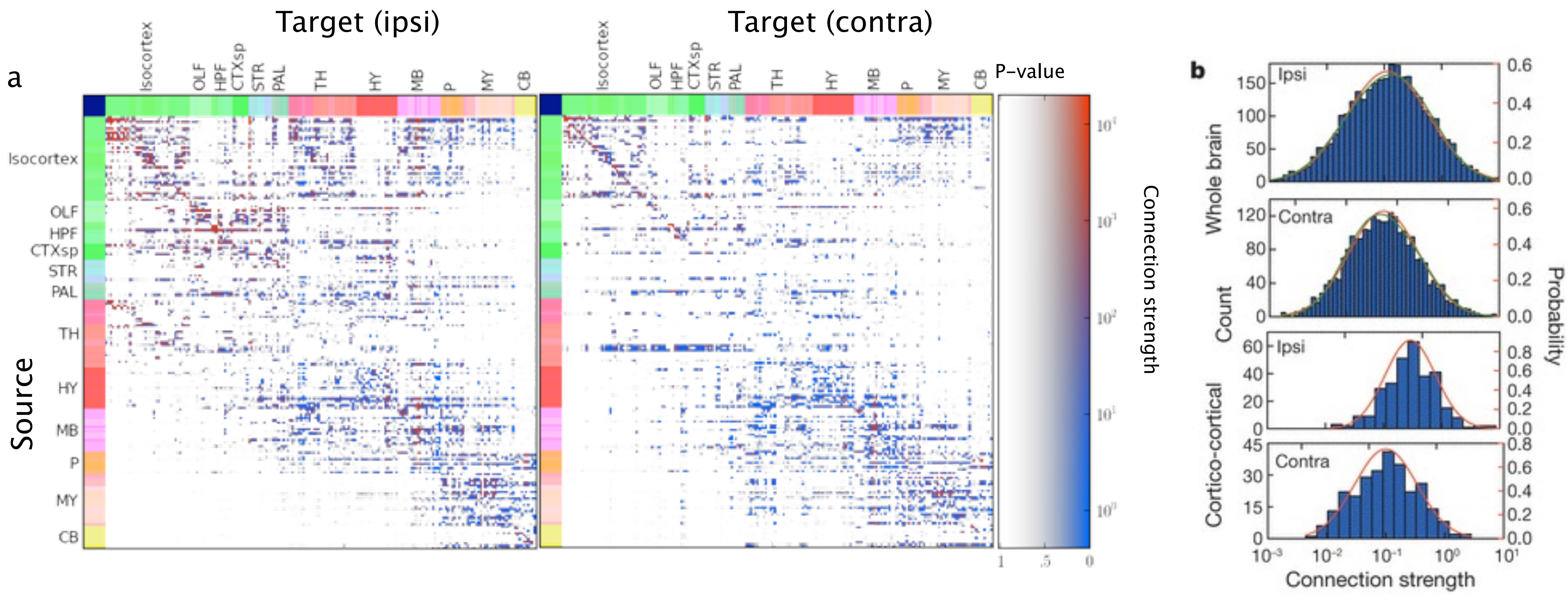
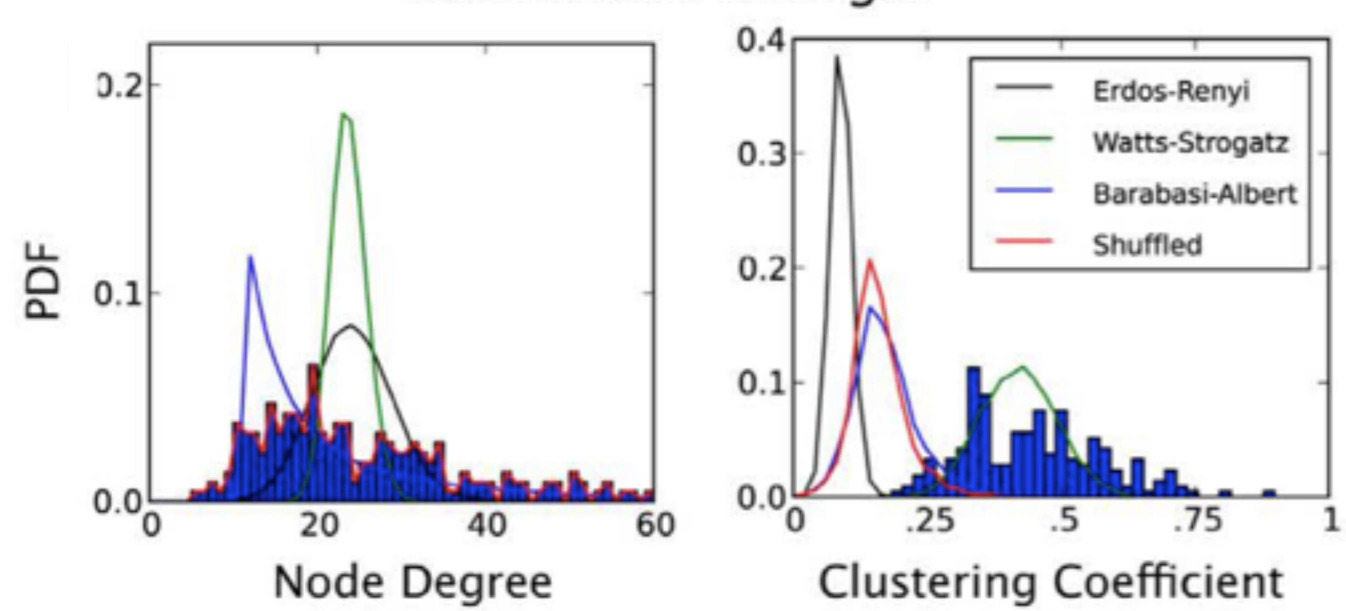


For each “target” Y



- Bidirectional, weighted, inter-area connectivity matrix.
- Log-normally distributed weights
- Topology does not fit the usual graph models.

Connection strength



Week 1 Projects: Connectivity

August 25, 2014

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Week 1 Project Introduction: Connectivity

- 3 Data sets provide the raw material for you project.
- The TA's have outlined 5 project areas to give you guidance, but you are not restricted to these areas (or within a single area).
- Can work individually or within a group (no more than 3-4 in a group). If you want, think about finding a partner (or partners) that compliment your skill set.
- If you have some ideas, go. If you don't have ideas, TA's are available to help start you and guide you. Projects are guidelines, not rules. Creativity in the problem direction and resolution is encouraged.
- Interim Project Presentations on Saturday (30 Aug.)
- After these weekend presentations, option to bail and start over on a project of your choice, or keep working on your first week project.
- Prizes (TBA)! Best in show and best visualization (voted on by your peers), and most likely to be published (voted by instructors/TA's)

A little about the TA's

- Hi my name is Lydia (and soon to be David!), and when it comes to your project, I can help you with:
  - Informatics processing for the Connectivity Atlas
  - Background on the voxelized data
  - Finding your way around the Allen Reference Atlas and ontology
  - How to access information from the Allen Brain Atlas API
  - Visualization of the 3D reference space and volume
  - Spatial and clustering analysis of the Connectivity data

A little about the TA's

- Hi my name is Nick, and when it comes to your project, I can help you with:
  - General python coding and configuration
  - Understanding the voxelized data code
  - Dynamical models of neurons and neuronal populations/coding
  - Network analysis
  - The inter-regional projection matrix (i.e the linear model)

A little about the TA's

- Hi my name is Michael, and when it comes to your project, I can help you with:
  - Python and coding
  - Statistical Data Modeling
  - Dynamical models of neurons and neuronal populations/coding
  - Network analysis
  - Algorithms

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A little about the TA's

- Hi my name is Shawn, and when it comes to your project, I can help you with:
  - General python coding and configuration
  - Understanding the voxelized data code
  - The inter-regional projection matrix (i.e the linear model)
  - Identifying/defining biological questions
  - Mouse neuroanatomy

A little about the TA's

- Hi my name is Wyeth, and when it comes to your project, I can help you with:
    - general programming and algorithms
    - biophysics and neural coding
    - visual system physiology and modeling
    - data analysis strategies (frequency domain, cross-correlation)

Voxel Clustering

The Allen reference provides a hierarchical ontology, that has been informatically aligned to voxeled data from the AAV injections. These structures provide an anatomists view of the brain, but what can the data itself tell us? Example questions:

- Use voxelized data to explore spatial connectivity patterns.
- In the reference atlas, the striatum is annotated as a single large structure. Can we use voxels to draw out the topography of the cortico-striatial pathway?
- There is evidence that the primary motor cortex (area MOp) is heterogeneous in its outgoing projections. Can we use the connectivity to map this out/subdivide this area?
- Other structures with known cortical projection topography includes thalamus, superior colliculus.
- Does an informatically-driven structure atlas look different when using projection-as-source data to define regions, as opposed to projection-as target?

Cell-type inter-region connectivity

Cre driver lines, combined with adeno-associated virus injections, allow cell-line specific anteriograde axonal tracing. Can we use cre line AAV injection experiments to determine brain-wide inter-areal projection patterns? Example questions:

- What cell lines project to where in the cortex? How can we best summarize this information (matrix, table, database, graph, something else)?

- What patterns emerge when looking across brain structures, but within cell types? Vice-versa?

- Can we construct a model that summarizes/explains the data (quantitatively and/or qualitatively)?

Network Analysis

Analysis of network topology can lead to insights about information routing and processing. Structural motifs can be found that are in common with other natural and artificial systems. Example questions:

- What structural motifs are present in the connectivity data set? How do they differ across regions?
- What are the functional correlates to the structural connectivity? How do they relate to models of information processing?
- At what scale (region, laminar, sublaminar) can we perform network analyses on the data?
- What do different cell types contribute to the network topology?

Virtual Tractography

The topology of the mouse connectome is supported by physical connections that provide constraints on possible connectivity. These spatial constraints can also impact dynamics through connectivity via resource considerations. Example questions:

- What is the relationship between projection distances, as grouped by anatomical region? Are there scaling/symmetry/invariance properties in the projection distance data?
- Does the tractography data inform/agree with theories of wiring efficiency?
- What is the relationship between the network topology and the physical topology?
- Although we have only one developmental time point in the data, does the tractography constrain models of how the connectome develops?

Mesoscale Dynamical Simulations

A connectivity matrix provides a static view of a brain network, and shapes the dynamic activity of the connected structures. What computational features emerge as a result of combining dynamics with realistic network topology?

- For models of different complexity, how dependent is dynamics on the particulars of the connectivity?
- How do conclusions differ when the models are deterministic versus stochastic?
- What does connectivity imply about cortical dynamics and information flow?
- How sensitive are the dynamics to choices of linear model parameters?
- Can use connectivity from the wild-type linear model: “A mesoscale connectome of the mouse brain”, Oh et al., Nature 2014.