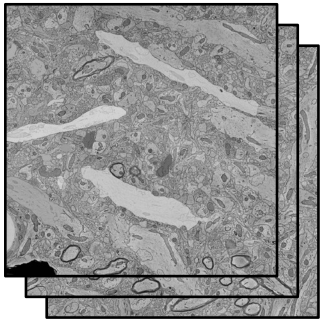
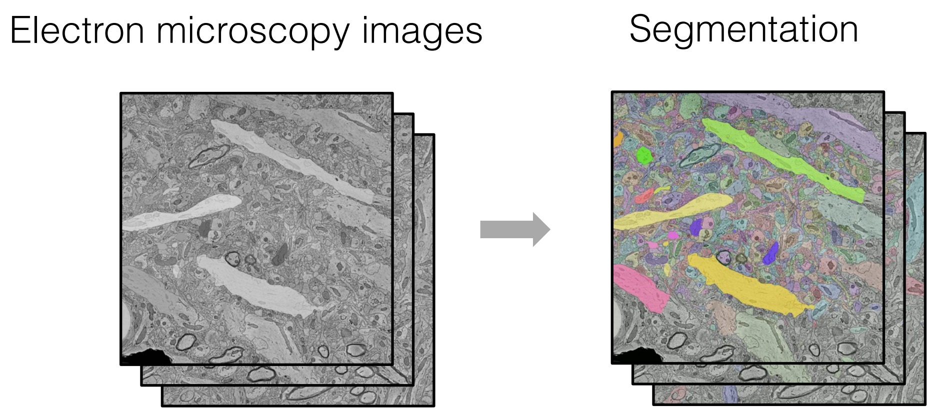
Electron microscopy images



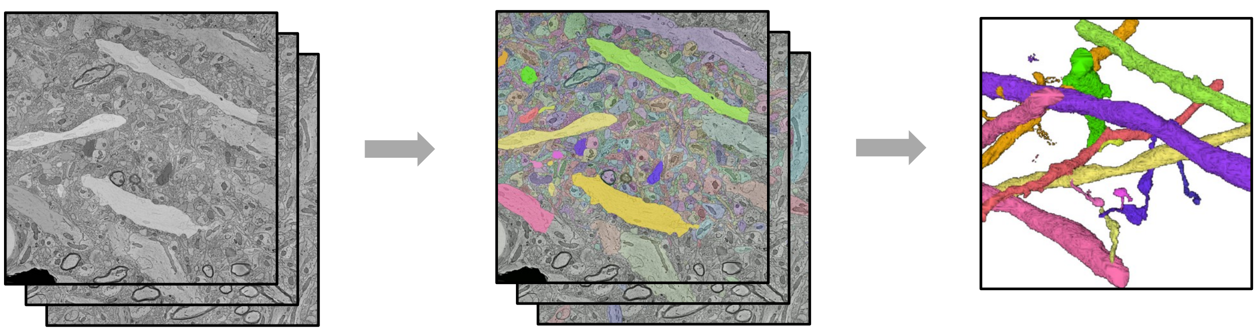


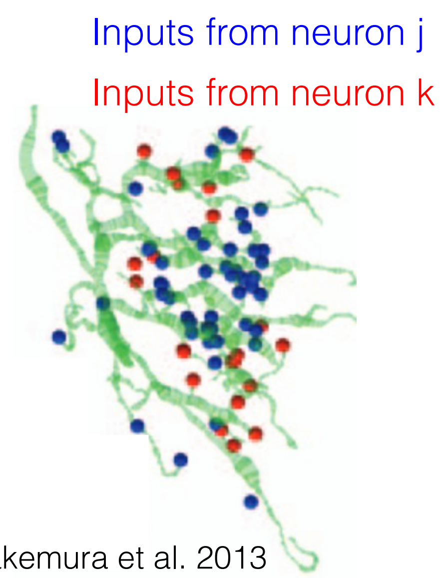
Electron microscopy images
Segmentation

Electron microscopy images

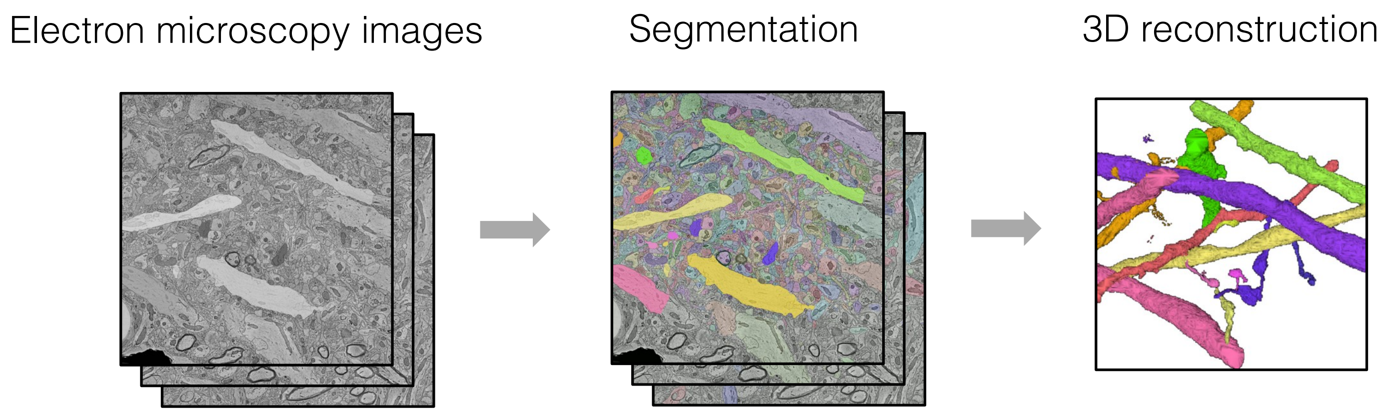
Segmentation

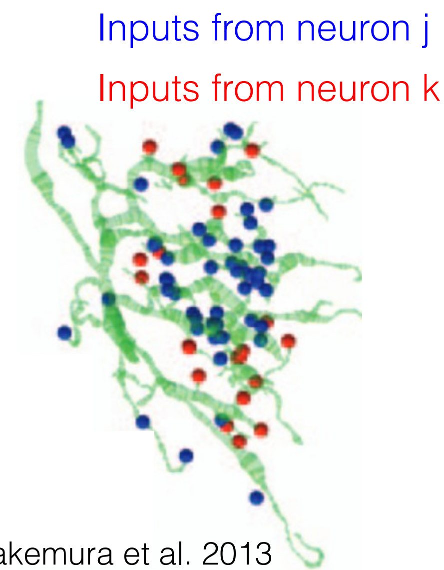
3D reconstruction



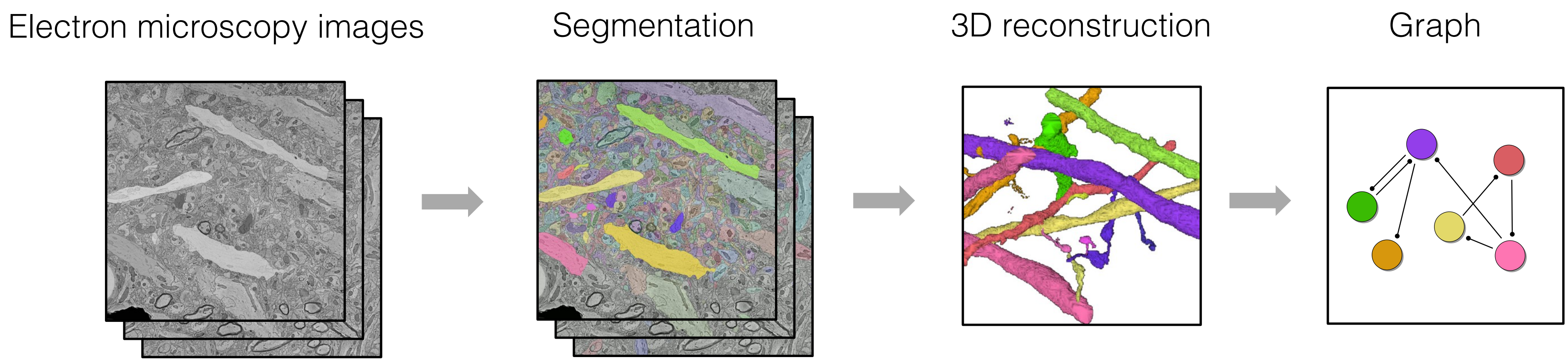


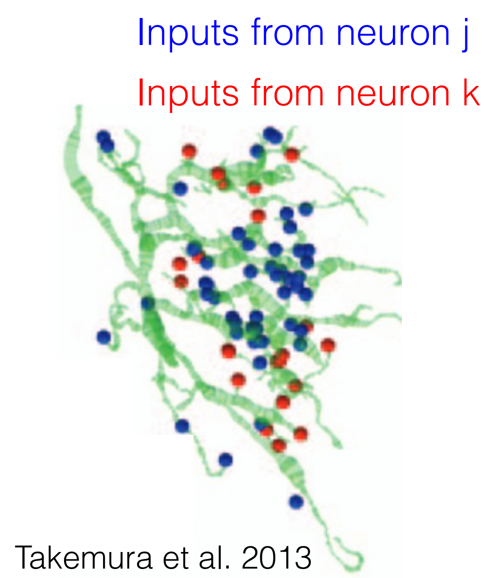
Takemura et al. 2013



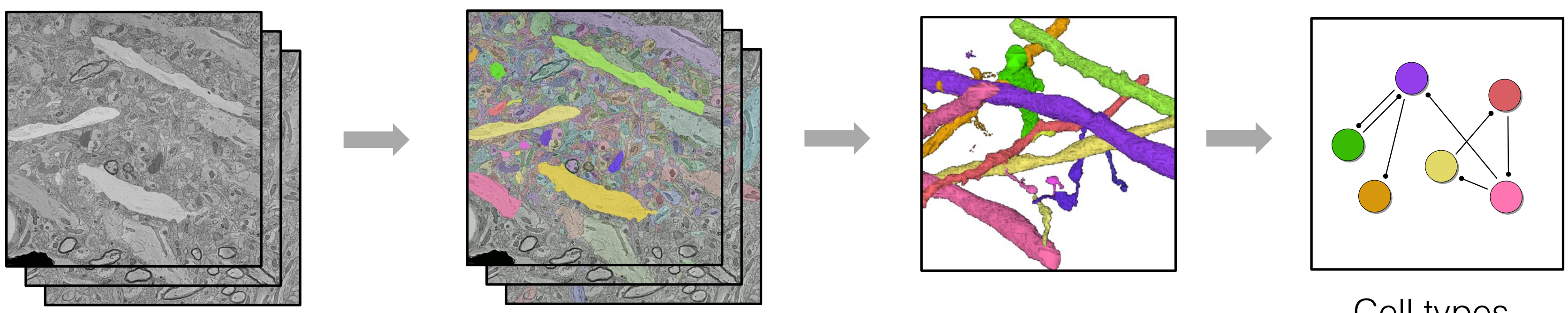


Takemura et al. 2013





Electron microscopy images → Segmentation → 3D reconstruction → Graph



Cell types
"Names"
Neurotransmitter types
Size/number of synaptic connections
Recordings/effects of activation/inactivation
Transcriptomic

C. elegans

~300 neurons

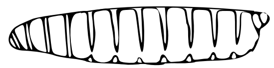
1986

C. elegans

~300 neurons

1986

Drosophila larva



~2,000 neurons

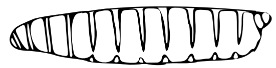
~2010-2023

C. elegans

~300 neurons

1986

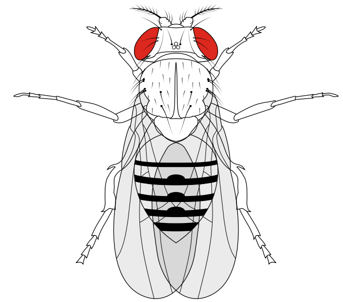
Drosophila larva



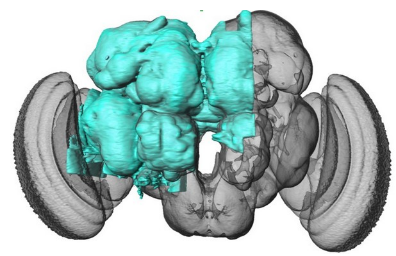
~2,000 neurons

~2010-2023

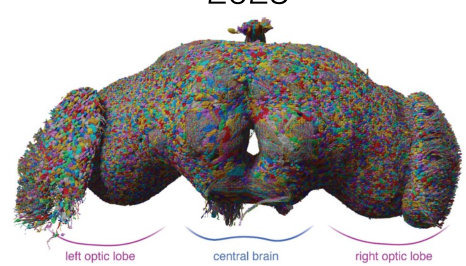
Drosophila adult



~20,000 neurons
2020



~120,000 neurons
2023

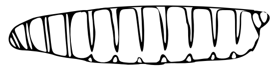


C. elegans

~300 neurons

1986

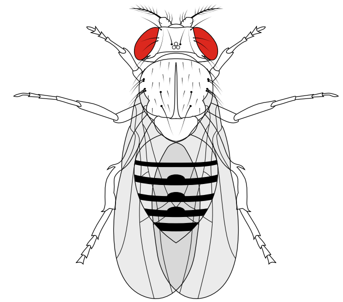
Drosophila
larva



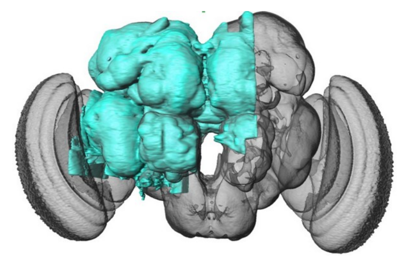
~2,000 neurons

~2010-2023

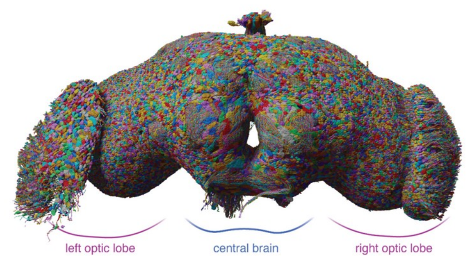
Drosophila
adult



~20,000 neurons
2020



~120,000 neurons
2023

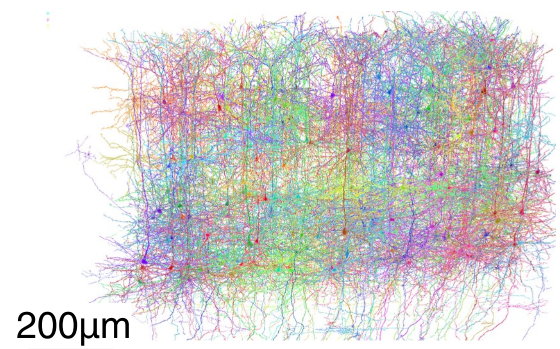


?

Mouse

~75,000,000 neurons

~200,000 neurons
2021



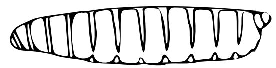
C. elegans

~300 neurons

1986

`wormwiring.org`

Drosophila
larva

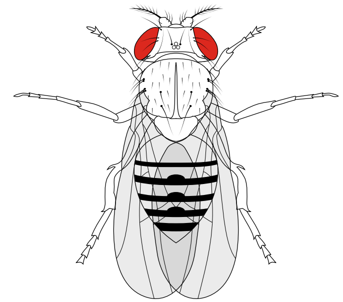


~2,000 neurons

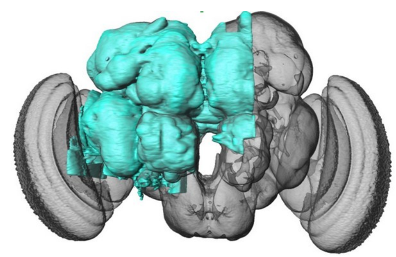
~2010-2023

`l1em.catmaid.`
`virtualflybrain.org`

Drosophila
adult

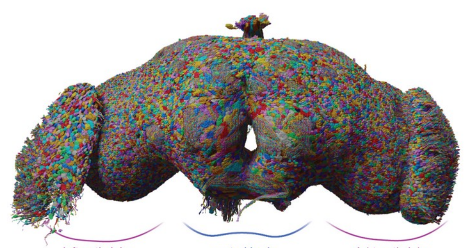


~20,000 neurons
2020



`neuprint.janelia.org`

~120,000 neurons
2023



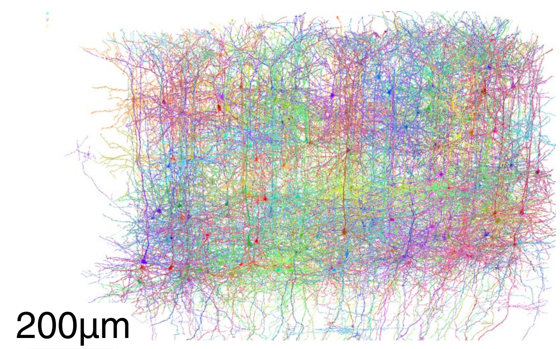
`codex.flywire.ai`

?

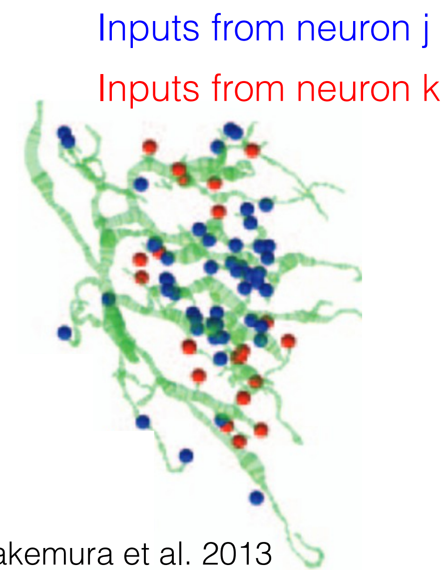
Mouse

~75,000,000 neurons

~200,000 neurons
2021

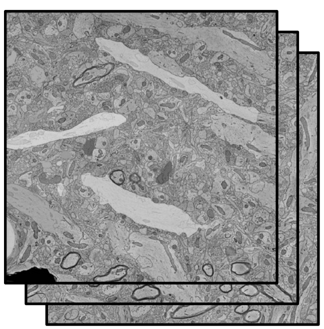


`microns-explorer.org`

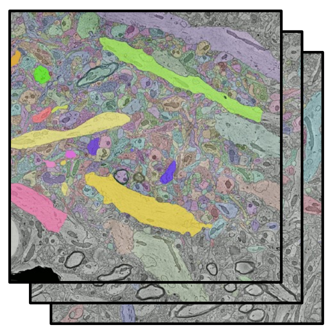


Takemura et al. 2013

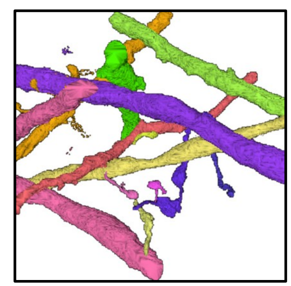
Electron microscopy images



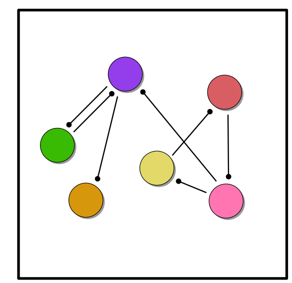
Segmentation



3D reconstruction



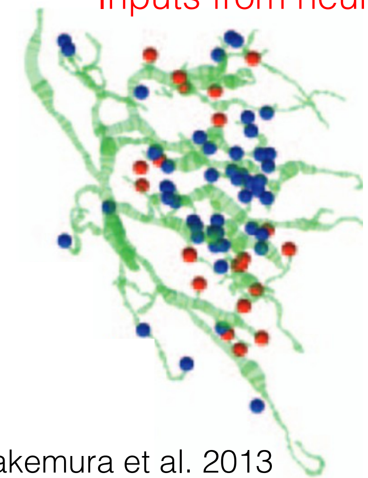
Graph



Cell types
“Names”
Neurotransmitter types
Size/number of synaptic connections
Recordings/effects of activation/inactivation
Transcriptomic

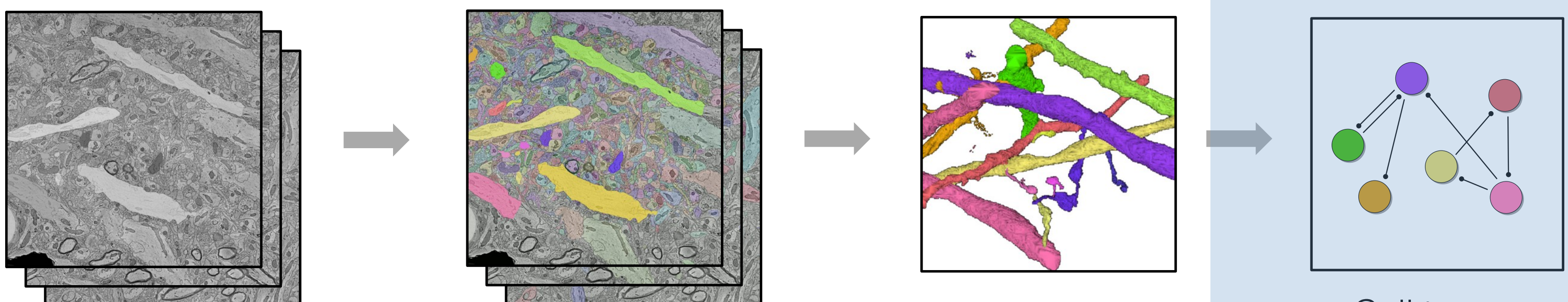
Inputs from neuron j

Inputs from neuron k

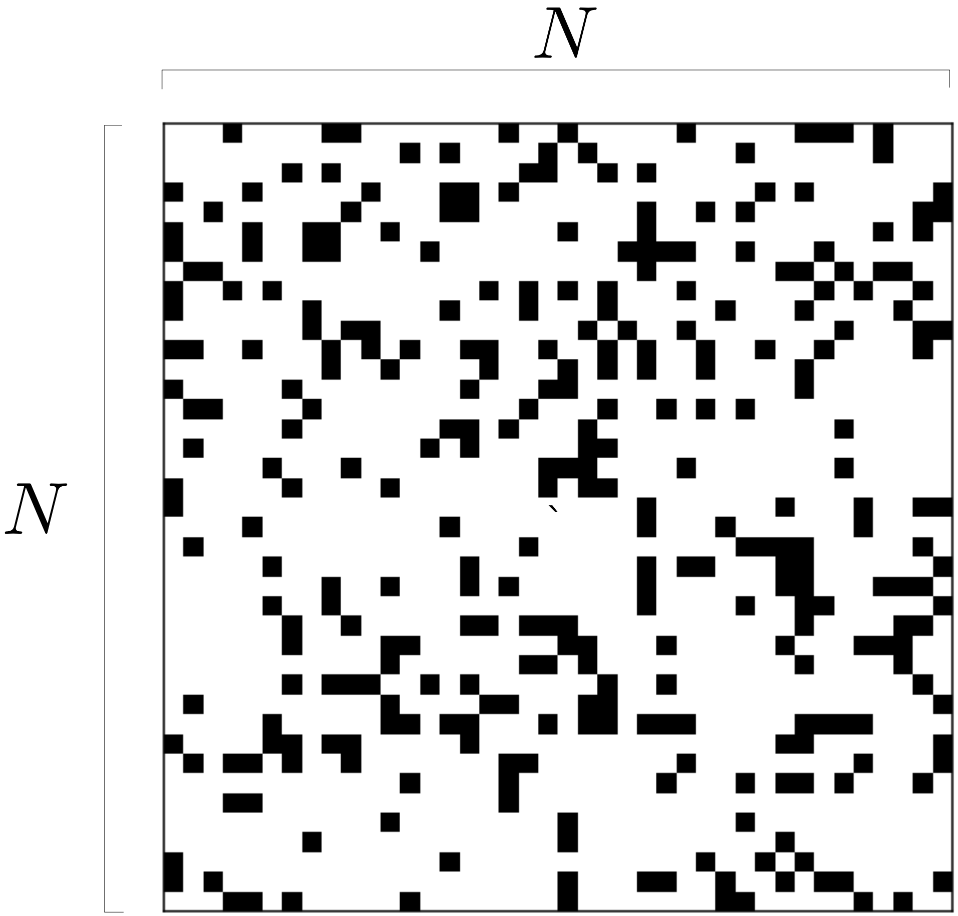


Takemura et al. 2013

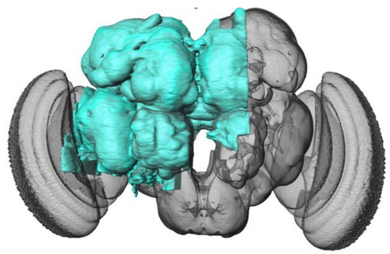
Electron microscopy images | Segmentation | 3D reconstruction | Graph



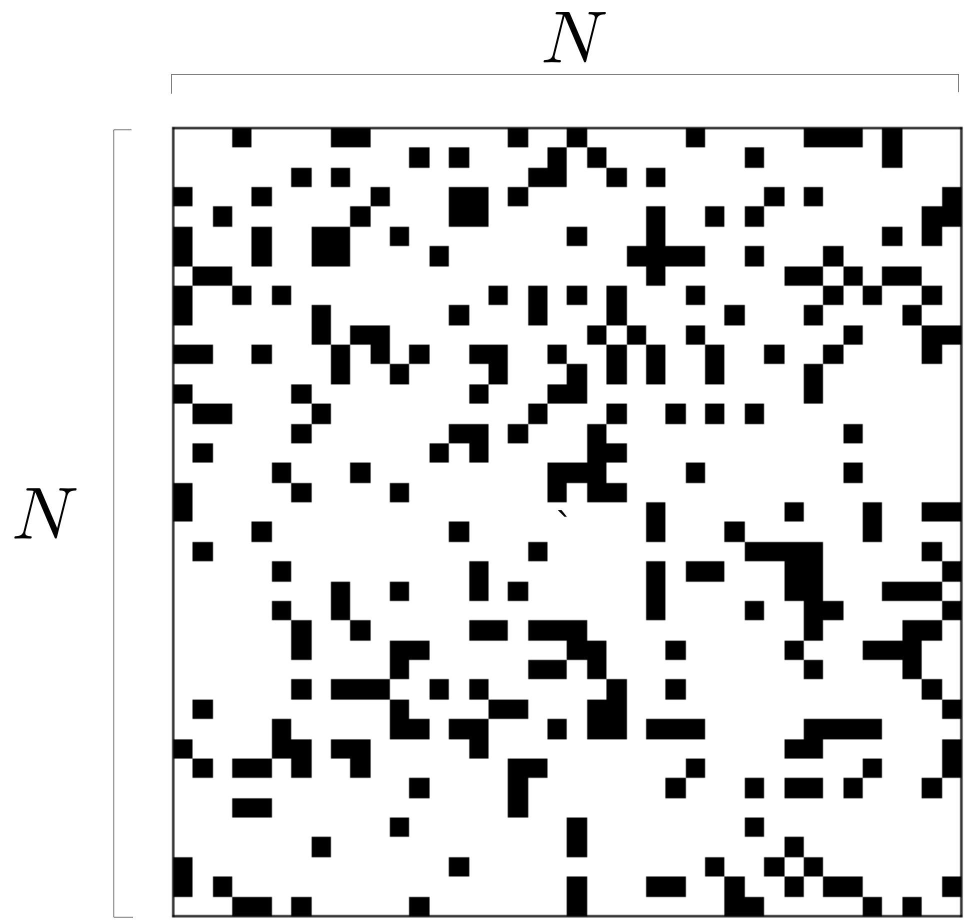
Cell types
“Names”
Neurotransmitter types
Size/number of synaptic connections
Recordings/effects of activation/inactivation
Transcriptomic

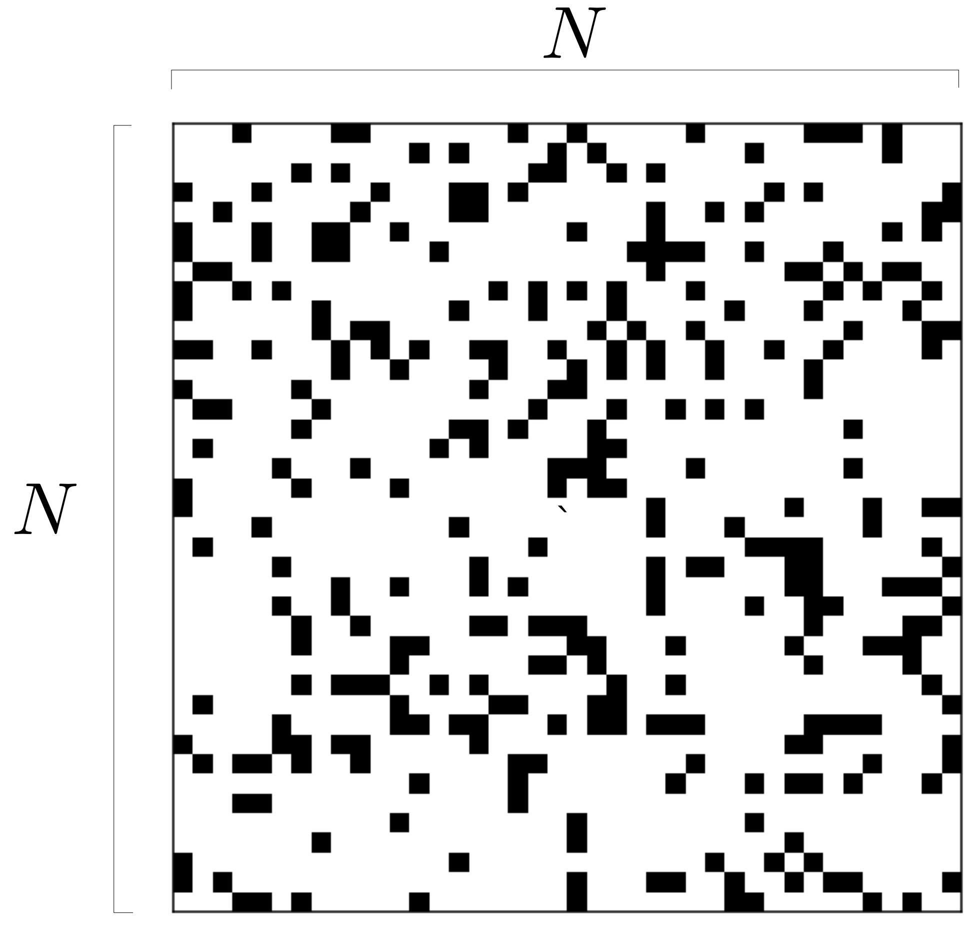

N
N

2020

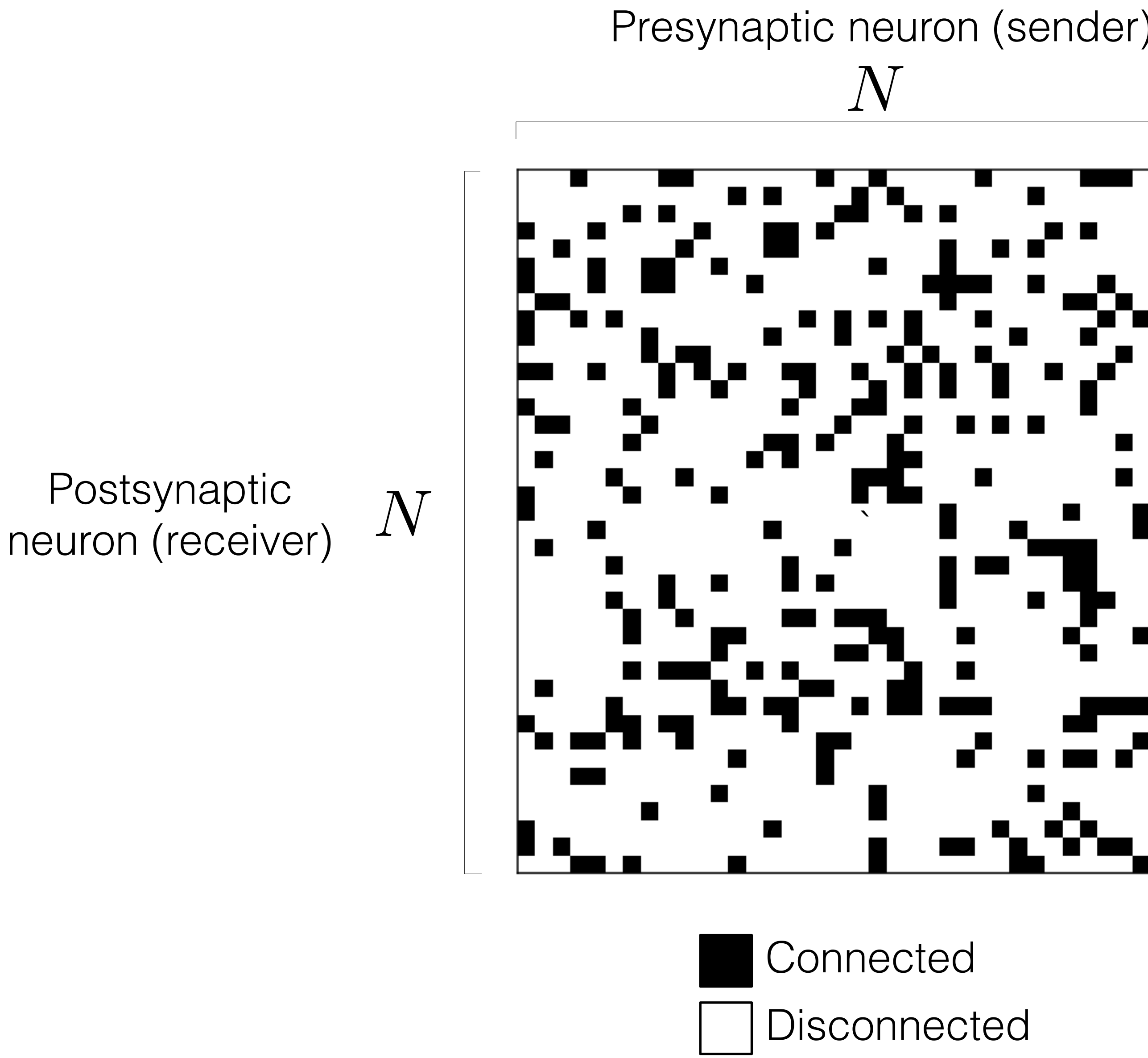


neuprint.janelia.org



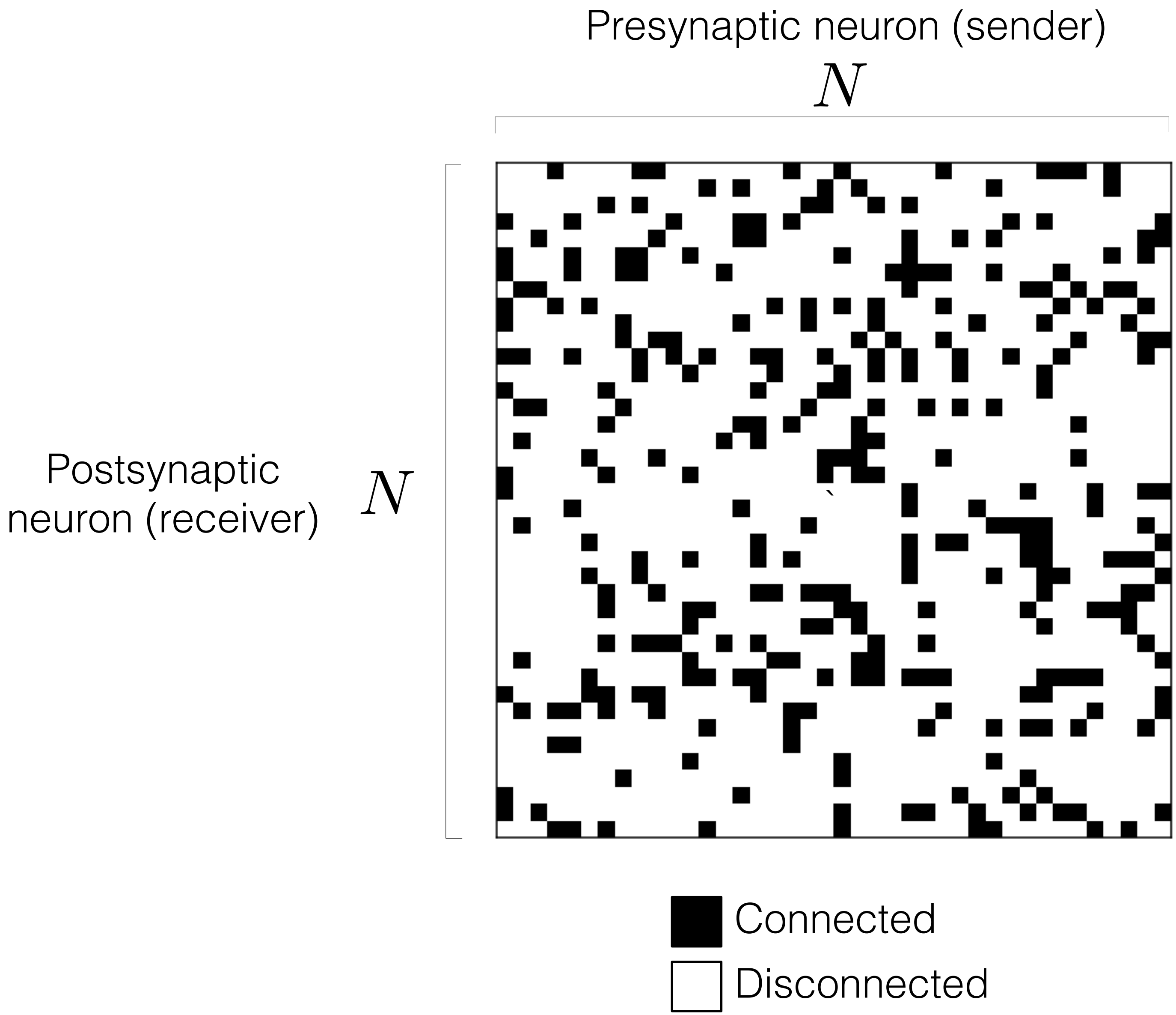

N
N

N
N
Connected
Disconnected

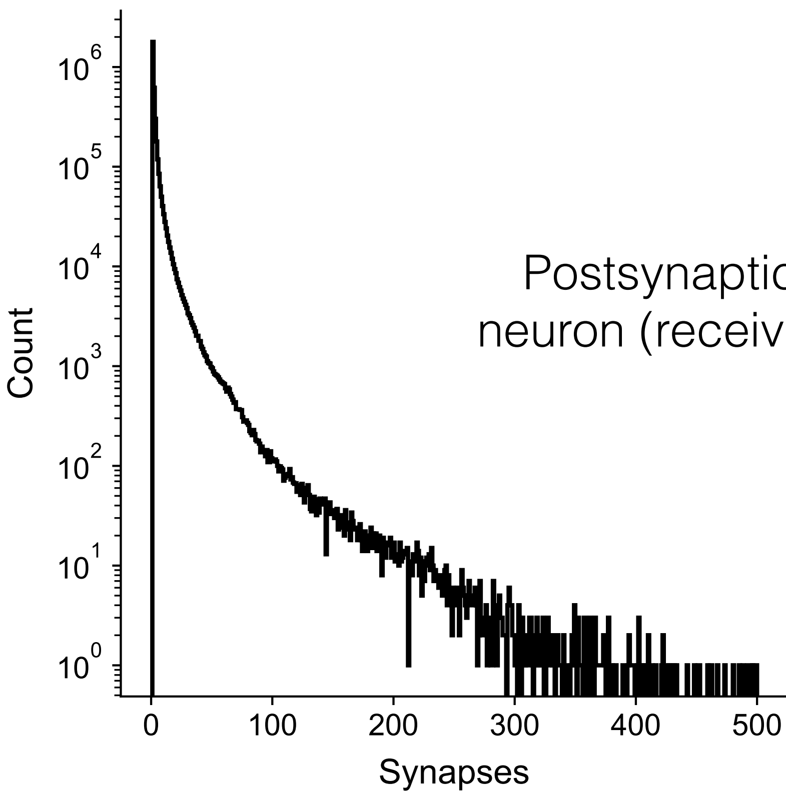


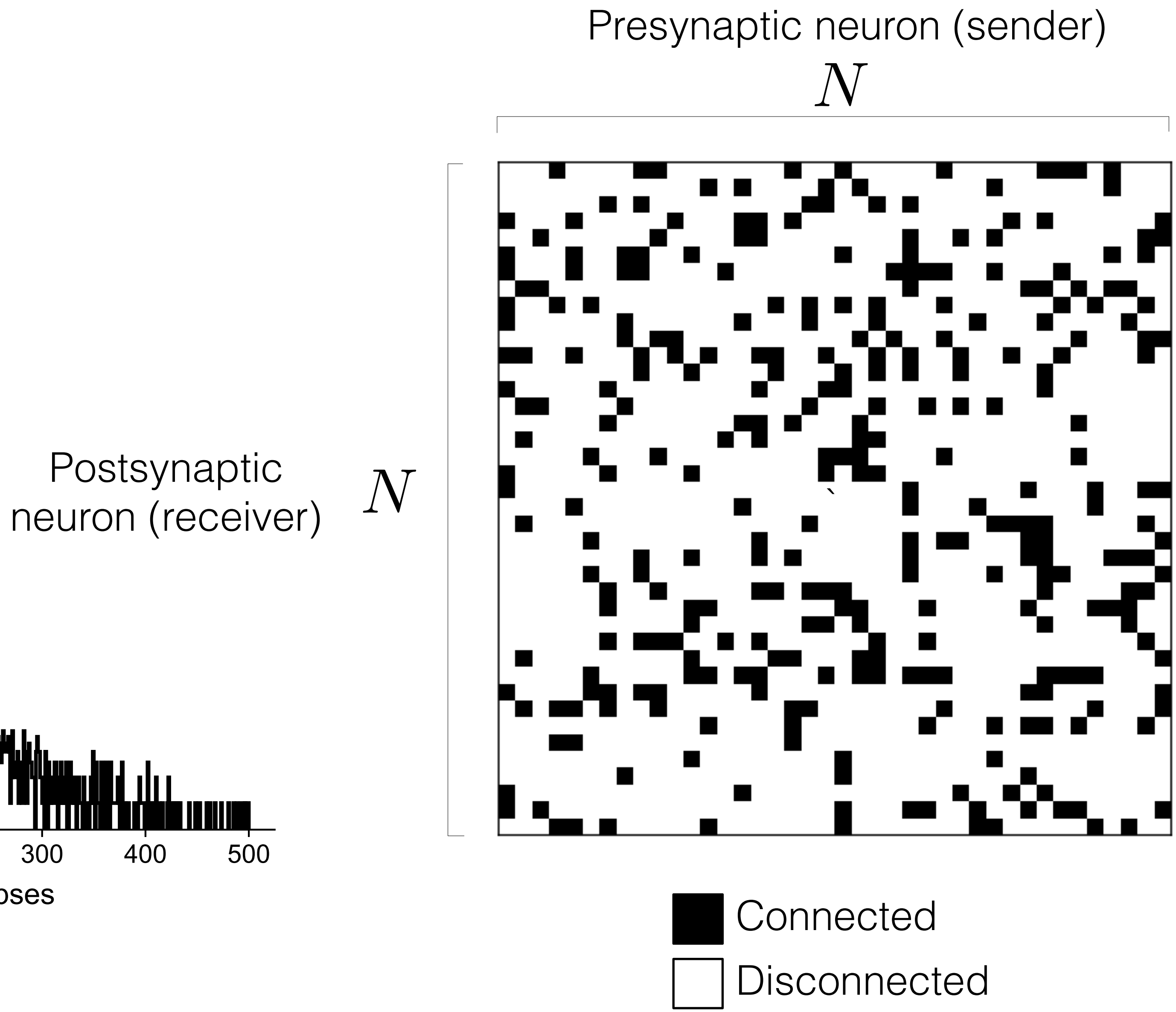
Presynaptic neuron (sender)
N
Postsynaptic neuron (receiver)
N
Connected
Disconnected

$$N = 21739$$
$$p = 0.0075$$

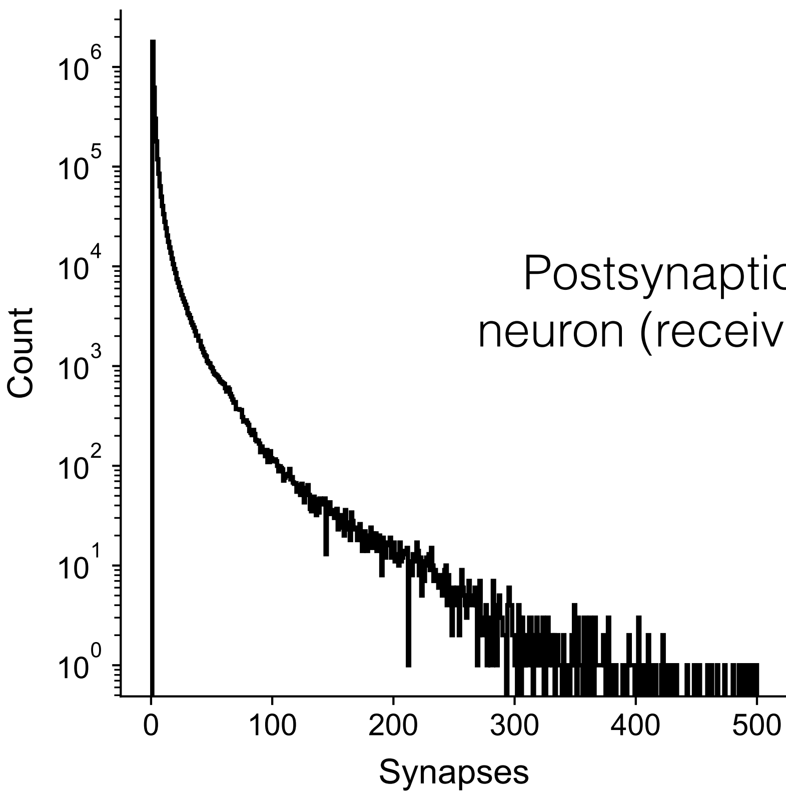


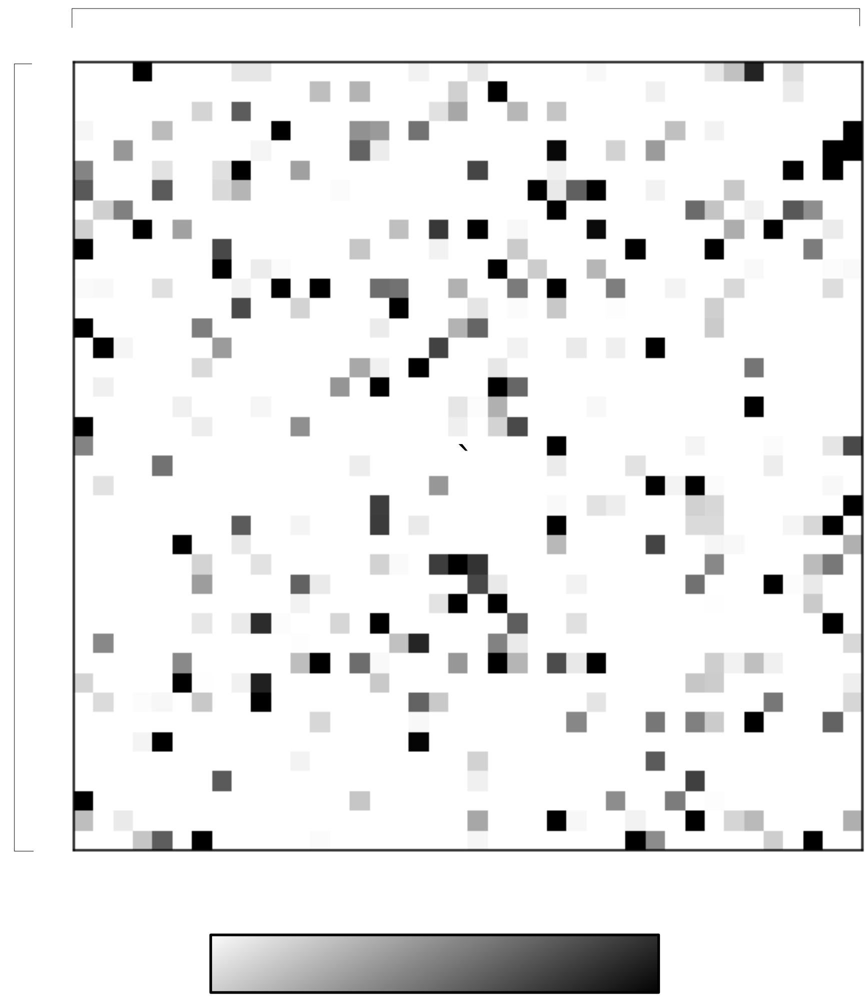
$N = 21739$
$p = 0.0075$



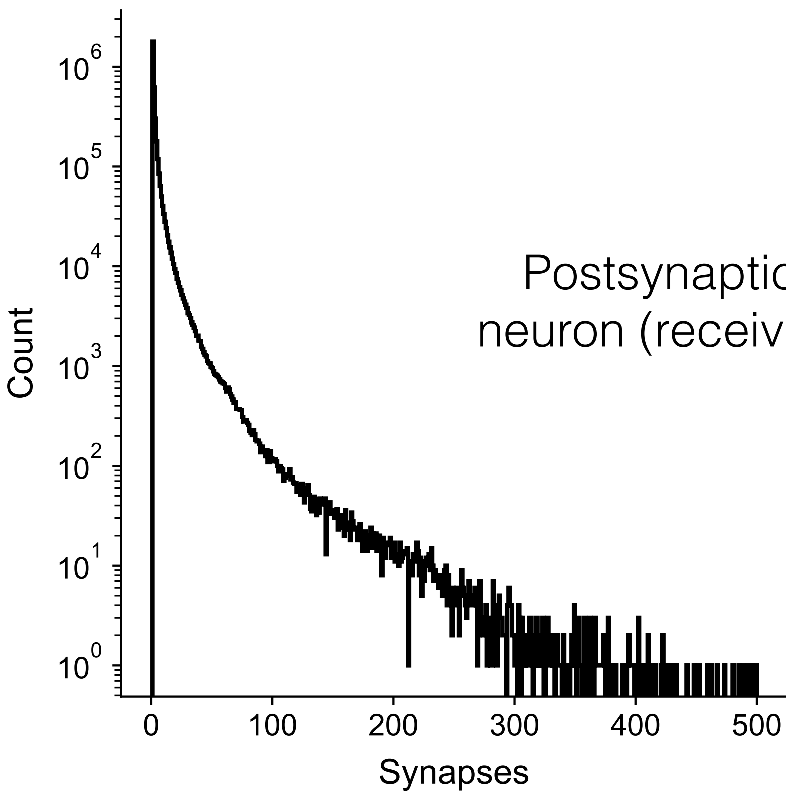


$$N = 21739$$
$$p = 0.0075$$

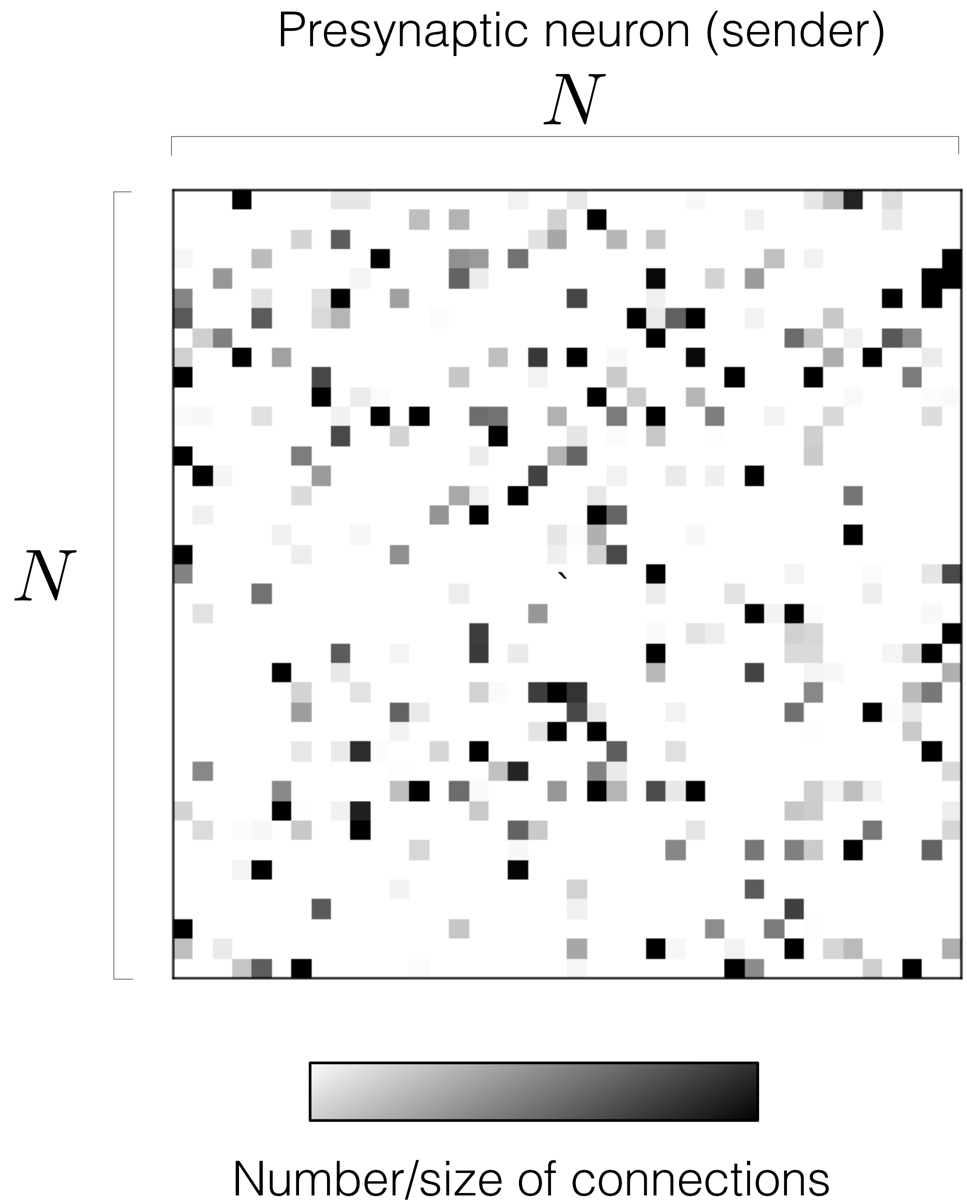




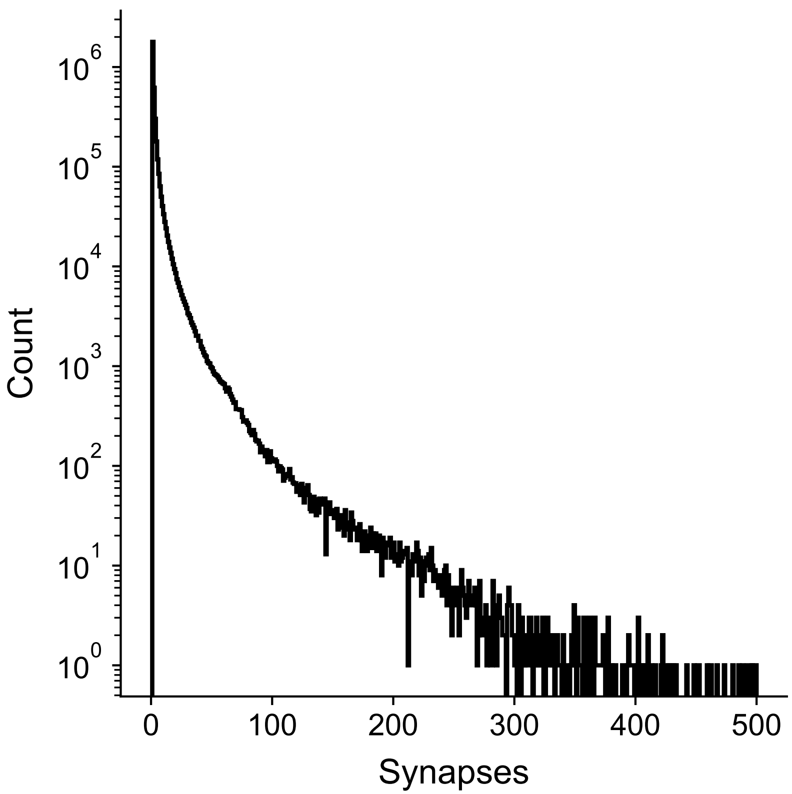
$$N = 21739$$
$$p = 0.0075$$
$$p(\geq 5) = 0.0014$$

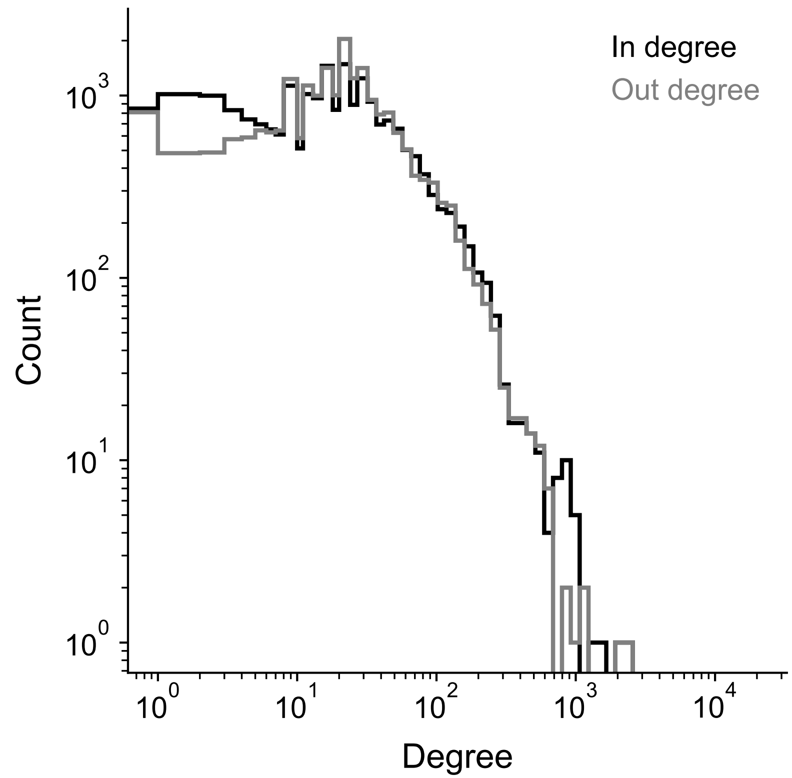


Postsynaptic neuron (receiver)

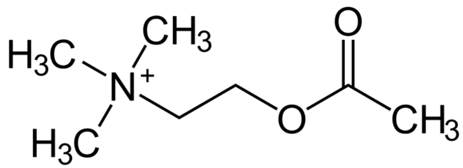


$$N = 21739$$
$$p = 0.0075$$
$$p(\geq 5) = 0.0014$$

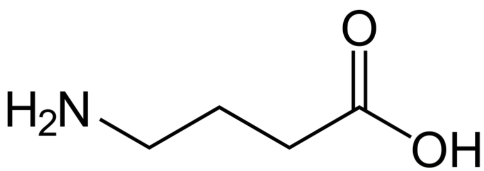




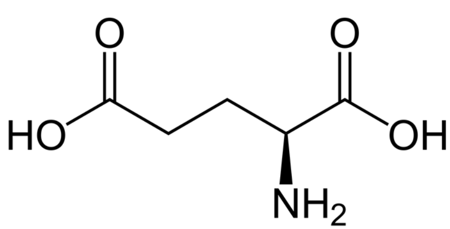
Acetylcholine (excitatory)



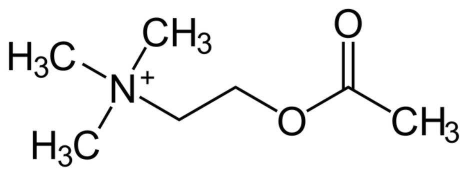
GABA (inhibitory)



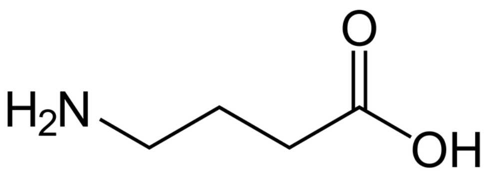
Glutamate (probably inhibitory)



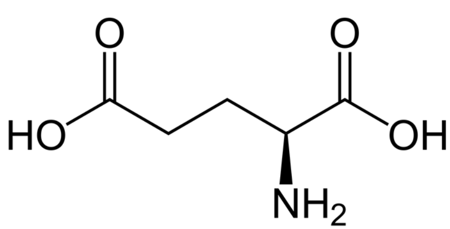
Acetylcholine (excitatory)



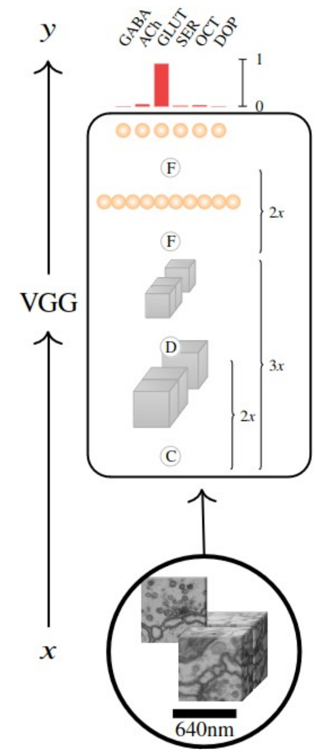
GABA (inhibitory)



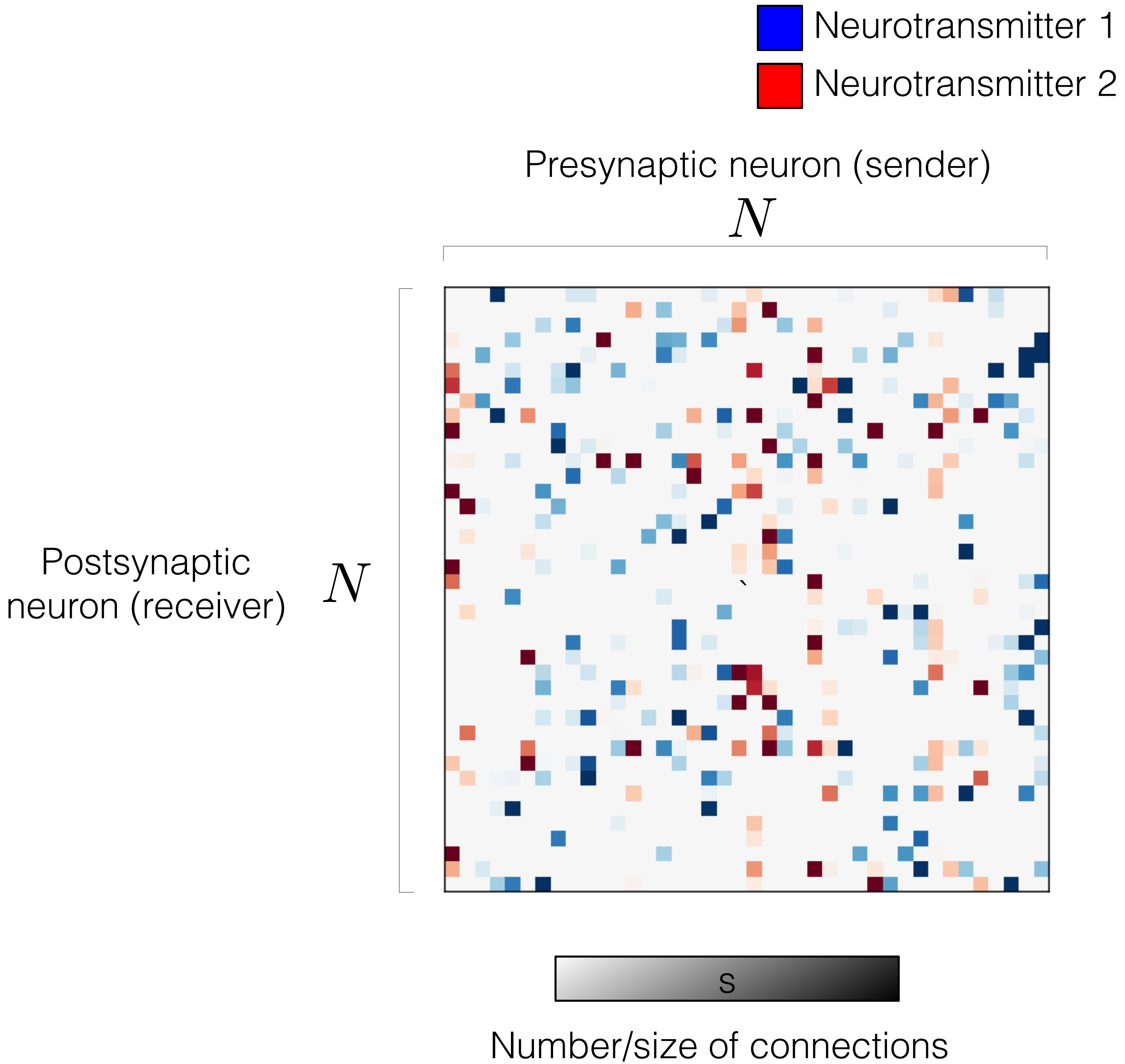
Glutamate (probably inhibitory)

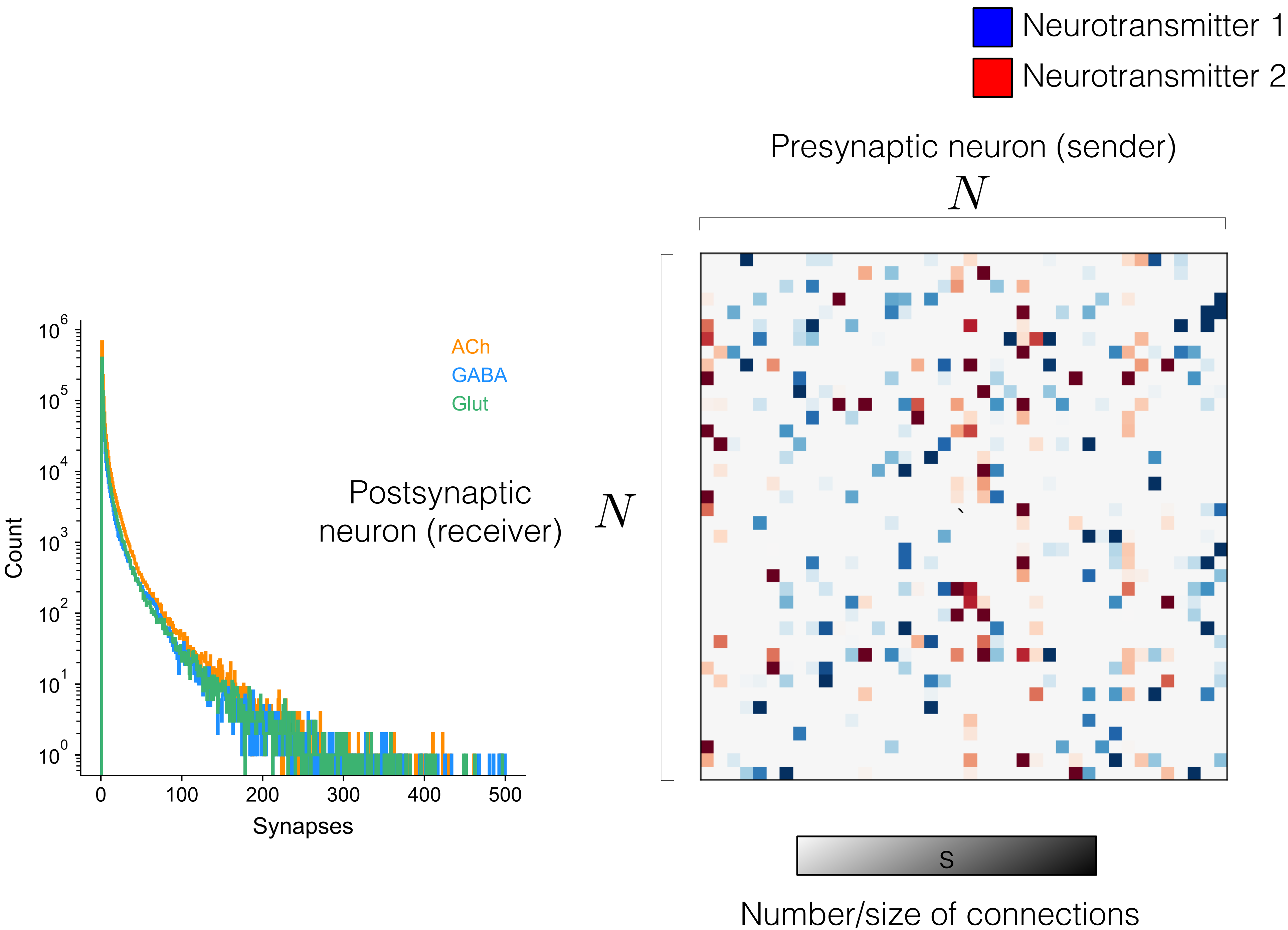


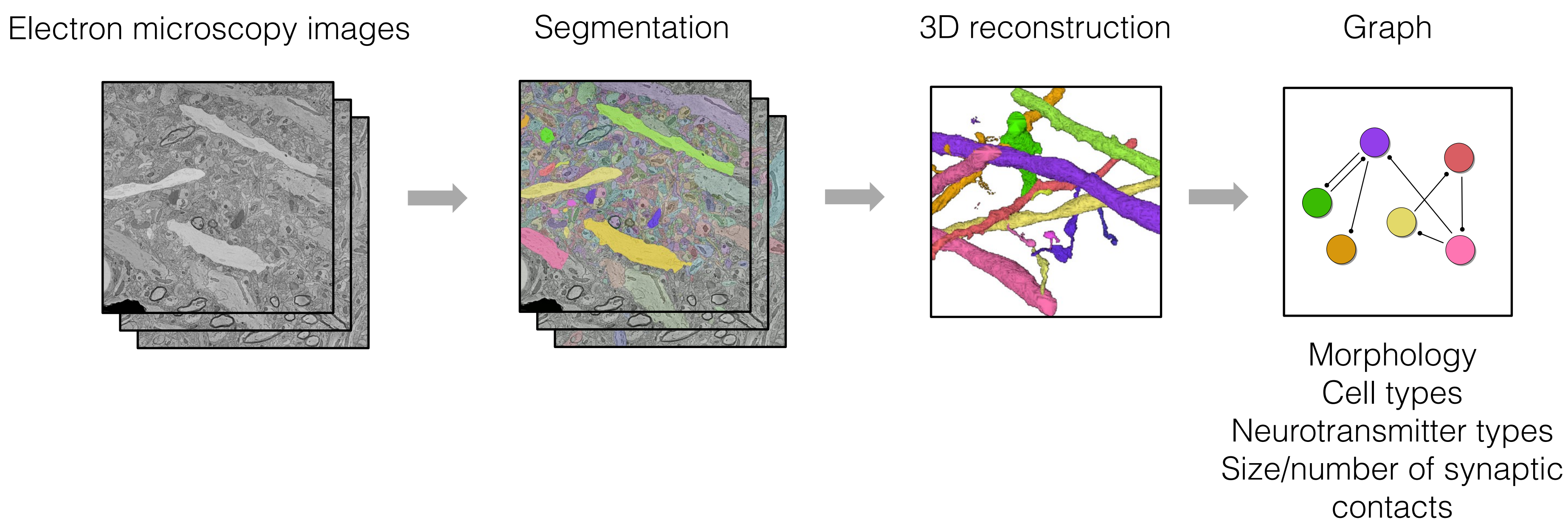
Predicted neurotransmitter



Eckstein et al. 2020


Neurotransmitter 1
Neurotransmitter 2
Presynaptic neuron (sender)
N
Postsynaptic neuron (receiver)
N
S
Number/size of connections


Neurotransmitter 1
Neurotransmitter 2
Presynaptic neuron (sender)
N
Postsynaptic neuron (receiver)
N
S
Number/size of connections
ACh
GABA
Glut
Count
Synapses
10^0
10^1
10^2
10^3
10^4
10^5
10^6
0
100
200
300
400
500

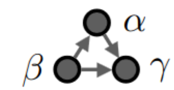
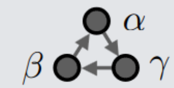
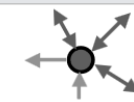
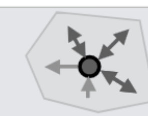
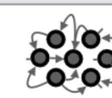
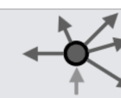
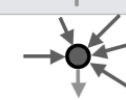
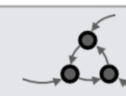
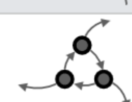


Graphical analysis

1) Cell types
2) Hierarchy
3) Null models

Dynamics

	Computed network statistics	
Connected components	strongly connected components	Figure 1d
	weak connected components	Figure 1e
Path length analysis	directed shortest path lengths	Figure 1d
	undirected shortest path lengths	Figure 1e
Percolation analysis	vertex percolation	Figures 1f, g; S1f
	edge percolation	Figure S1a
Rich-club analysis	total-degree rich club	Figure 1h
	in-degree rich club	Figure S1g
	out-degree rich club	Figure S1g
Small-word analysis	clustering coefficient	Table 2
	small-wordness	Equation 1
2-neuron motifs	reciprocity	Table 2; Figures 5c; S5c
	connection strength	Figures 2a, d; 5f, S6a
	neurotransmitter types	Figures 2c, e, f; 5d, e; S5
3-neuron motifs	motif frequencies	Figures 3a; 6a, d; S7a
	motif strength	Figures 3b; 6c; S7b
	neurotransmitter types	Figures 3c, d, e
Large-scale connectivity	degree distribution	Figure 1c
	cell categories	Figure 4
Spectral analysis	forward random walk	Figure S1d
	reversed random walk	Figure S1e
Neuropil subgraphs	internal/external connection weights	Figure S4
	2-neuron motifs	Figures 5, S5, S6
	3-neuron motifs	Figures 6, S7

	Neuron lists available on Codex		# of neurons
2-neuron motifs	reciprocal connection participants		77,607
3-neuron motifs	feedforward loop participants		113,978
	3-unicycle participants		66,835
N-neuron motifs	highly reciprocal neurons		2,183
	neuropil-specific highly reciprocal neurons (NSRNs)		704
Rich-club analysis	rich-club neurons		40,218
	broadcasters		676
	integrators		638
Spectral analysis	attractors		3,469
	repellers		3,469

Lin et al. 2023

1) Cell types

eLIFE
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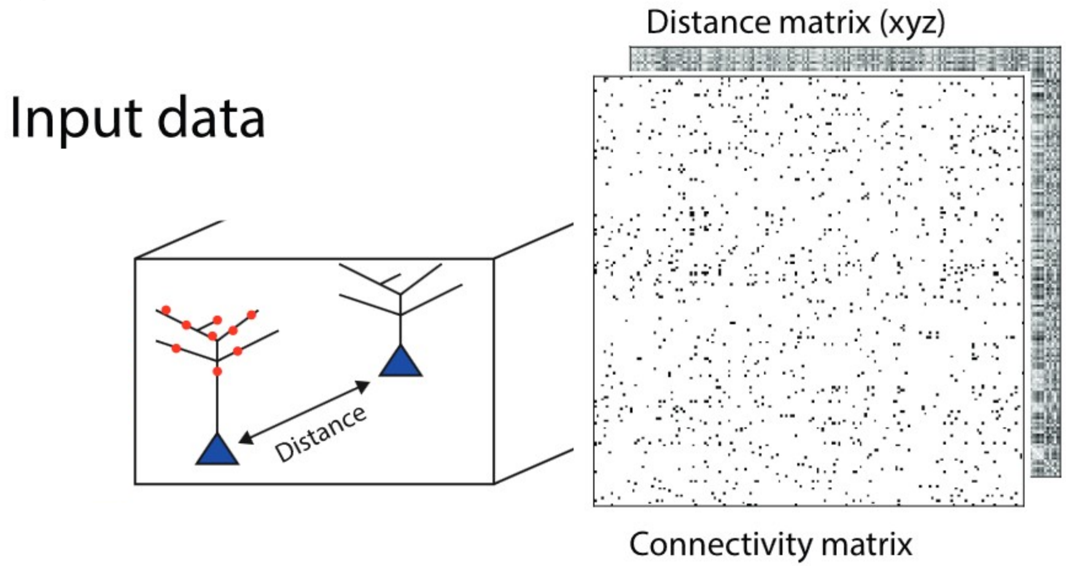
TOOLS AND RESOURCES

Automatic discovery of cell types and microcircuitry from neural connectomics

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

Jonas & Kording 2015

1) Cell types



Jonas & Kording 2015

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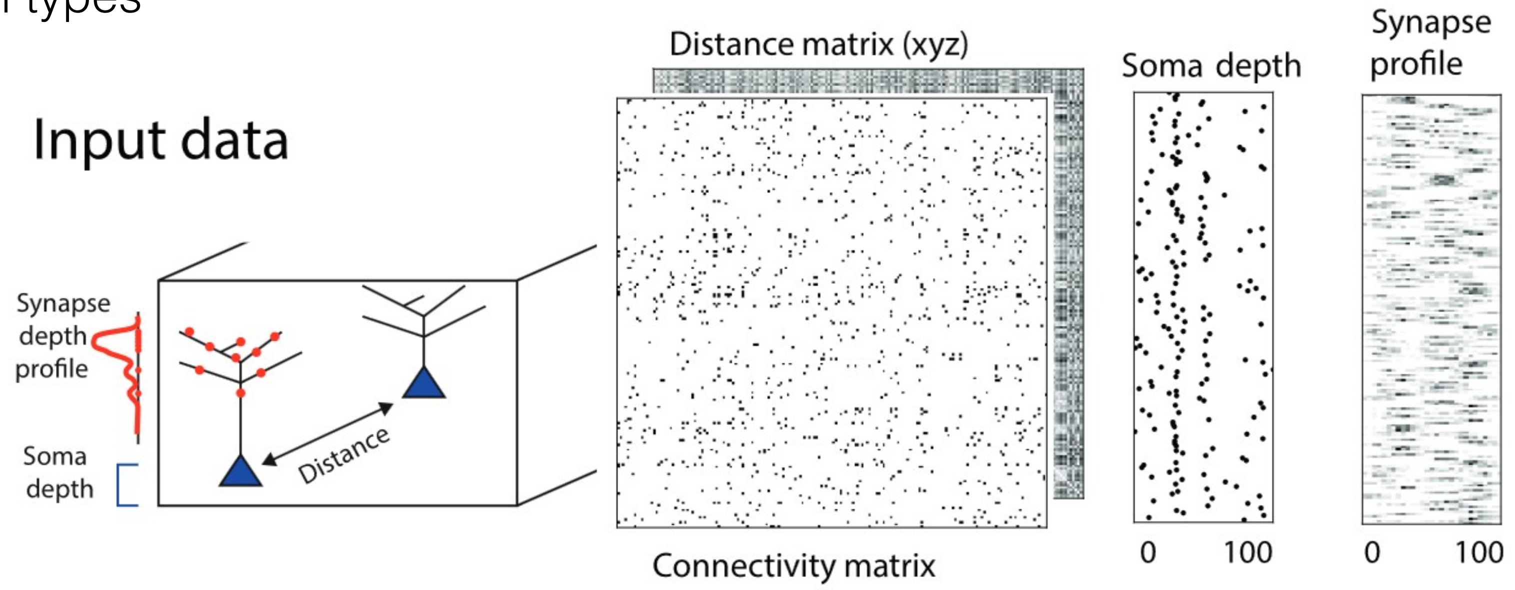

Jonas & Kording 2015

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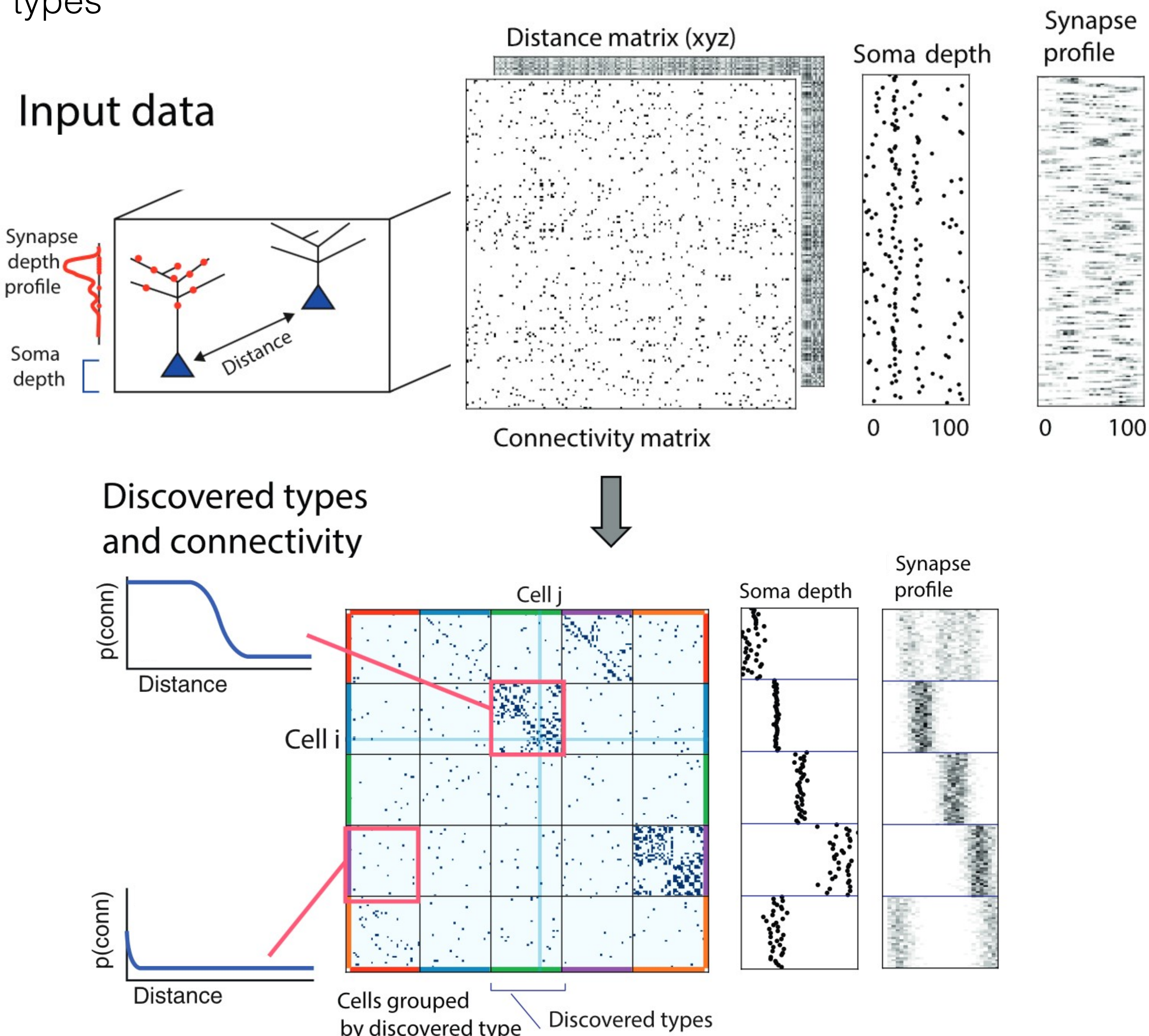
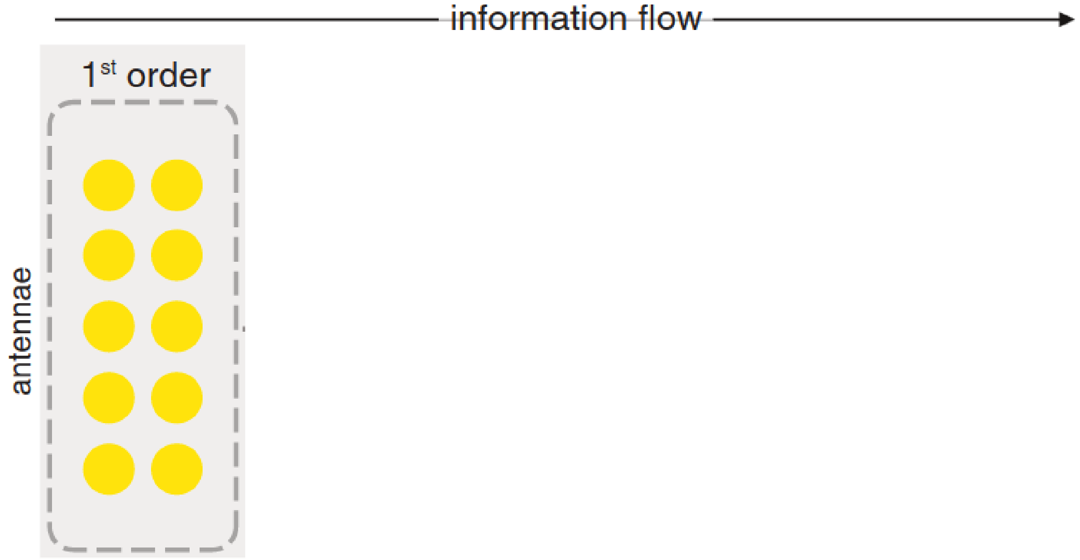


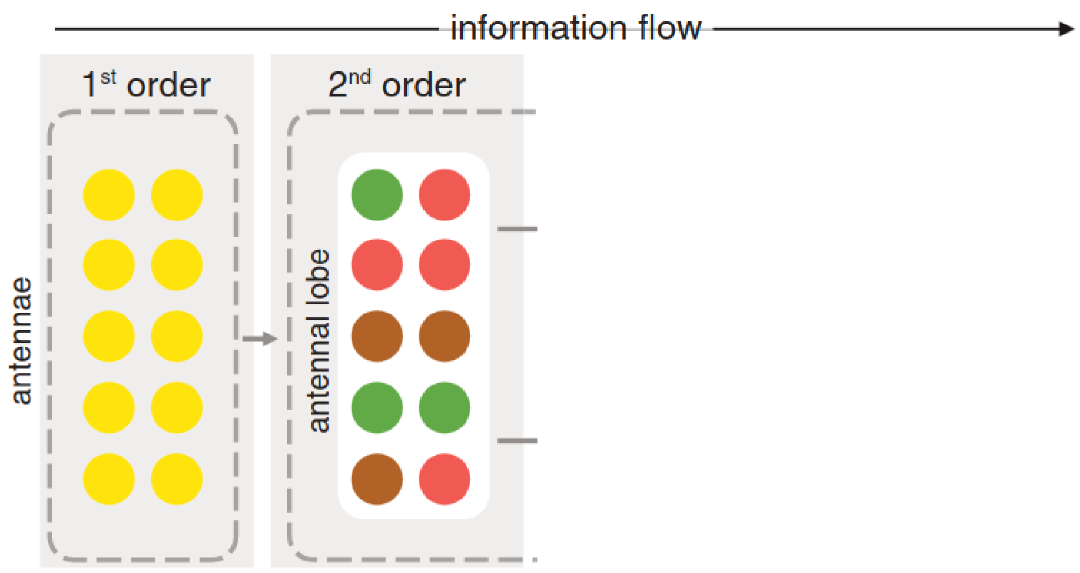
Jonas & Kording 2015

2) Hierarchy



Schlegel et al. 2021

2) Hierarchy



Schlegel et al. 2021

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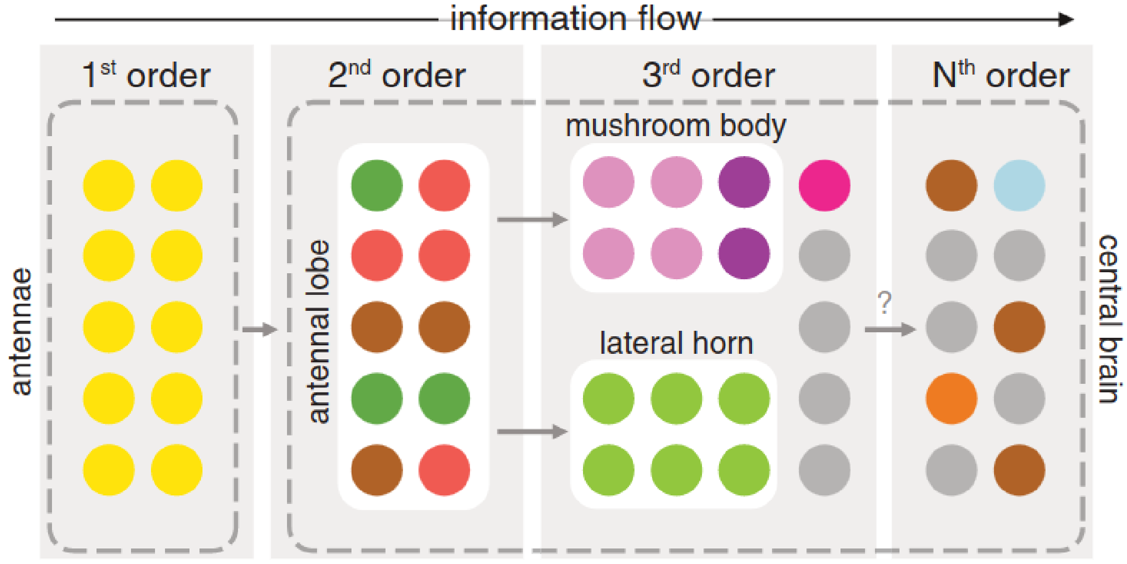

Schlegel et al. 2021

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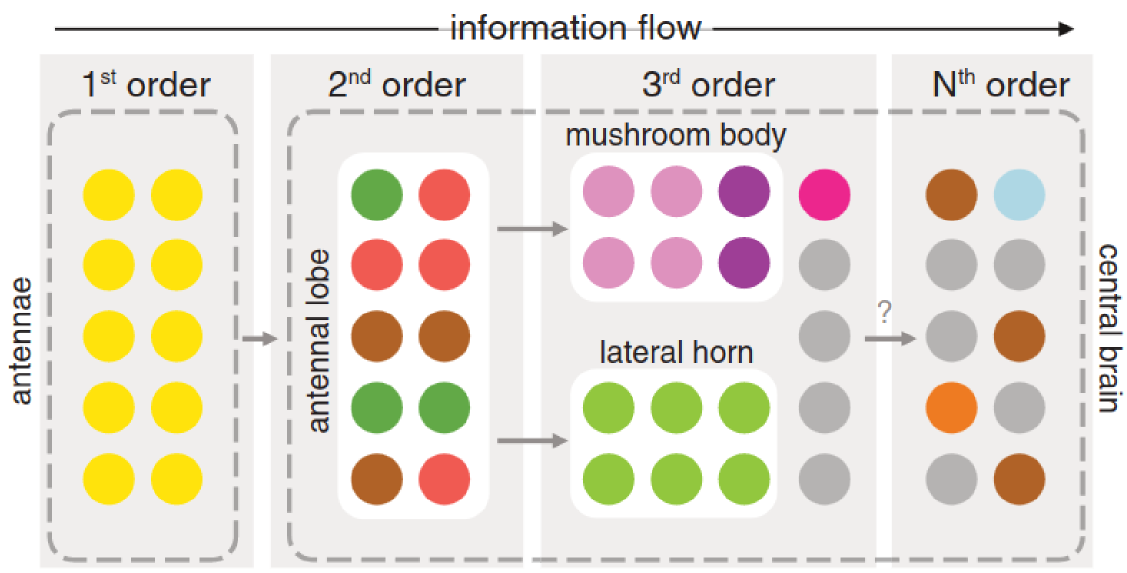

Schlegel et al. 2021

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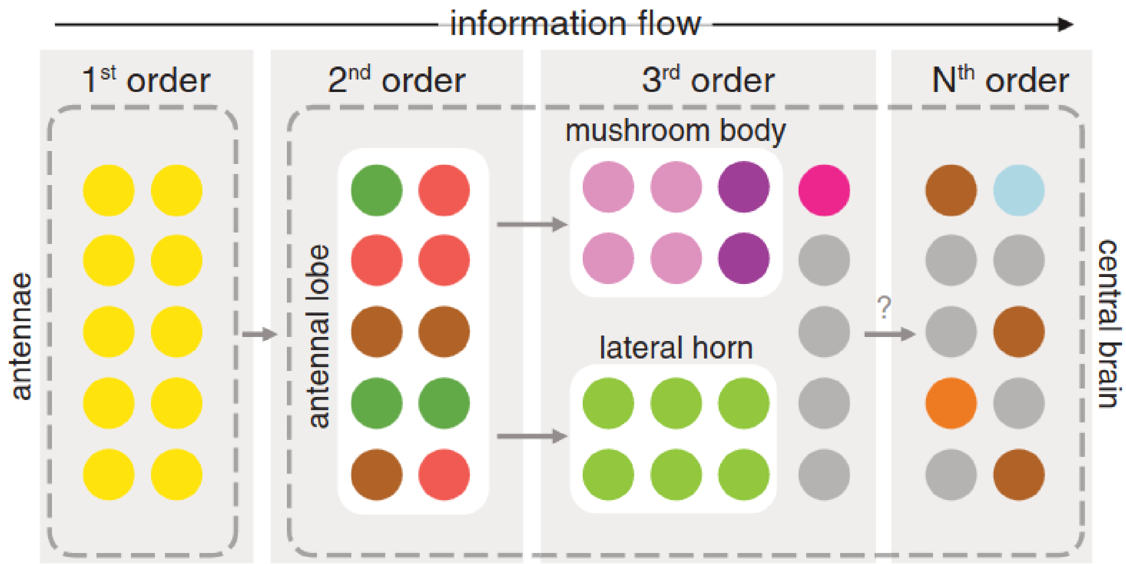

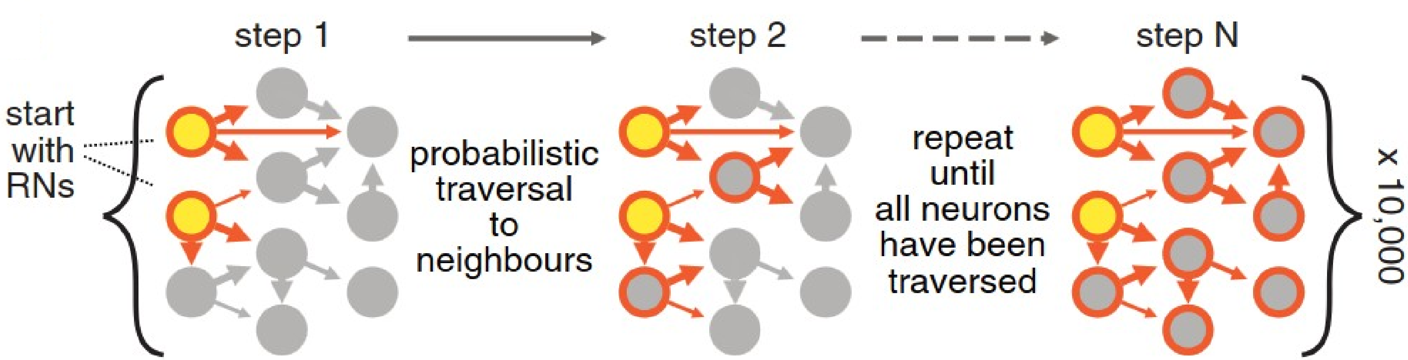

Schlegel et al. 2021

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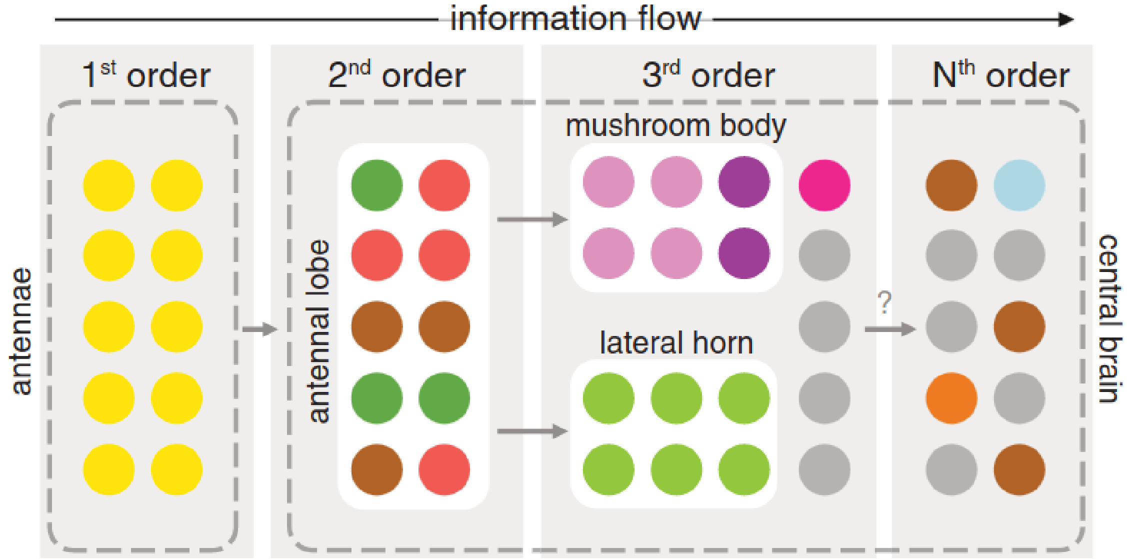
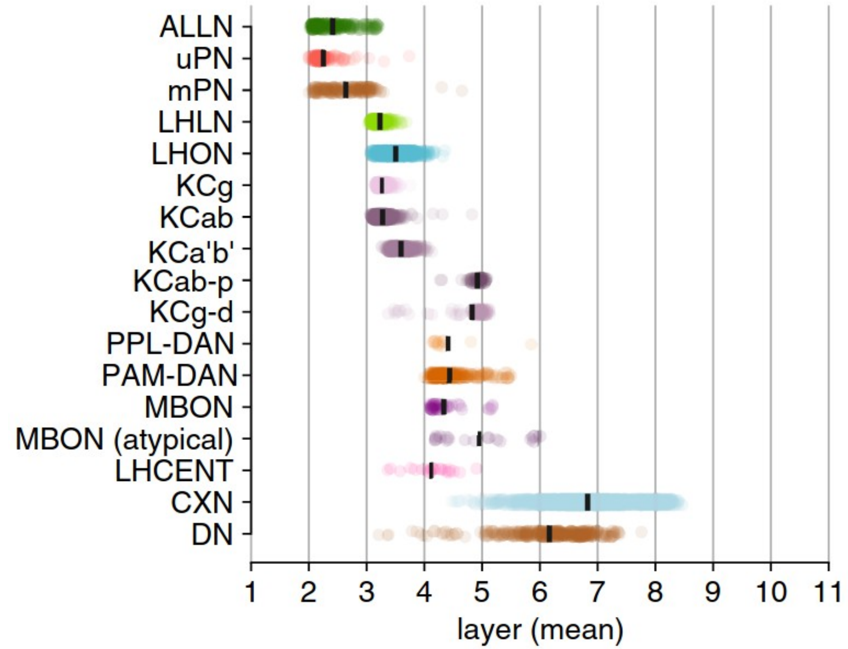
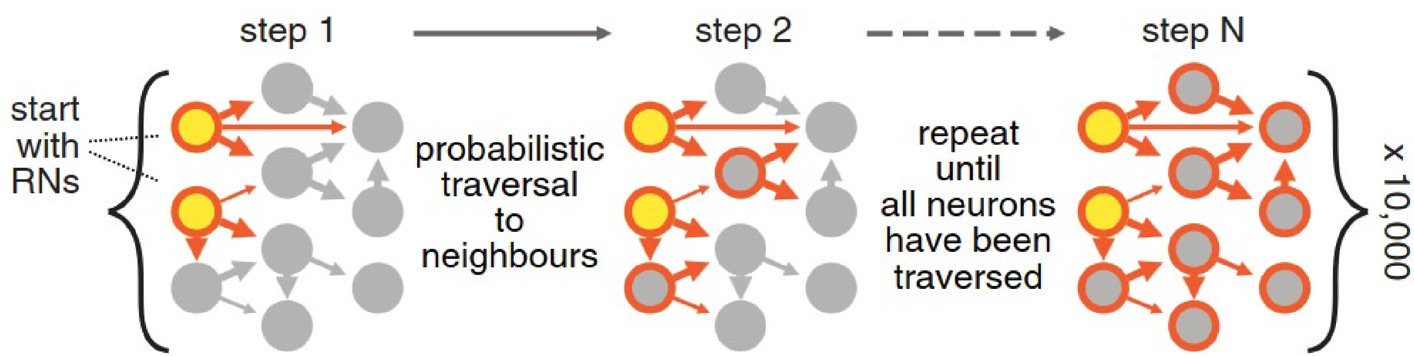




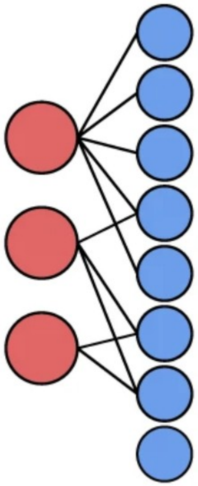


Schlegel et al. 2021

3) Null models

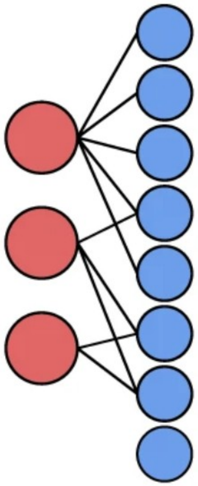
3) Null models

Cell type 1 Cell type 2



3) Null models

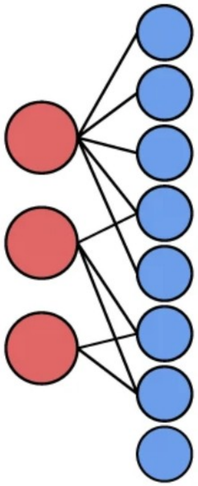
Cell type 1 Cell type 2



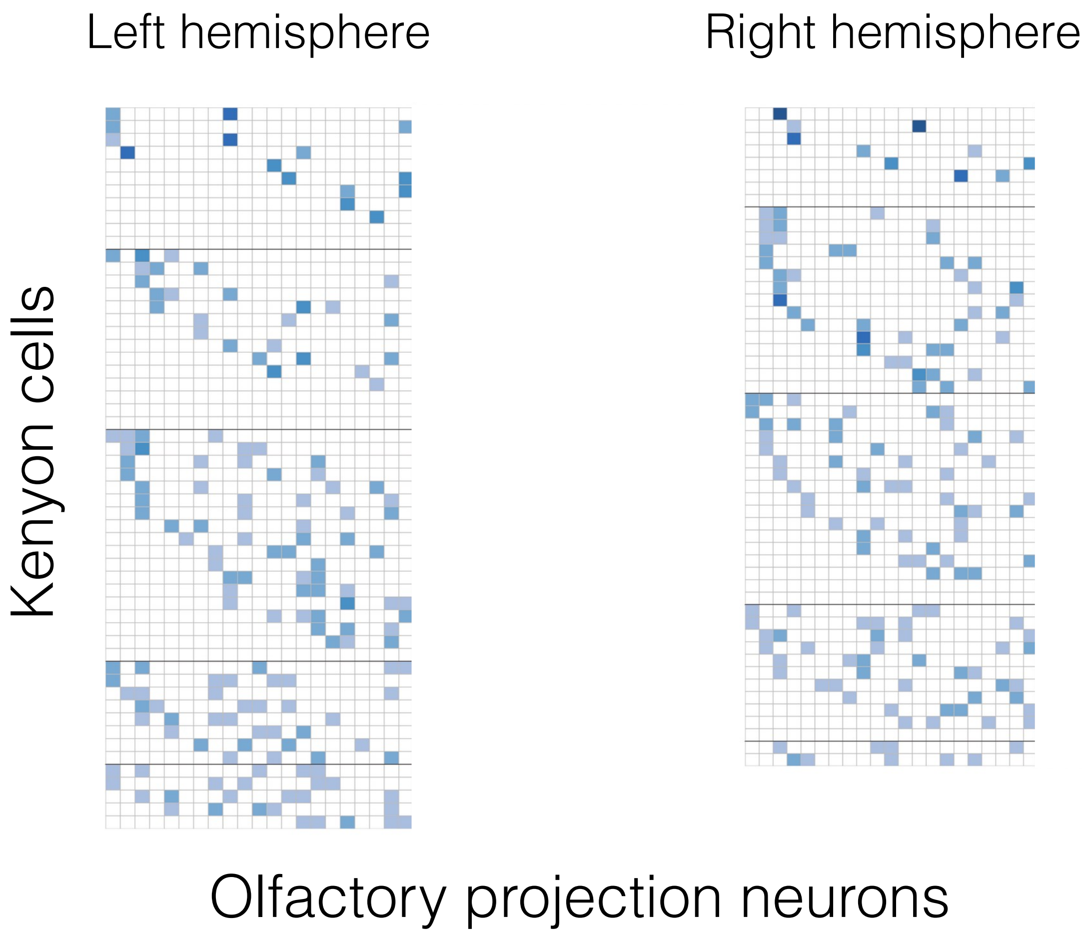
Random?

3) Null models

Cell type 1 Cell type 2



Random?



Eichler et al. 2017

3) Null models

$$A = USV^T$$

Caron et al. 2013, Eichler et al. 2017, Li et al. 2020, Zheng et al. 2022, Nguyen et al. 2023

3) Null models

Adjacency matrix (unweighted) $$A = USV^T$$

Caron et al. 2013, Eichler et al. 2017, Li et al. 2020, Zheng et al. 2022, Nguyen et al. 2023

3) Null models

Adjacency matrix (unweighted)
Degree-matched random matrices

$$A = USV^T$$

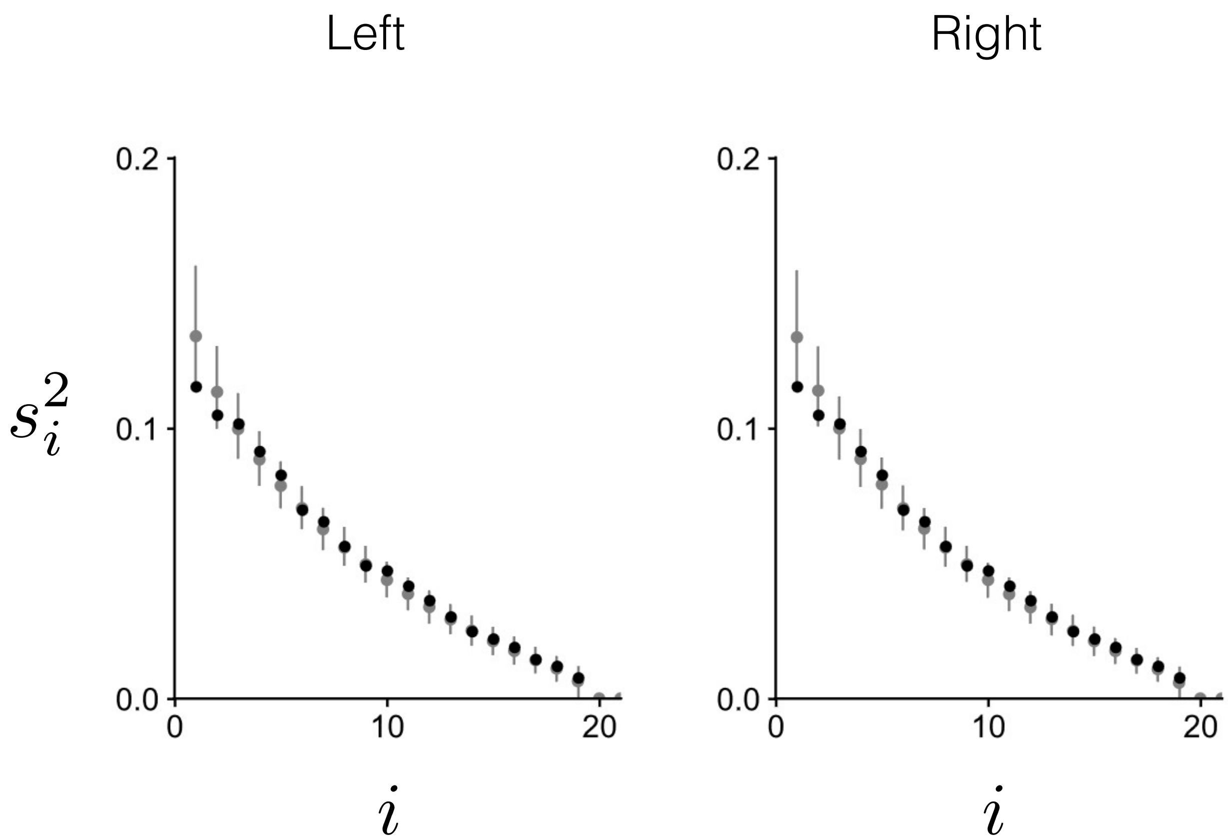
Caron et al. 2013, Eichler et al. 2017, Li et al. 2020, Zheng et al. 2022, Nguyen et al. 2023

3) Null models

Adjacency matrix (unweighted)

Degree-matched random matrices

$$A = USV^T$$



Caron et al. 2013, Eichler et al. 2017, Li et al. 2020, Zheng et al. 2022, Nguyen et al. 2023

Future directions

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Null models incorporating cell types, distance dependence, synaptic weights, neurotransmitters

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Identifying structure beyond stochastic blockmodels

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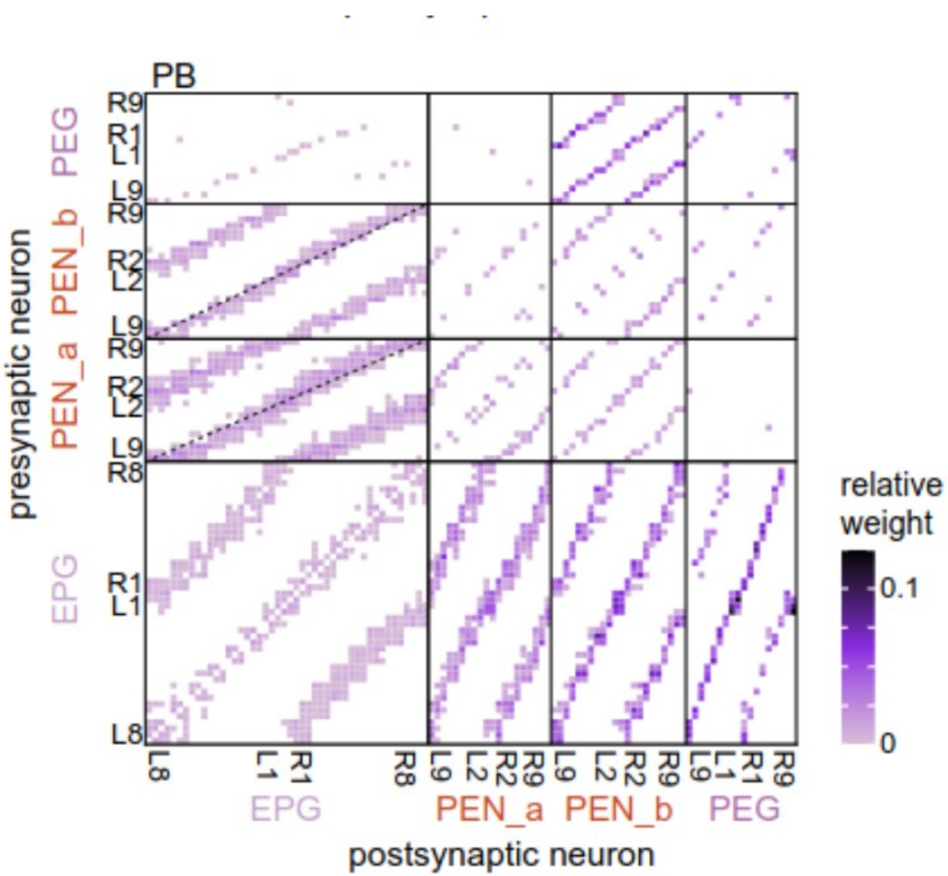
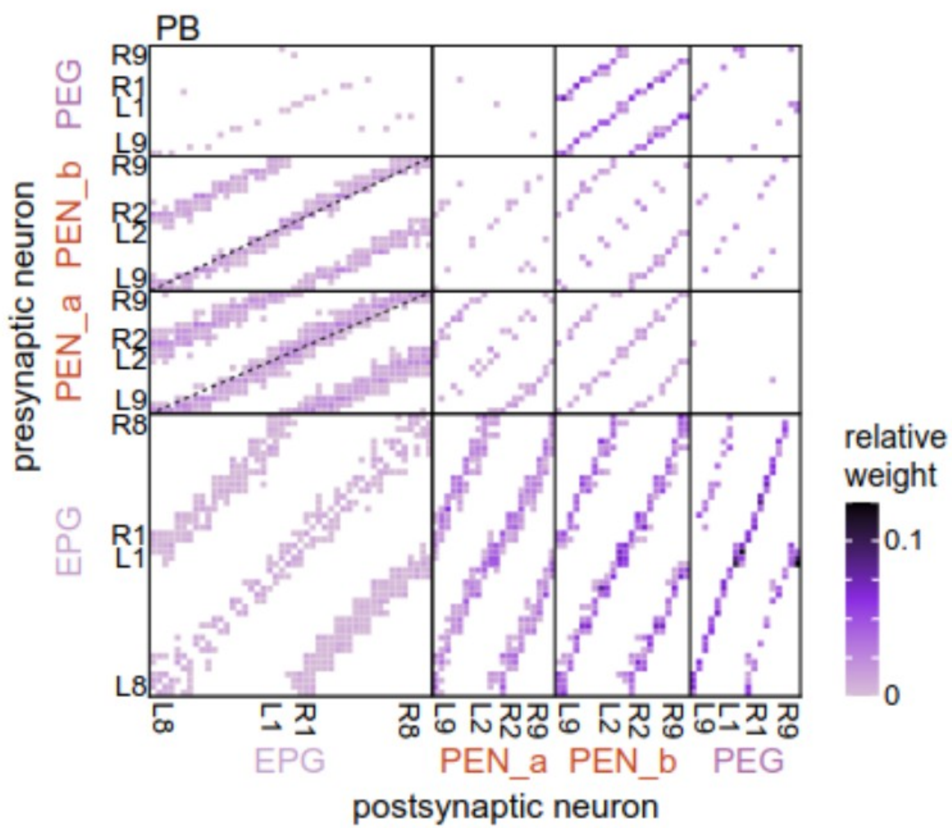


Hulse et al. 2021

Future directions

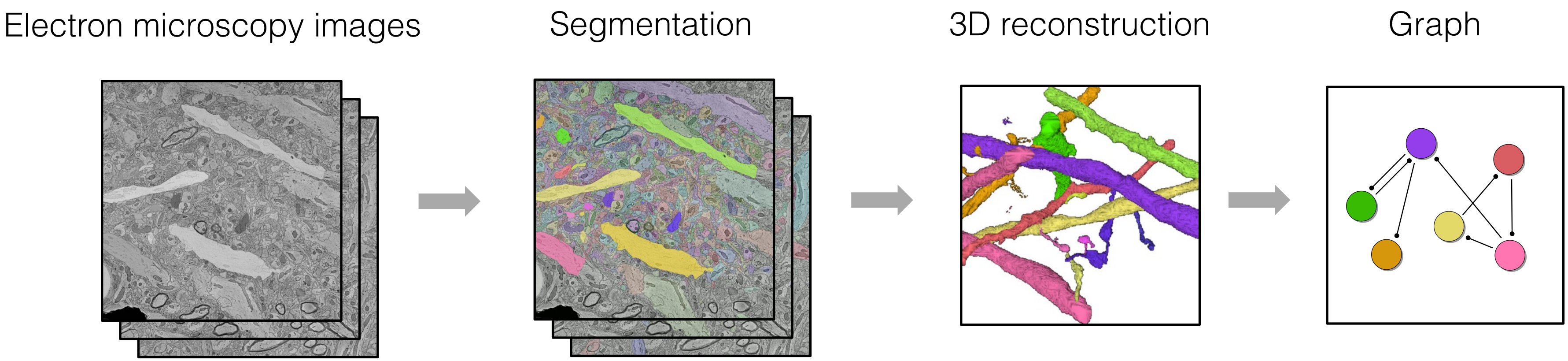
Null models incorporating cell types, distance dependence, synaptic weights, neurotransmitters

Identifying structure beyond stochastic blockmodels



Comparing connectomes (n=1, 2)

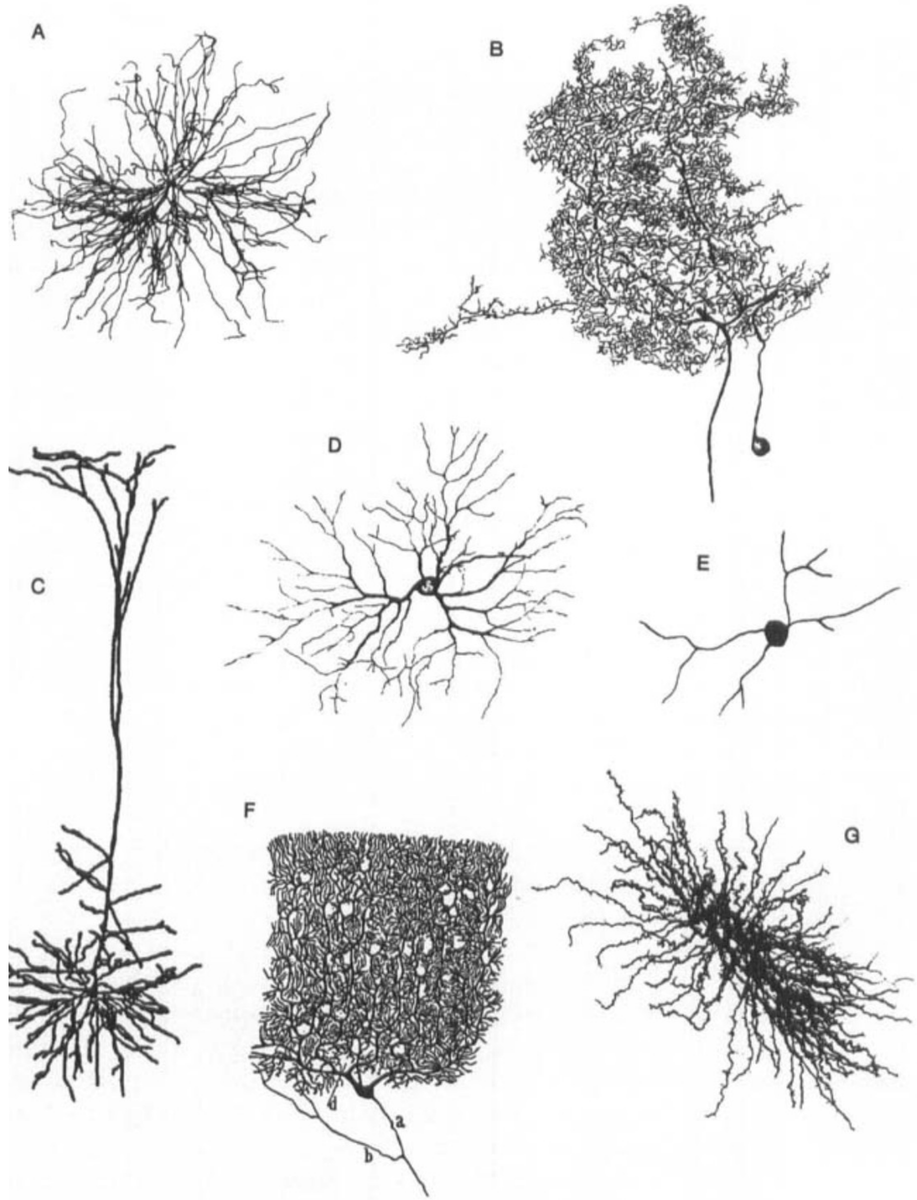
Hulse et al. 2021



Graphical analysis

1) Cell types
2) Hierarchy
3) Null models

Dynamics



Mel 1994

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

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$x_i(t)$: Activity level (e.g. voltage), $\quad i = 1 \ldots N$

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$x_i(t)$: Activity level (e.g. voltage), $i = 1 \ldots N$

b_i: Baseline activity level

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$f_i > 0$: Nonlinearity (e.g. voltage to firing rate mapping)

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$I_i(t)$: External input

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$x_i(t)$: Activity level (e.g. voltage), $i = 1 \dots N$

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W_{ij}: Interactions

$f_i > 0$: Nonlinearity (e.g. voltage to firing rate mapping)

$I_i(t)$: External input

Assumptions: First-order, 1-d dynamics per neuron, additive interactions

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

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$$W_{ij} \propto g_{ij} A_{ij}$$

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$$W_{ij} \propto g_{ij} A_{ij}$$

$g_{ij} = g$ Global scale factor

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$$W_{ij} \propto g_{ij} A_{ij}$$

$g_{ij} = g$ Global scale factor

$g_{ij} = \pm g$ Excitatory/inhibitory

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

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Global scale factor

$$g_{ij} = \pm g$$

Excitatory/inhibitory

$$g_{ij} = \pm g / \sum_j A_{ij}$$

Normalized by incoming weights

$$\tau_i \frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

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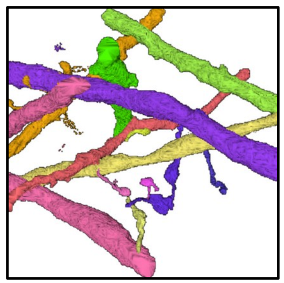
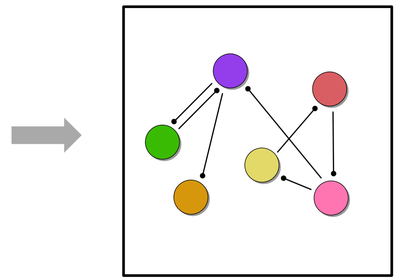
$g_{ij} = g$	Global scale factor
$g_{ij} = \pm g$	Excitatory/inhibitory
$g_{ij} = \pm g / \sum_j A_{ij}$	Normalized by incoming weights
$g_{ij} = \pm g_{(\mathrm{NT})} / \sum_j A_{ij}$	Neurotransmitter-specific gain

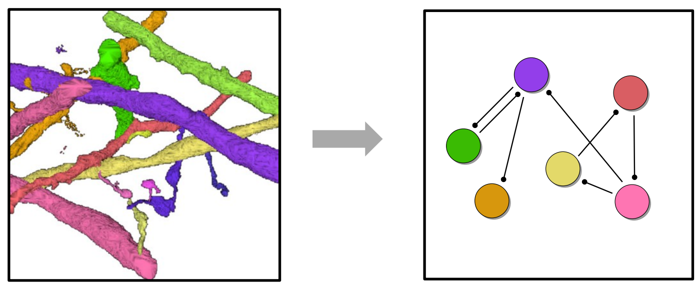
3D reconstruction



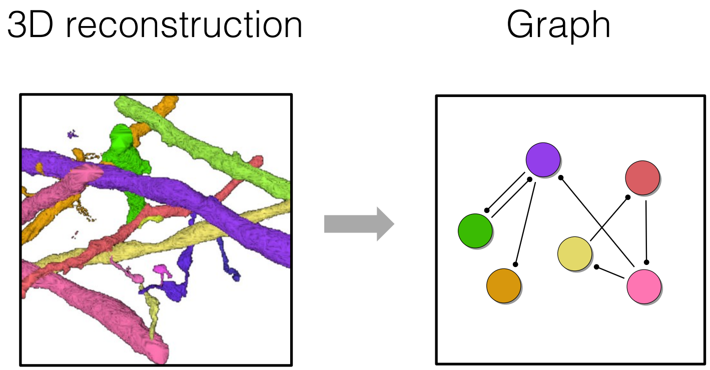
Graph



3D reconstruction Graph

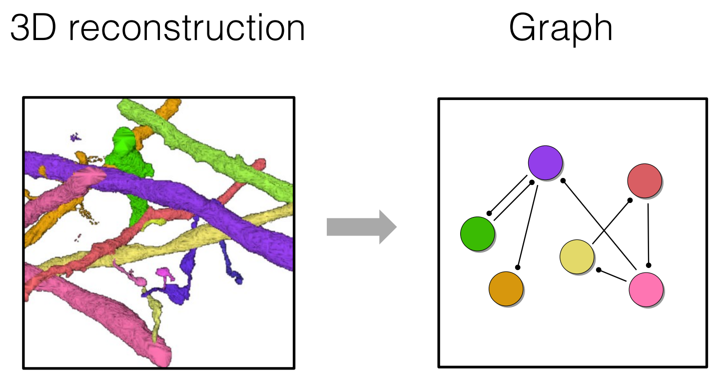


Approaches:



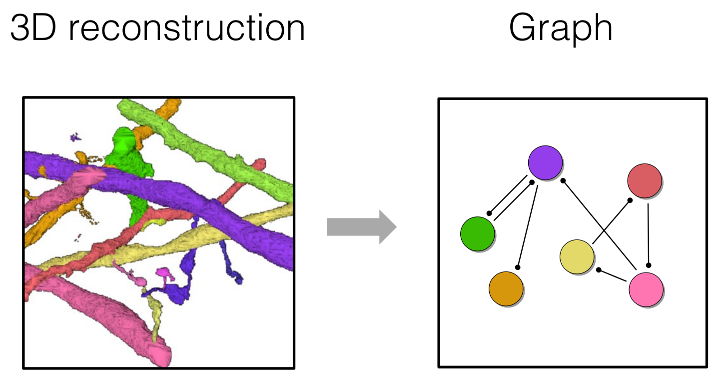
Approaches:

1) Direction simulation with hand-chosen parameters (often)



Approaches:

1) Direction simulation with hand-chosen parameters (often)
2) Fit to perform a task and/or reproduce neural data (recorded $x_i(t)$)

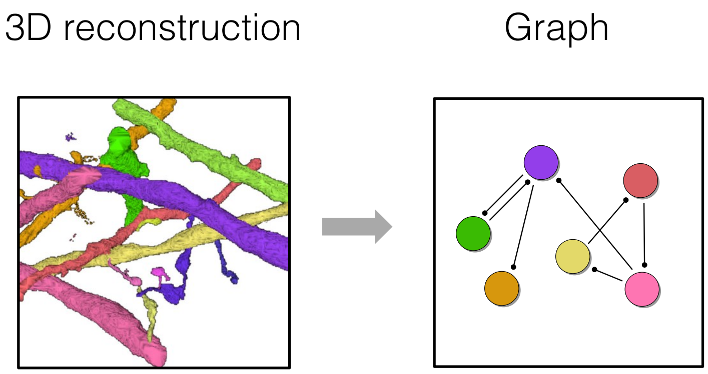


Approaches:

1) Direction simulation with hand-chosen parameters (often)

2) Fit to perform a task and/or reproduce neural data (recorded $x_i(t)$)

   a) W fixed, other parameters trained (Turaga)



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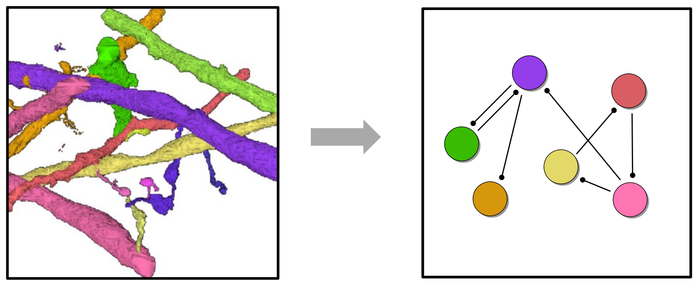
3D reconstruction Graph



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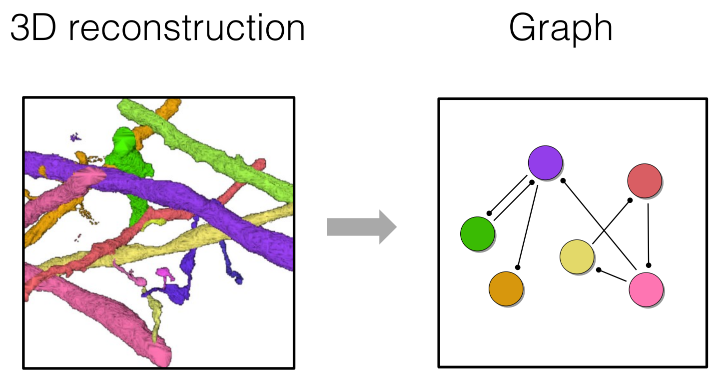
3) Analysis of fixed points/attractors (Curto)



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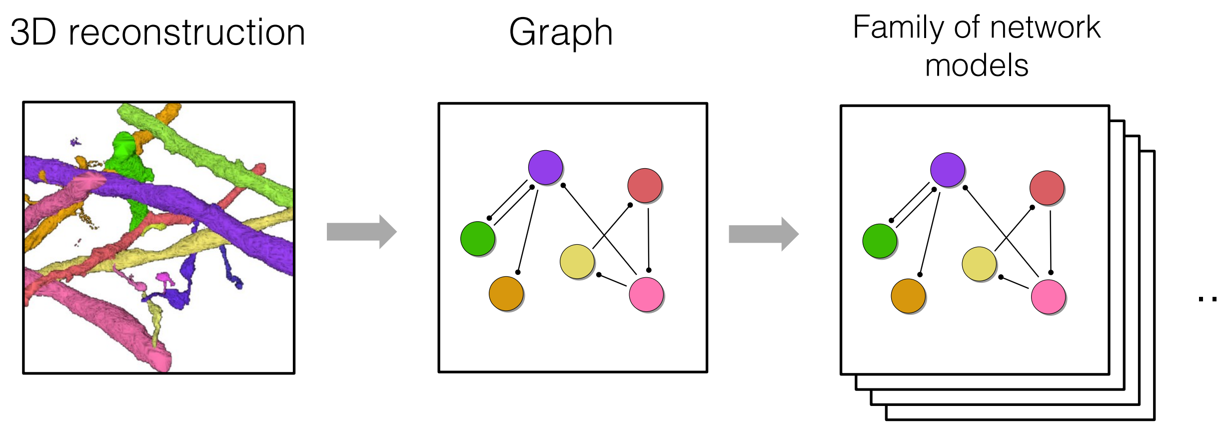
4) Mean-field approaches/low-rank approximations (Solla)



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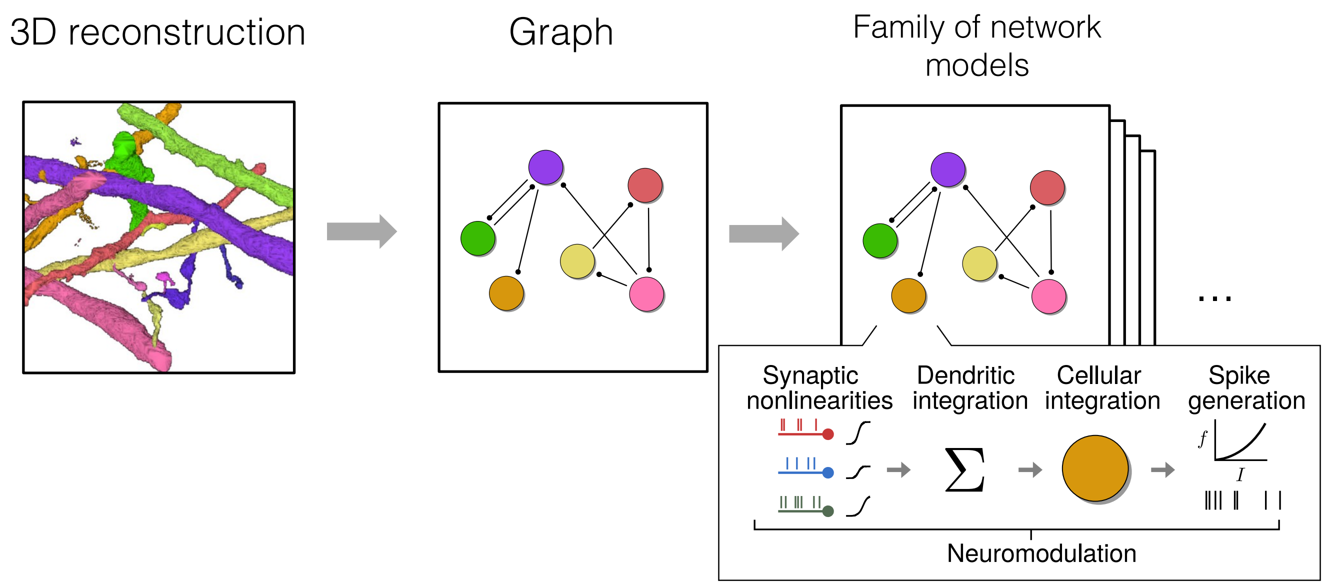

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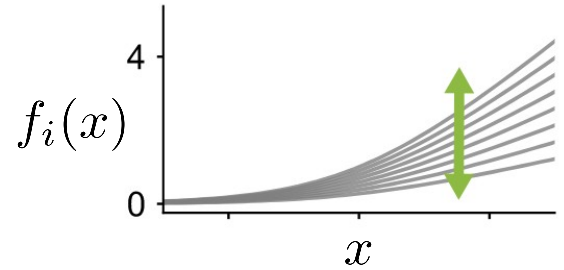
$$\frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$$f_i(x) = \mathrm{Softplus}(g_i x)$$



Manuel Beiran

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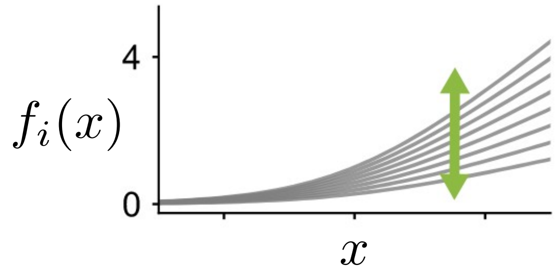

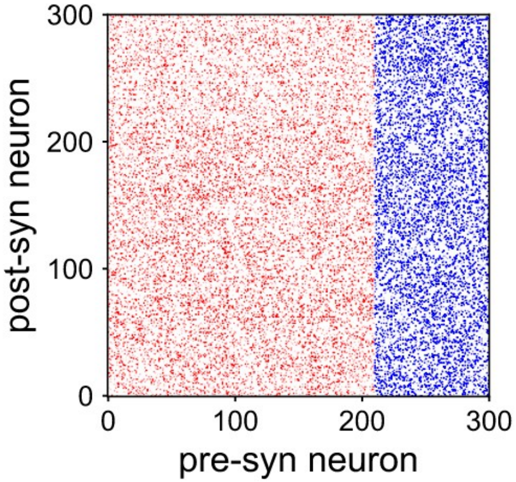

Manuel Beiran

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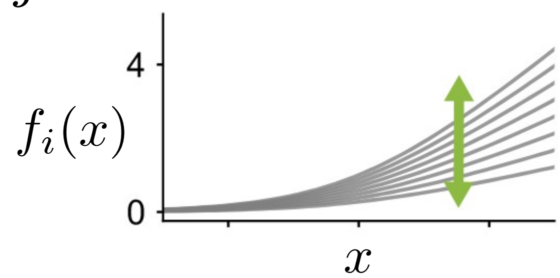

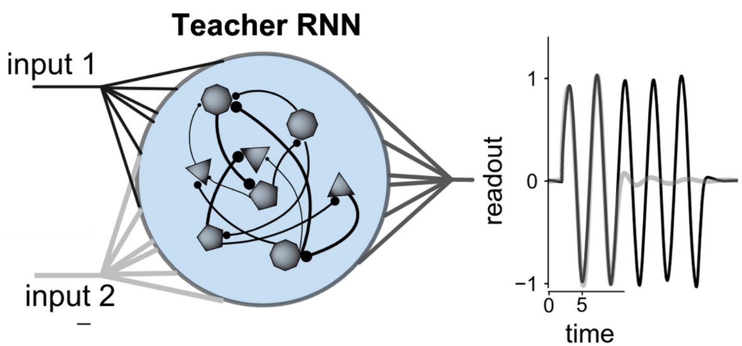

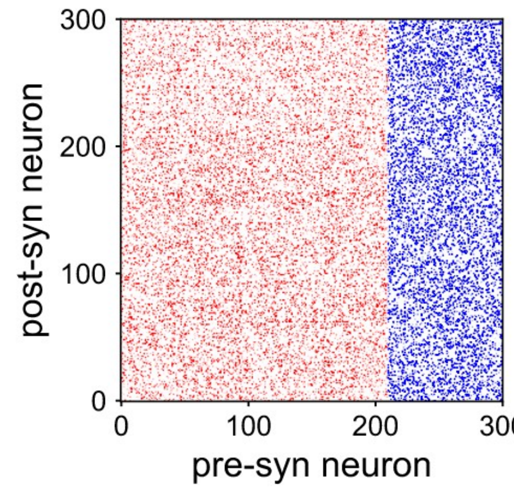

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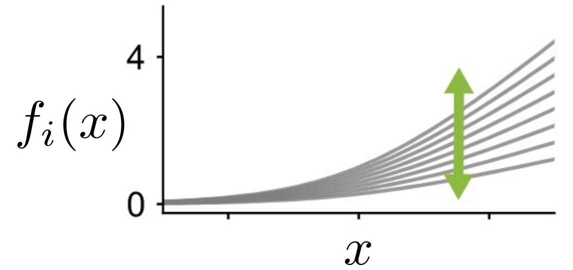

“Student” networks: Same W, other parameters initialized randomly, trained through gradient descent to match teacher readout.

$$\frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

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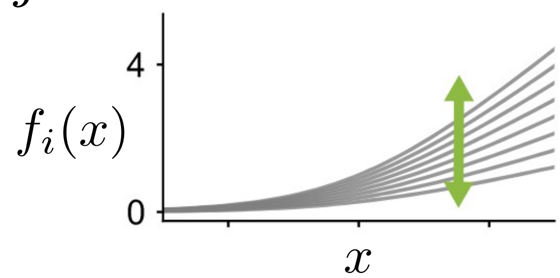

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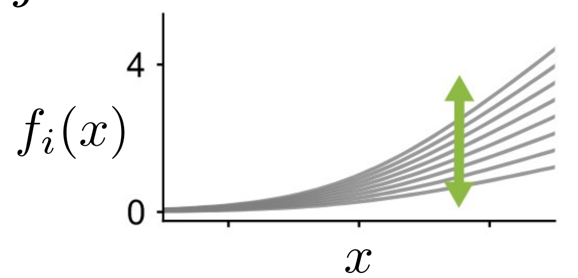
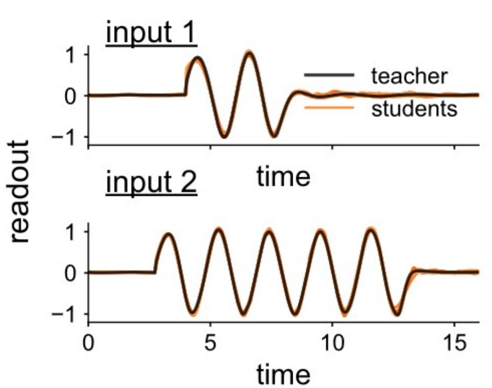


"Student" networks: Same W, other parameters initialized randomly, trained through gradient descent to match teacher readout.



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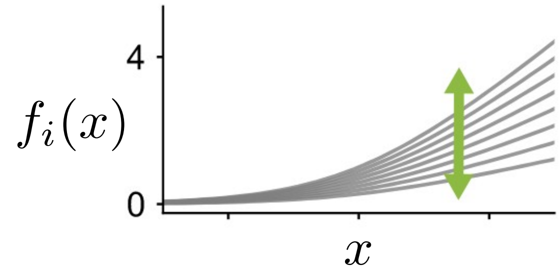
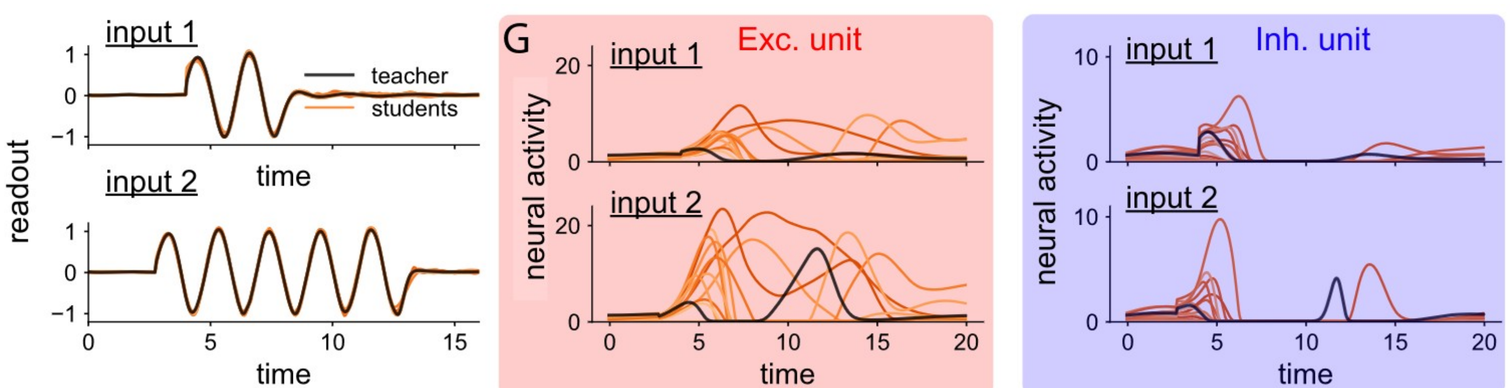
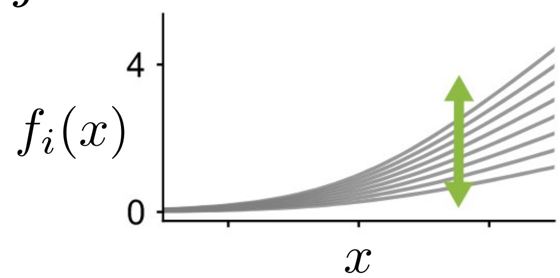


“Student” networks: Same W, other parameters initialized randomly, trained through gradient descent to match teacher readout.



$$\frac{dx_i(t)}{dt} = -x_i(t) + \boxed{b_i} + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$$f_i(x) = \mathrm{Softplus}(\boxed{g_i} x)$$



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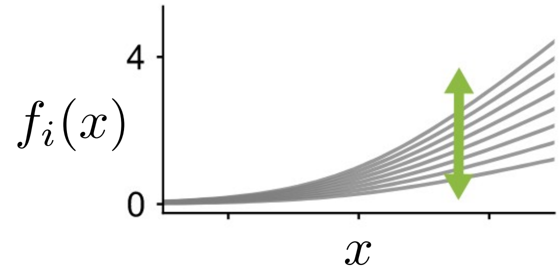
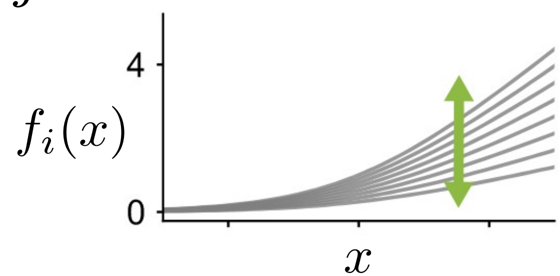


“Student” networks: Same W, other parameters initialized randomly, trained through gradient descent to match subset of activity in teacher.

$$\frac{dx_i(t)}{dt} = -x_i(t) + b_i + \sum_j W_{ij} f_j(x_j(t)) + I_i(t)$$

$$f_i(x) = \text{Softplus}(g_i x)$$



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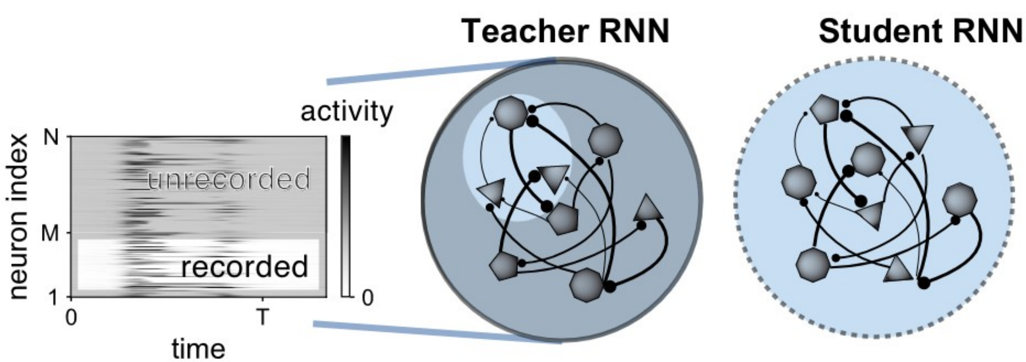

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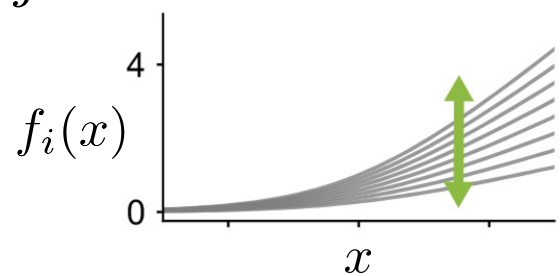
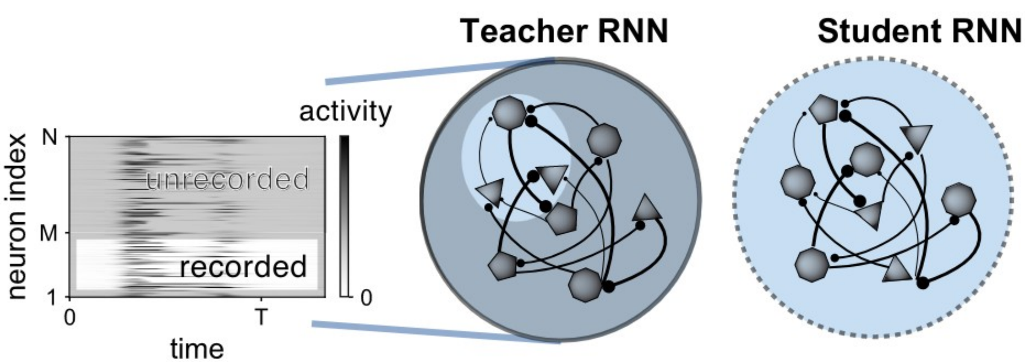
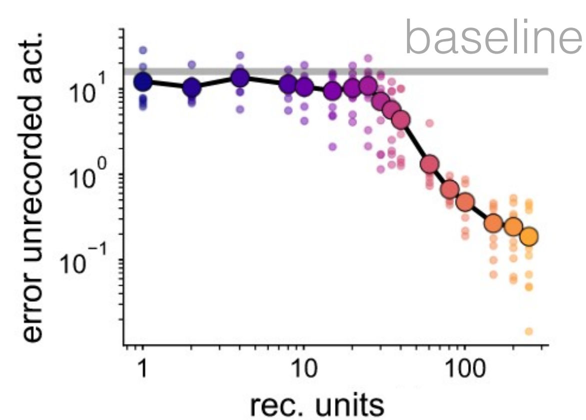


“Student” networks: Same W, other parameters initialized randomly, trained through gradient descent to match subset of activity in teacher.





What are the right model classes?

What are the right benchmarks?

When can we be confident our models are sufficiently constrained?