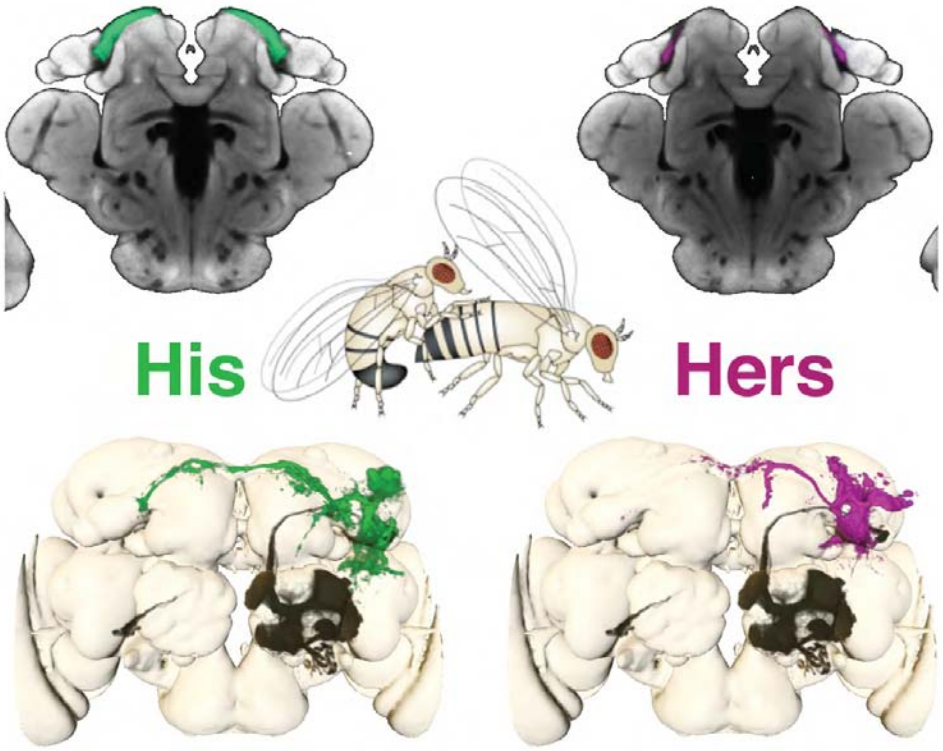
Mapping Neural Networks in the Fly

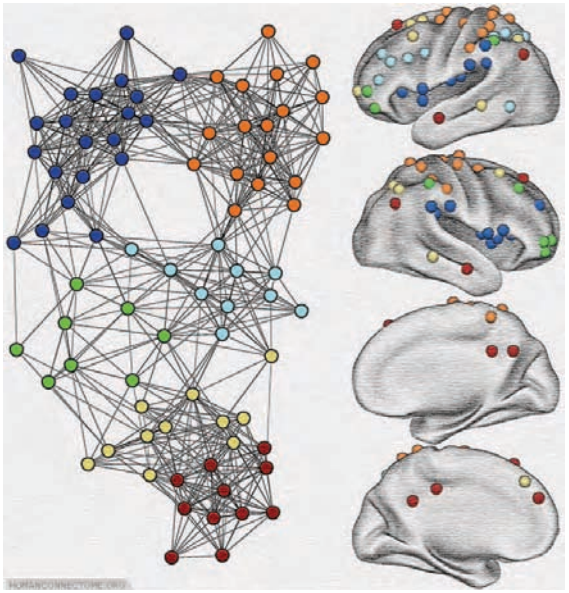


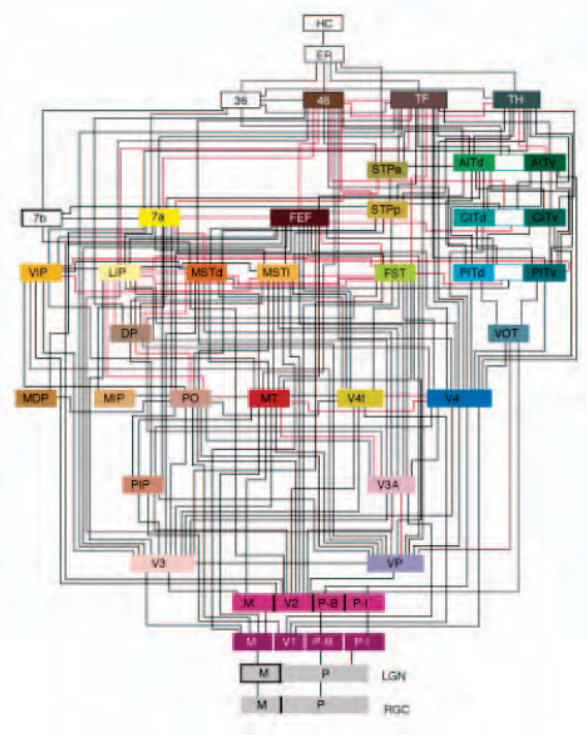
Greg Jefferis, MRC Laboratory of Molecular Biology
Cambridge Networks Day 18th May 2012

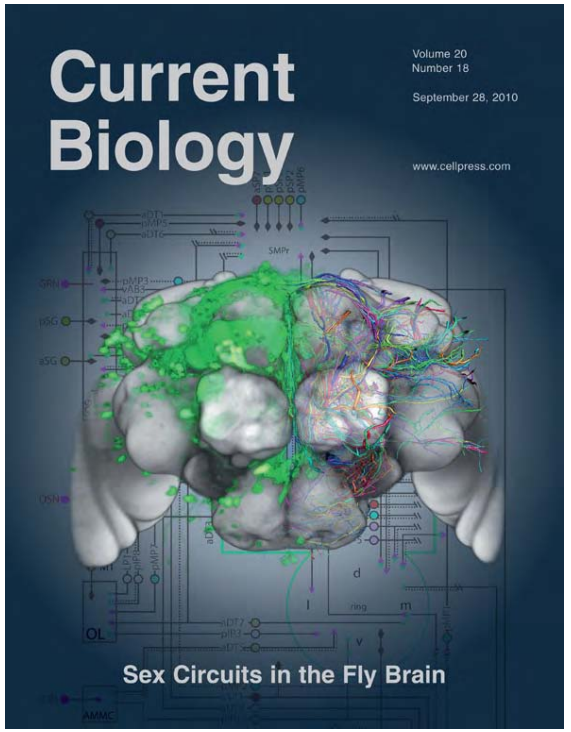
Menu

- Brains
- Neurons
- Fruit fly behaviour
- Neural Networks in the fly
- Sex Differences in Networks and
- … how these can change behaviour
- Current Network Analysis Problems in Field

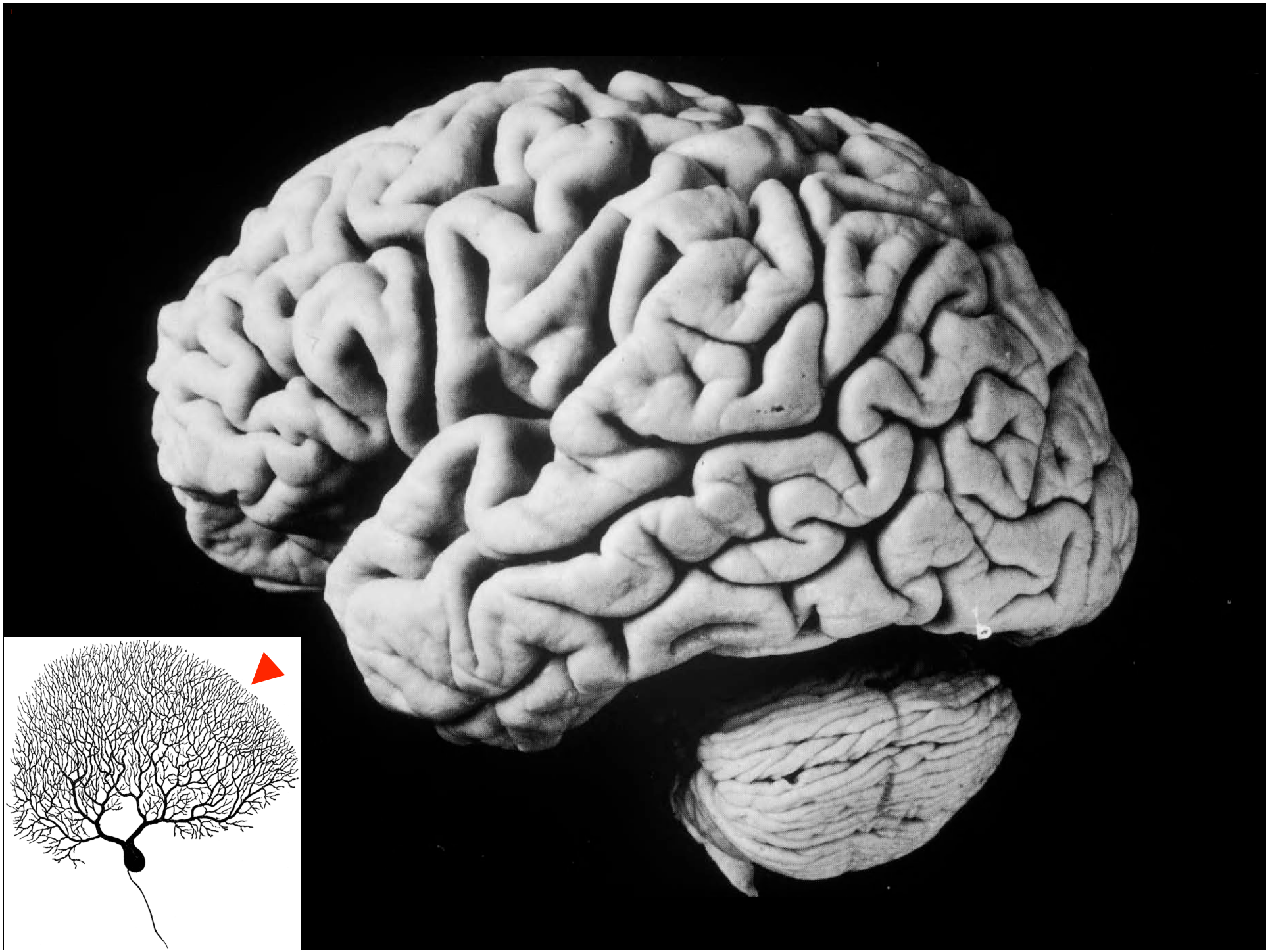
Networks In Neuroscience

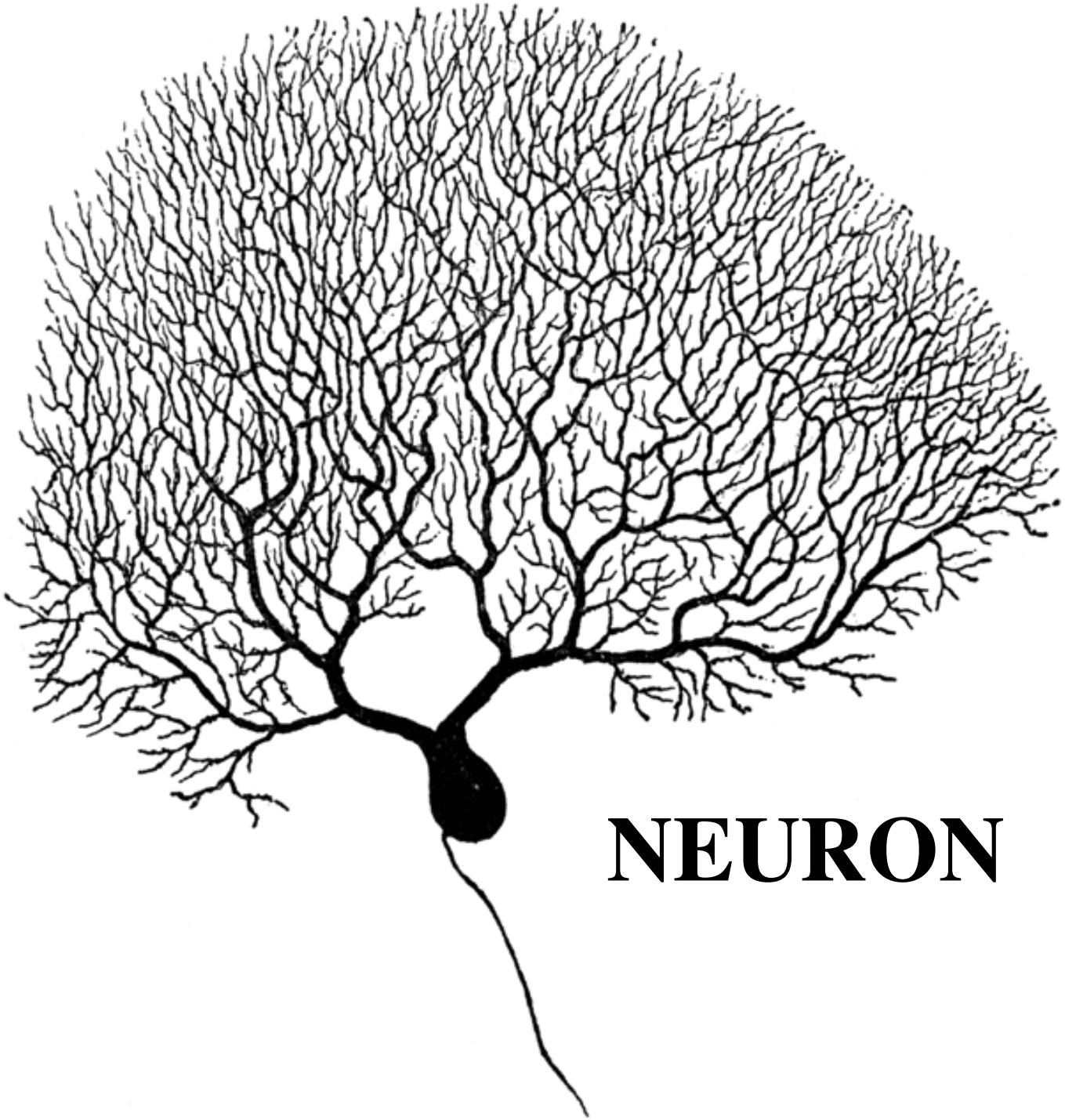




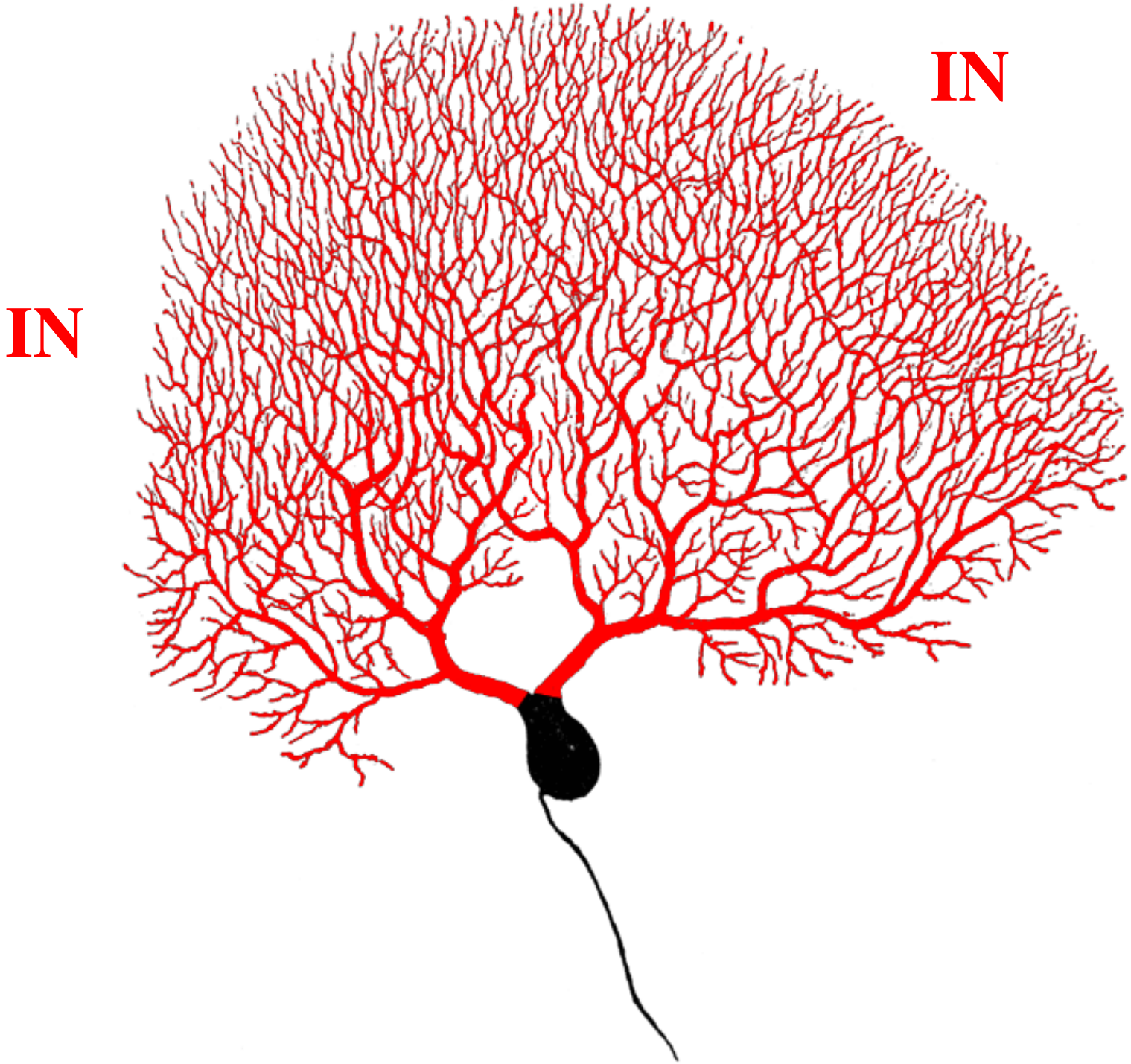


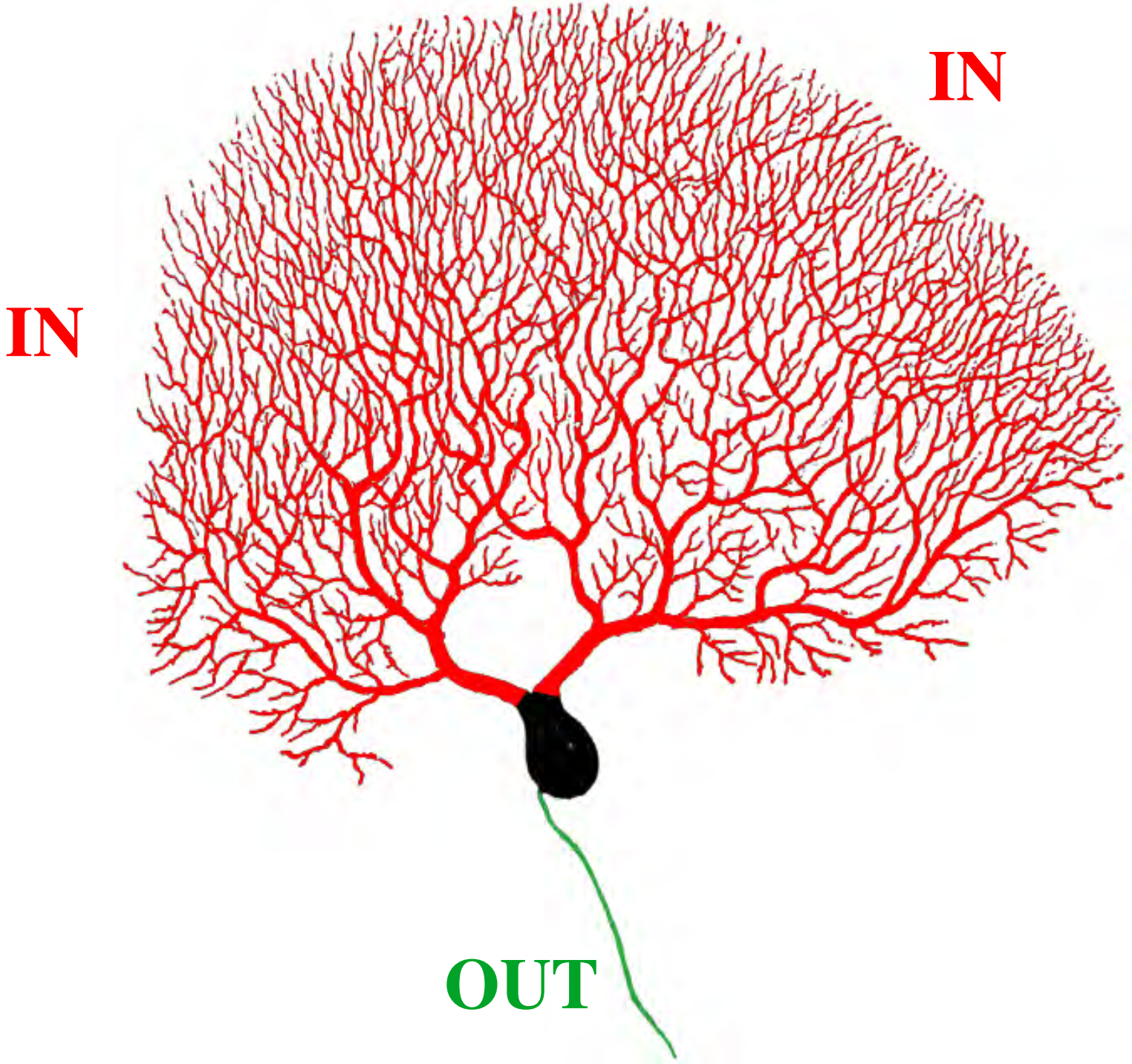
Networks of connected brain modules (or individual cells) embedded in 3D space

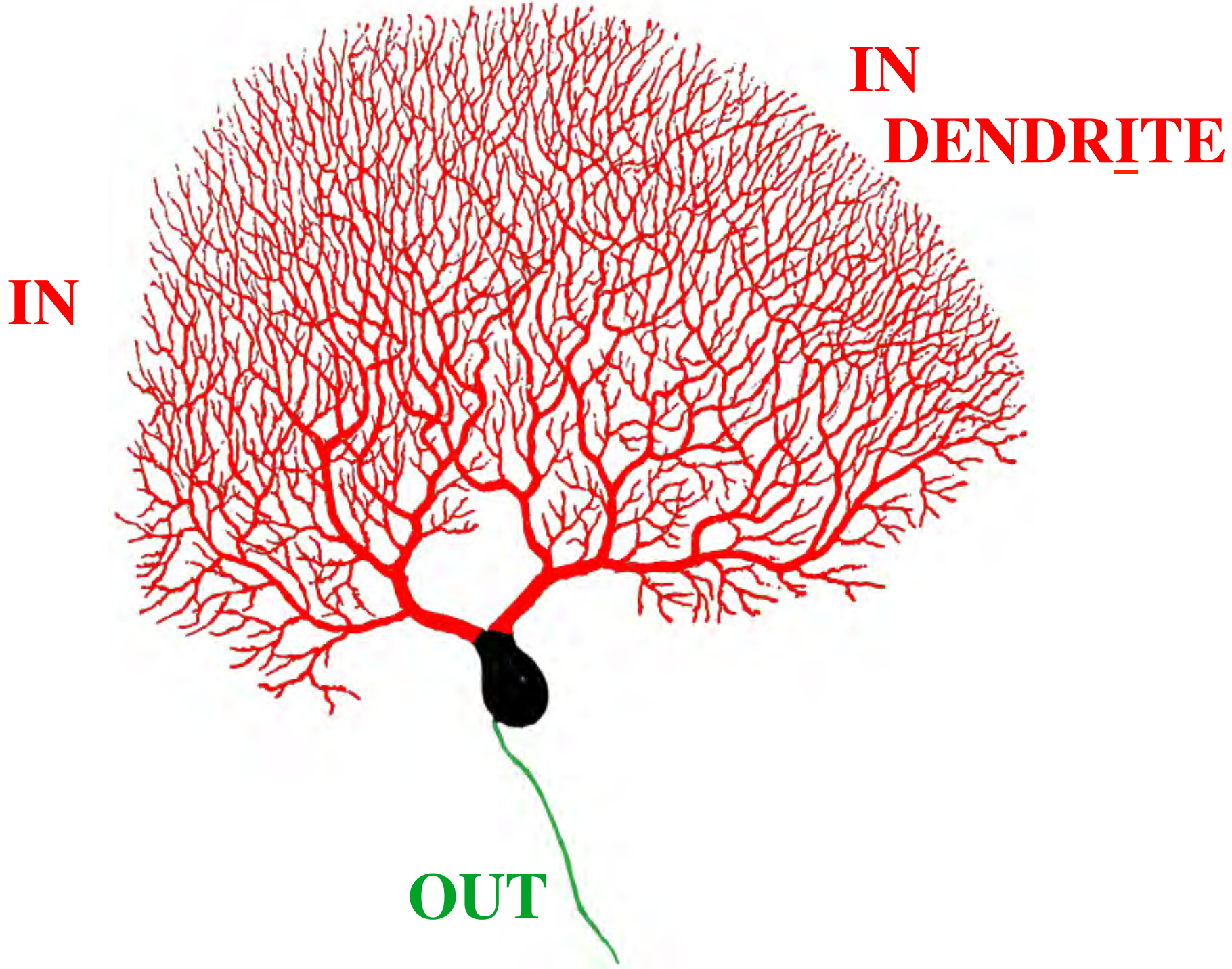


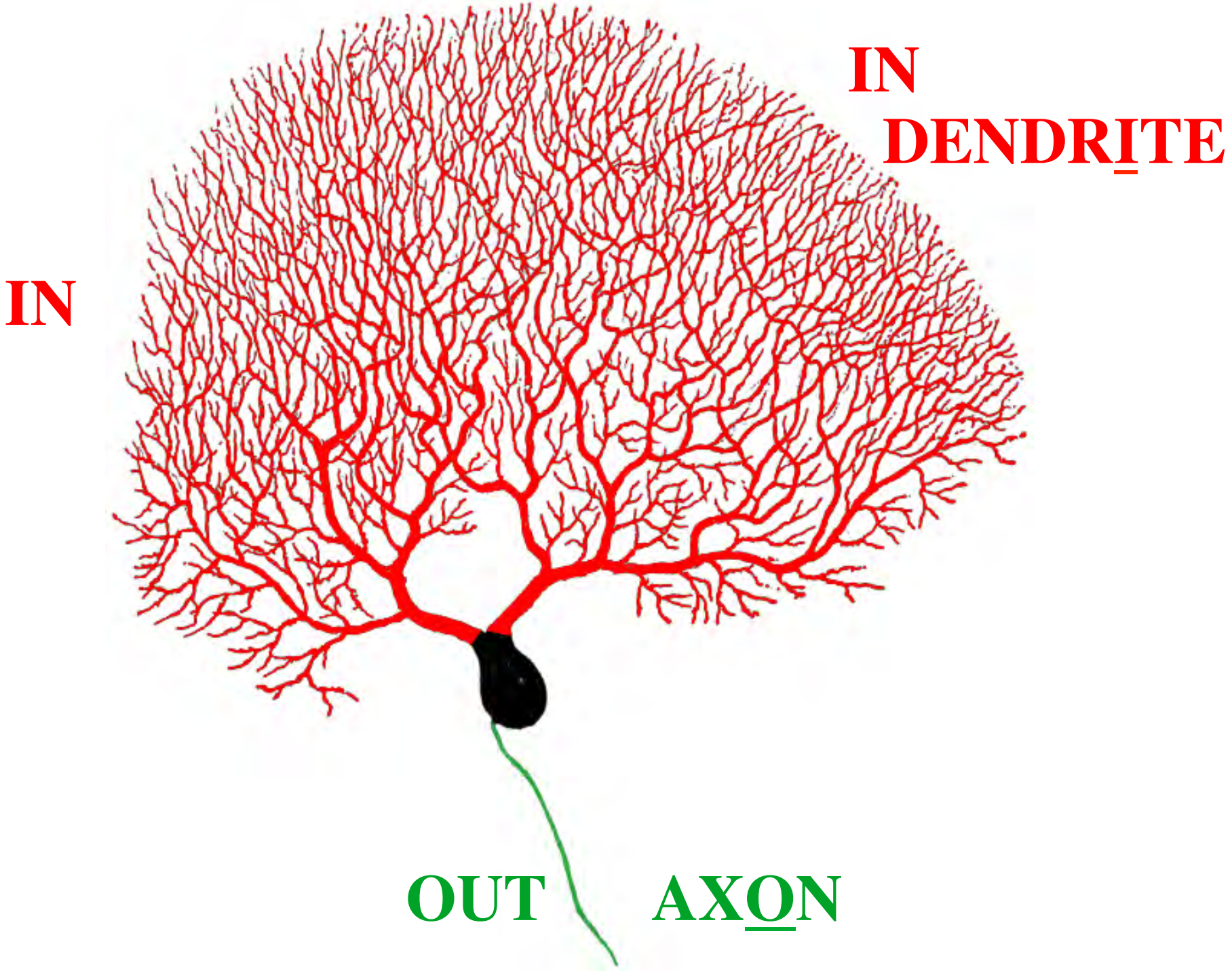


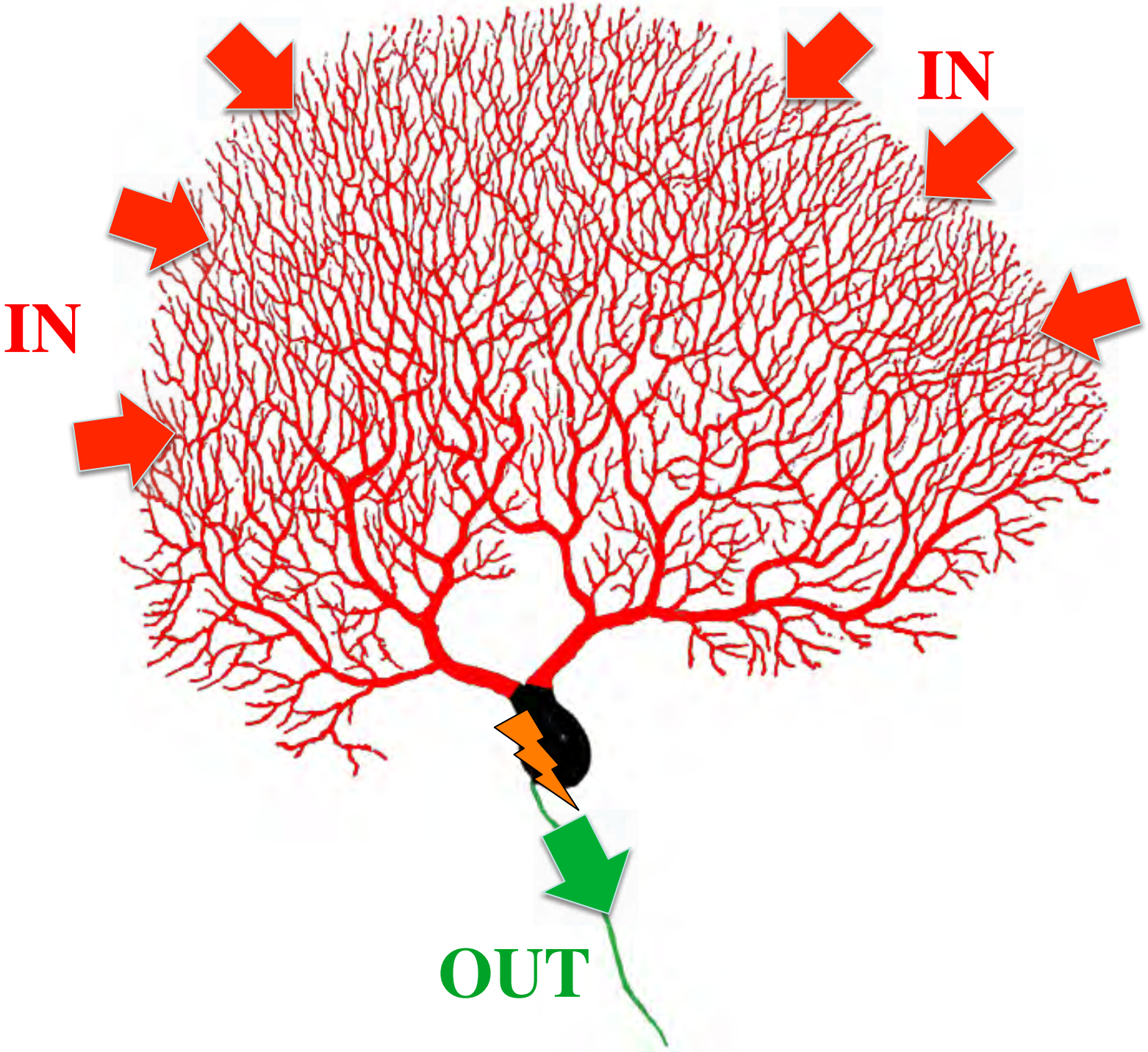
NEURON


IN
IN


IN
IN
OUT


IN
IN
DENDRITE
OUT

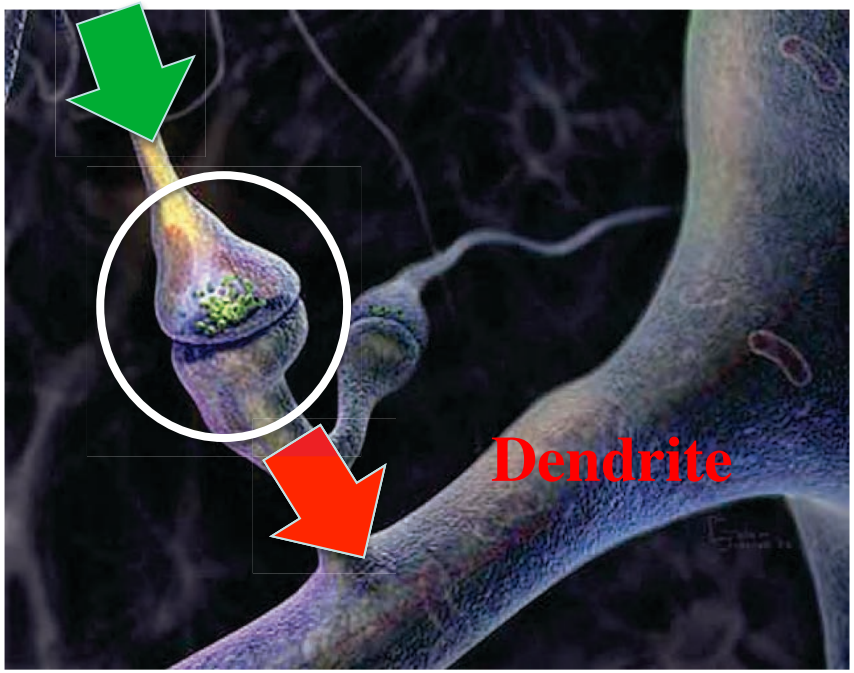

IN
IN
DENDRITE
OUT
AXON

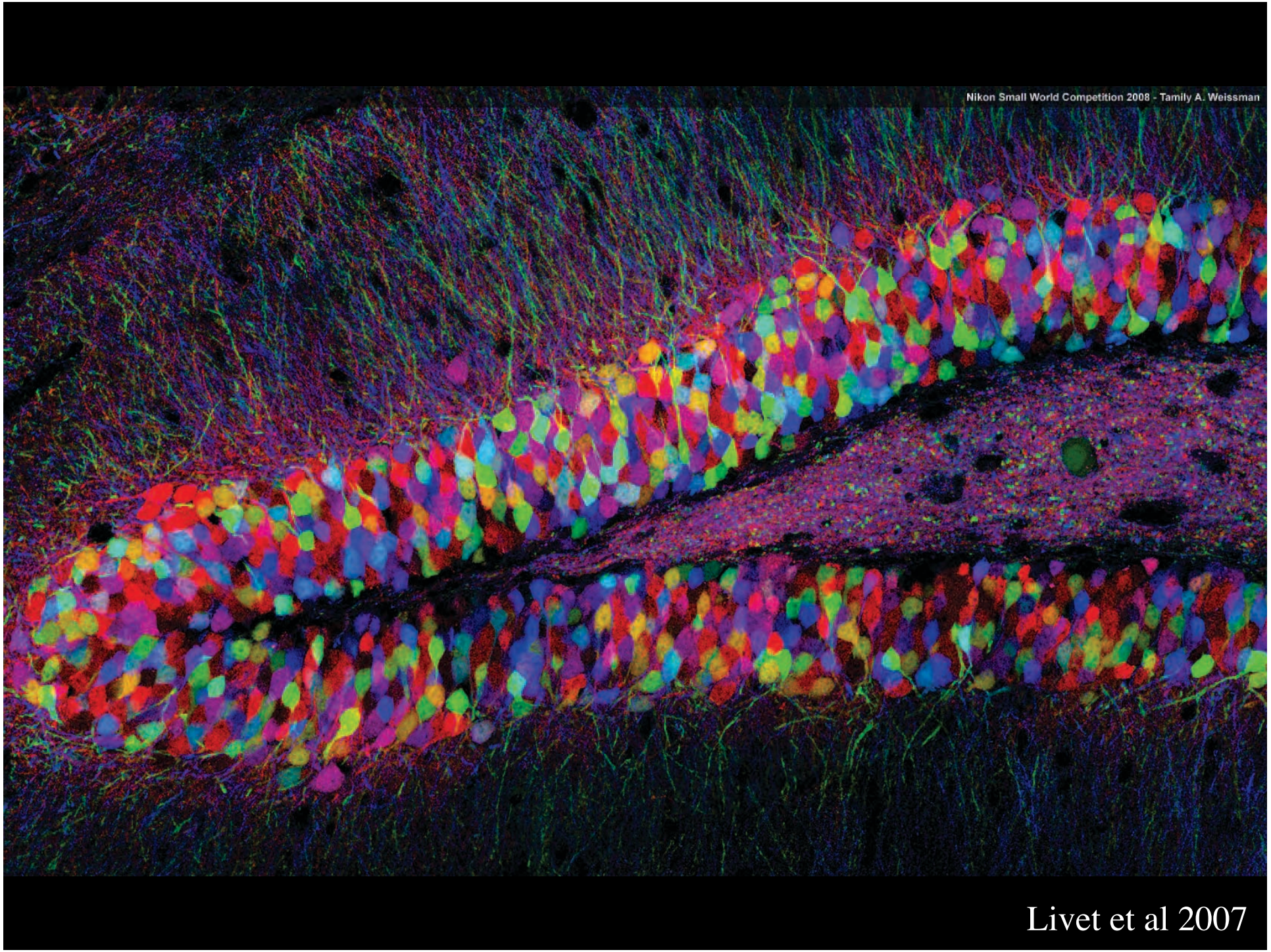

IN
IN
OUT

Synapse

where one neuron plugs in to another

Axon





Livet et al 2007

Key Questions

- How are all these neurons connected?
- How does this let them work together to solve complex problems?
- **Anatomical** and **Functional** Neural Networks

Fruit fly (*Drosophila*)

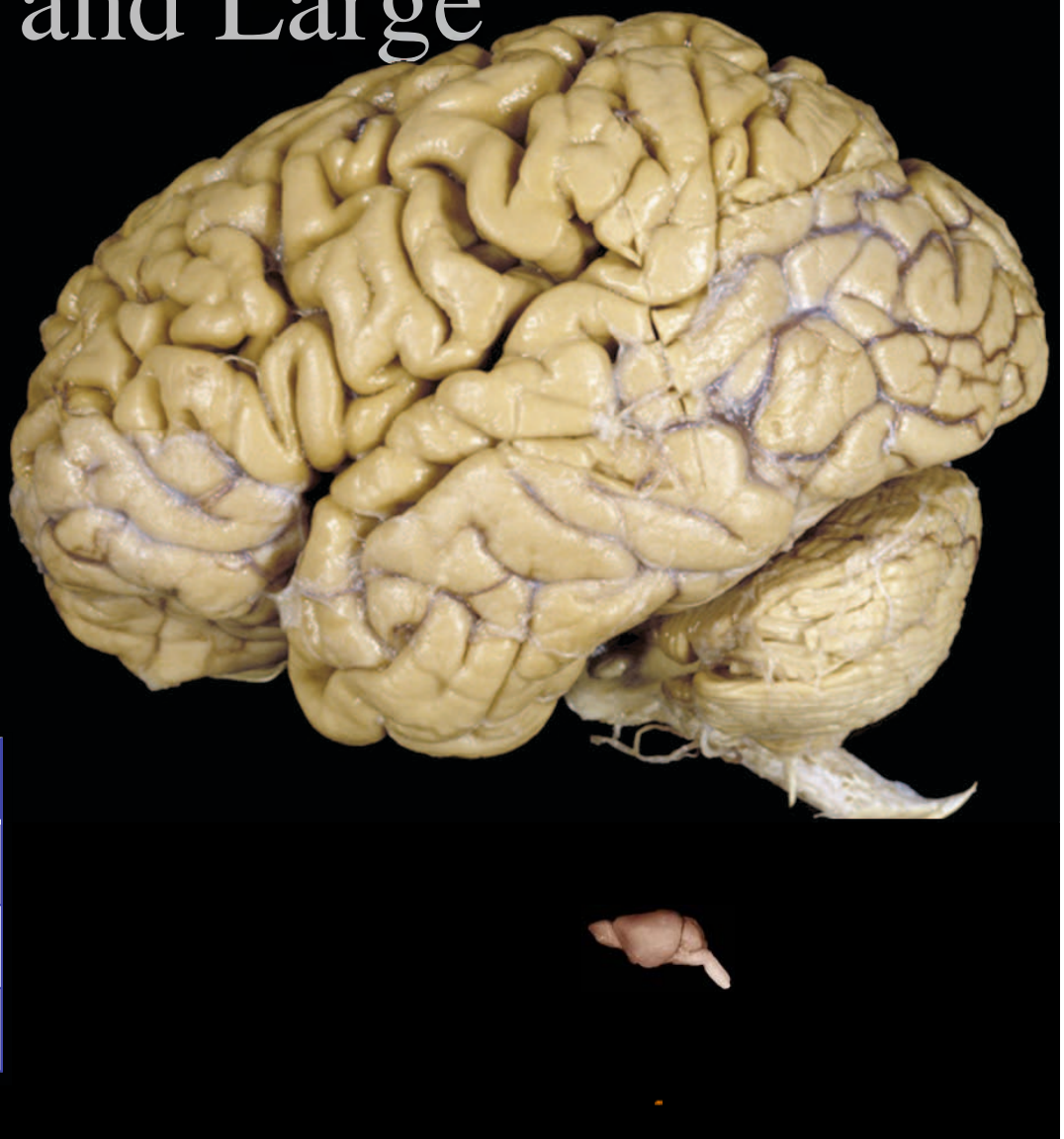
Why study the fly brain?

- Simple
- Powerful experimental tools

- Built with most of the same genes as our brain

- Surprisingly complex behaviour

Little and Large



Species	Neurons
Human	100 Billion
Mouse	100 Million
Fly	100 Thousand

Why study the fly brain?

- Simple
- Powerful experimental tools

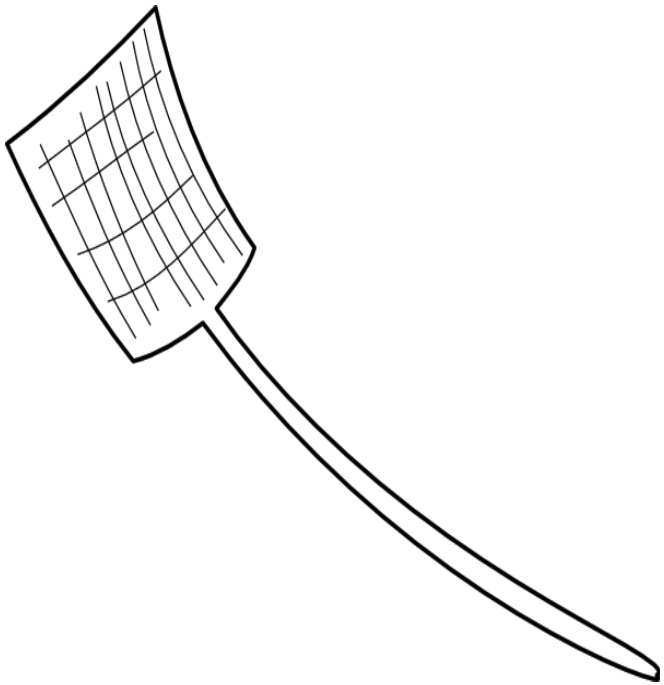
- Built with most of the same genes as our brain

- Surprisingly complex behaviour

Mmm
Feeding
Flying

Planning an Escape

Slowed down 50x



Watch how she moves her middle legs
to jump away from approaching fly swat!

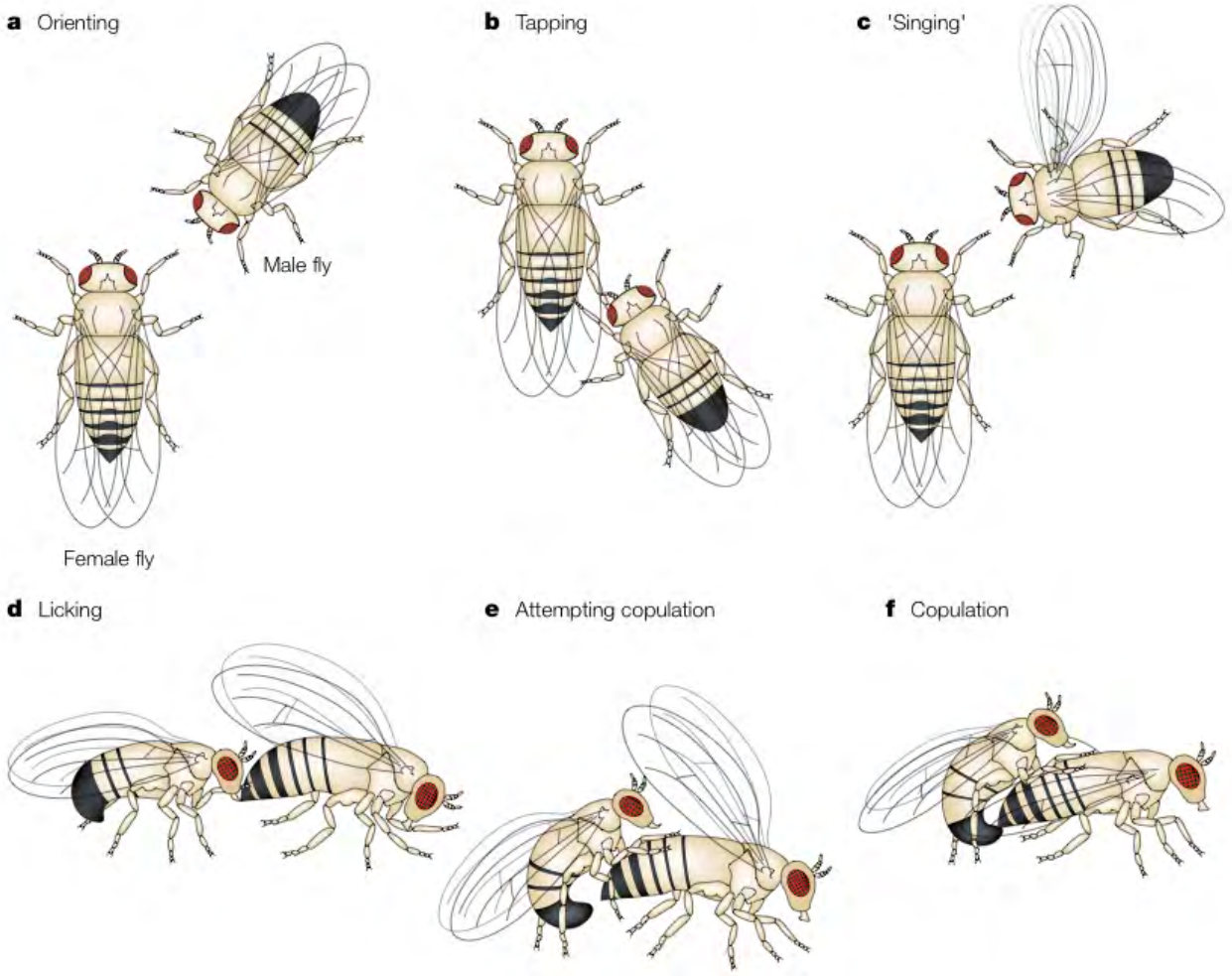
Card and Dickinson, 2008

Fighting

Rare unless food and females are nearby

Hoyer et al (2008)

… Mating



Sokolowski (2001)

Why do males and females behave differently?

fruitless mutant males

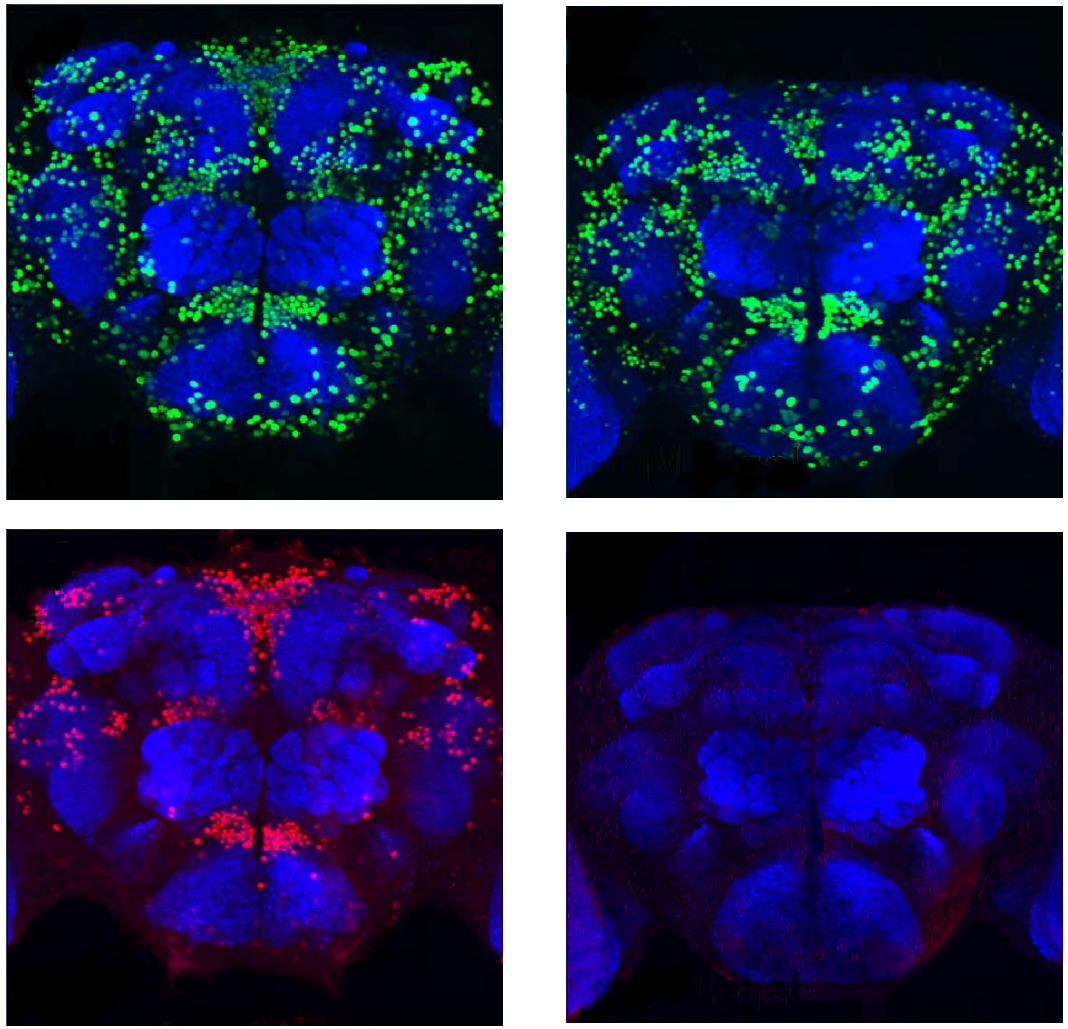
Demir and Dickson (2005)

Male

Female

Gene Expression

Protein

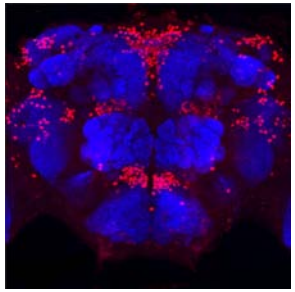


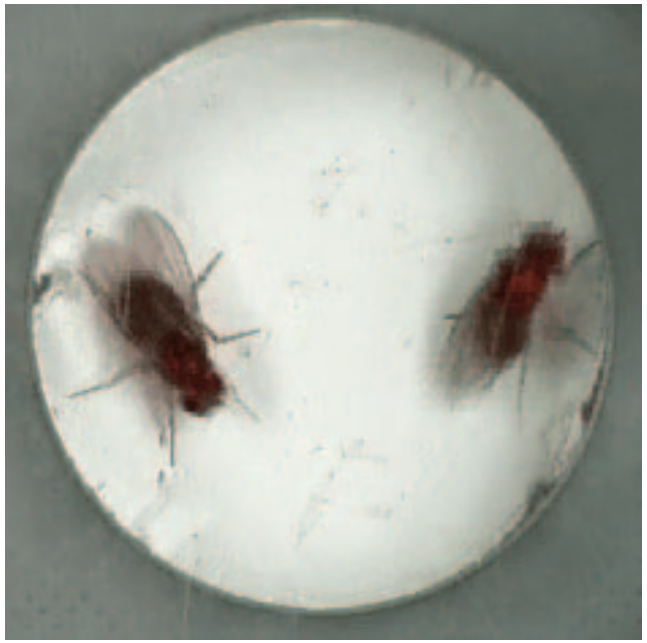
0.3 mm

Stockinger et al. (2005)

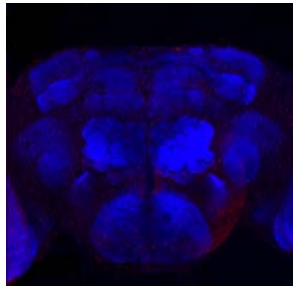
Fruitless is sufficient for early steps of male courtship

Female engineered to express Fru^M protein





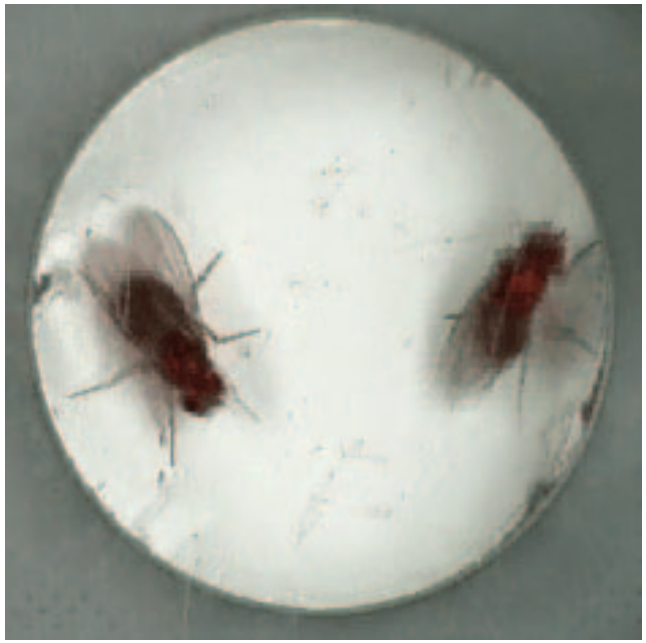
Female



Demir and Dickson (2005)

Fruitless is sufficient for early steps of male courtship

Shemale



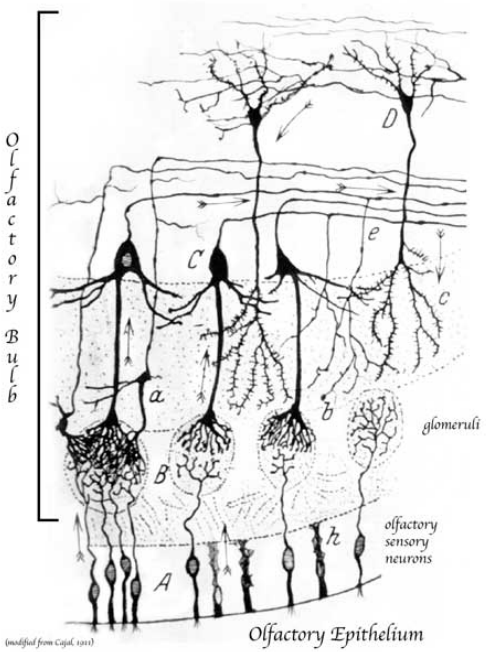
Female

Demir and Dickson (2005)

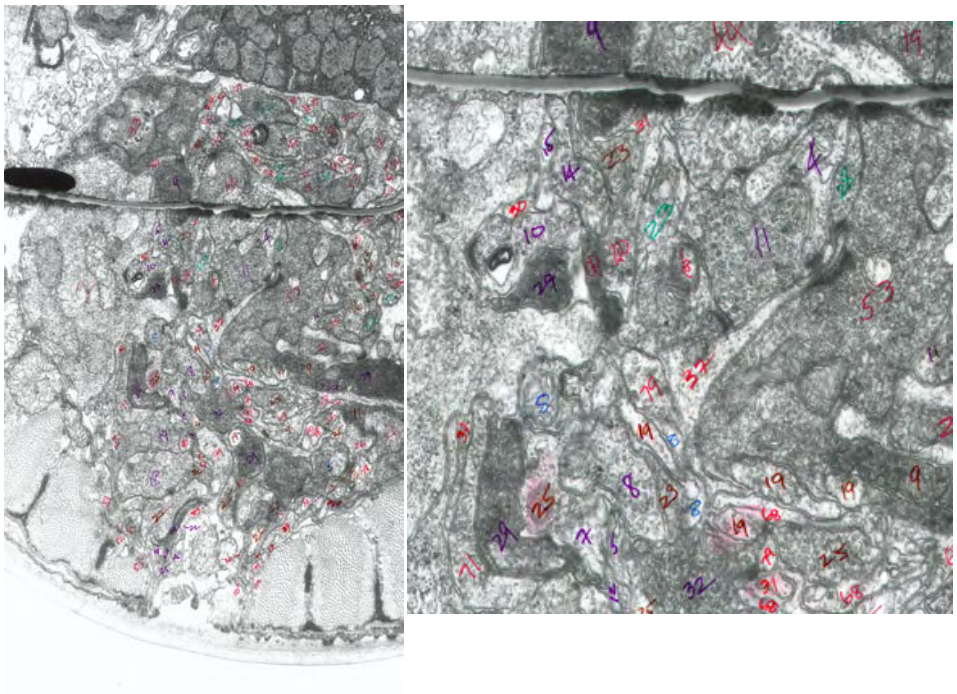
Fruitless is expressed in 2000/100,000 male neurons

Determining a wiring diagram

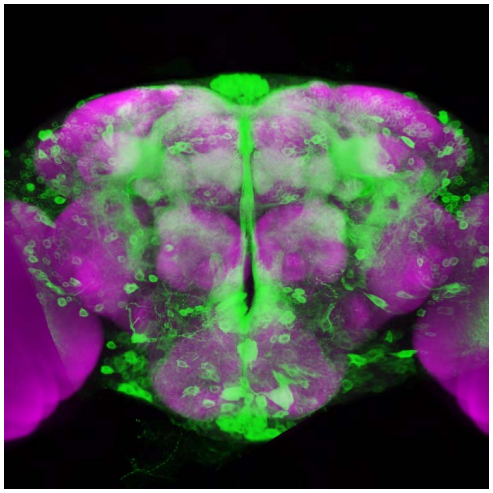
- Label a small number of neurons in many brains



- Label many neurons in one brain (or a few brains)

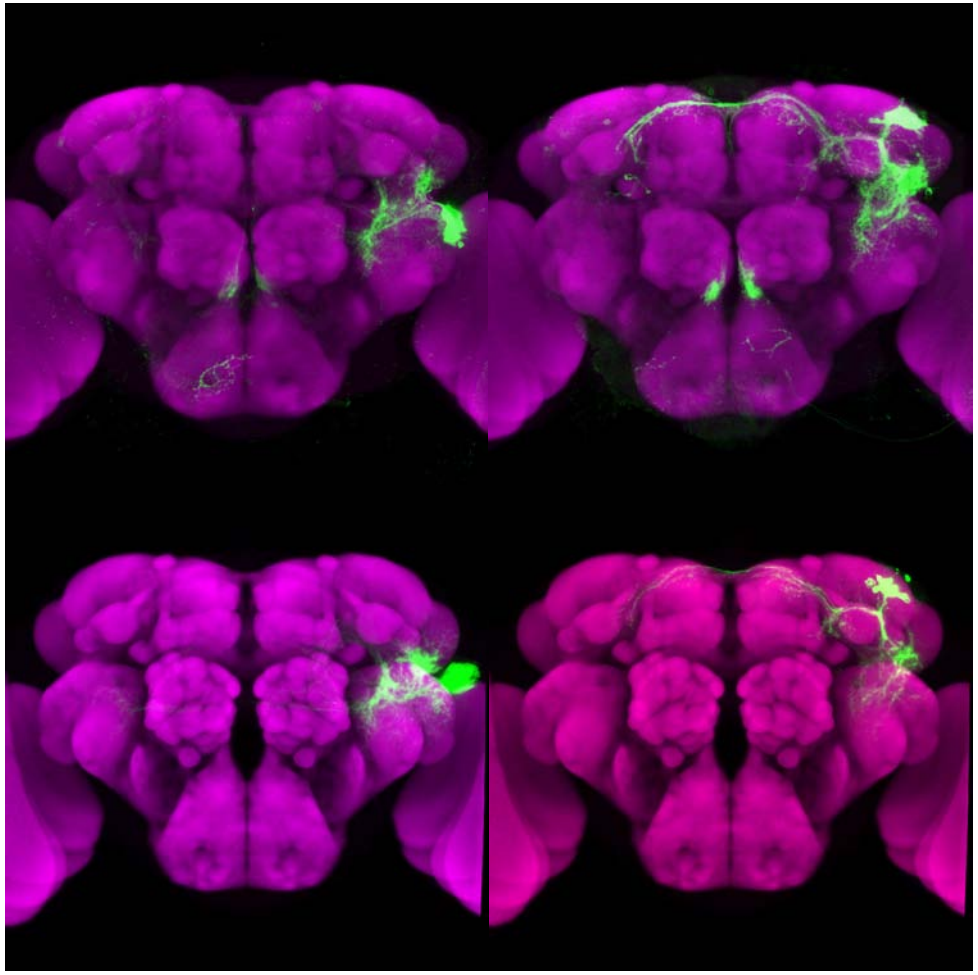


Separate fruitless neurons into 100 developmental lineages



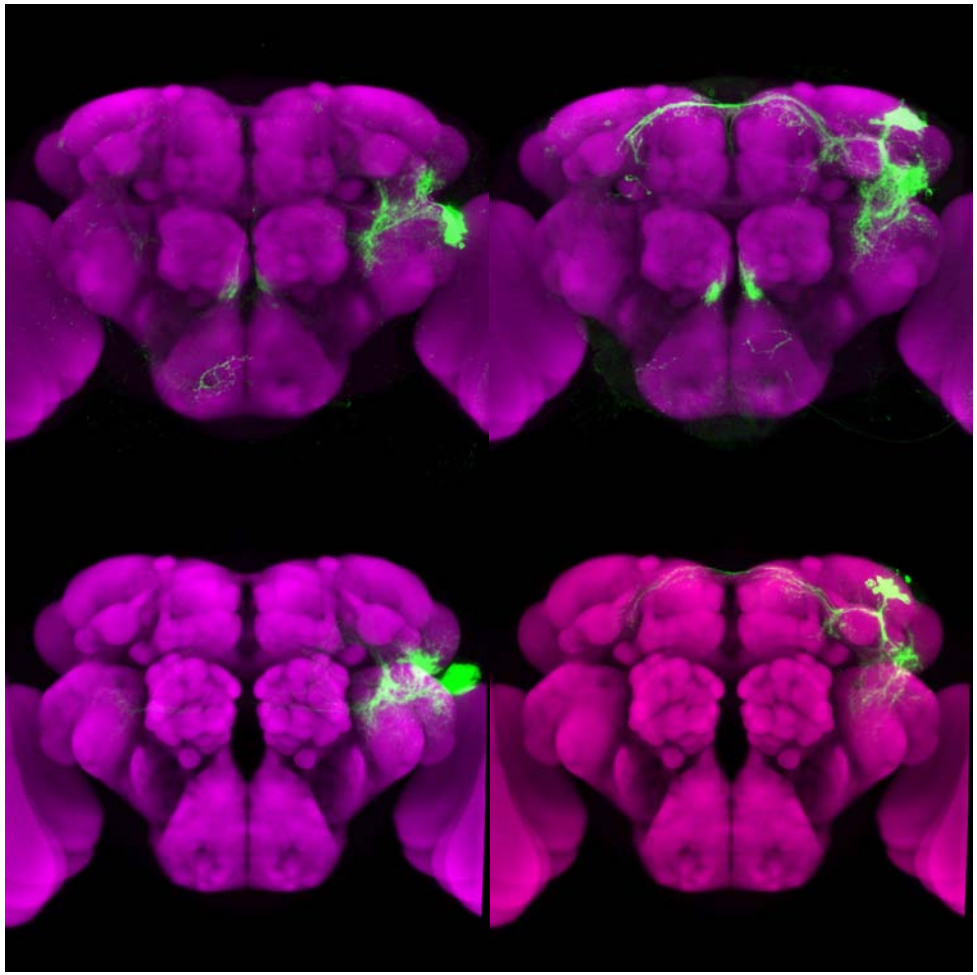
All Neurons

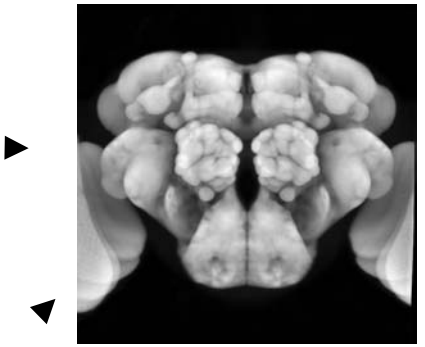
>



Cluster 1 Cluster 2 …

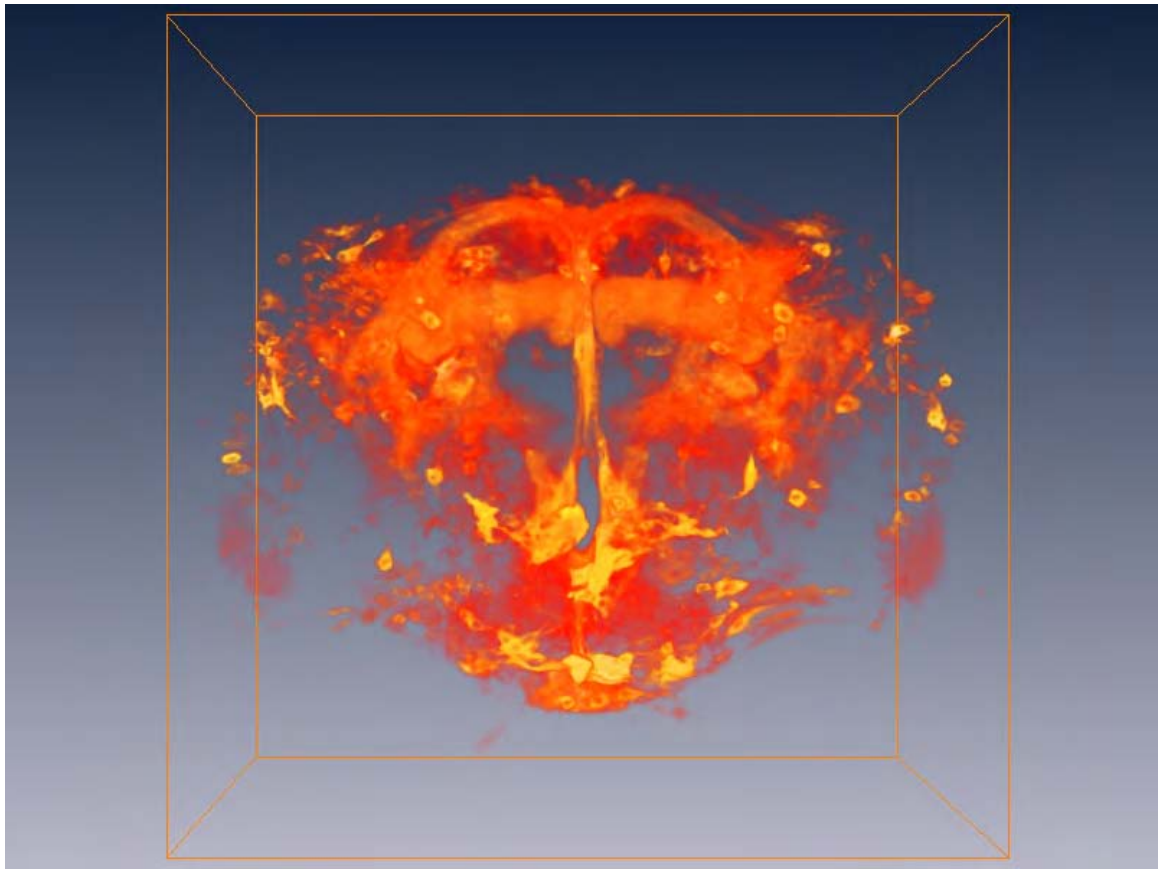
Reassemble with 3D Registration



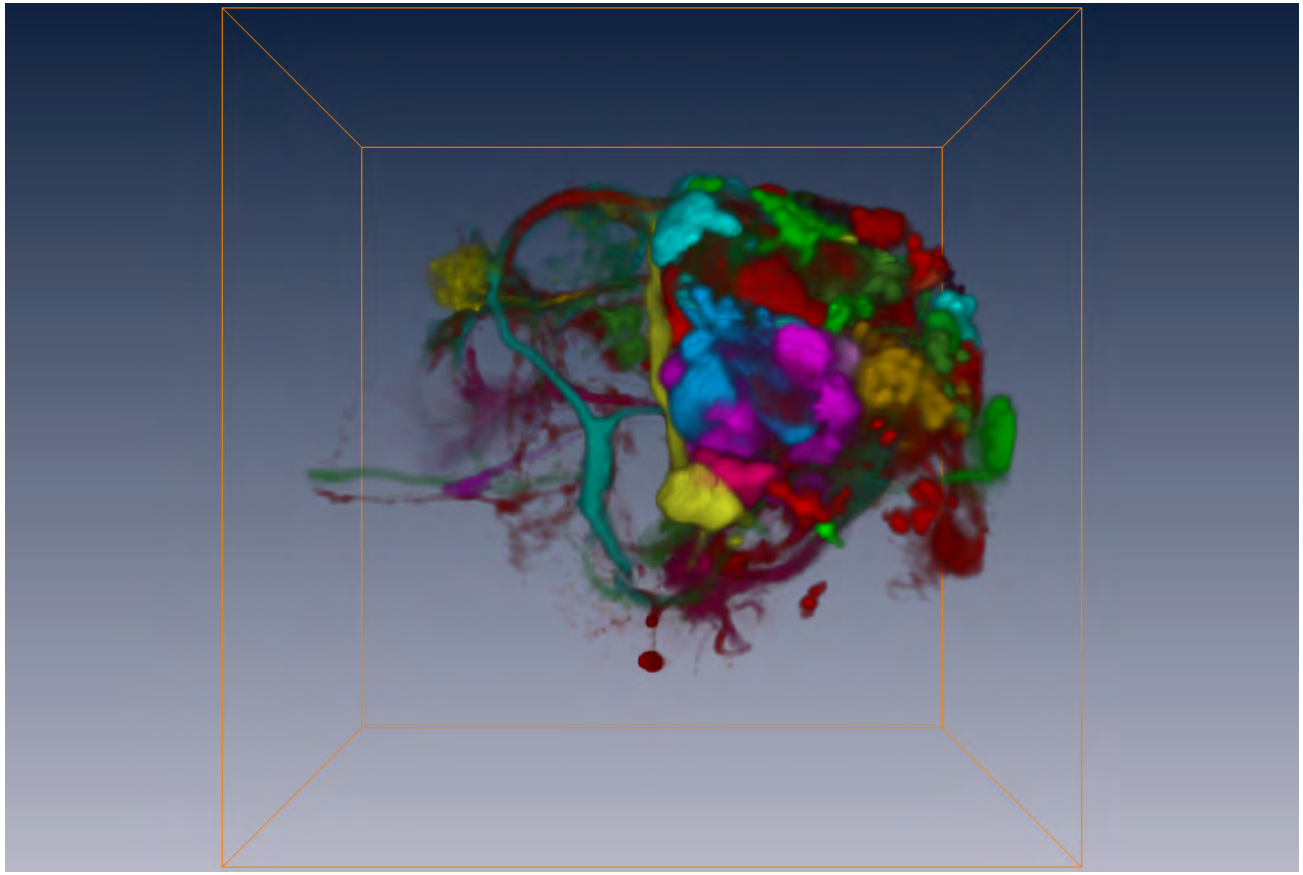


Template brain
(intersex)

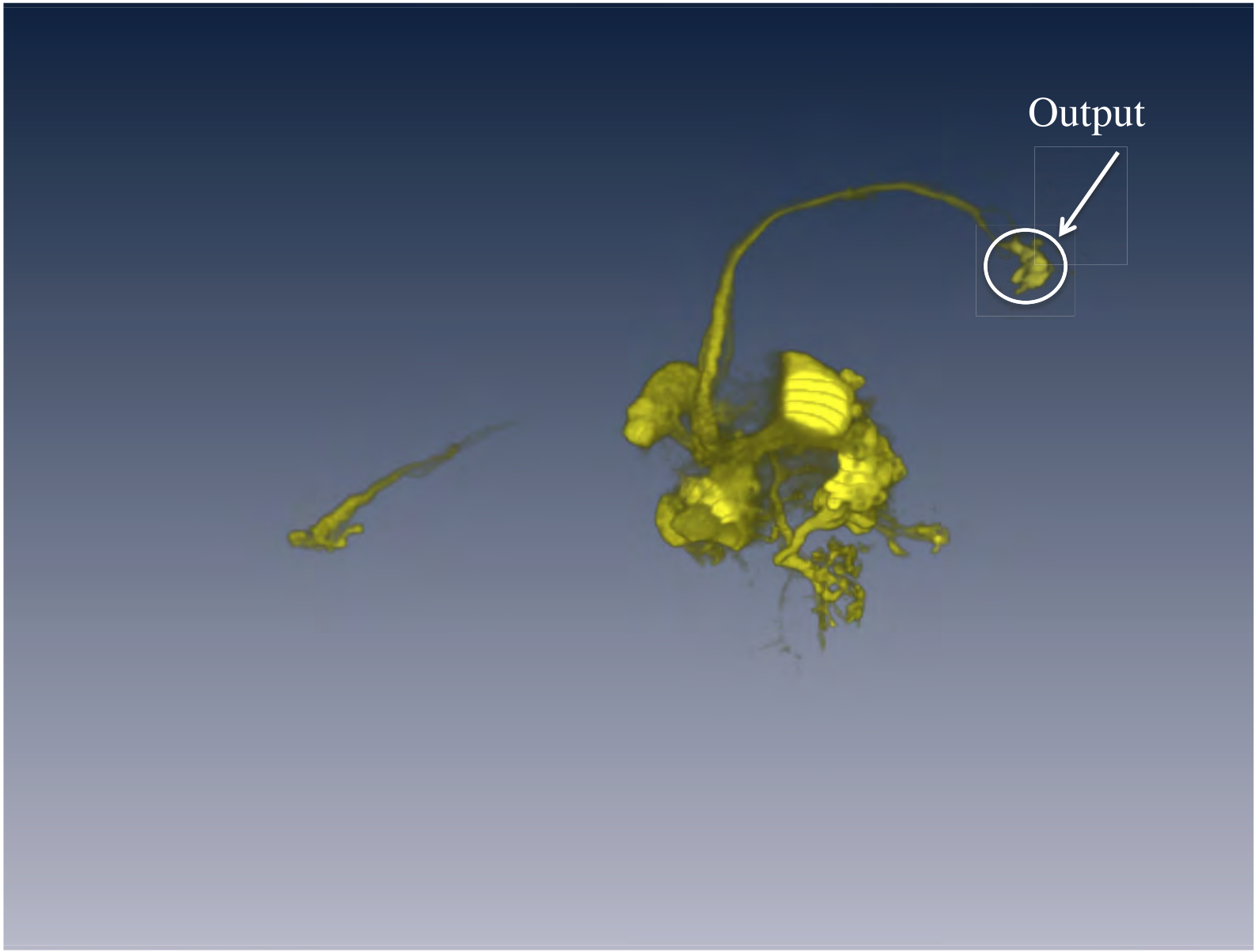
Clickable atlas of 110 *fruitless* clusters



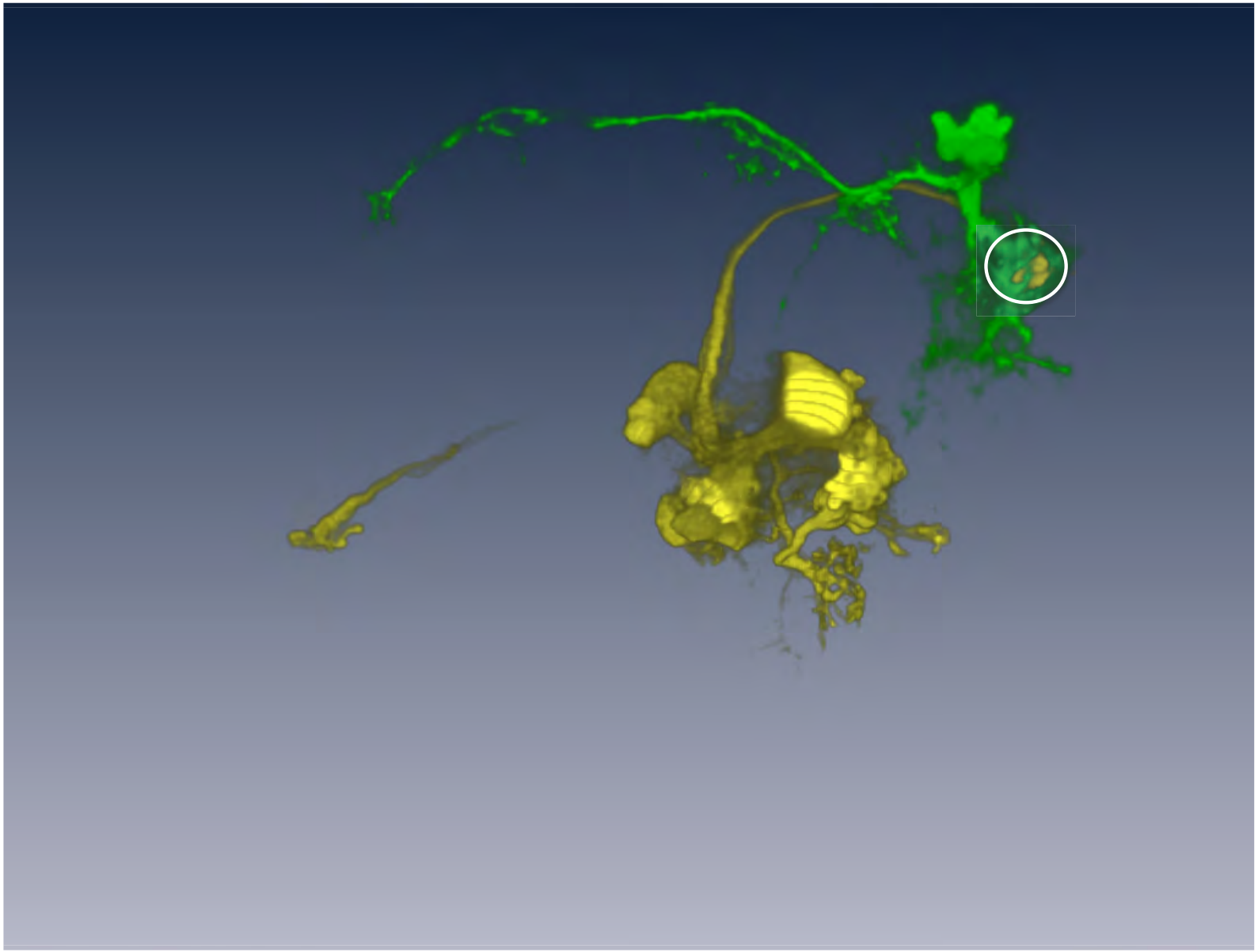
Clickable atlas of 110 *fruitless* clusters



3D overlap defines potential connectivity



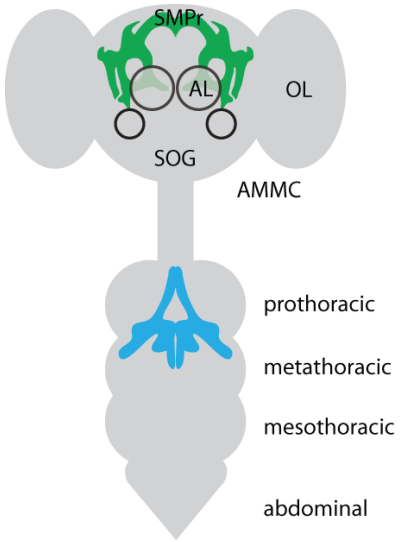
3D overlap defines potential connectivity



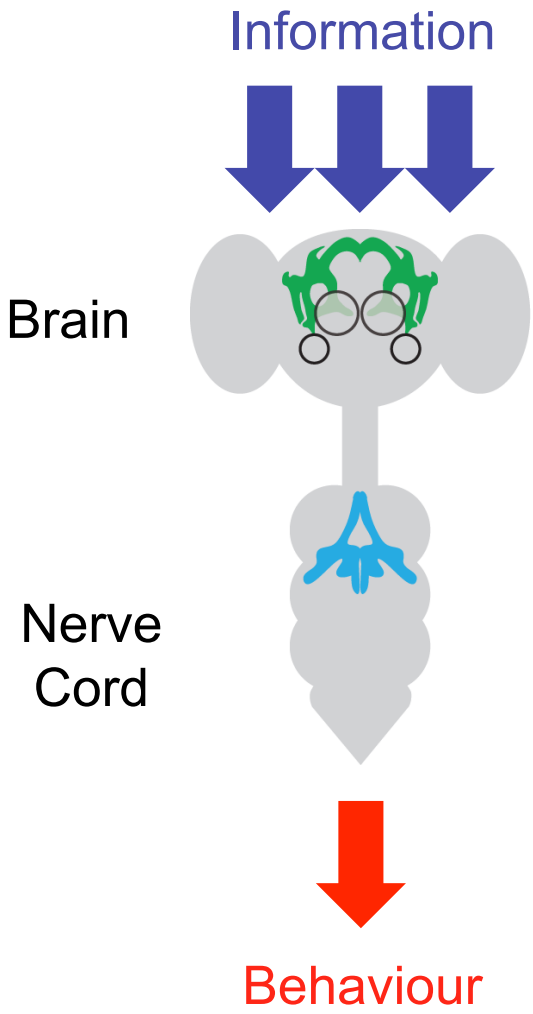
Fruitless Neuron Network

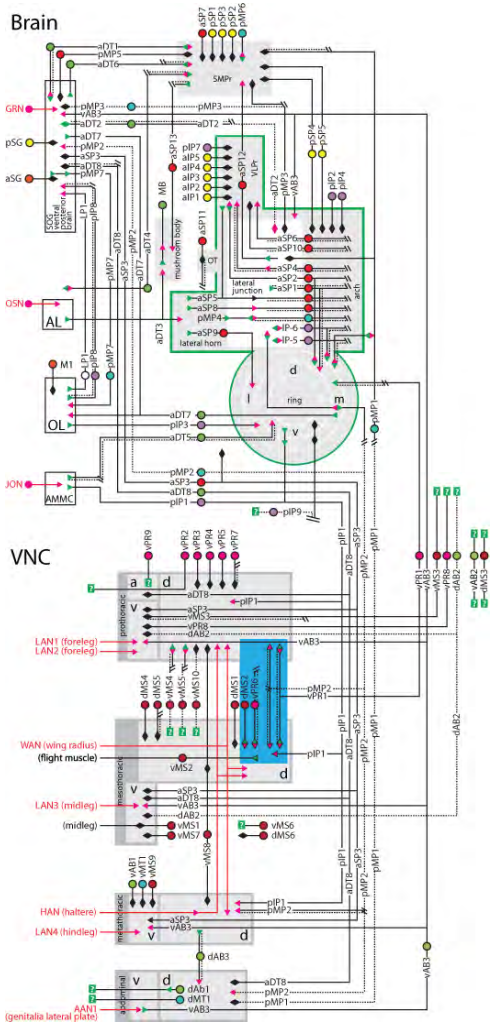
Brain

Nerve Cord



Fruitless Neuron Network



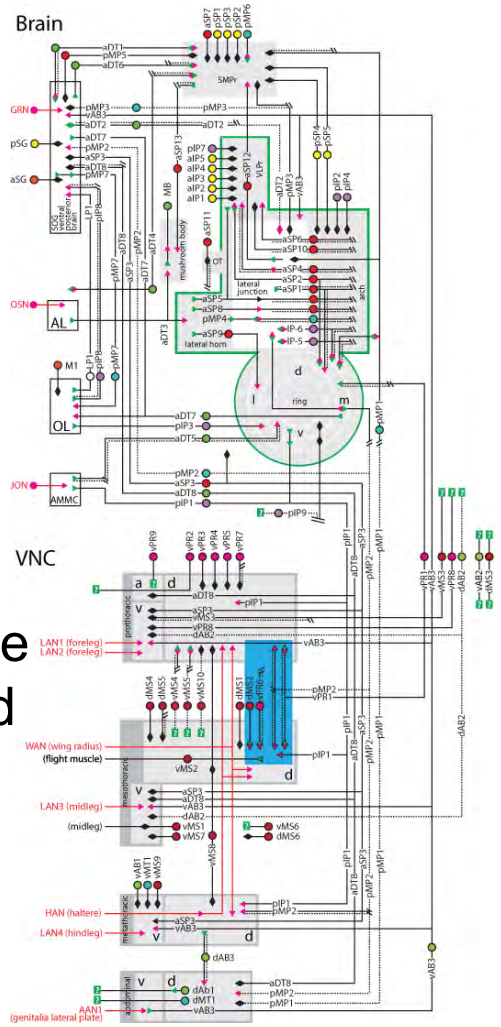


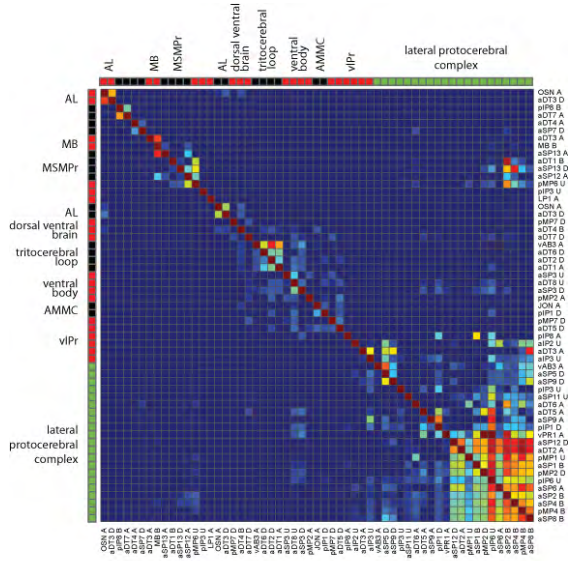
Yu et al. (2010)

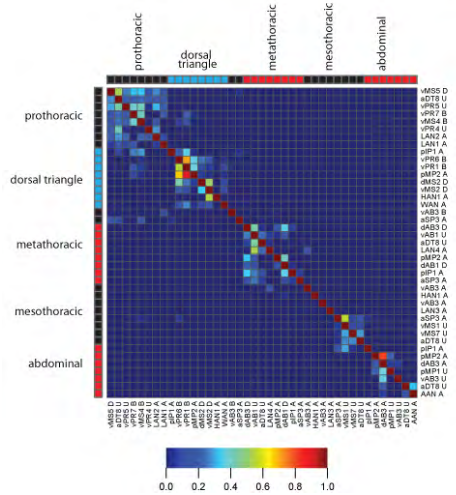
Fruitless Neuron Network

Brain

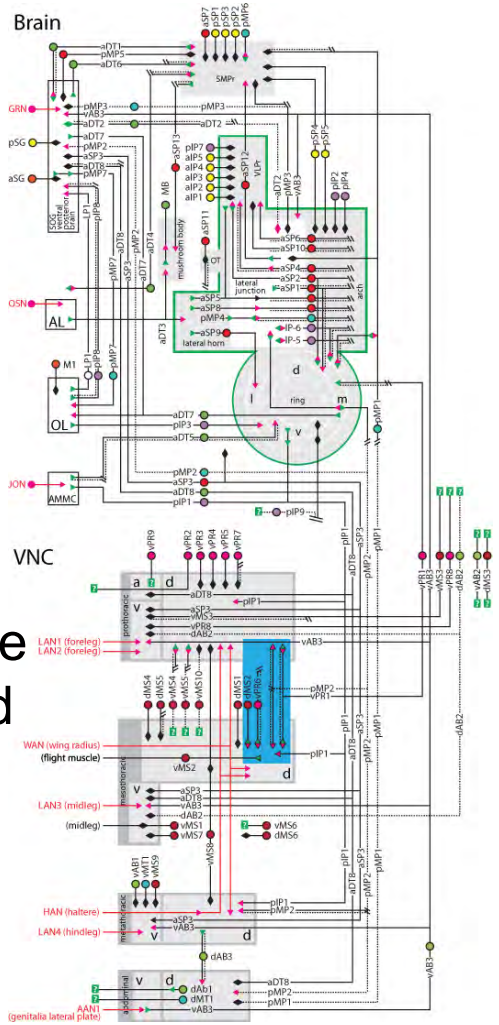
Nerve Cord





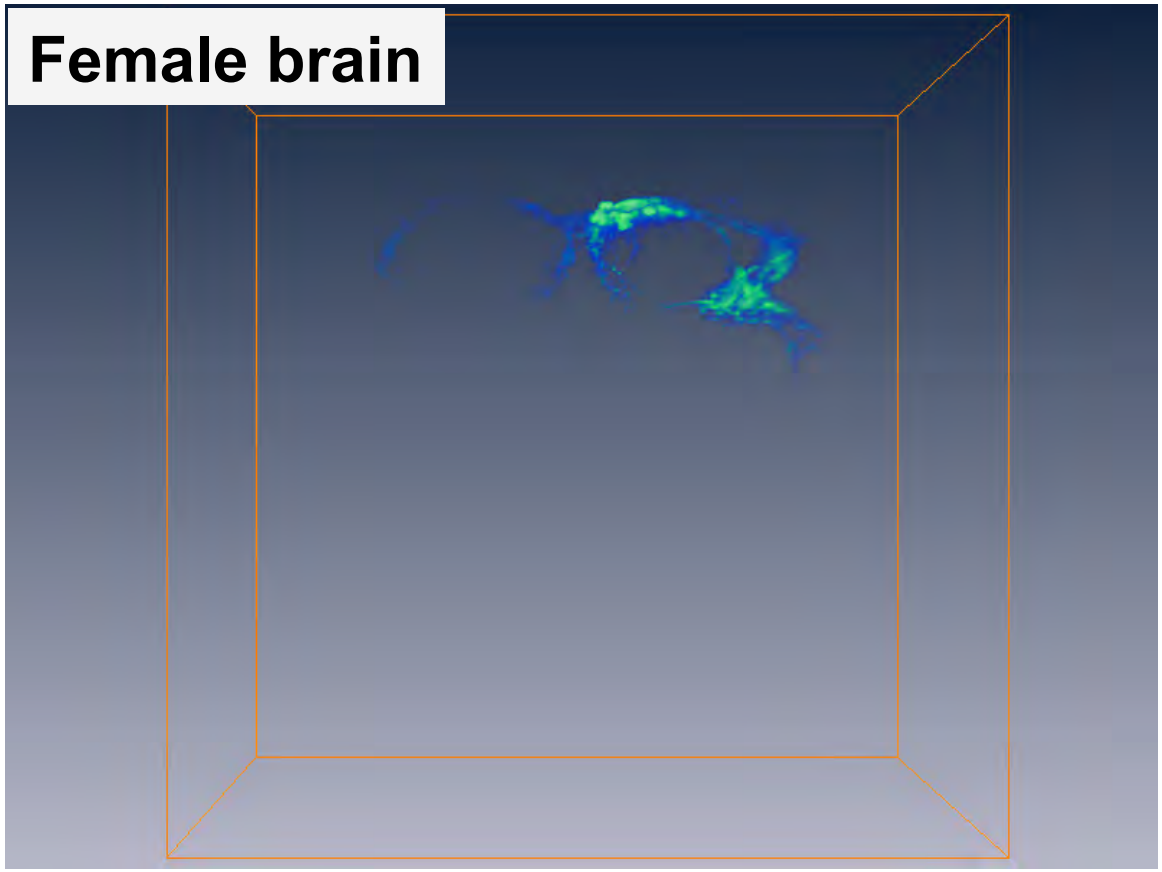


Fruitless Neuron Network

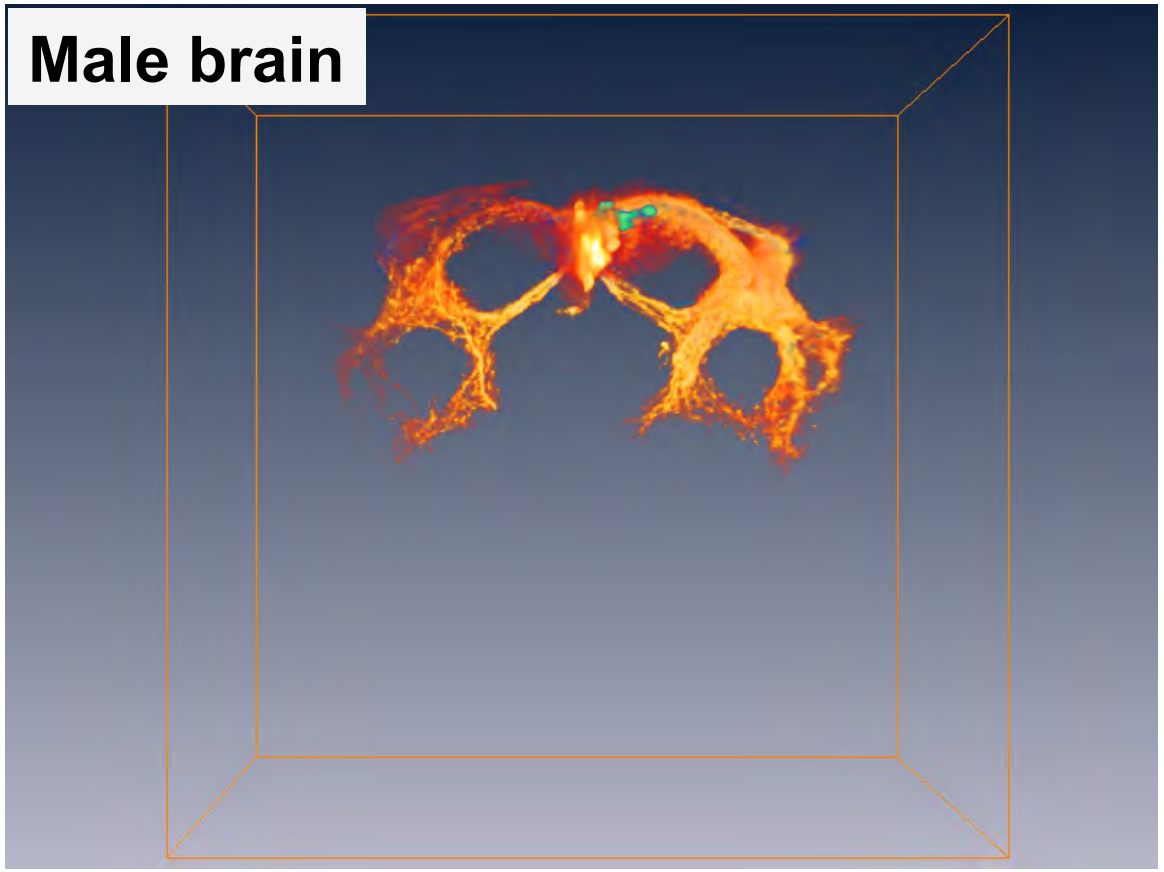


But where are the sex differences?

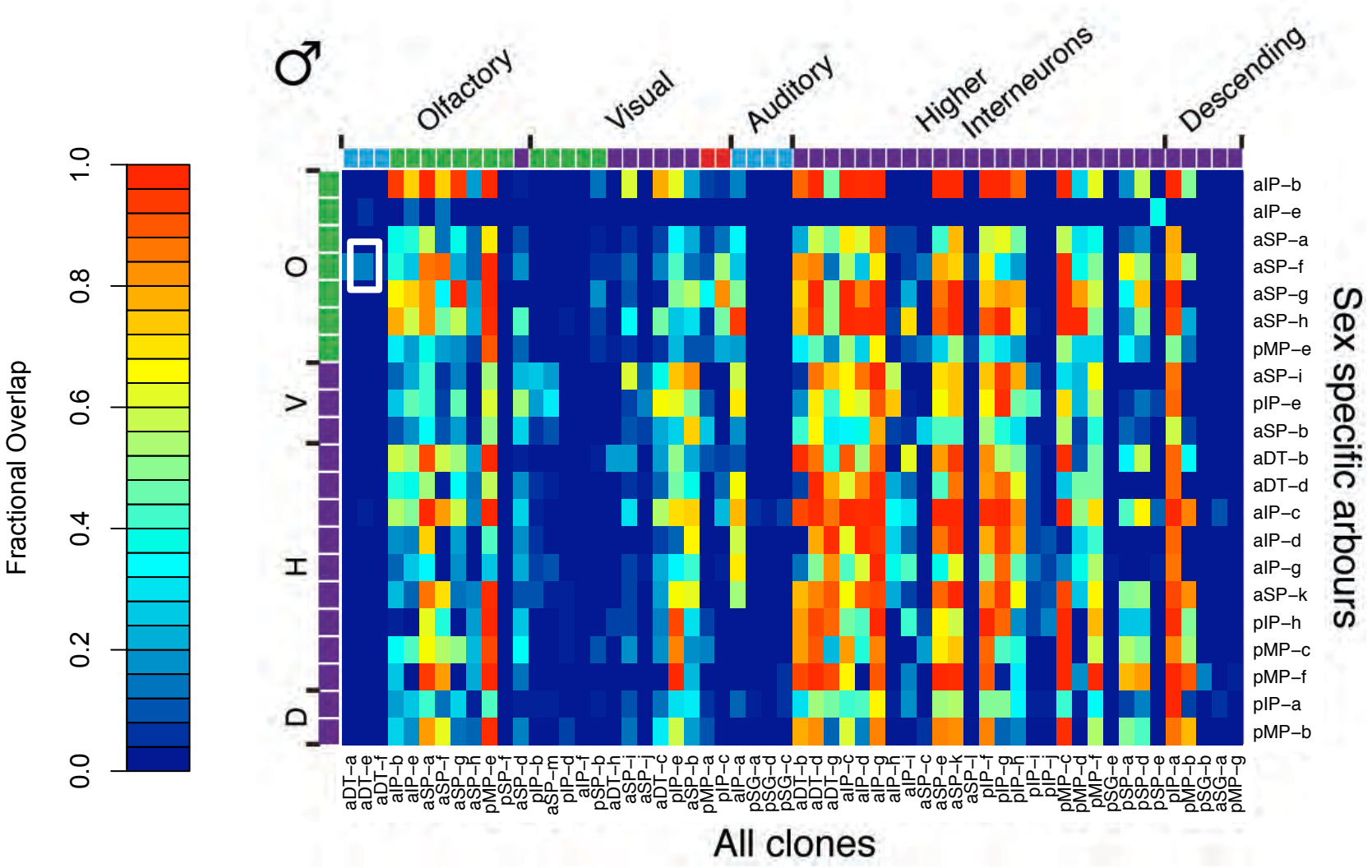
Atlas allows easy comparison …



of neurons between the sexes



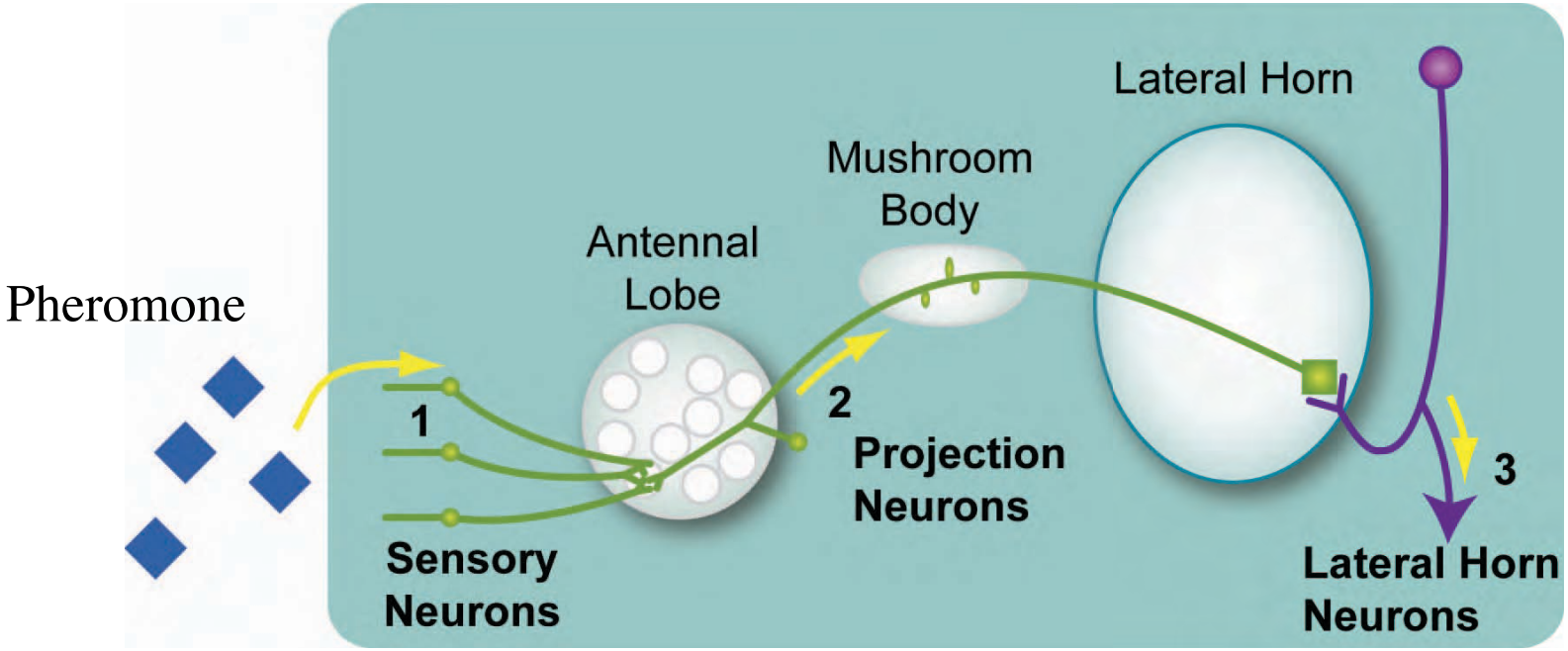
>700 Overlap Differences



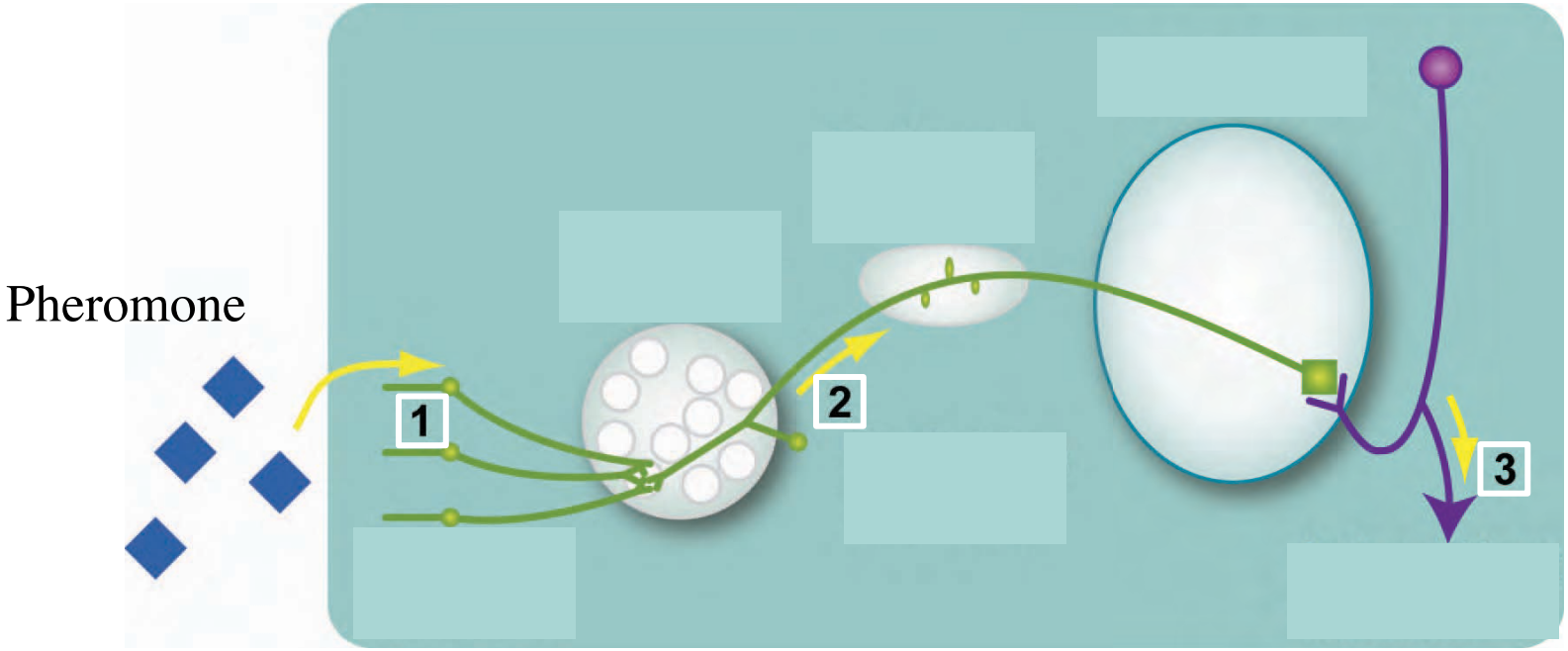
Fly Pheromones

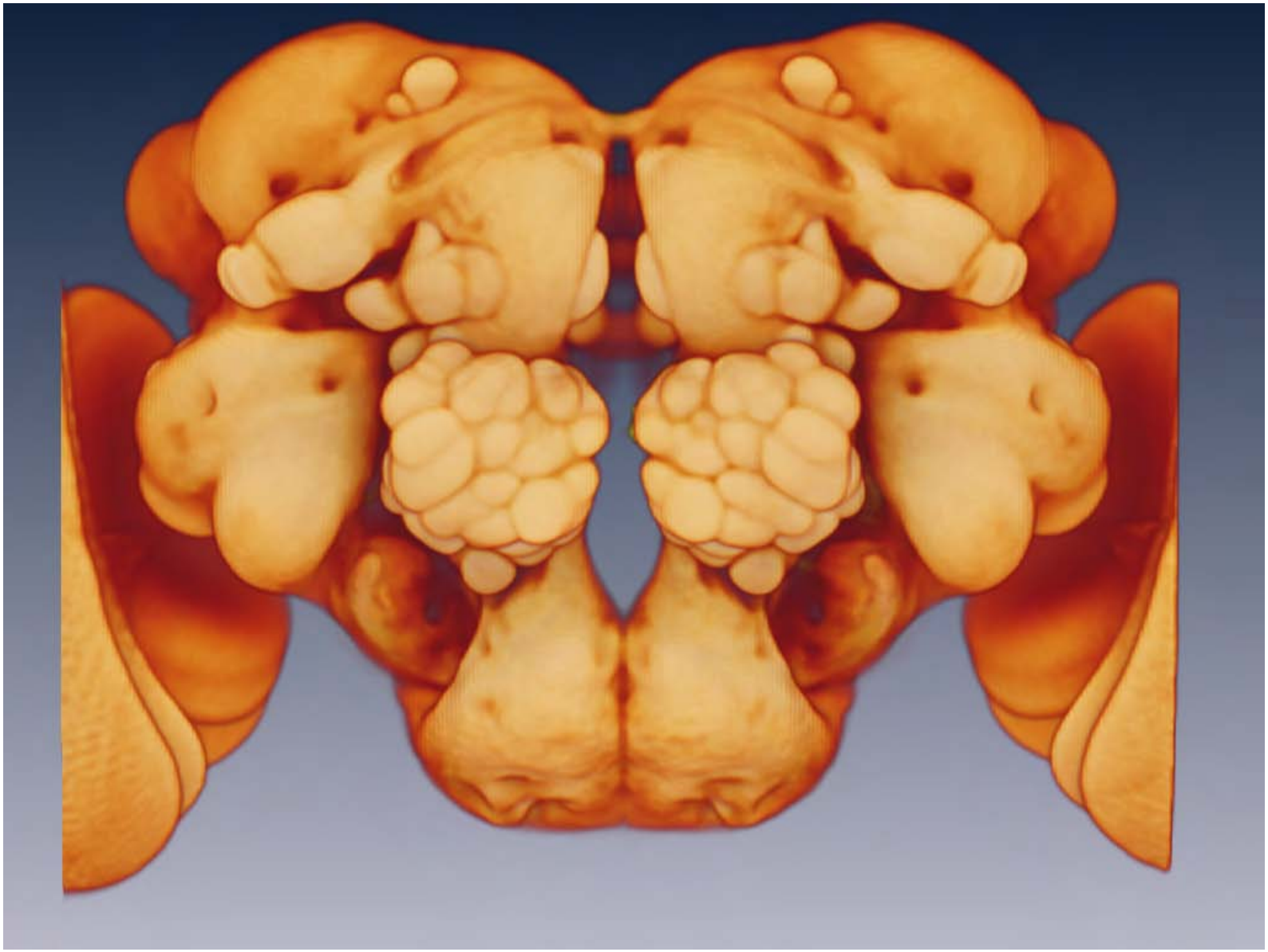
- Odour produced by one animal to signal to another
- Recently fly neurobiologists have identified a male pheromone
- Repels other males but increases chance that females will mate

Olfactory Circuits

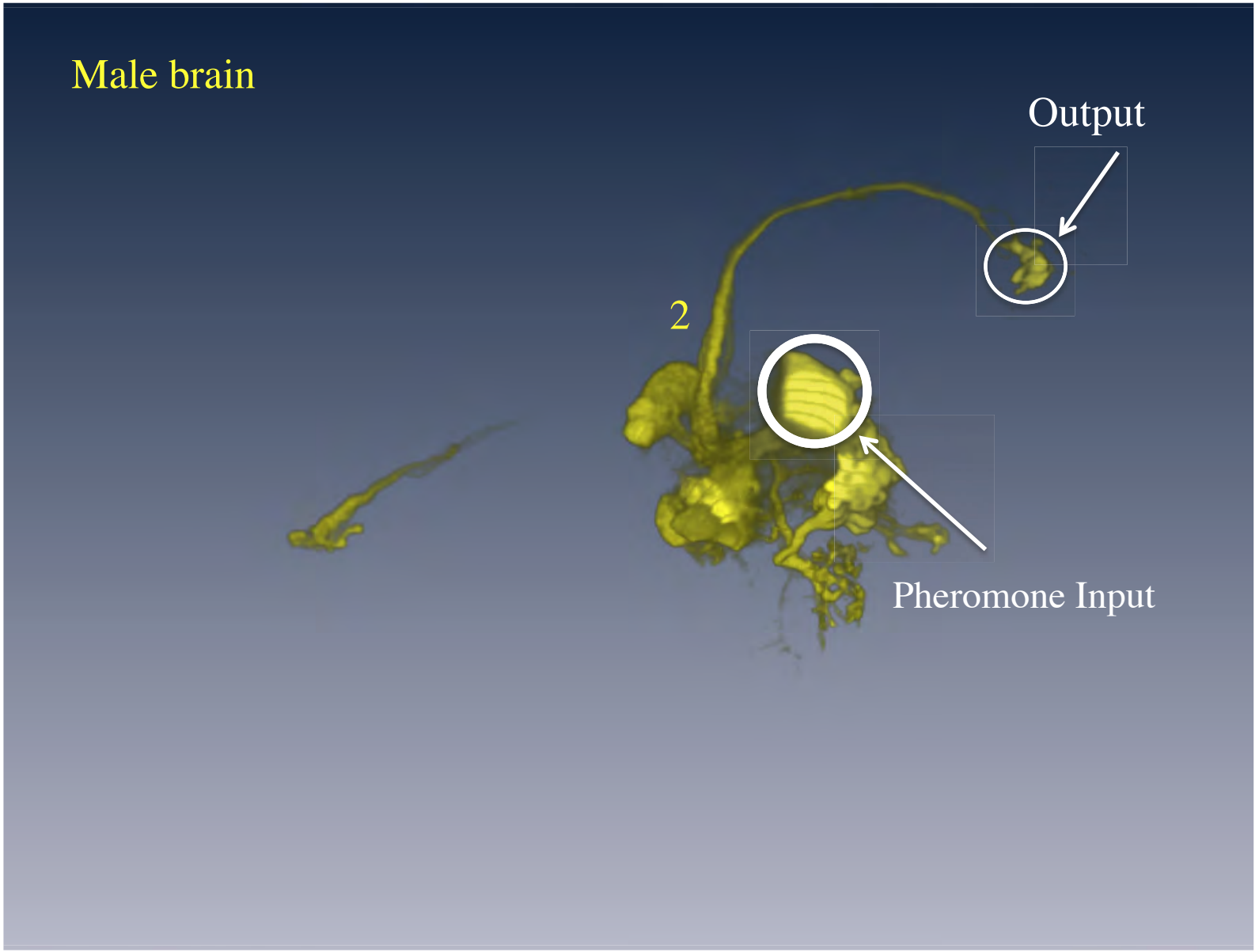


Olfactory Circuits

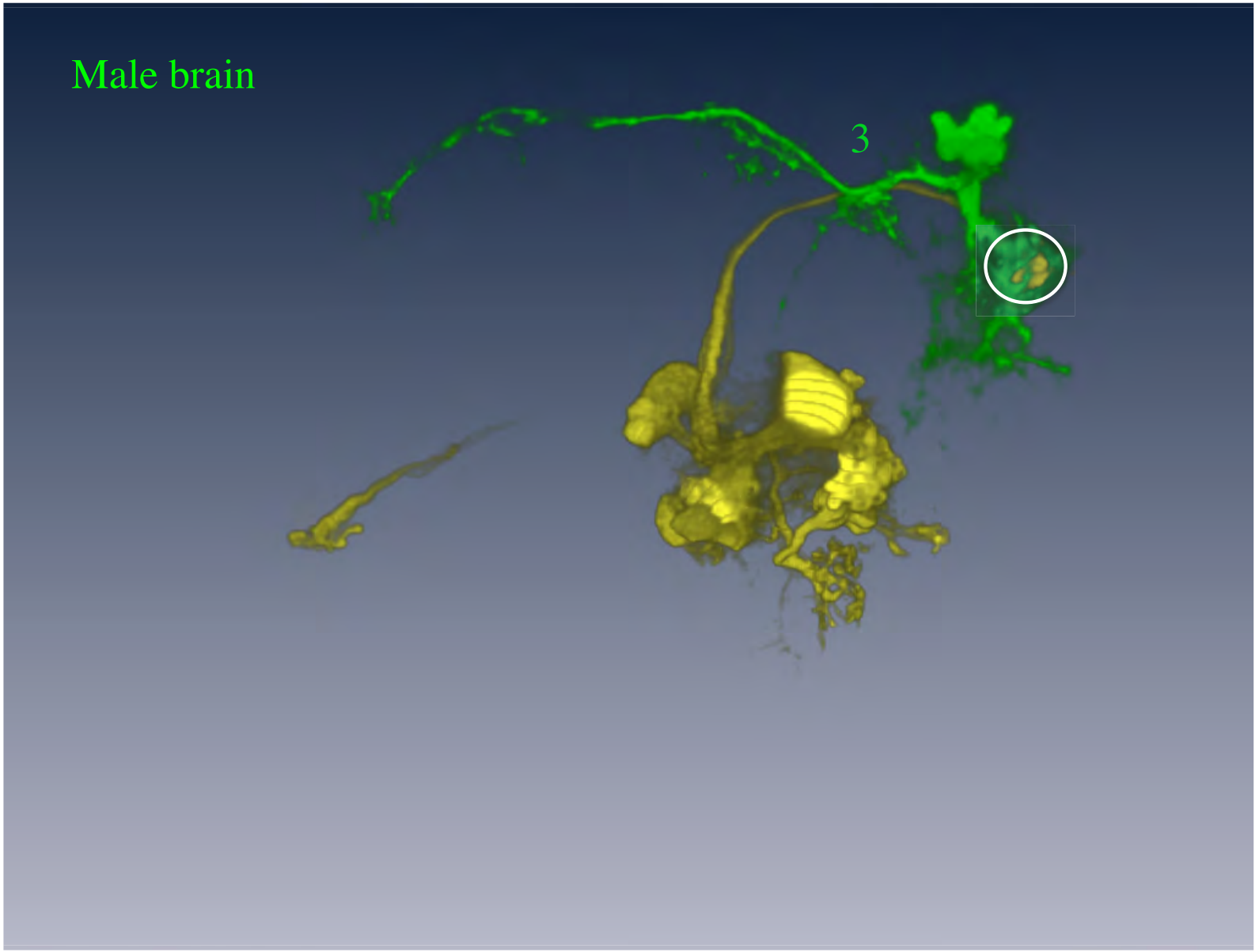




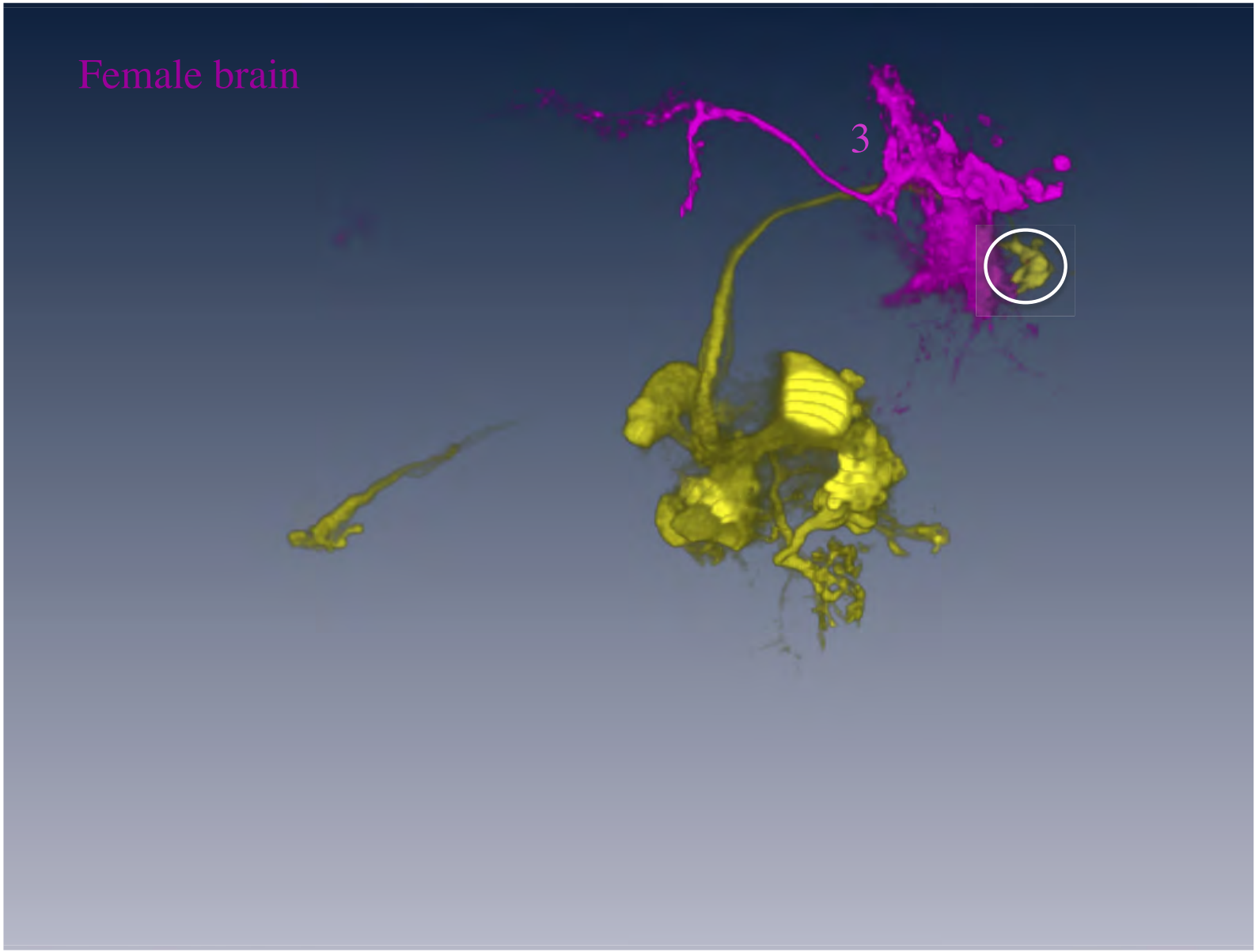
Circuit Differences



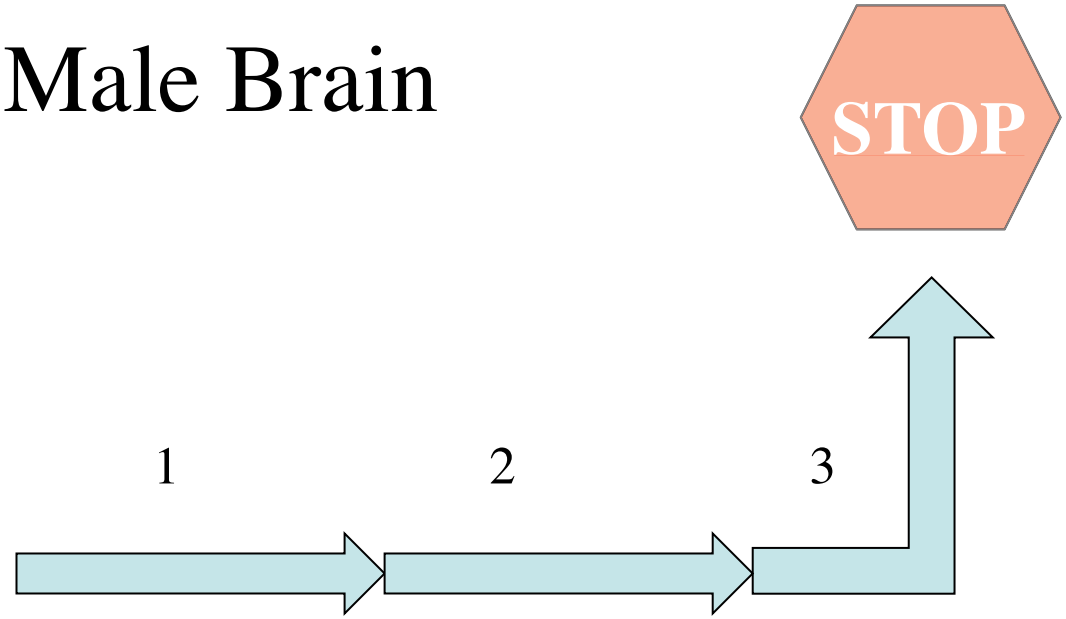
Circuit Differences

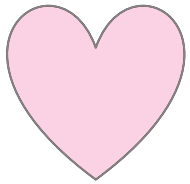


Circuit Differences

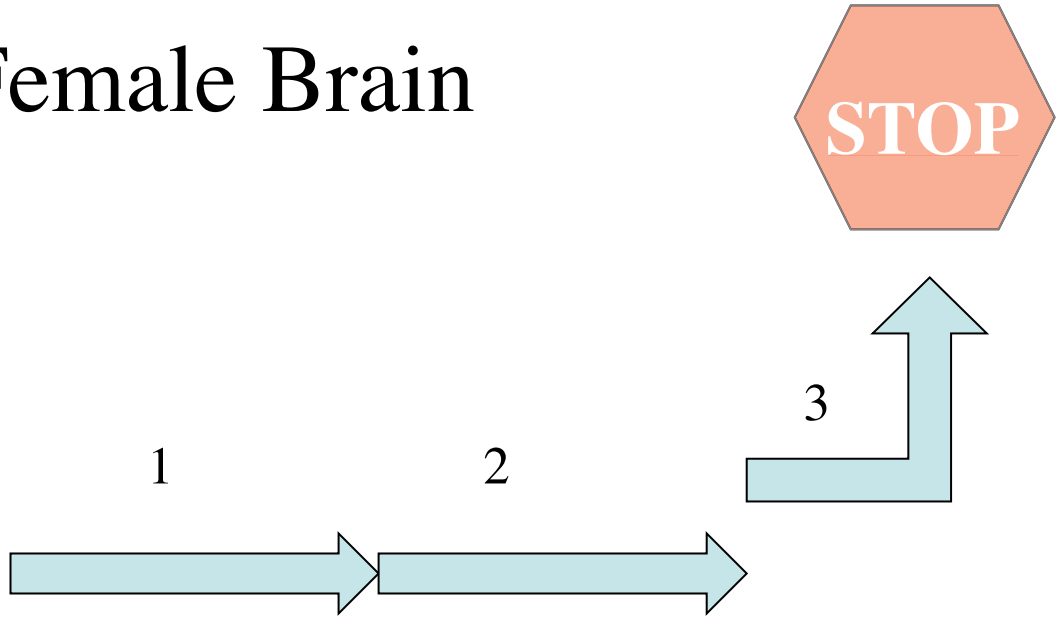


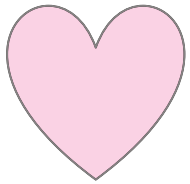
Male Brain



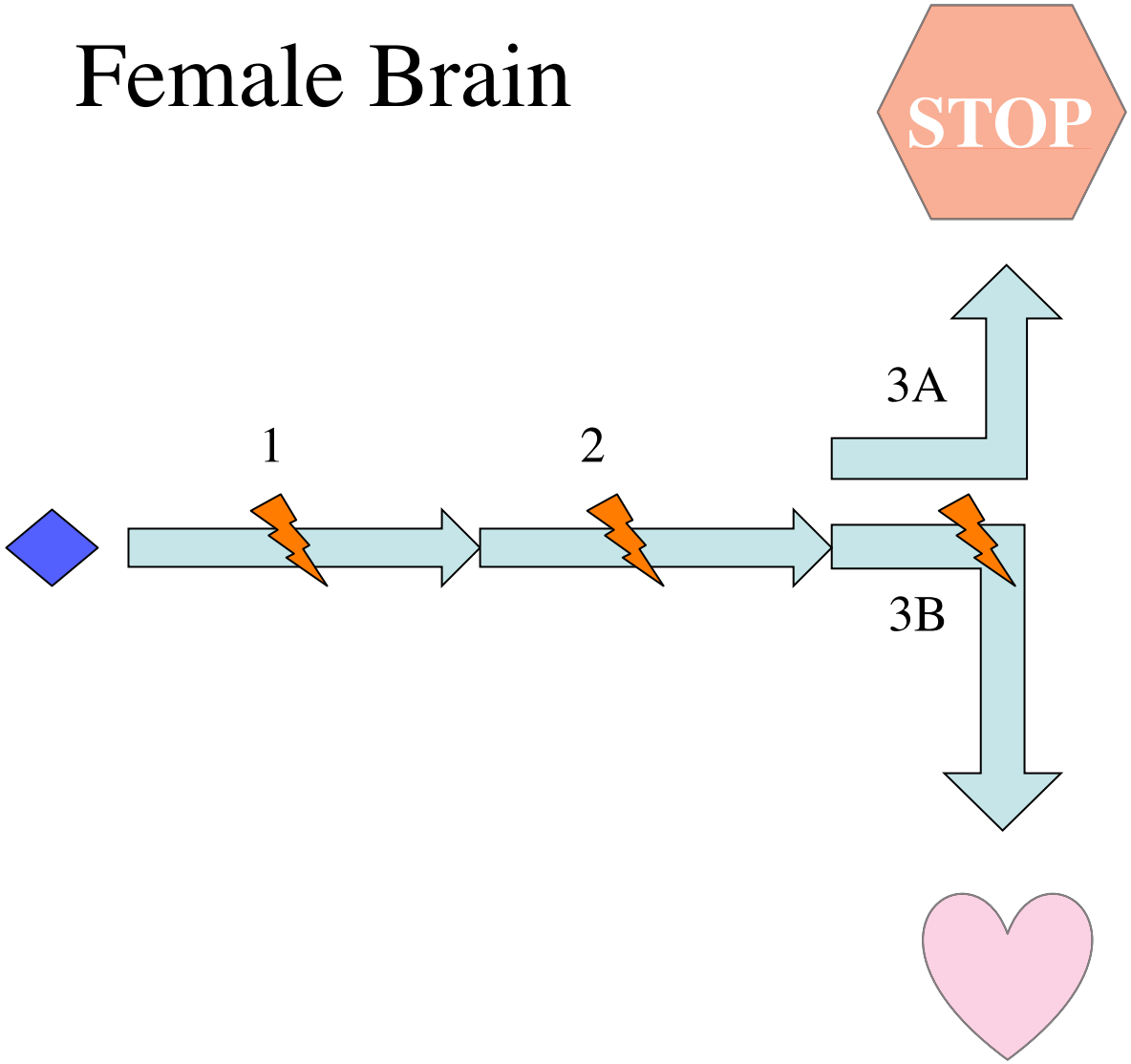


Female Brain

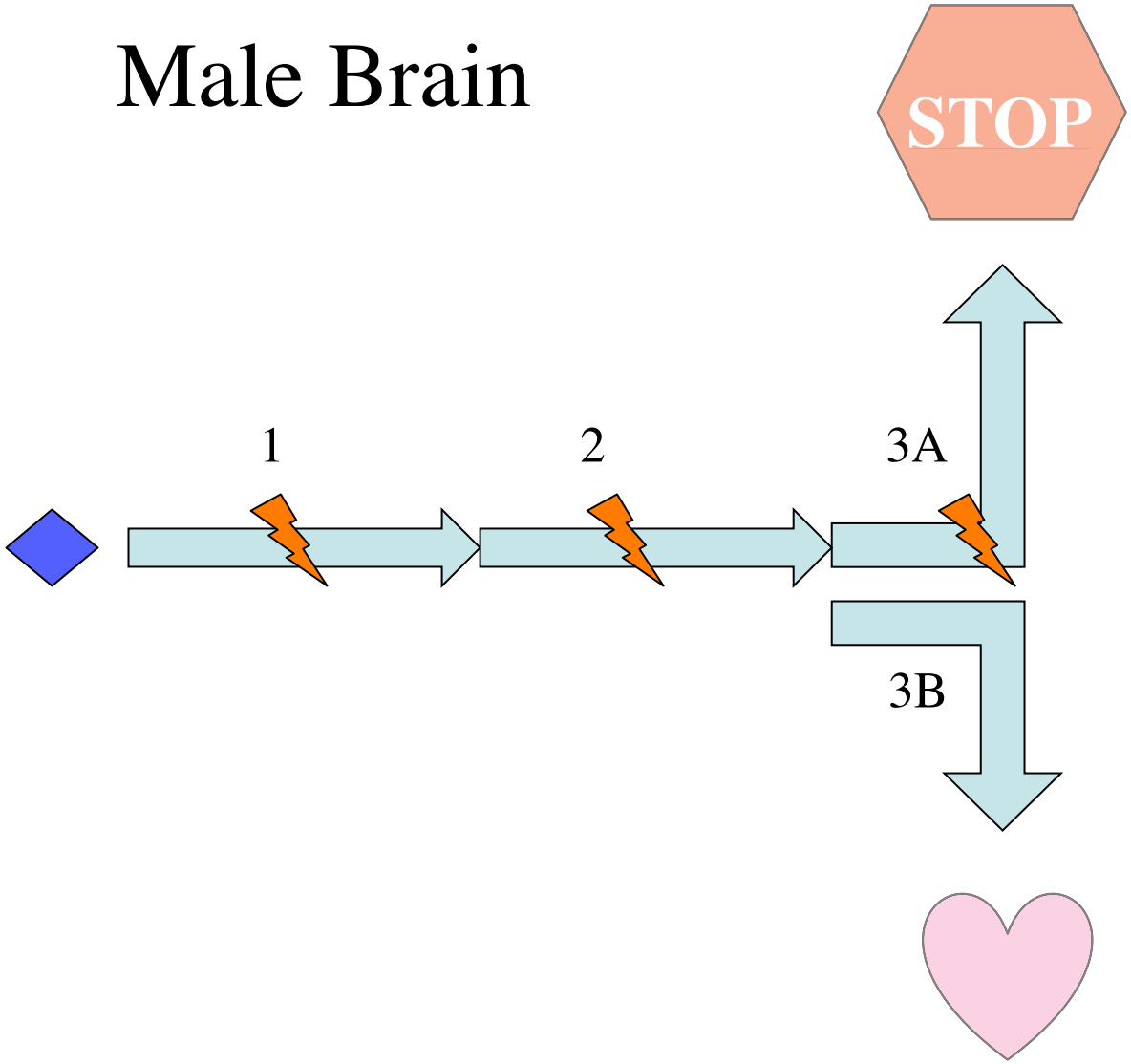




Female Brain

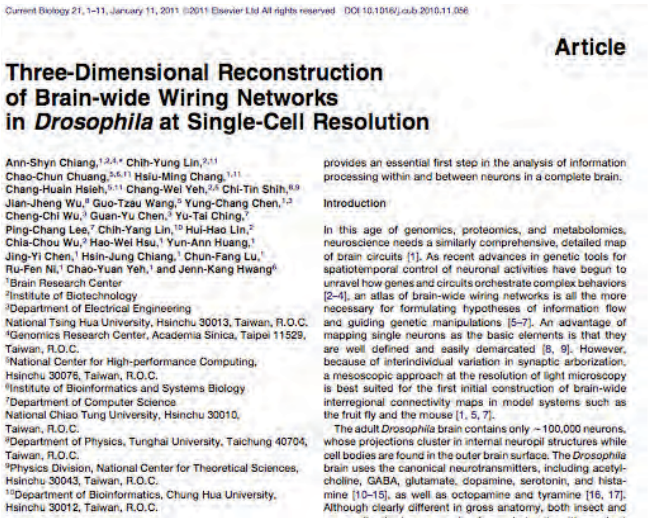


Male Brain



Networks In Neuroscience 2

Large Scale Data



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Article

Three-Dimensional Reconstruction of Brain-wide Wiring Networks in *Drosophila* at Single-Cell Resolution

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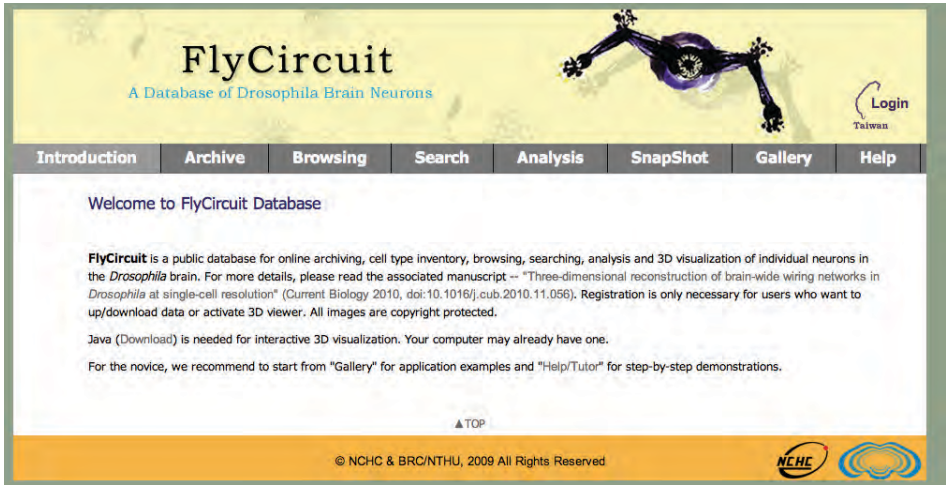
provides an essential first step in the analysis of information processing within and between neurons in a complete brain.

Introduction

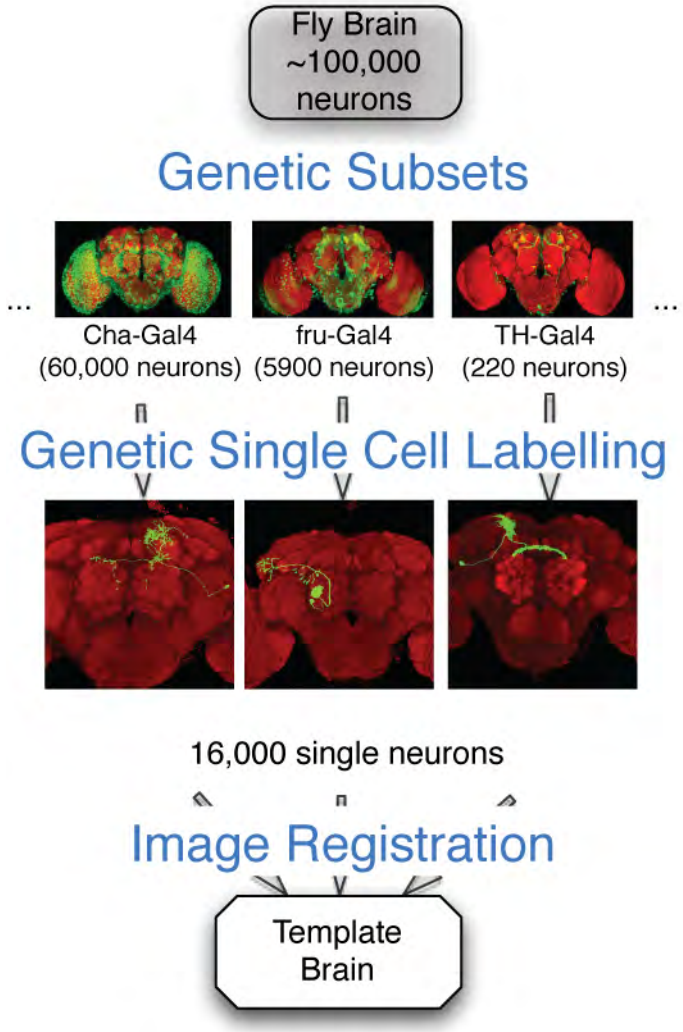
In this age of genomics, proteomics, and metabolomics, neuroscience needs a similarly comprehensive, detailed map of brain circuits [1]. As recent advances in genetic tools for spatiotemporal control of neuronal activities have begun to unravel how genes and circuits orchestrate complex behaviors [2–4], an atlas of brain-wide wiring networks is all the more necessary for formulating hypotheses of information flow and guiding genetic manipulations [5–7]. An advantage of mapping single neurons as the basic elements is that they are well defined and easily demarcated [8, 9]. However, because of interindividual variation in synaptic arborization, a mesoscopic approach at the resolution of light microscopy is best suited for the first initial construction of brain-wide interregional connectivity maps in model systems such as the fruit fly and the mouse [1, 5, 7].

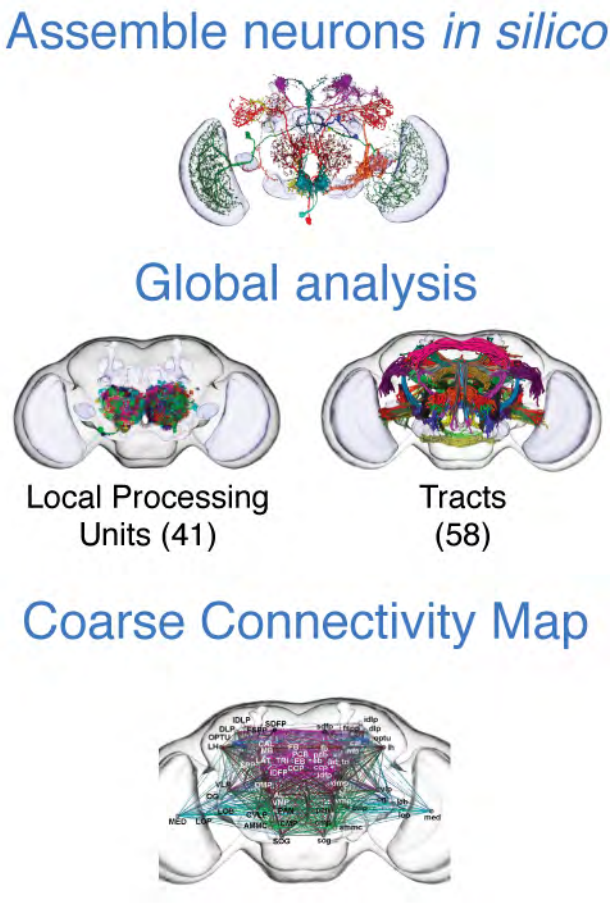
The adult *Drosophila* brain contains only ~100,000 neurons, whose projections cluster in internal neuropil structures while cell bodies are found in the outer brain surface. The *Drosophila* brain uses the canonical neurotransmitters, including acetylcholine, GABA, glutamate, dopamine, serotonin, and histamine [10–15], as well as octopamine and tyramine [16, 17]. Although clearly different in gross anatomy, both insect and



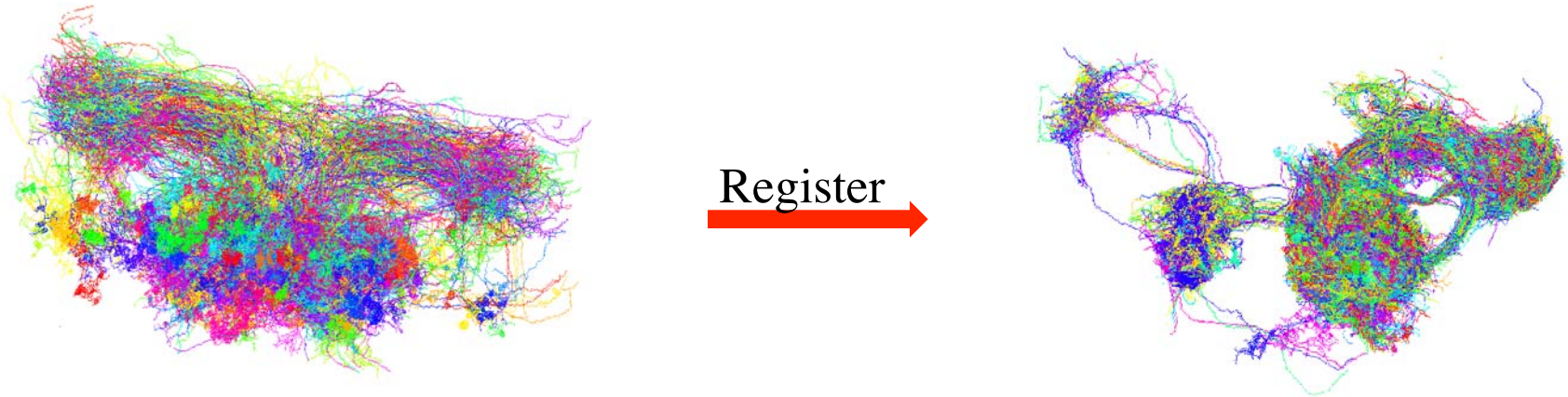
16,000 registered single fly neurons – 10 Tb image data

Networks In Neuroscience 2





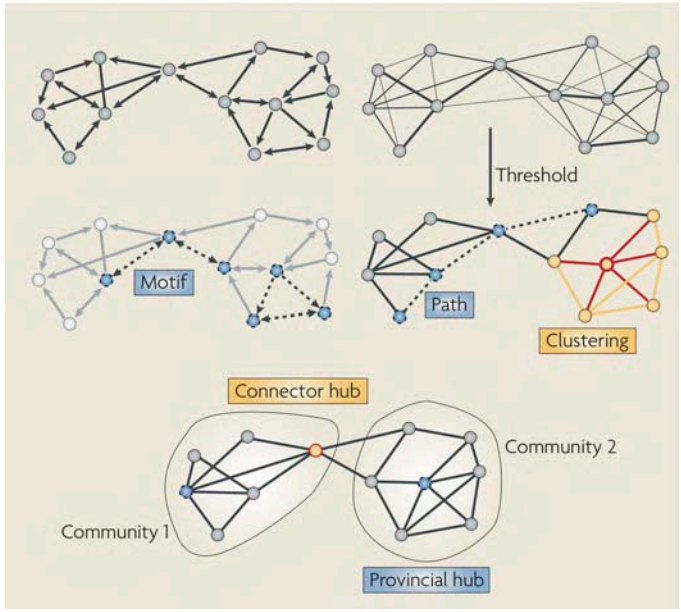
Have reassembled raw data



Example: 634 Olfactory Projection Neurons

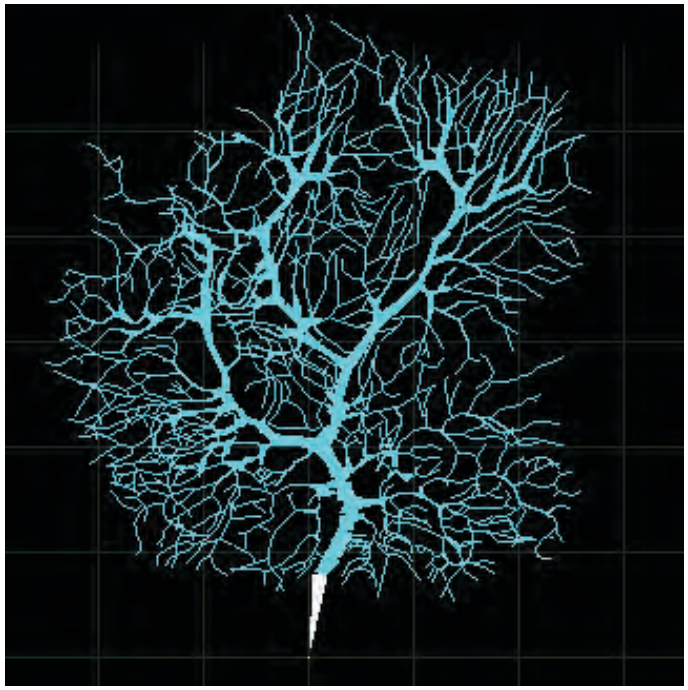
15198 neurons ready for overlap-based reconstruction of fly neural circuits

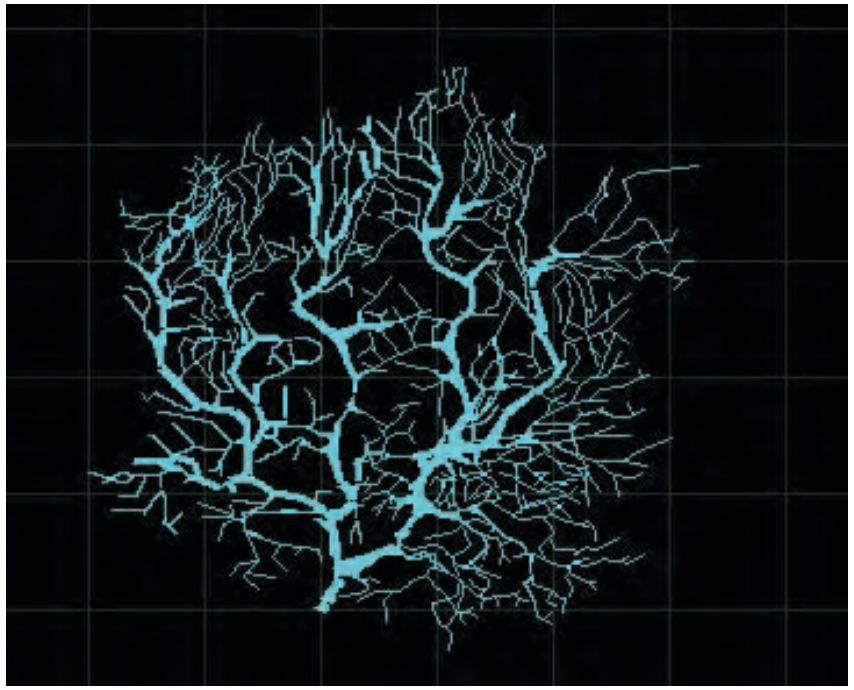
What would you do?



Networks in Neuroscience 3

Neuron similarity

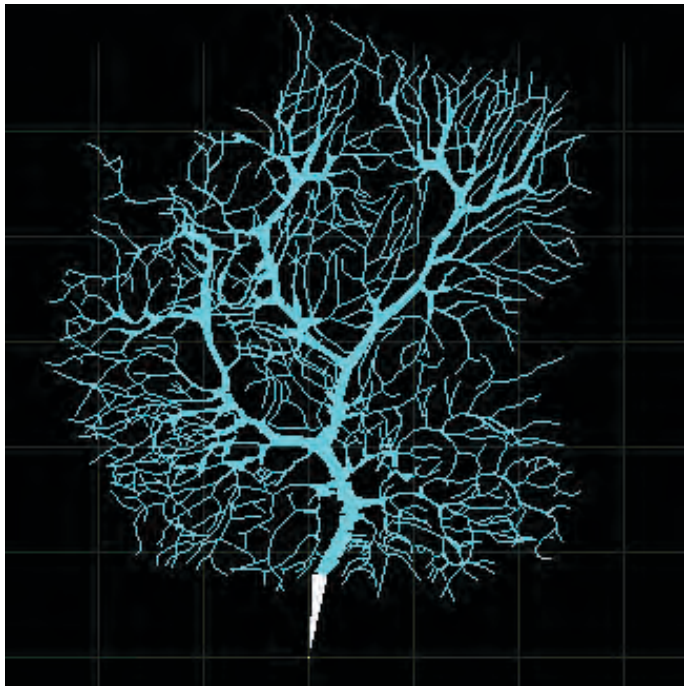


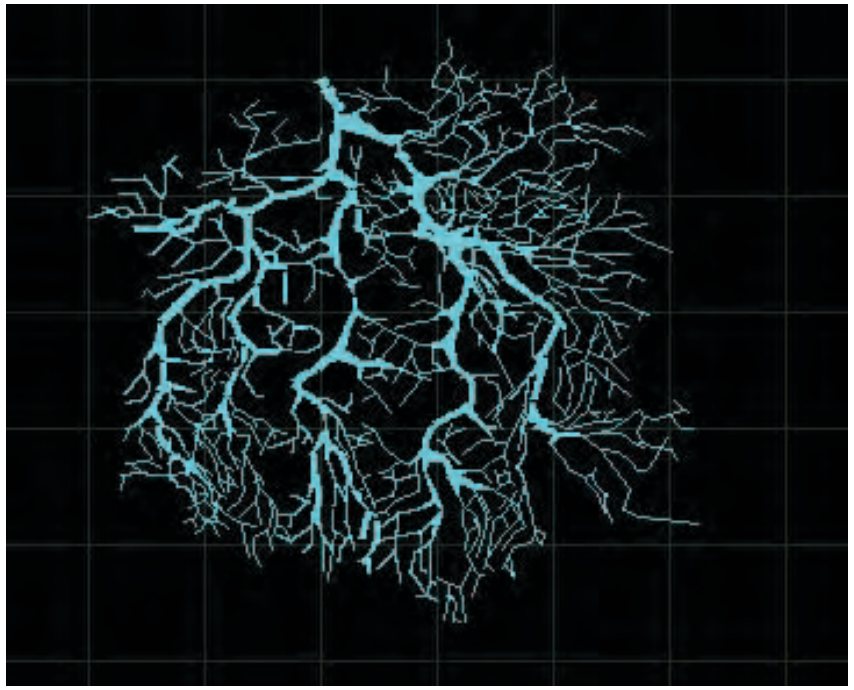


A graph matching problem – embedded in 3D space

Networks in Neuroscience 3

Neuron similarity





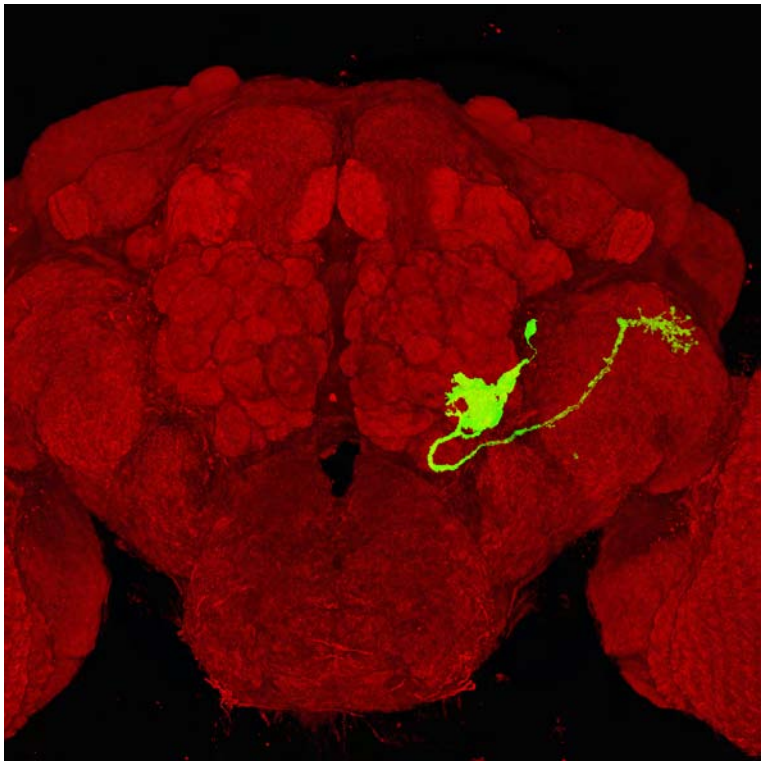
A graph matching problem – embedded in 3D space

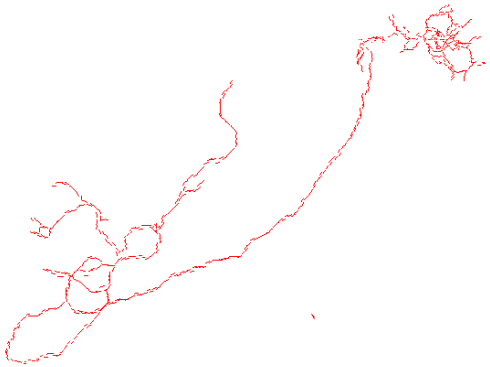
Networks in Neuroscience 4

Analytic tools related to network analysis – compare bioinformatics

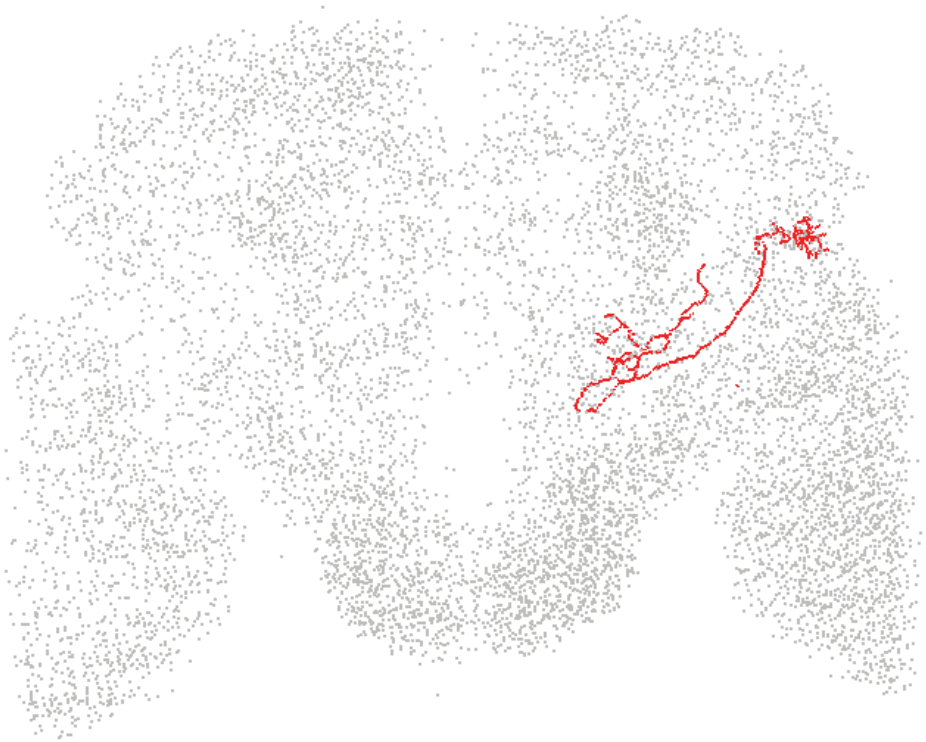
- Similarity measures for neurons
- Use to search databases (cf BLAST)
- Identify neuron families (cf PFAM)

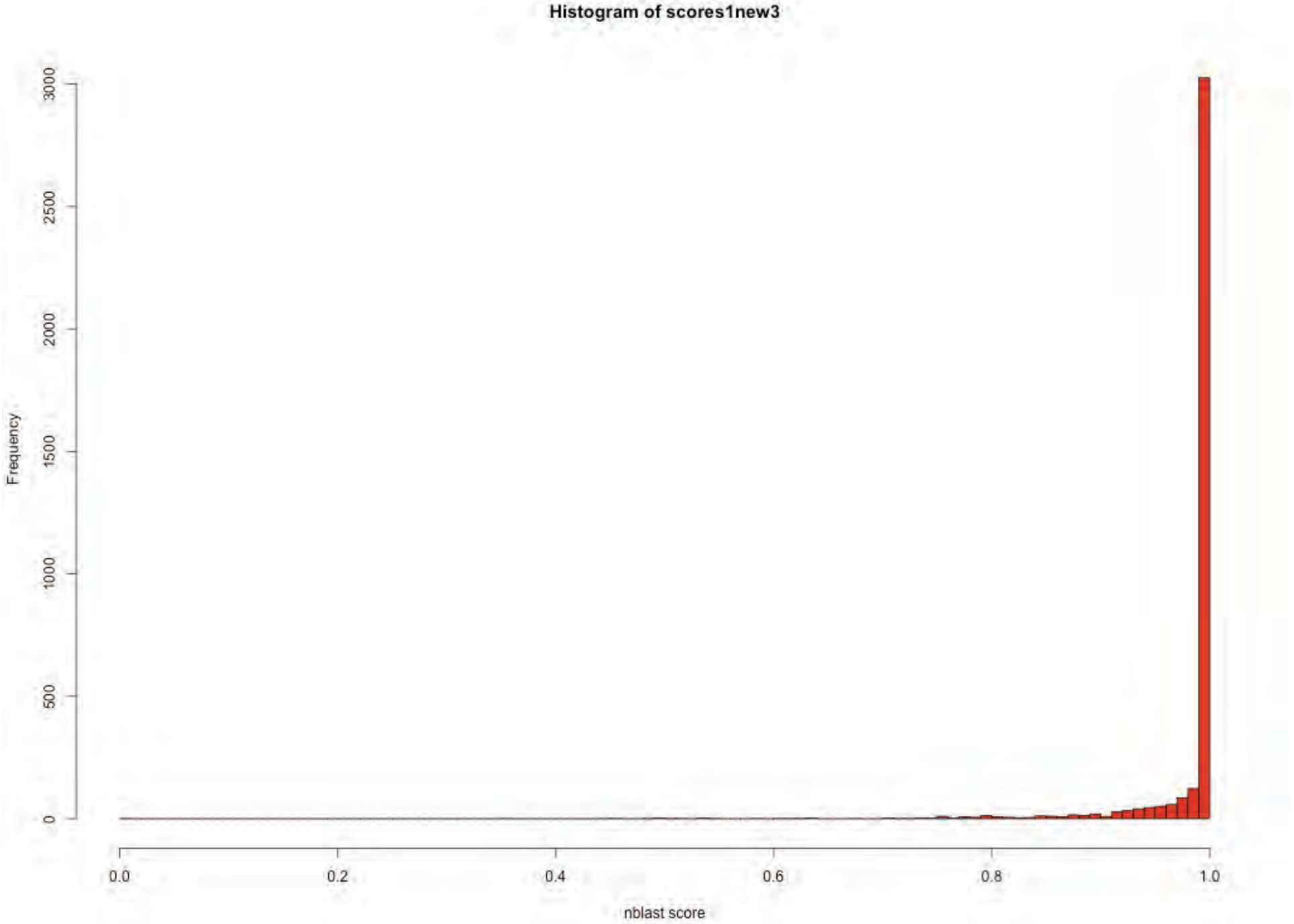
Convert image to (3D) skeleton

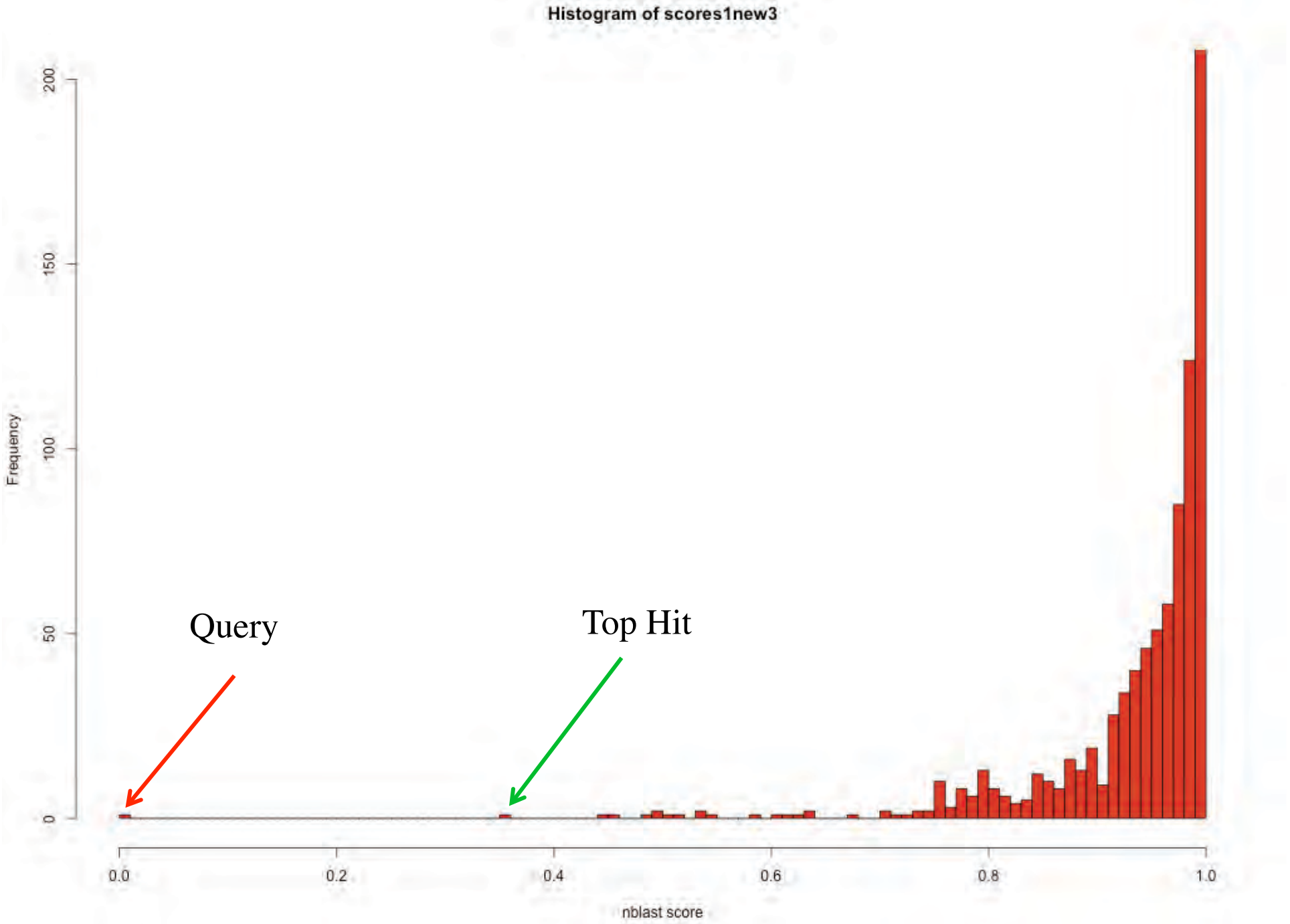




NBlast




Histogram of scores1new3
Frequency
0
500
1000
1500
2000
2500
3000
0.0
0.2
0.4
0.6
0.8
1.0
nblast score


Histogram of scores1new3
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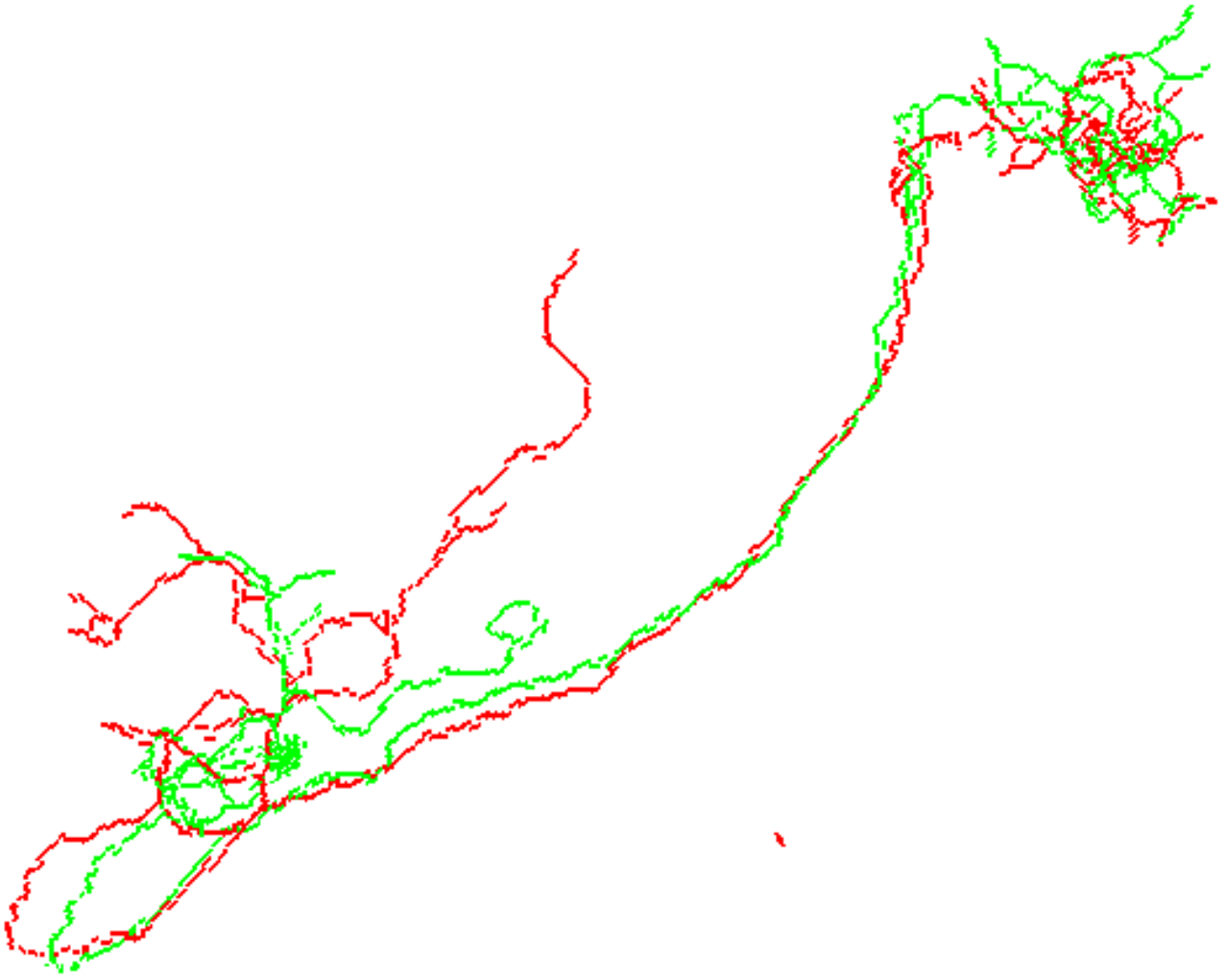
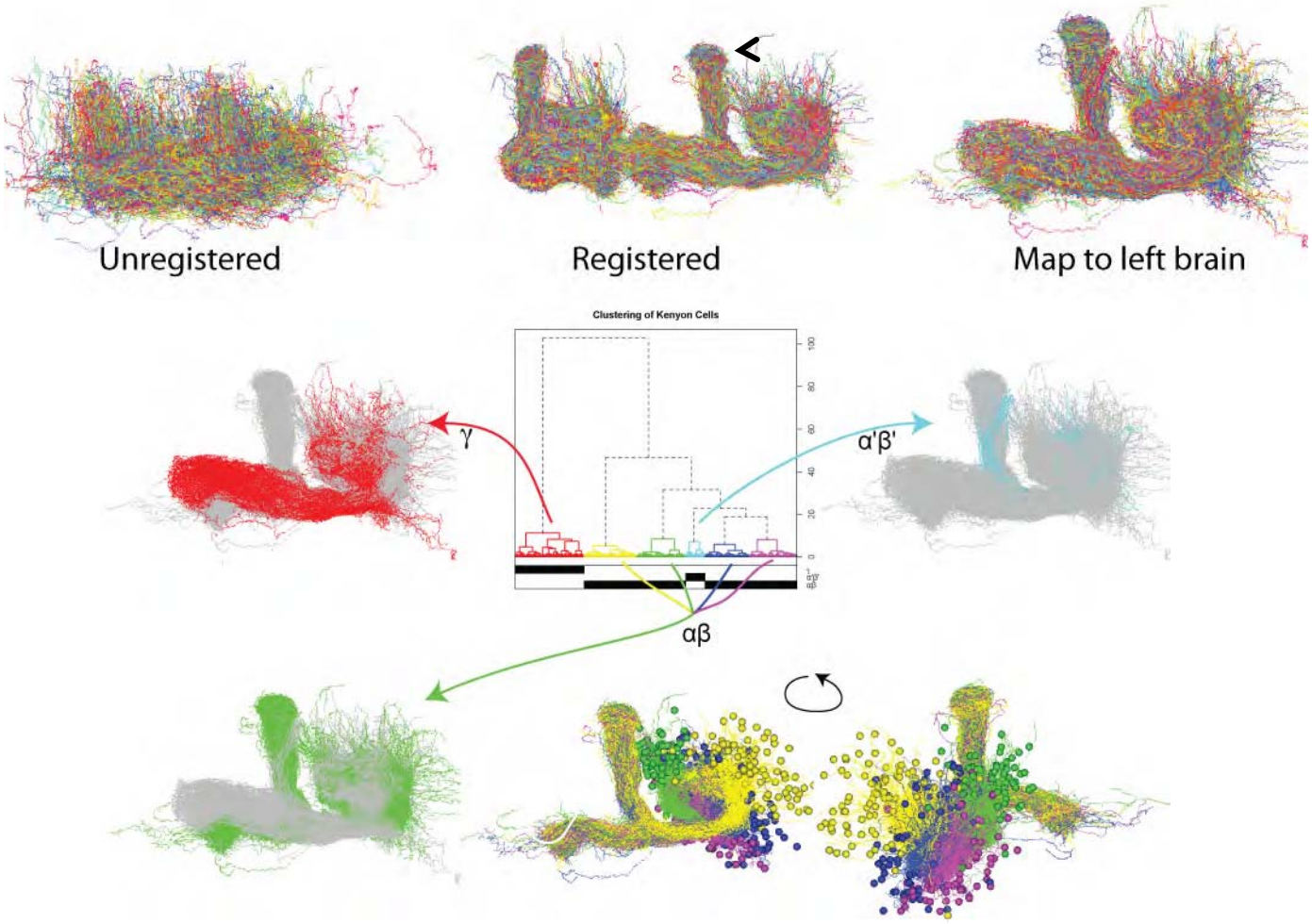
50
100
150
200
Query
Top Hit
0.0
0.2
0.4
0.6
0.8
1.0
nblast score

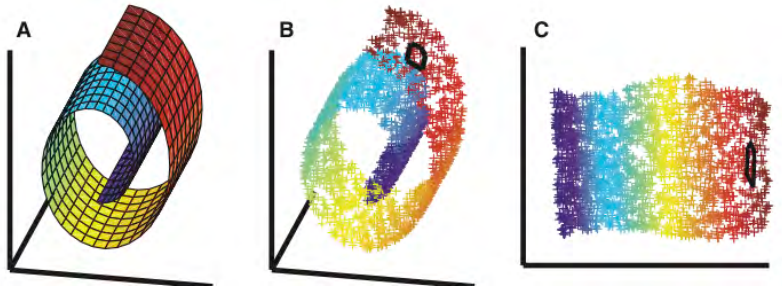


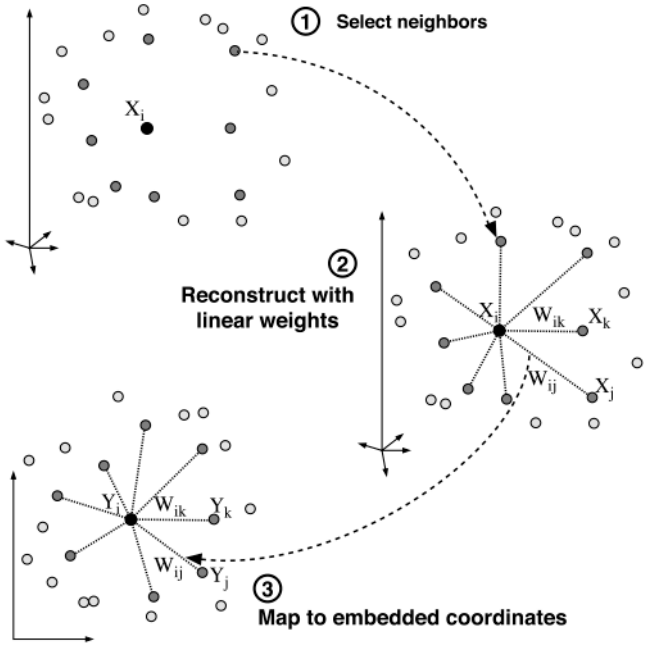
Clustering by Search Score

Example: 1500 Mushroom Body Neurons (required for olfactory memory)



Local Neighbourhood Methods



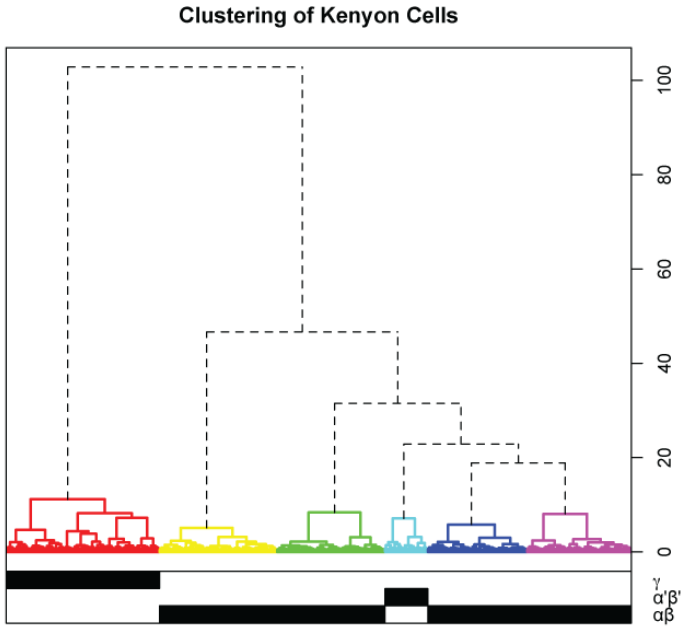


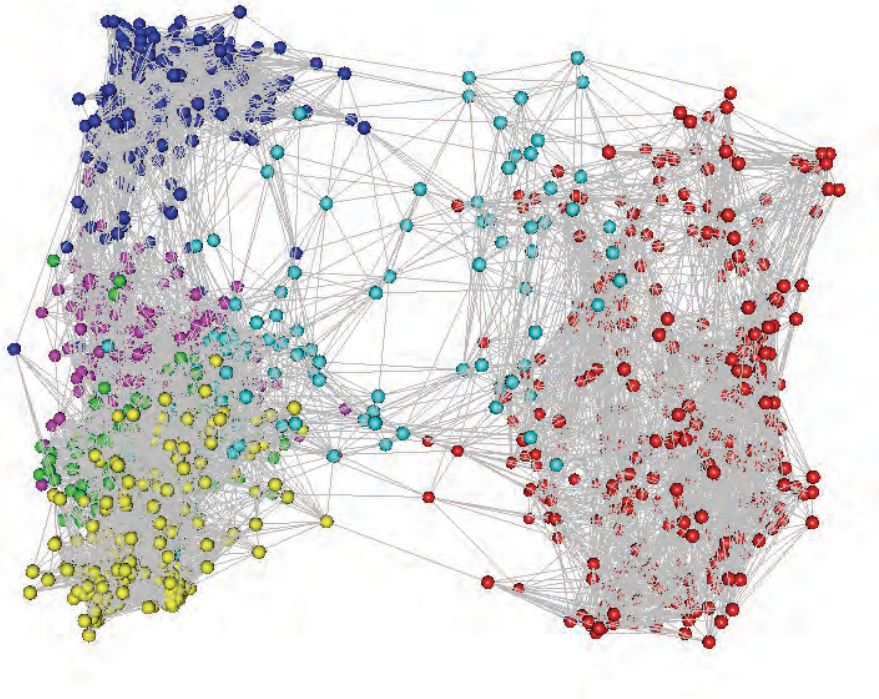
e.g. LLE, ISOMAP etc

- Convert all x all distance matrix into local neighbourhood graph
- Can visualise structure in high-dimensional data
- Can improve clustering results and time/space constraints for large data

Clustering vs ISOMAP

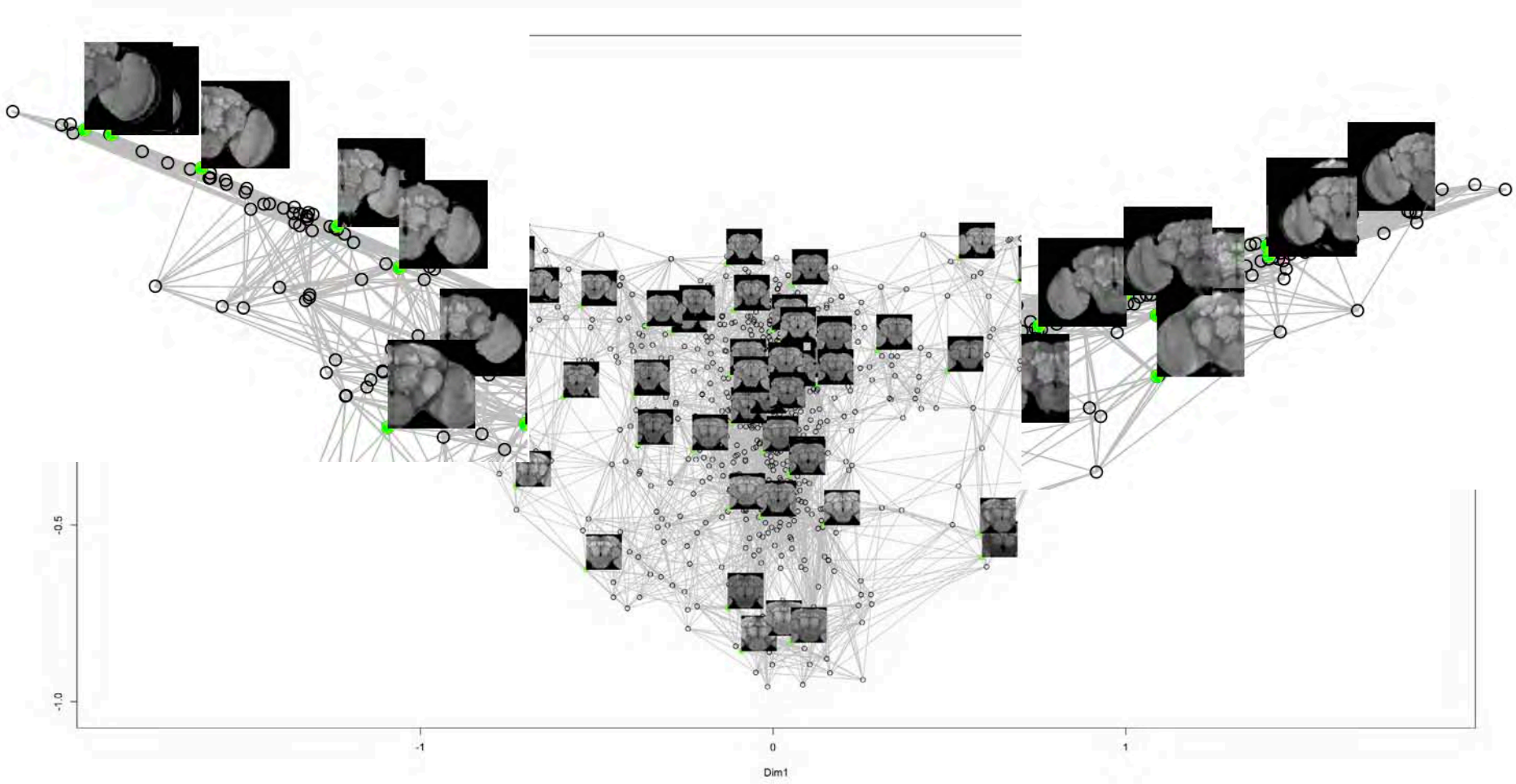
Non-linear dimension reduction allows visualisation of individuals in context of whole data structure





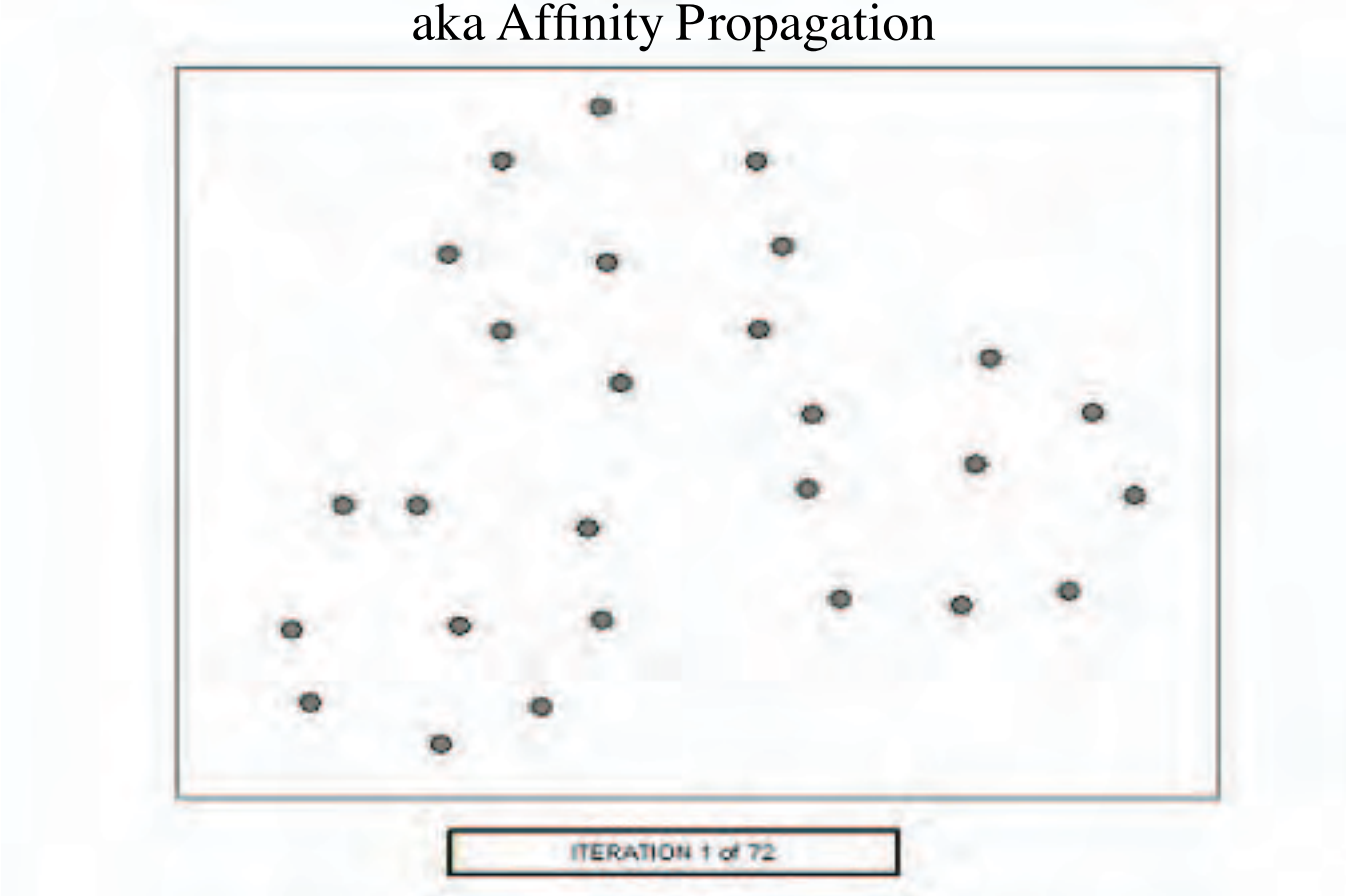
ISOMAP embedding
of distance matrix

ISOMAP and Registration Pose Problem



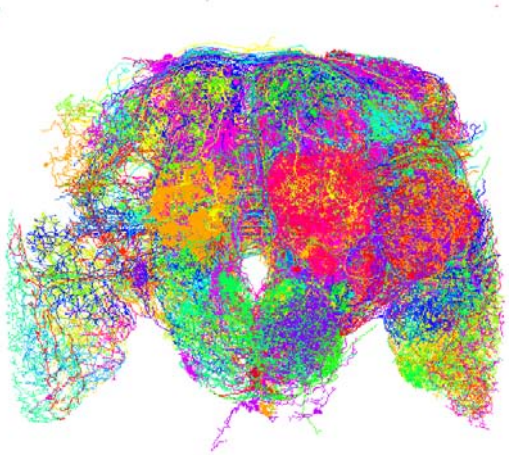
Message Passing Clustering

aka Affinity Propagation

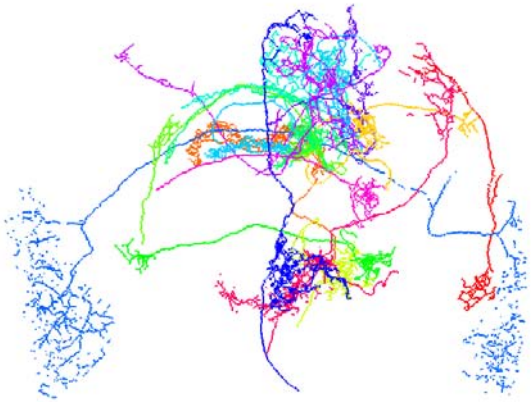


Frey and Dueck 2007

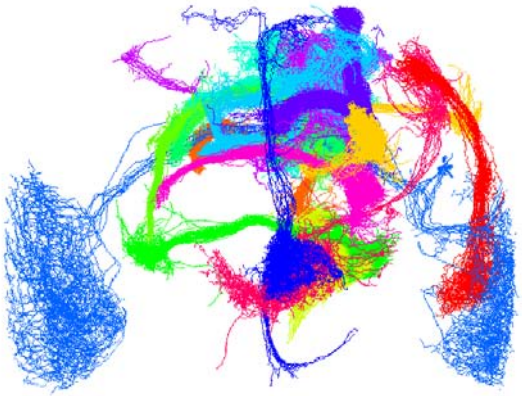
Message Passing Clustering



286 exemplars
(for 15198 neurons)



15 exemplars



Clusters for 15 exemplars
(total of 743 neurons)

Conclusions

- Neural Networks in the fly are highly stereotyped and can be mapped to single cell level
- Differences in network structure can explain some features of sexually dimorphic behaviour
- Neuron mapping data present interesting problems in analysis both of neural connectivity networks and to tame high dimensional neuronal structure data.

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Barry Dickson

Other Lab Members

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Shahar Frechter
Julian Ng
Mike Dolan

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National Tsing Hua University, flycircuit.tw

European Research Council | erc

jefferislab.org
github.com/jefferis
flybrain.stanford.edu
www.nitrc.org/projects/cmtk

MRC | Laboratory of Molecular Biology