Of Mice and Men

Seminar in Mathematics, Physics & Machine Learning

IST

6 June 2024

EPFL

Project leader: Lida Kanari (Blue Brain Project)

The topology of neuron morphologies

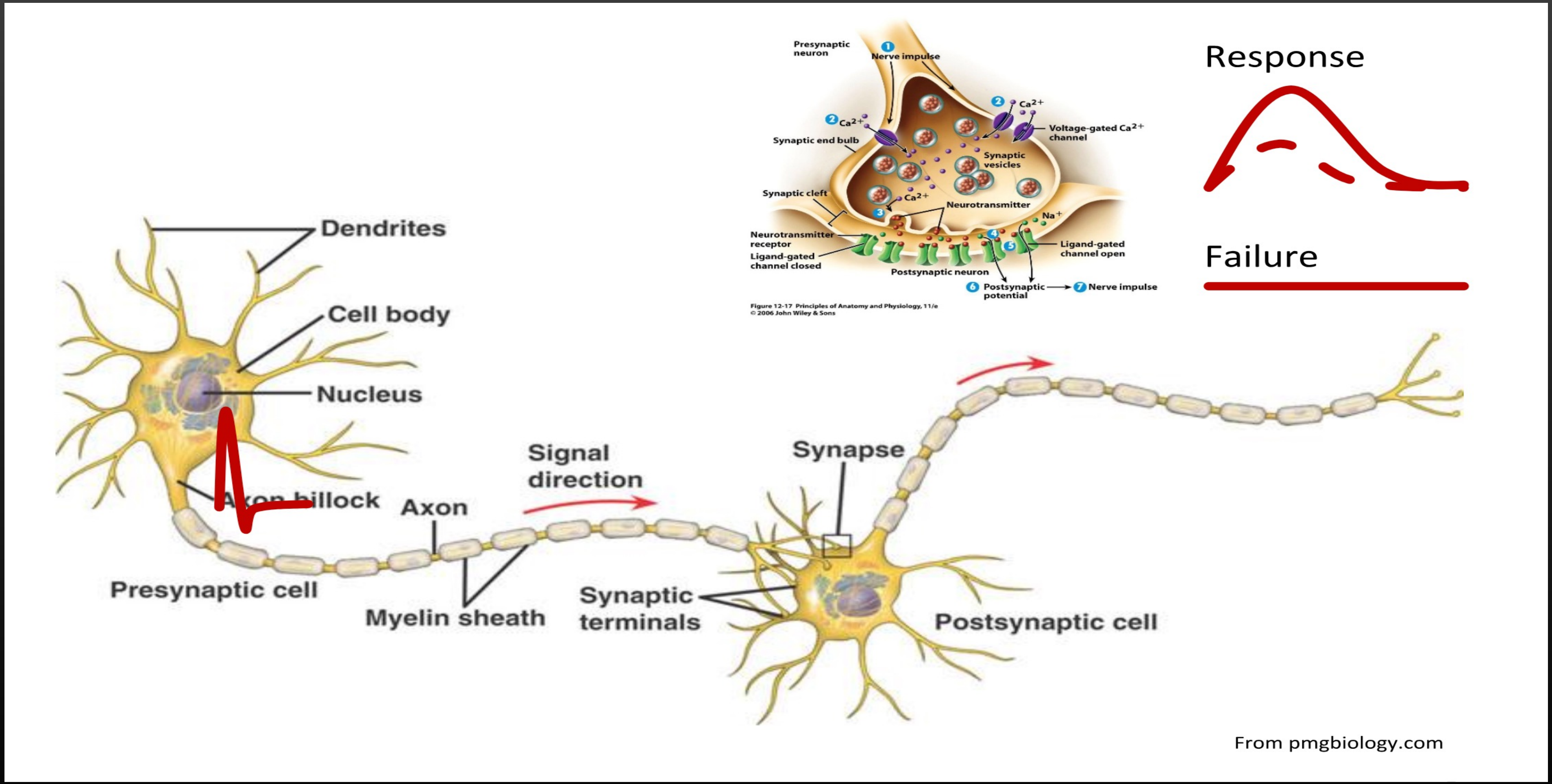
Y. Deitcher et al, Cerebral Cortex, 2017.

L. Kanari et al, Neuroinformatics, 2018.

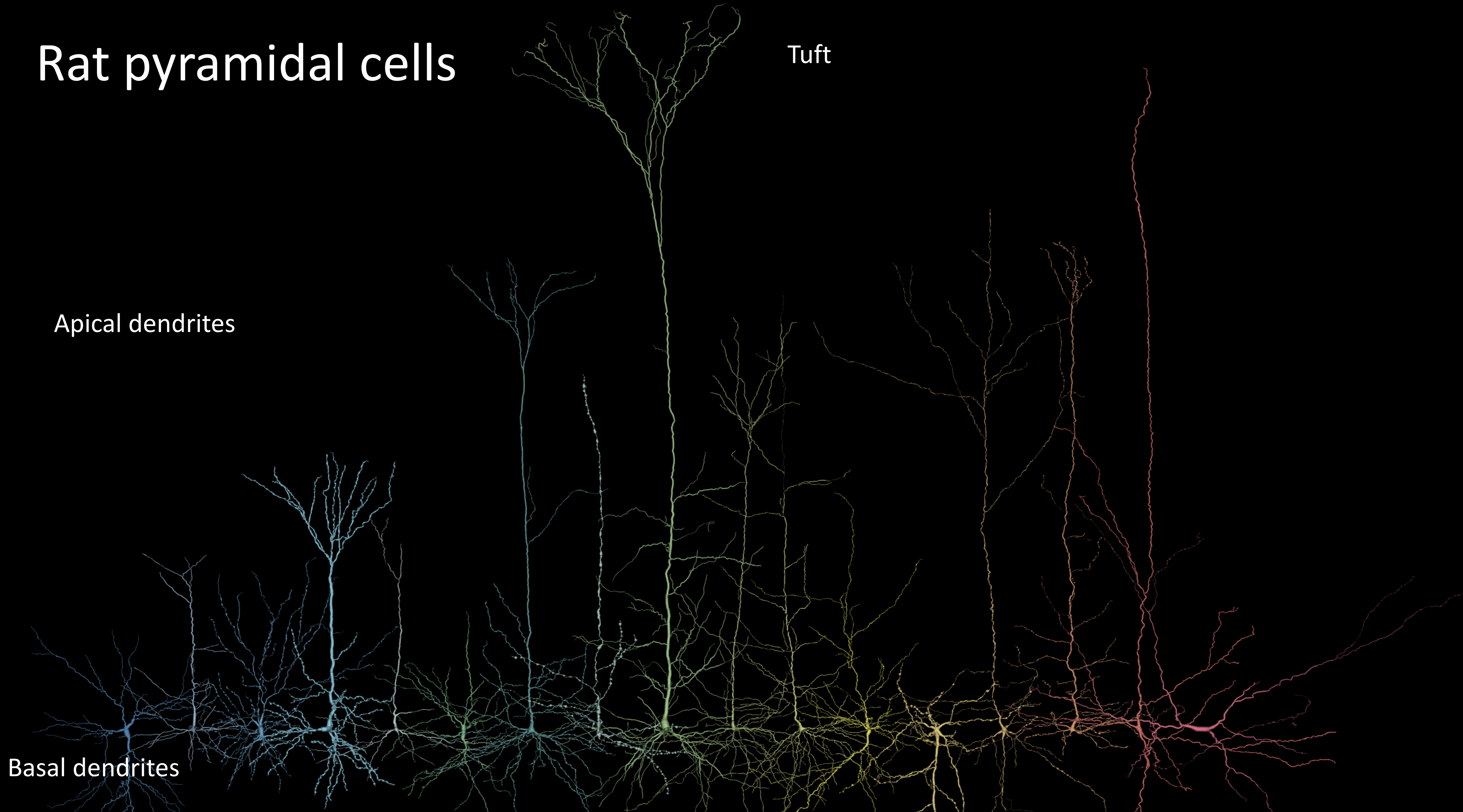
L. Kanari et al, Cerebral Cortex, 2019.

G. Colombo et al, Nature Neuroscience, 2022.

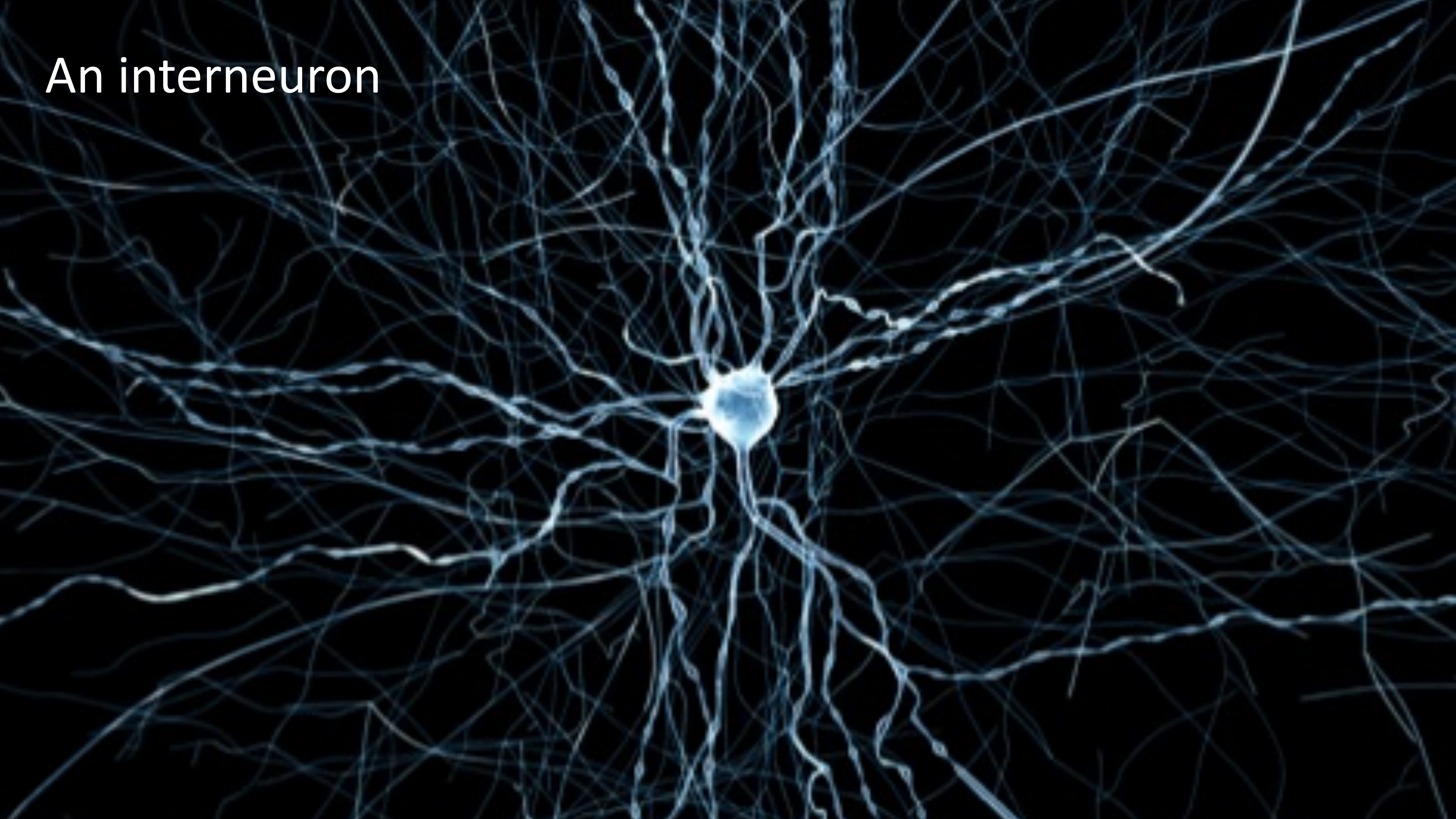
A (very) brief intro to neurobiology



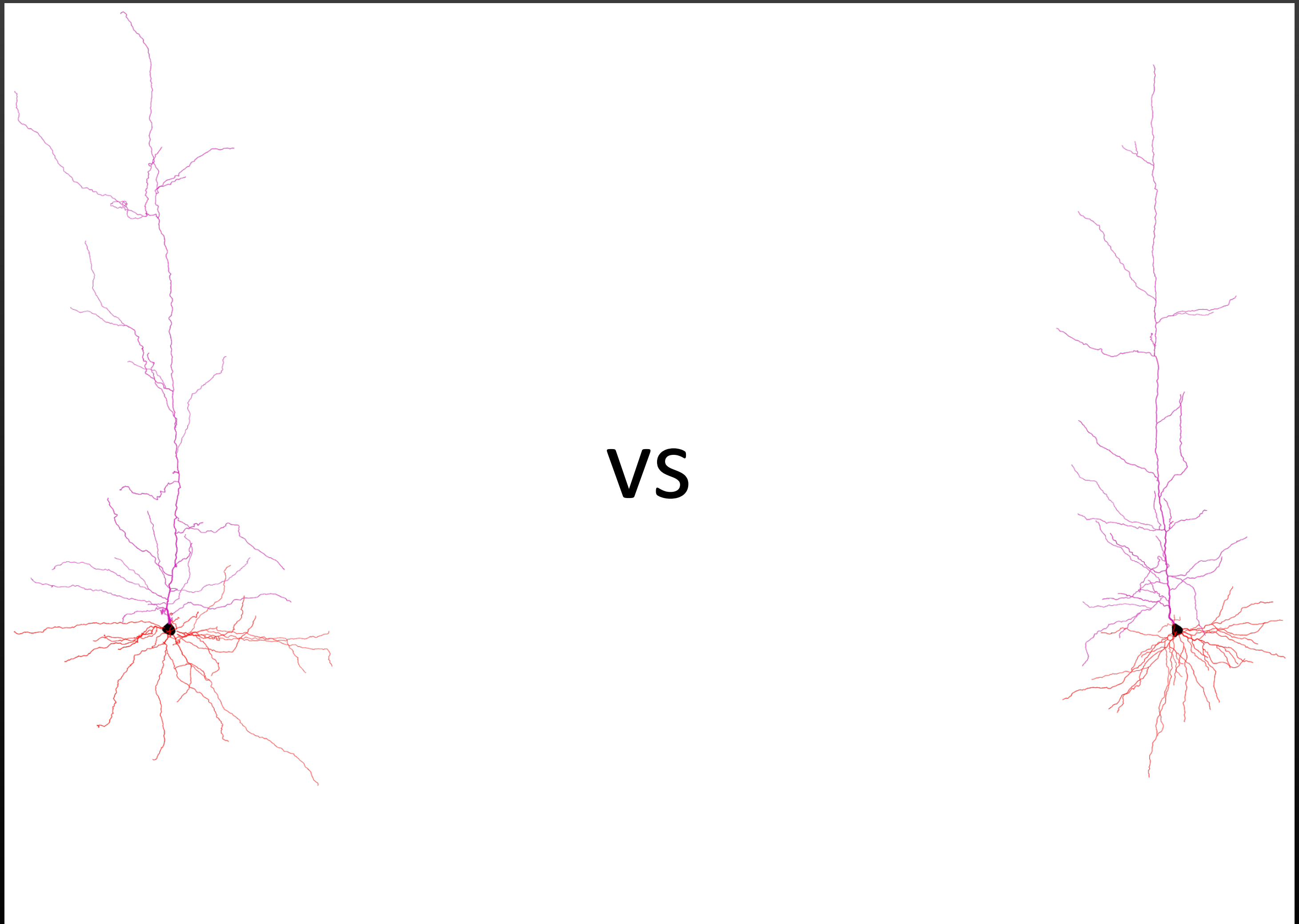
Rat pyramidal cells



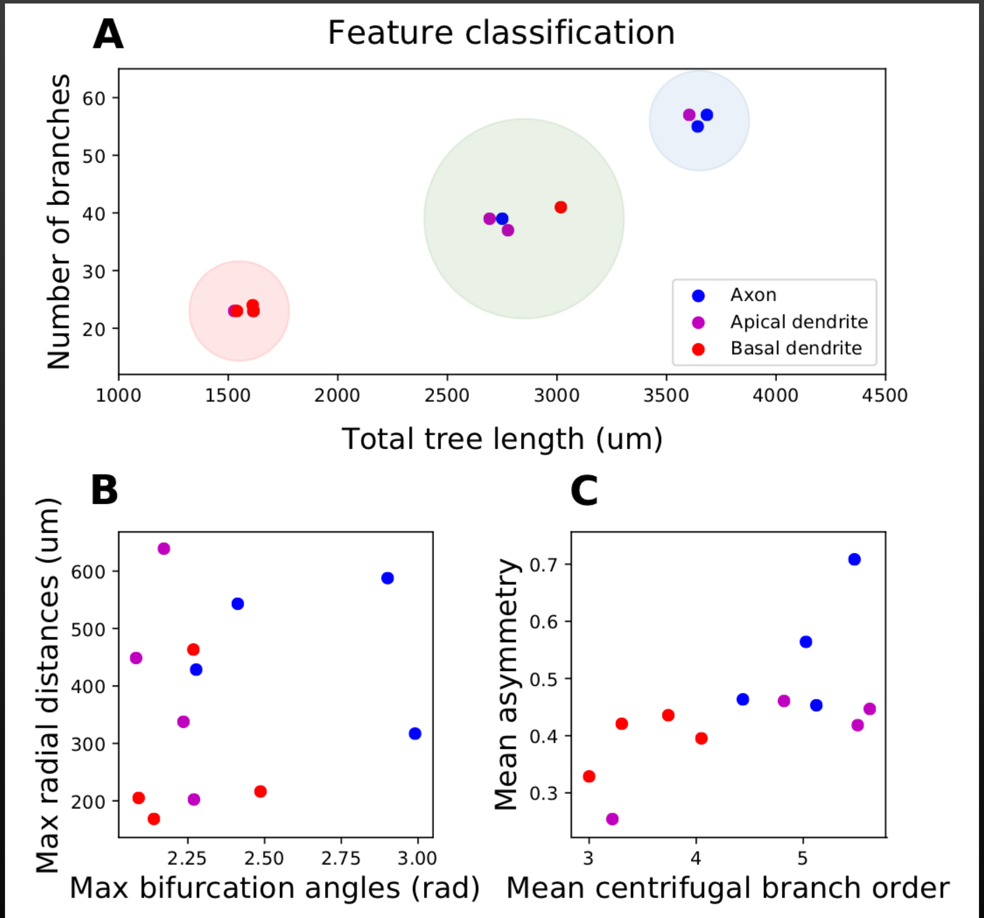
An interneuron

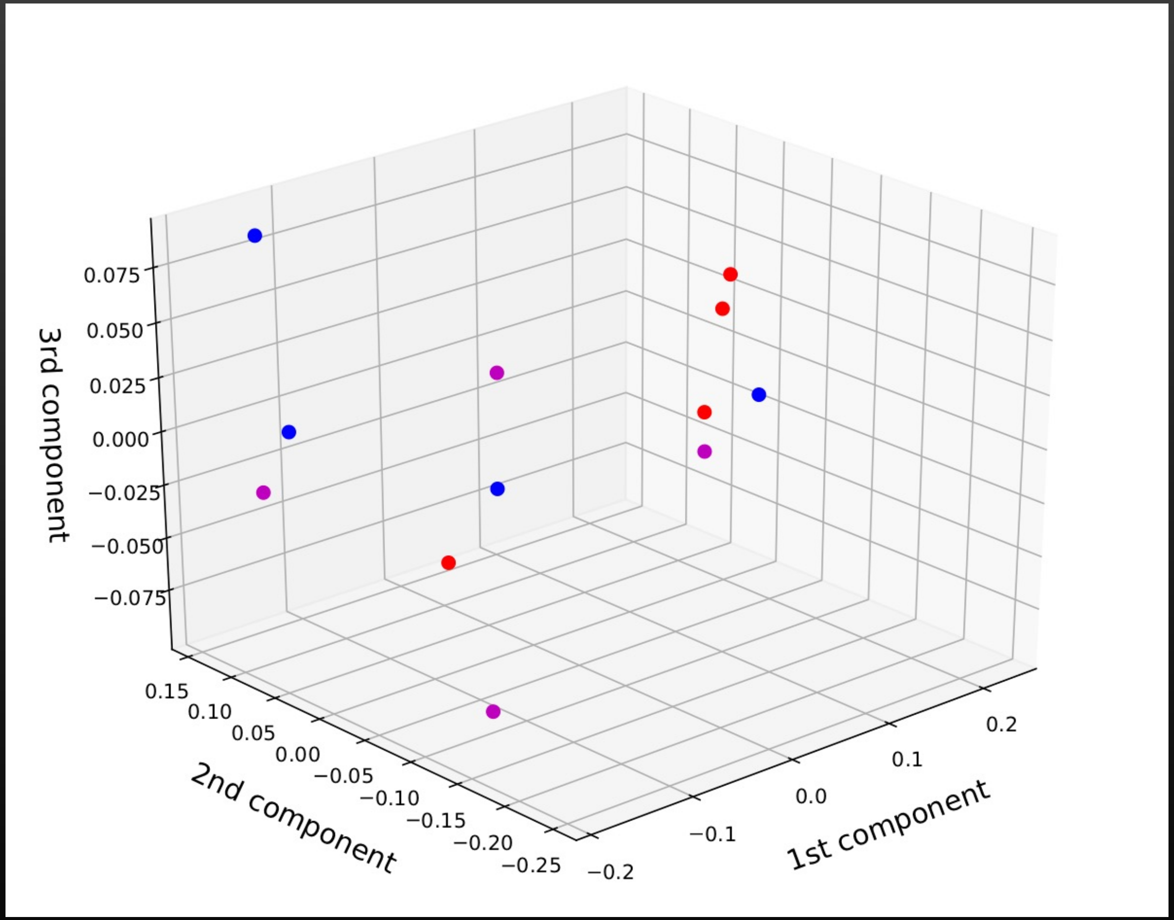


How to classify neuron morphologies?



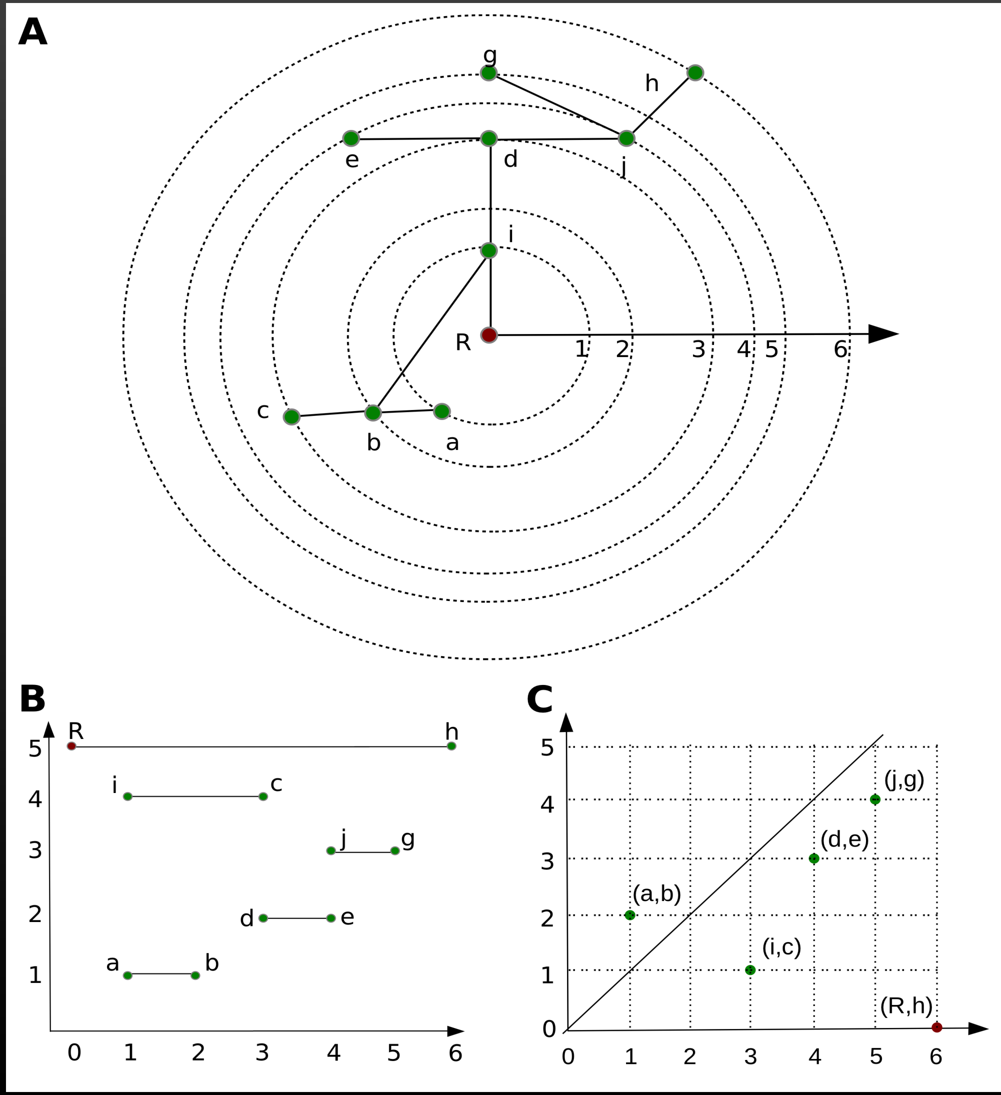
Standard morphometrics don't suffice





i) The TMD

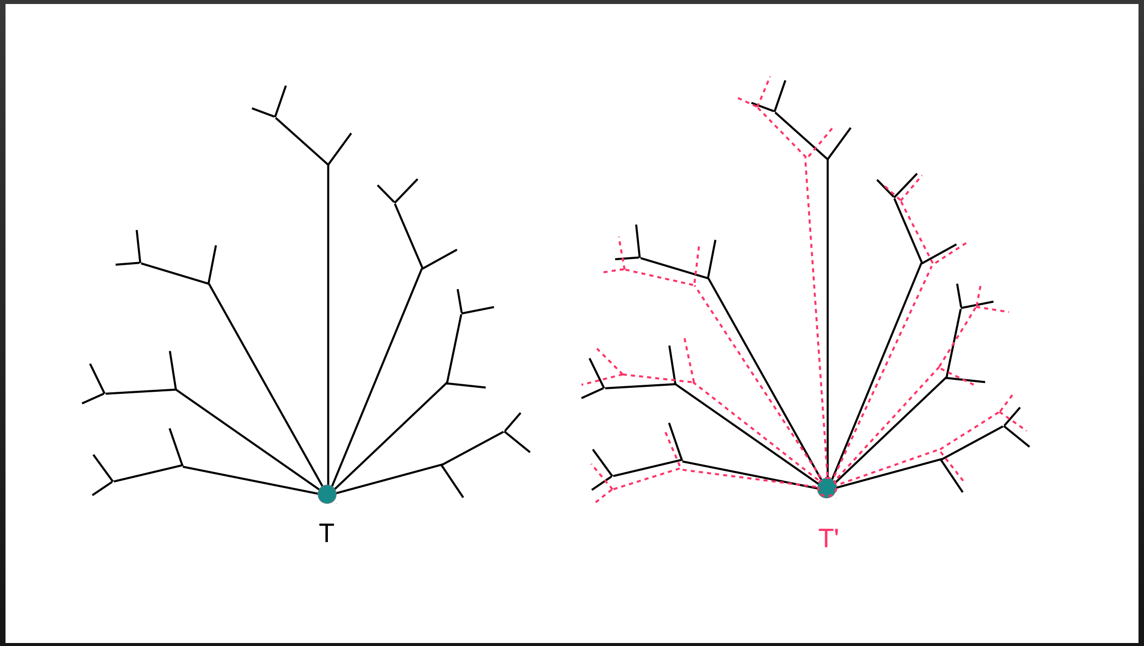
The TMD algorithm

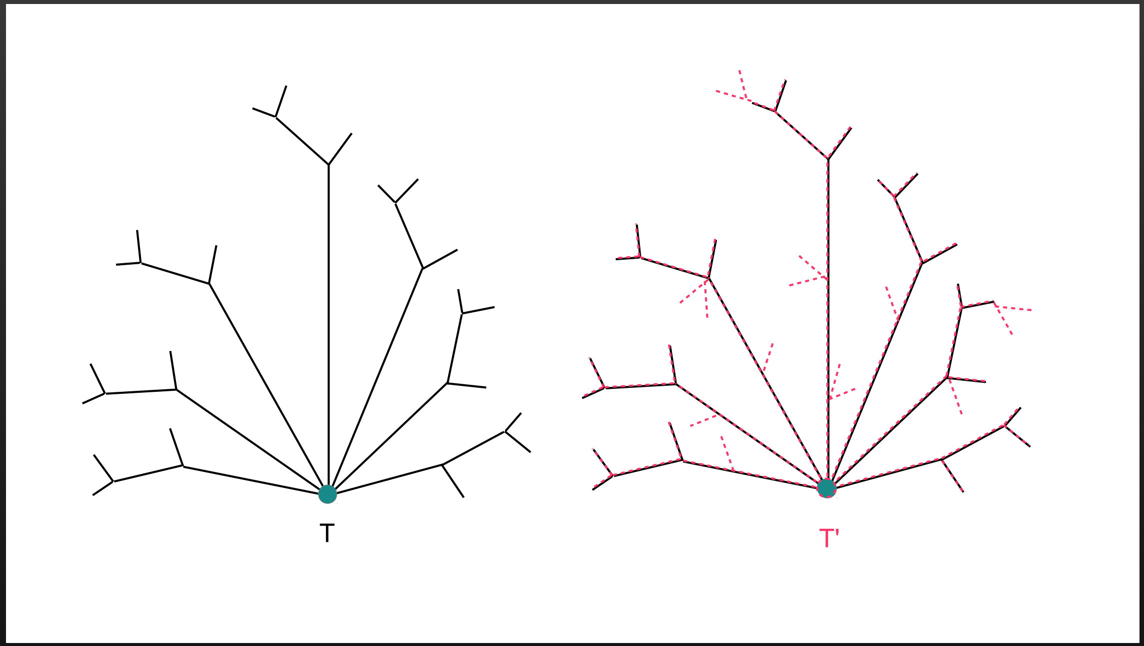


Idea: Starting at the leaves and descending recursively to the root, decompose the tree into branches, while respecting the Elder Rule, i.e., at any bifurcation, the elder (longer) branch survives and the younger branch is broken off.

Integrate the topology of the tree and the geometry of its embedding in space into a surprisingly powerful global descriptor.

Possible small errors and stability

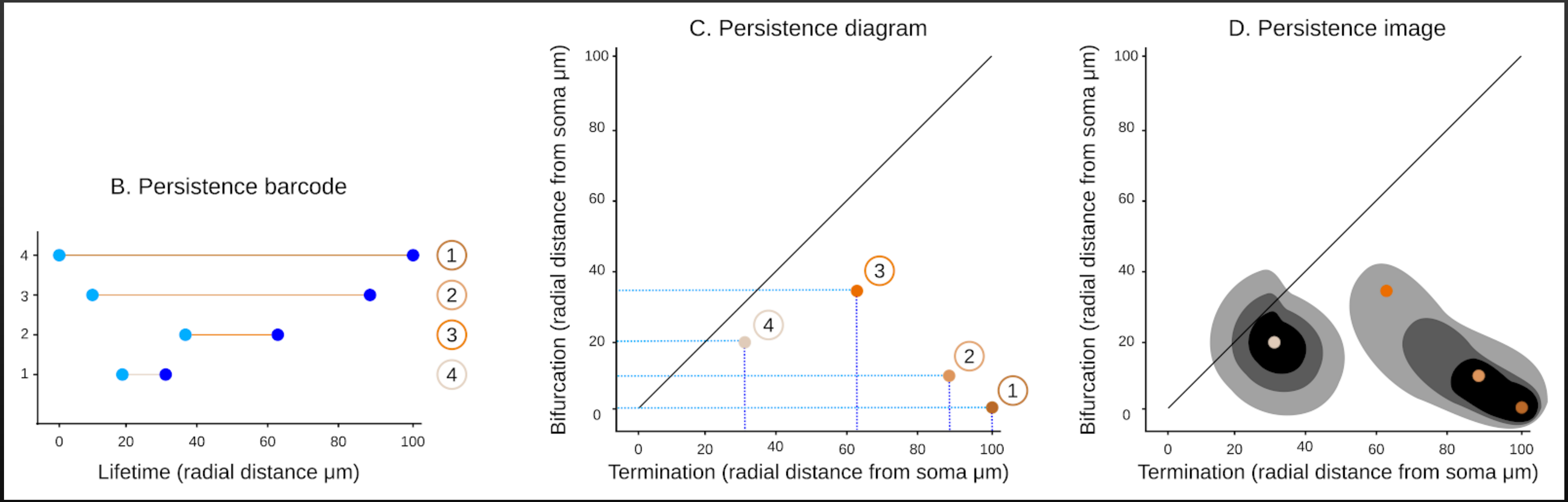




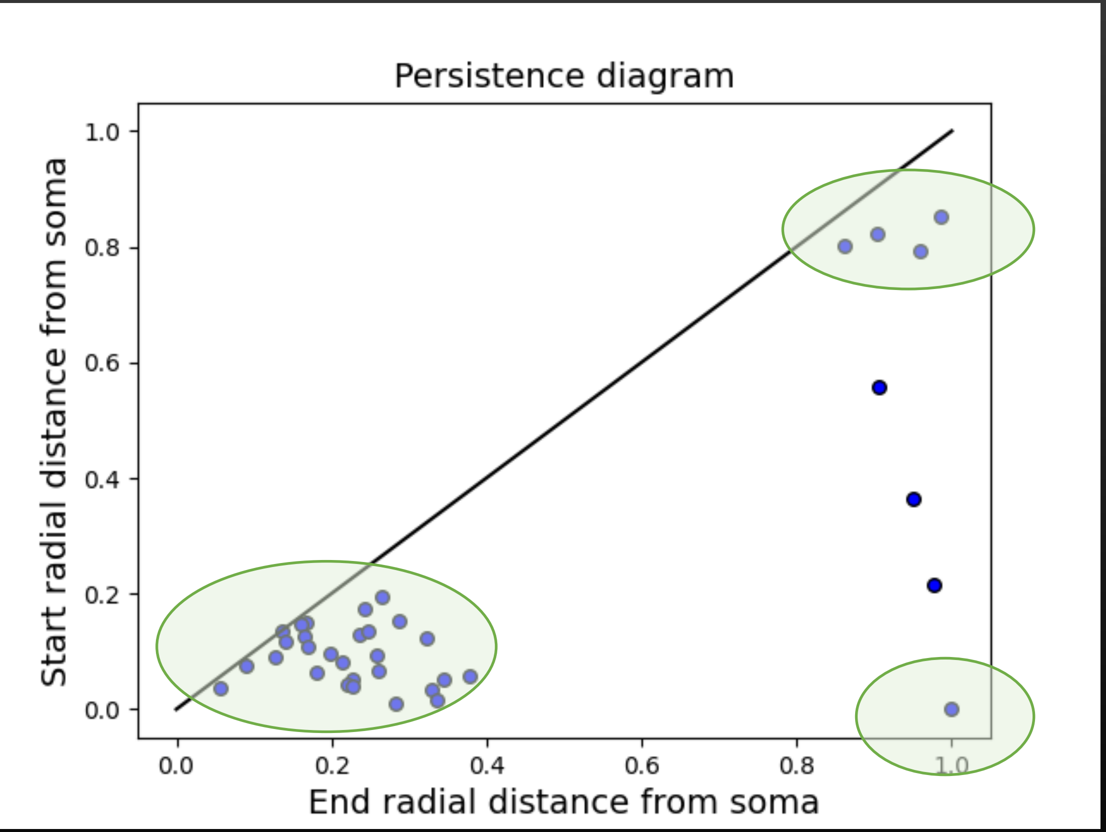
Theorem: The TMD is stable with respect to small errors of reconstruction, for both the bottleneck and the 1-Wasserstein distances.

Kanari et al. (2017), Beers et al. (2022)

Alternative representations

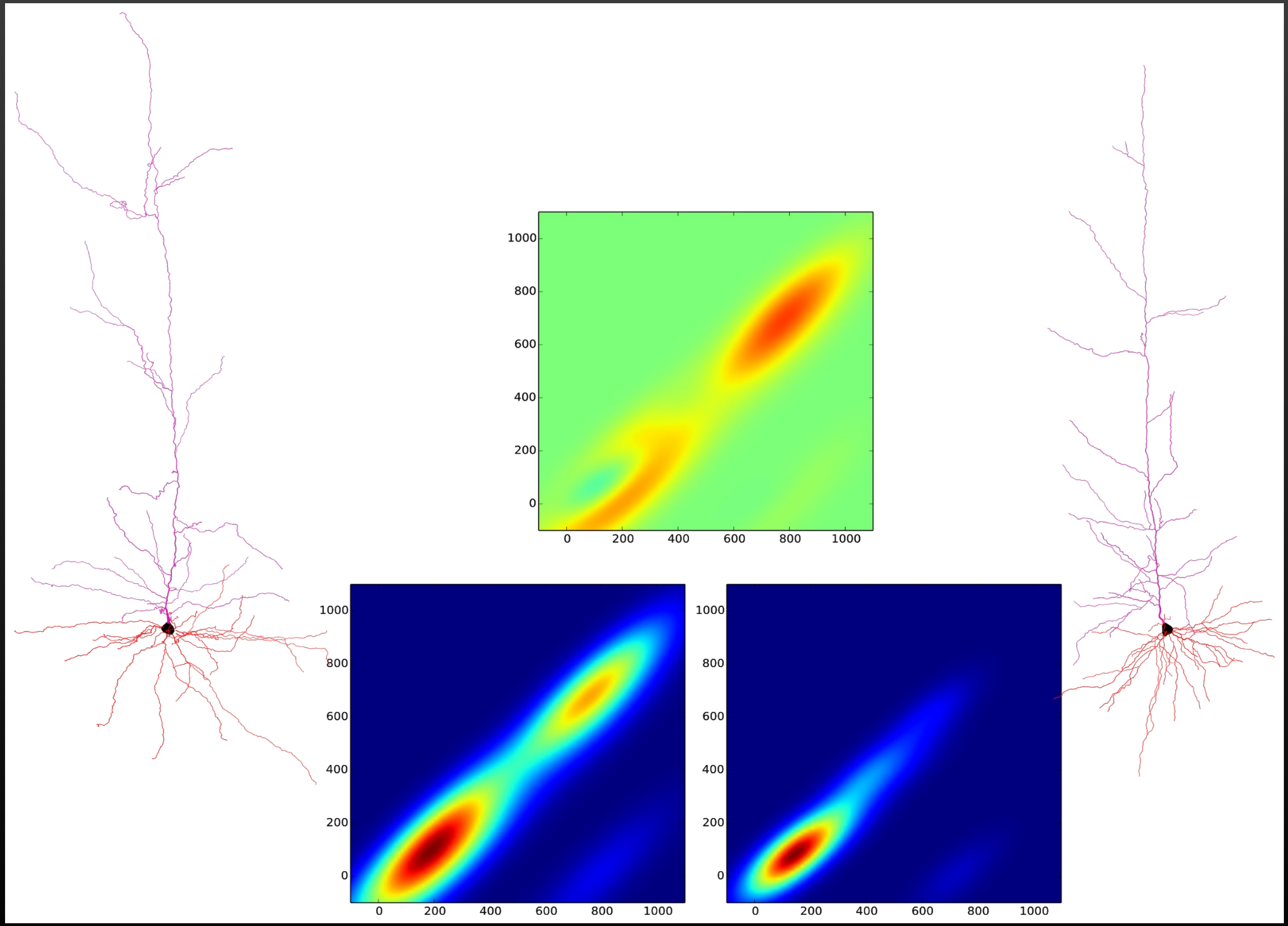


Interpretation of the TMD



- Number of points = number of branches
- Distance from the diagonal = length of the branch
- Point farthest from the diagonal = apical main trunk
- Points near the origin = obliques near the soma
- Points far from the origin, near the diagonal = apical tuft far from the soma

The TMD in our motivating example



ii) Applications of the TMD

Interspecies comparison

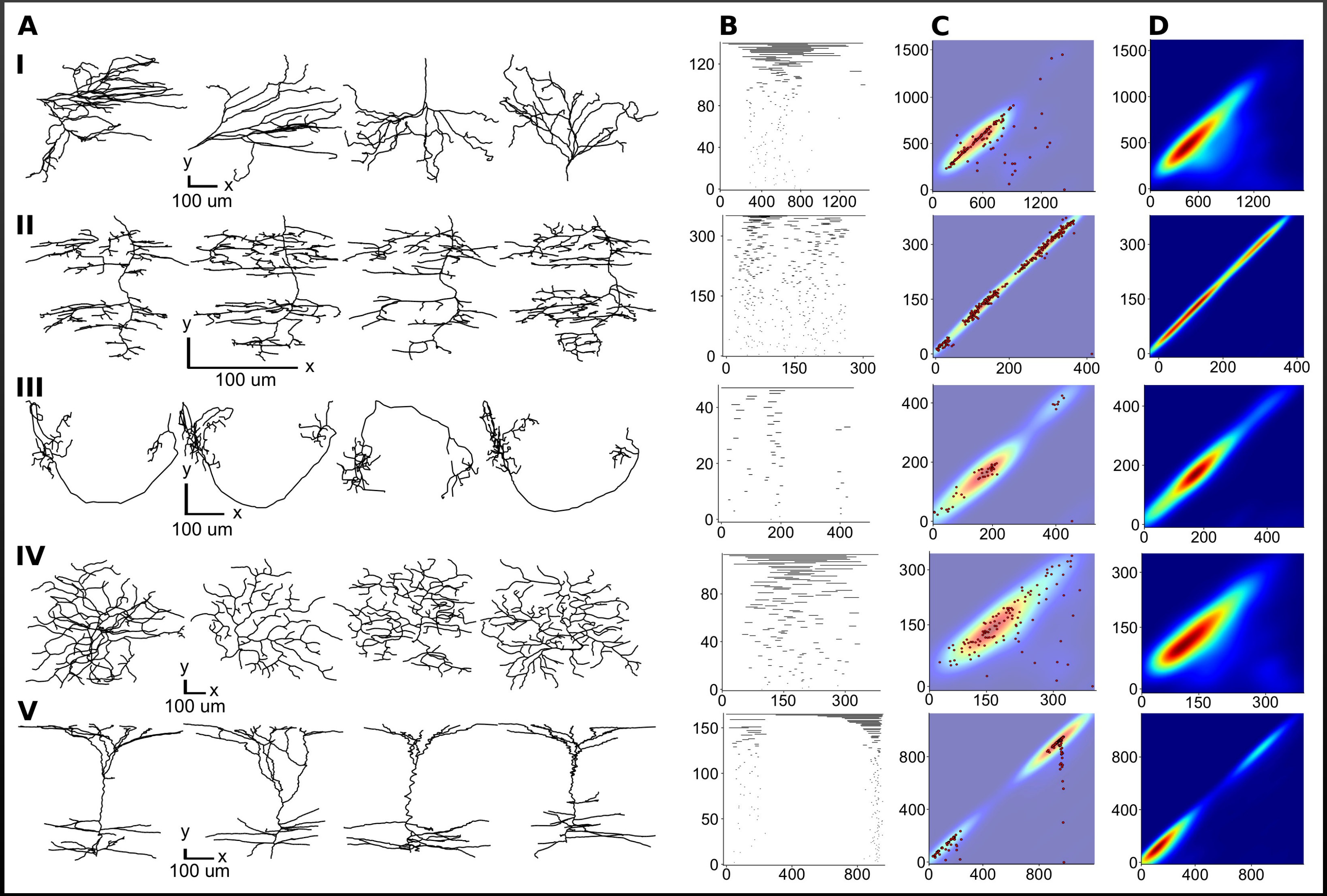
Cat

Dragonfly

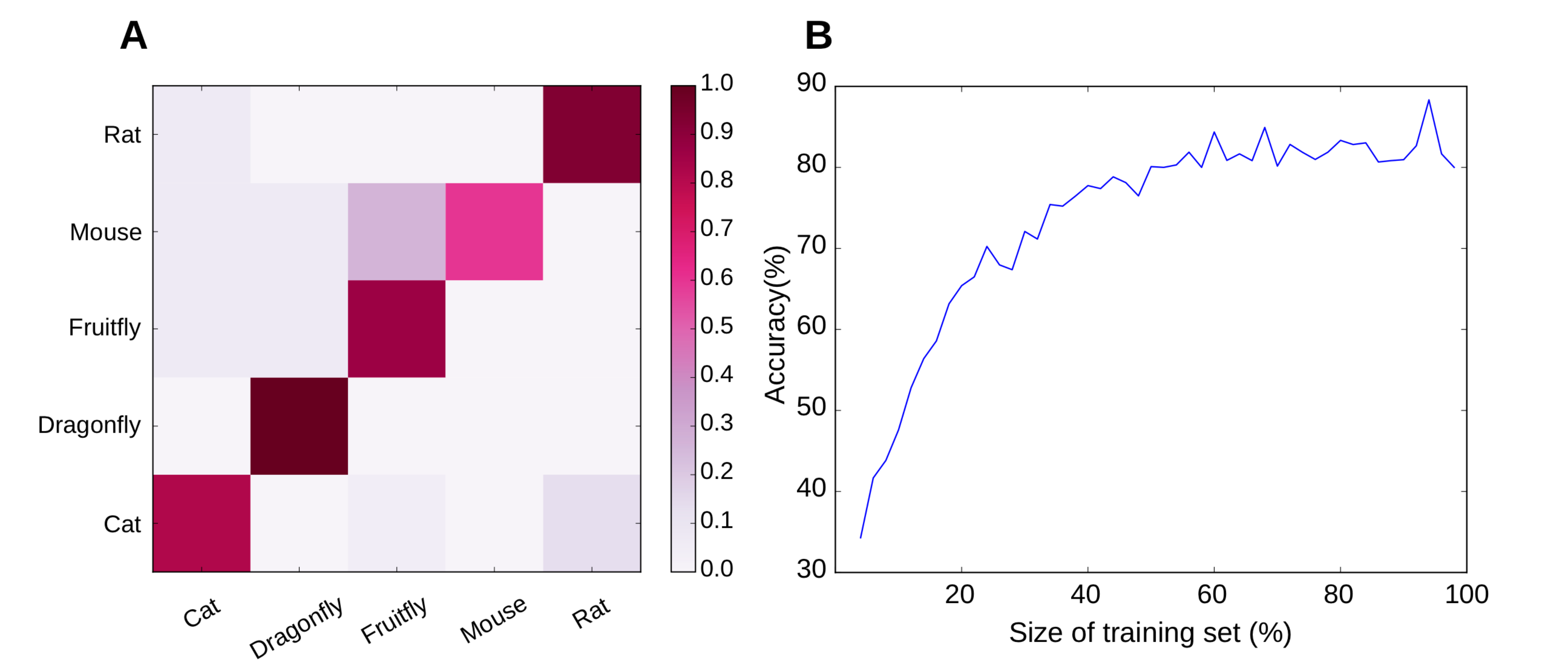
Fruitfly

Mouse

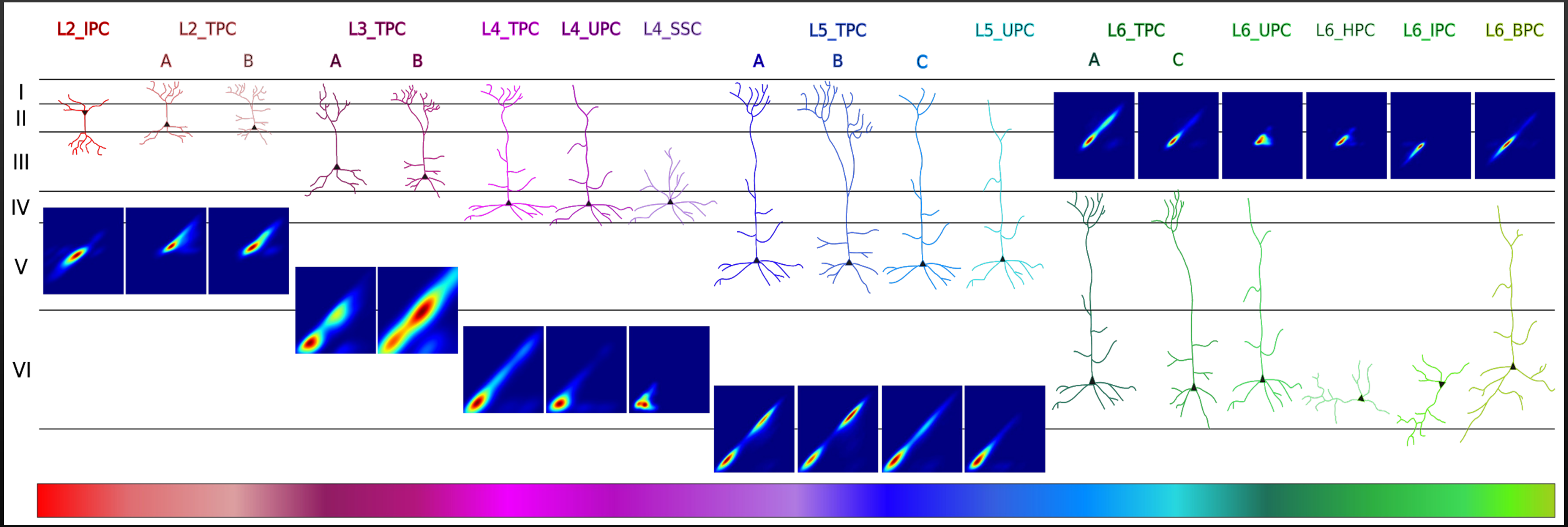
Rat



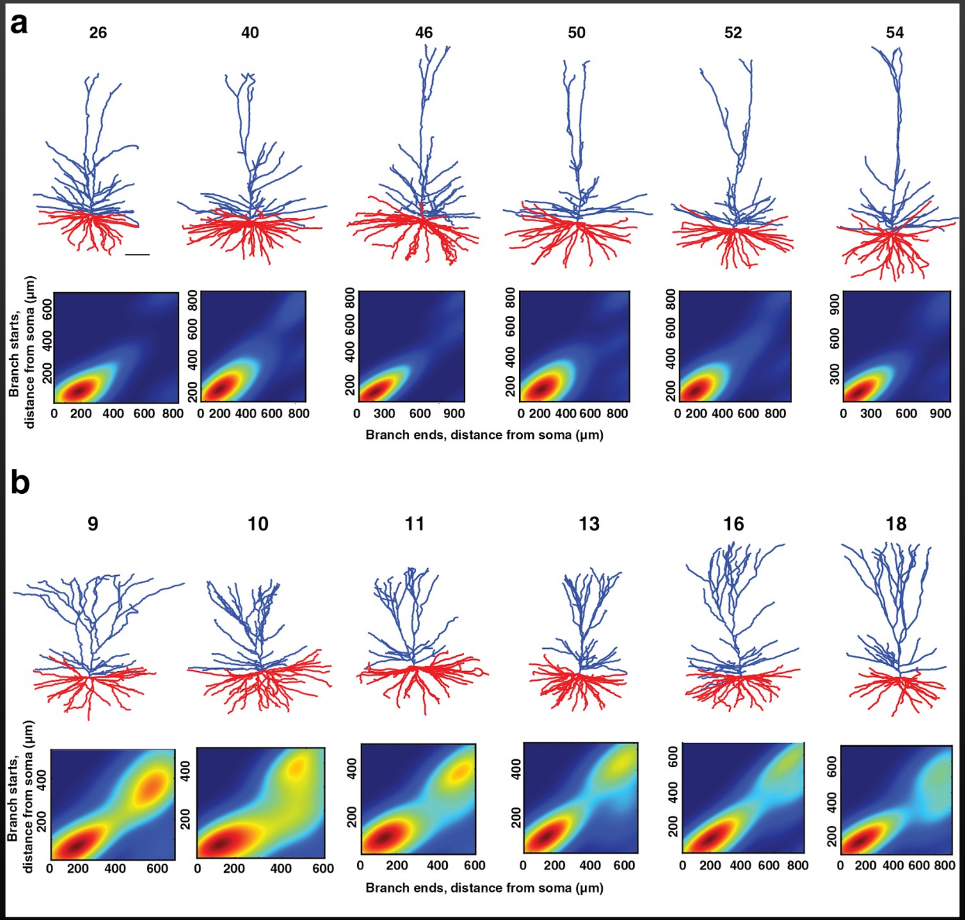
Training the classifier

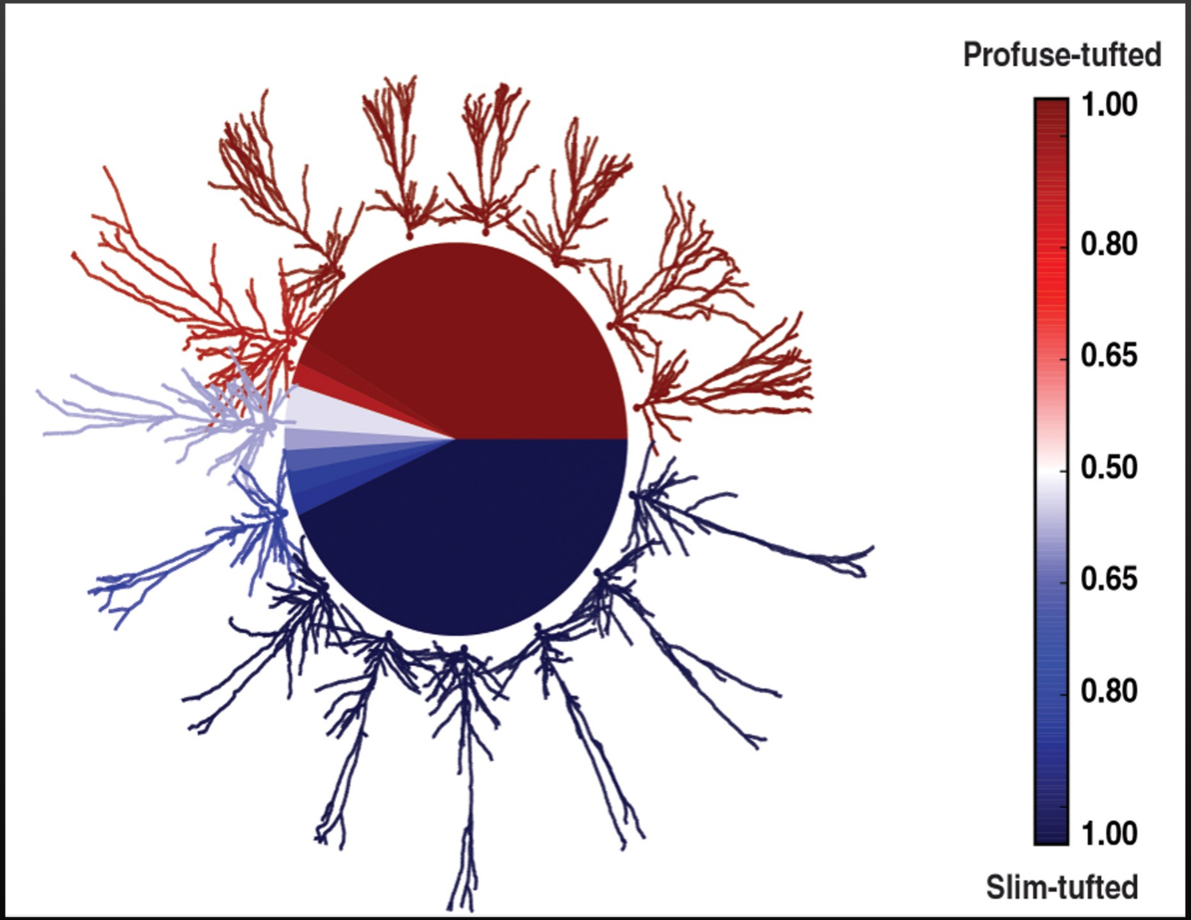


TMD of rat pyramidal cells

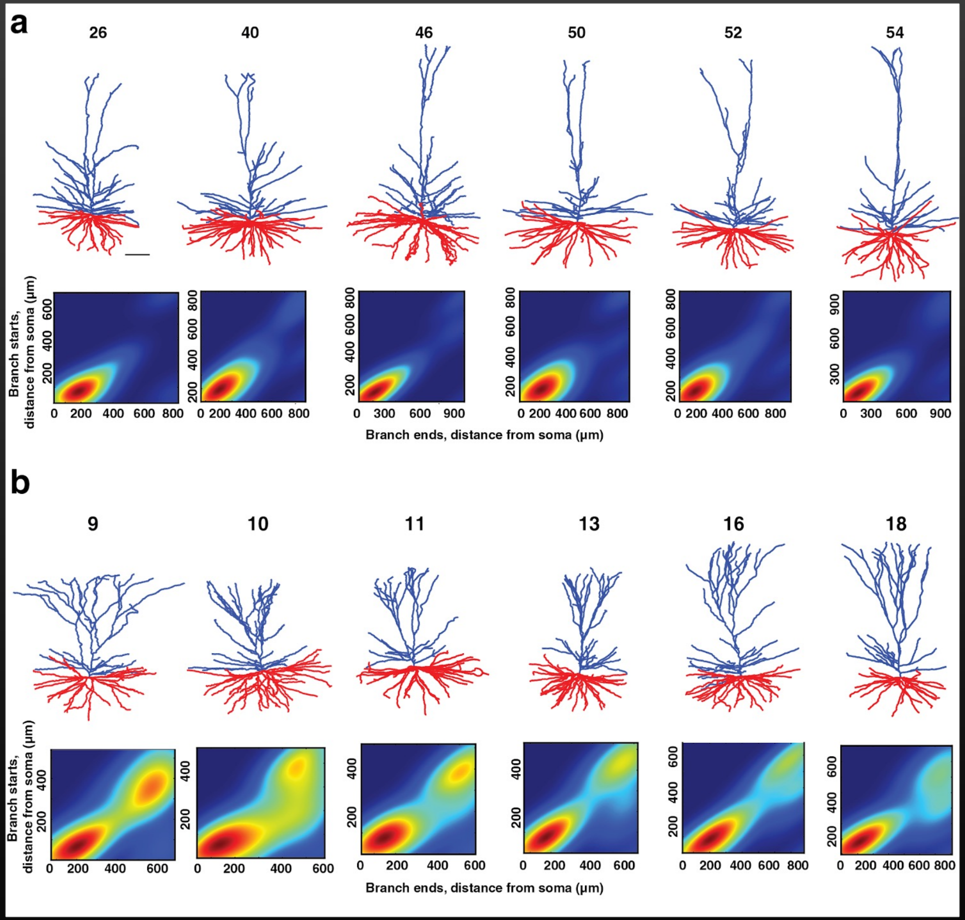


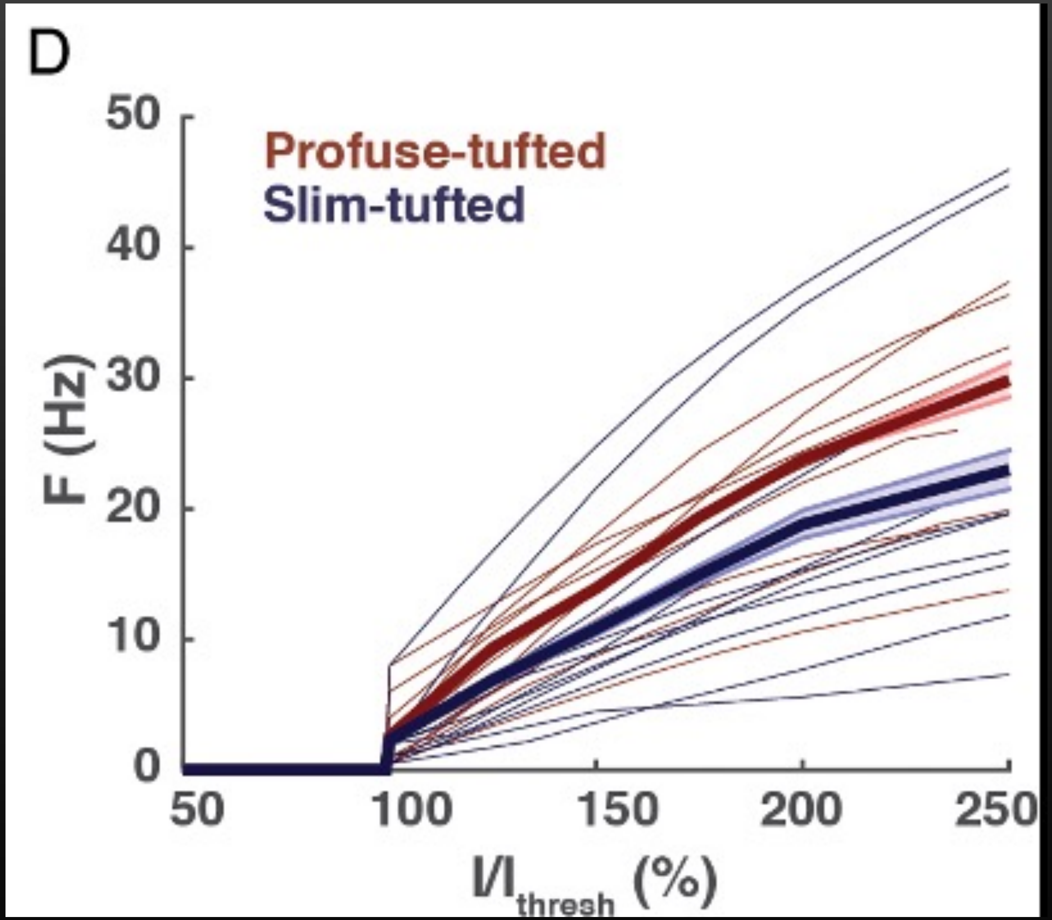
Clustering of human pyramidal cells



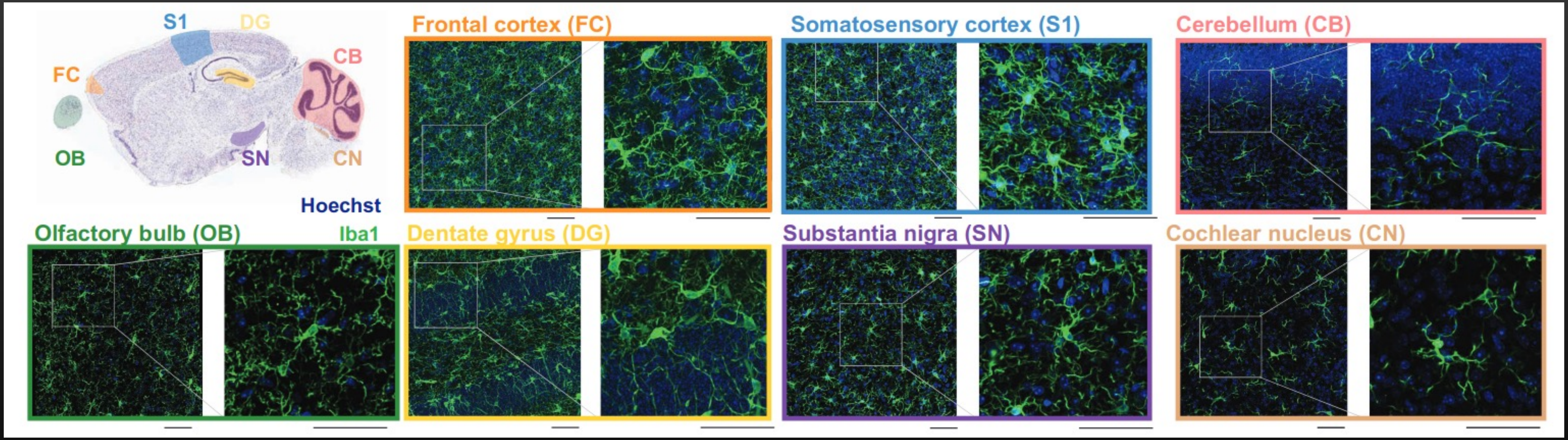


Clustering of human pyramidal cells

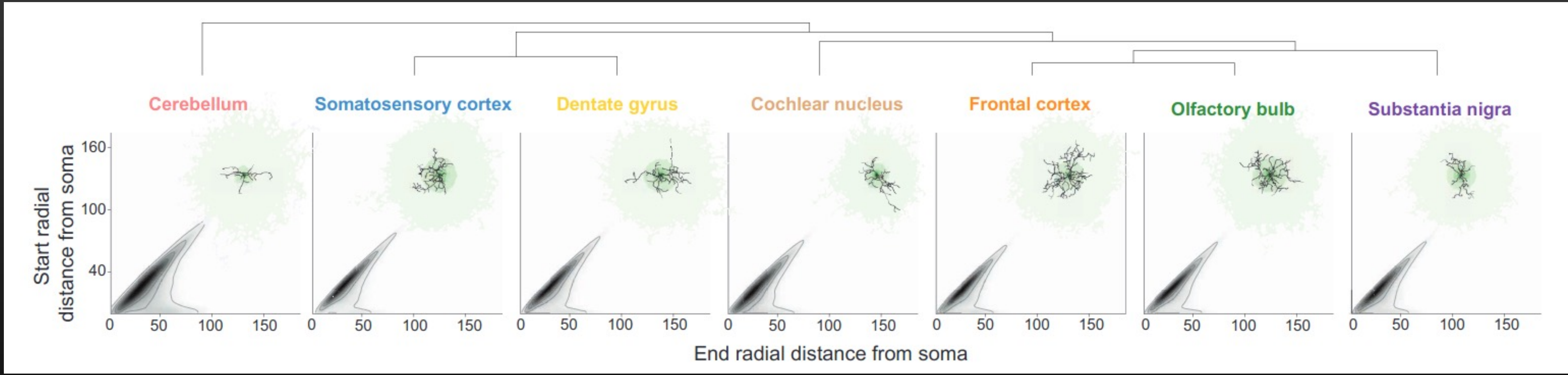




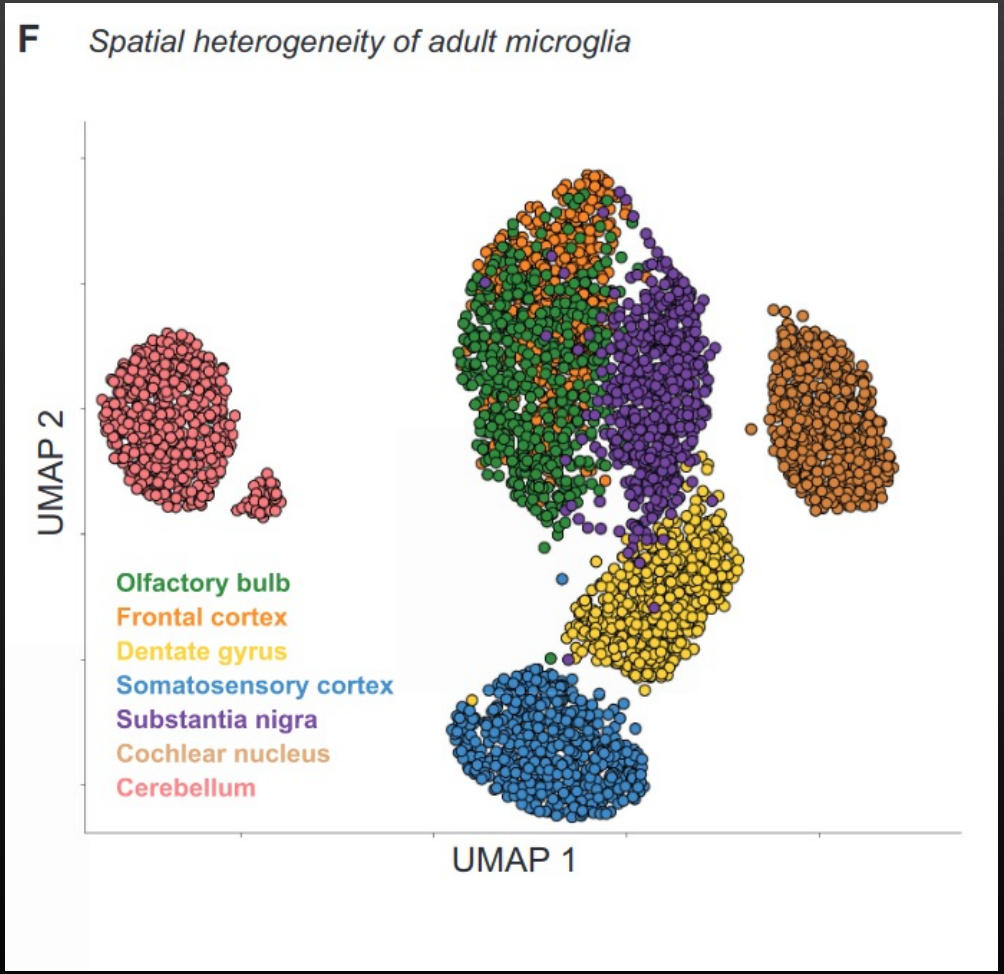
Morphological characterization of microglia



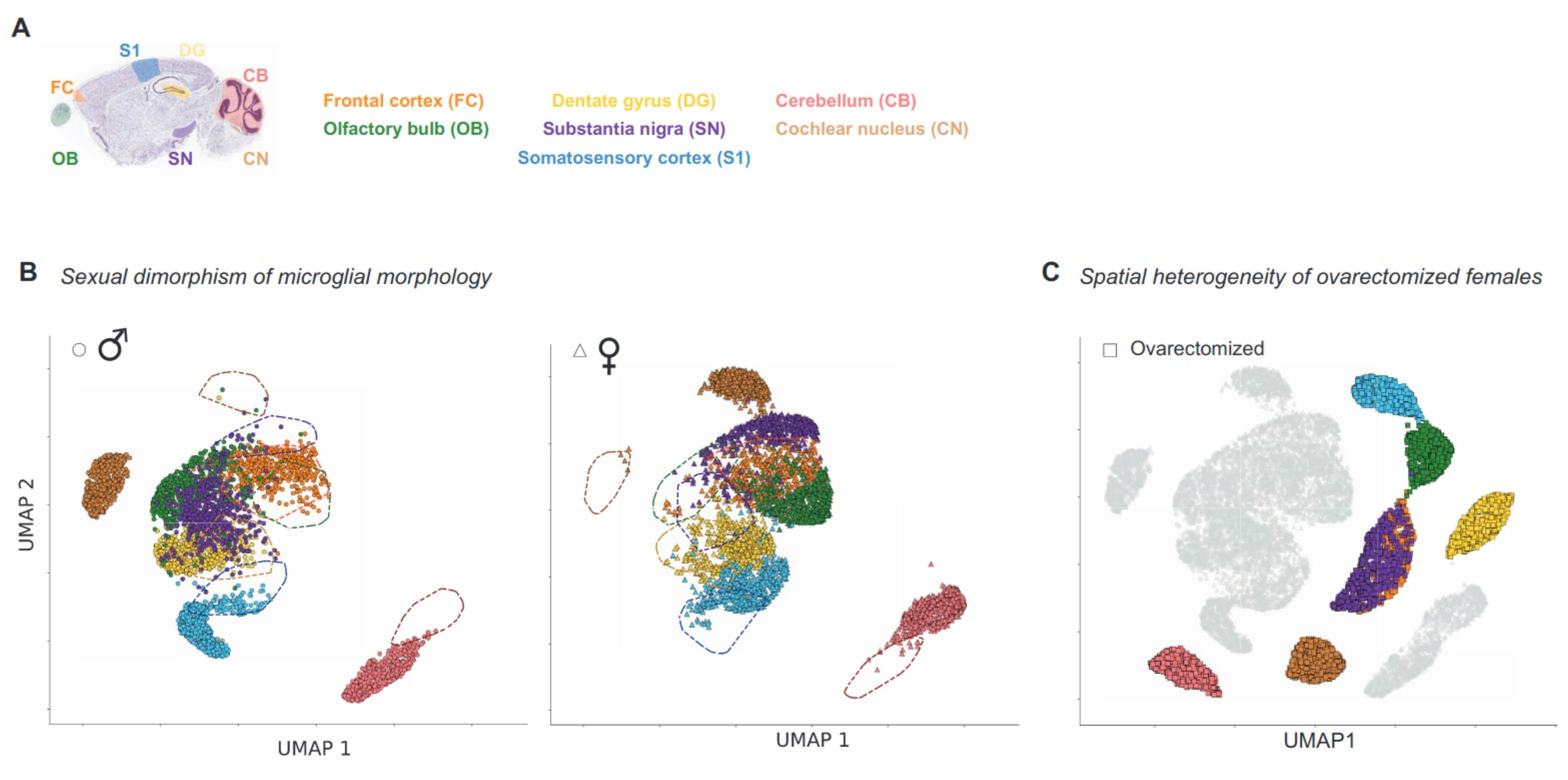
Morphological characterization of microglia



Morphological characterization of microglia



Morphological characterization of microglia



Of mice and men

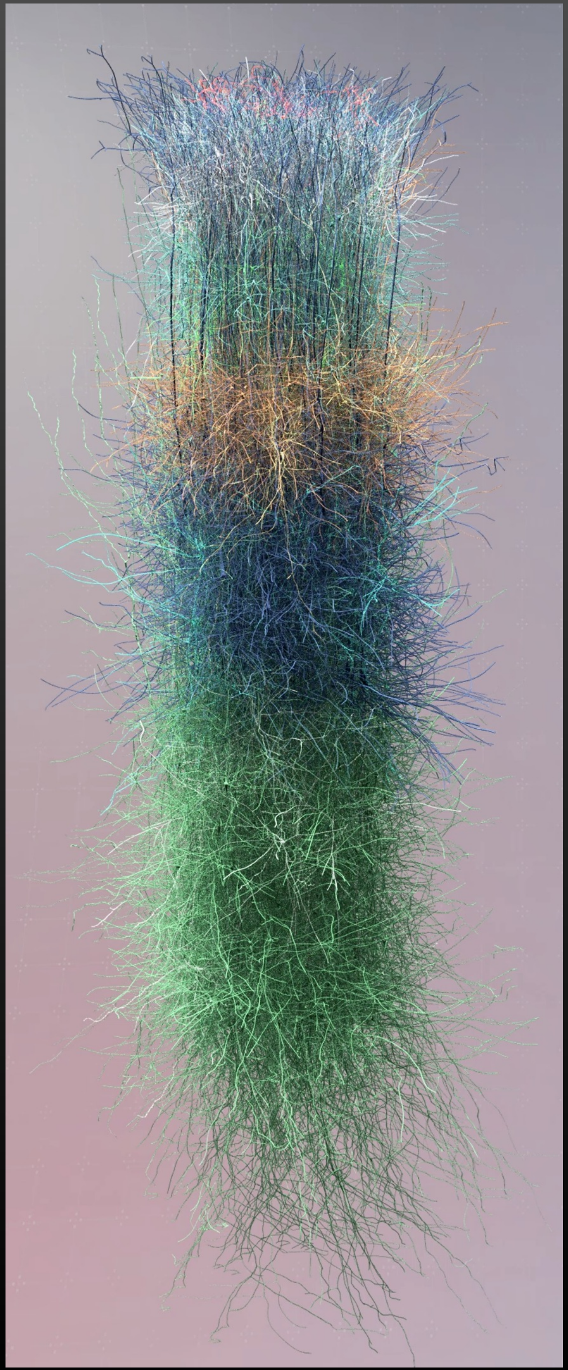
L. Kanari, et al., bioRxiv, 2023.

Questions

- What distinguishes human from mouse neurons?
- Are the differences merely a matter of scale?
- What are the consequences of these differences for the structure and function of human and mouse connectomes?

A connectome core sample

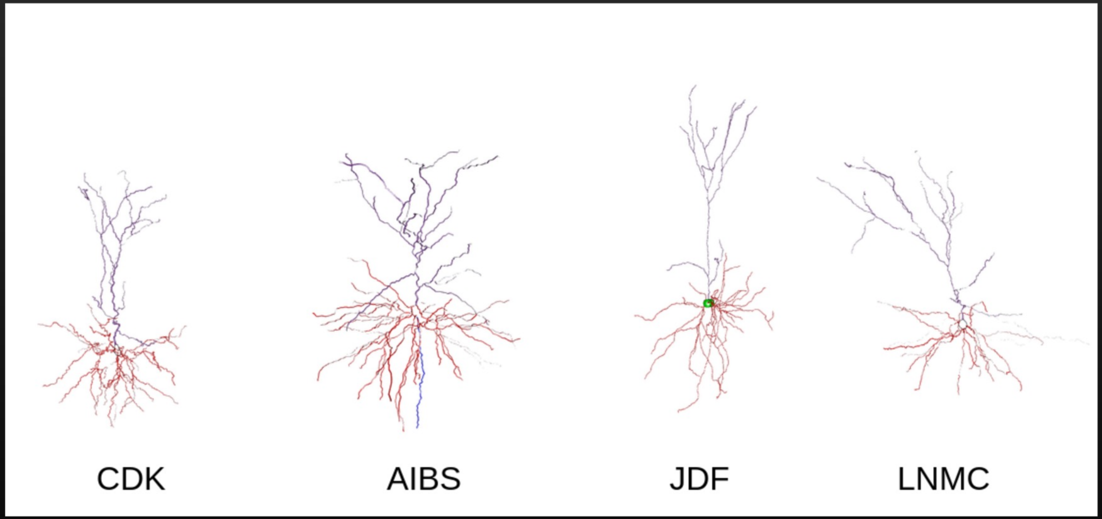
In the cortex:
six structurally and functionally distinct layers



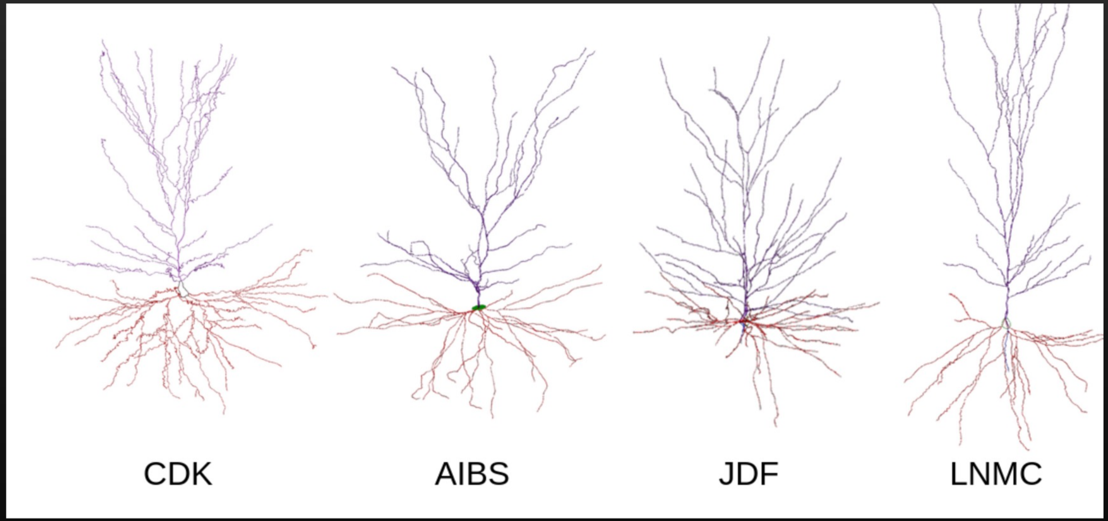
i) Comparison of neurons

Visual comparison

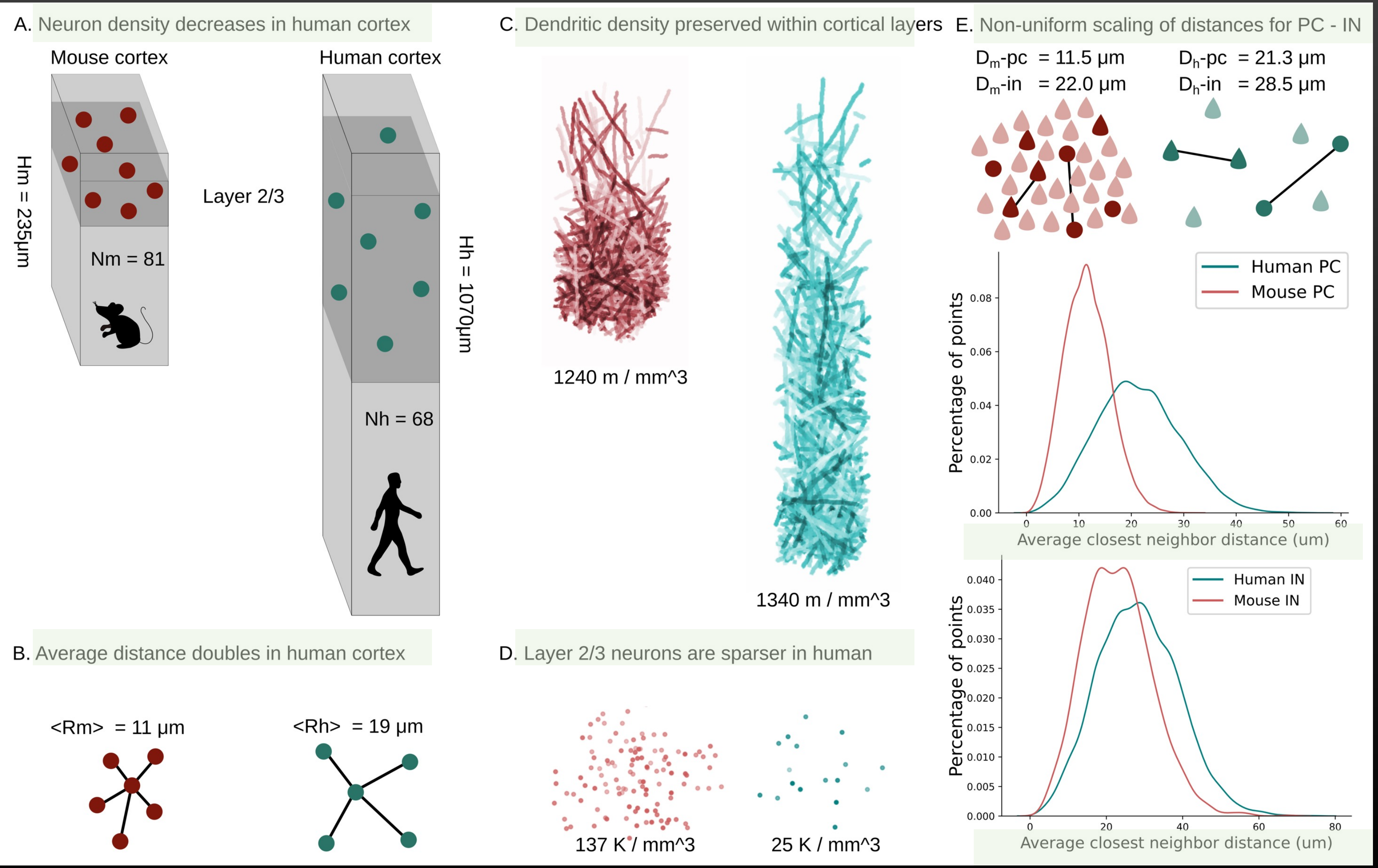
Mouse



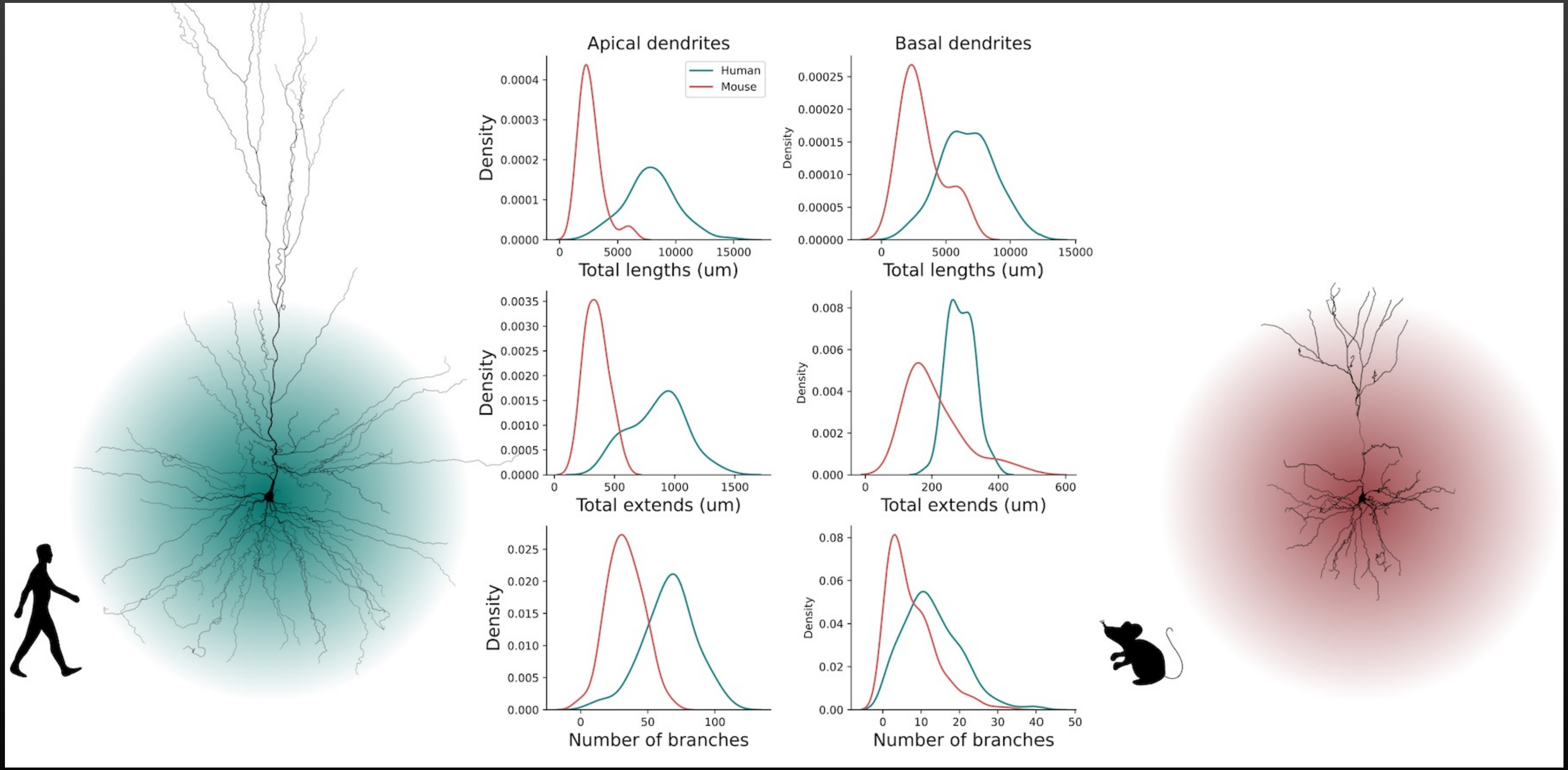
Human



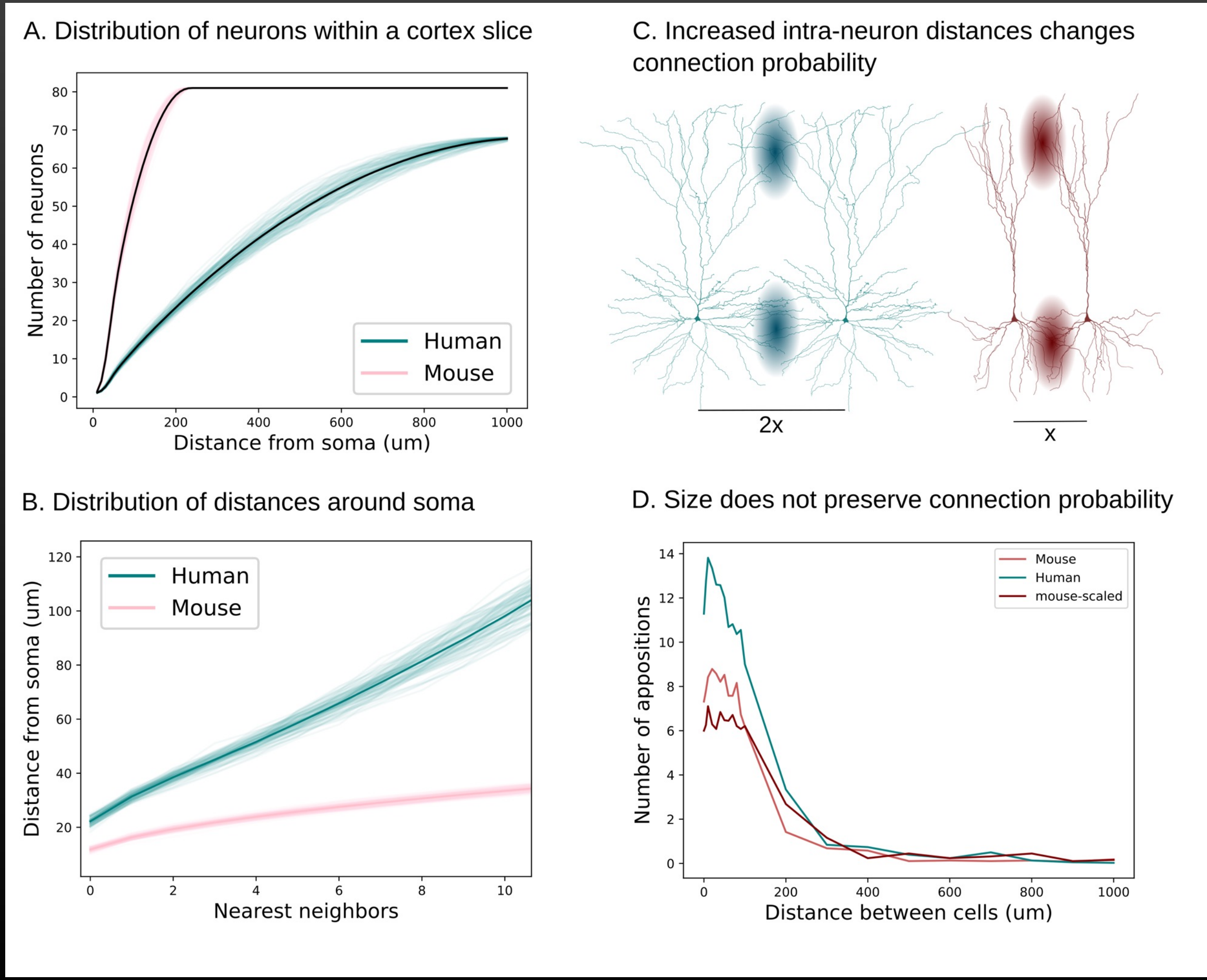
Anatomical comparison



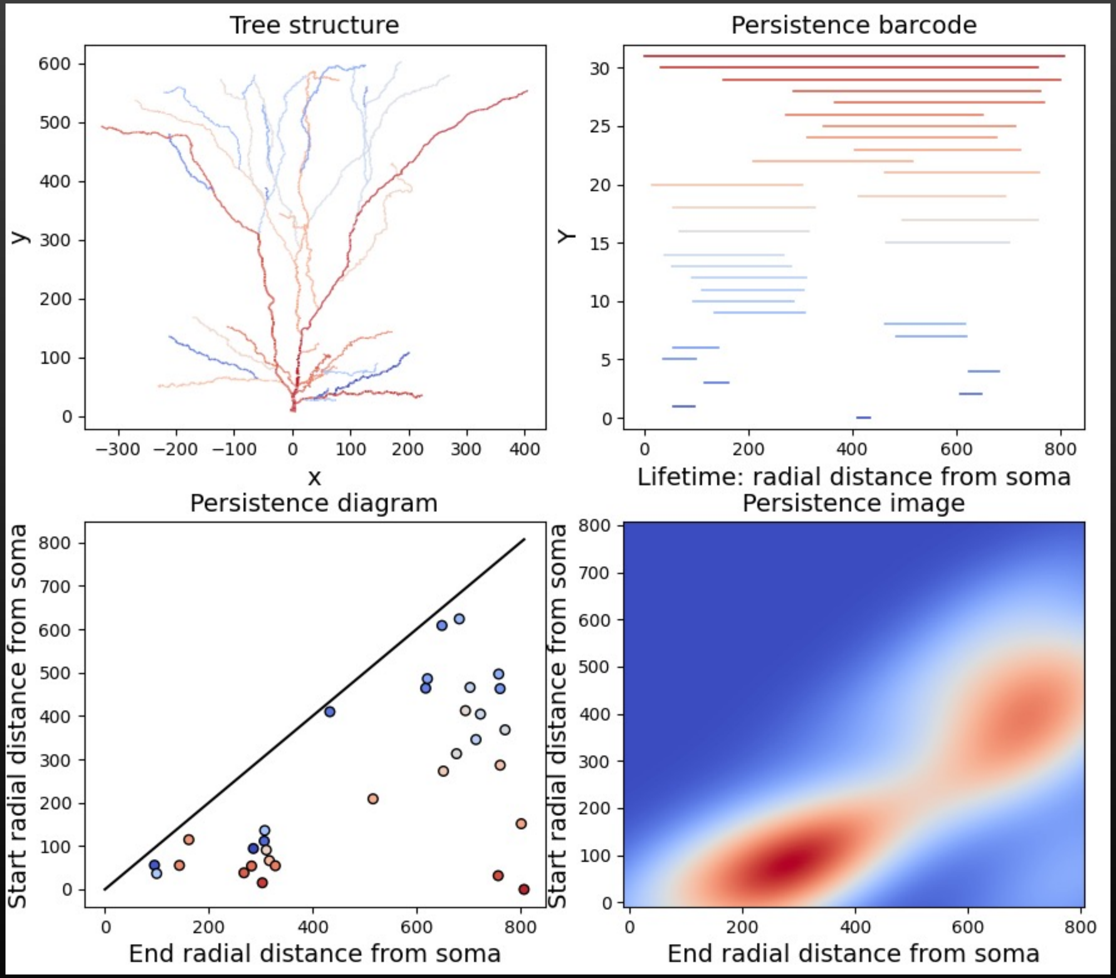
Anatomical comparison



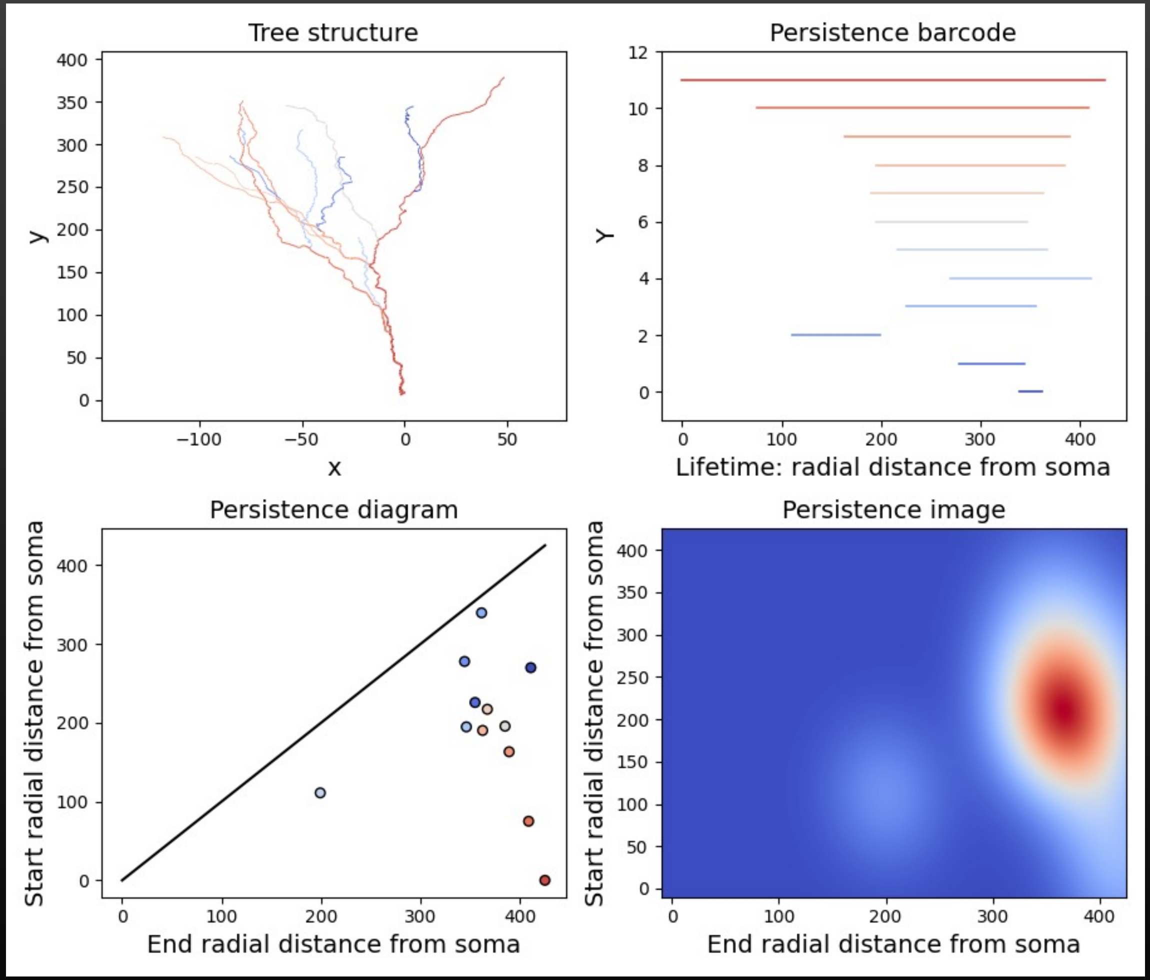
Anatomy and connectivity



Topological comparison

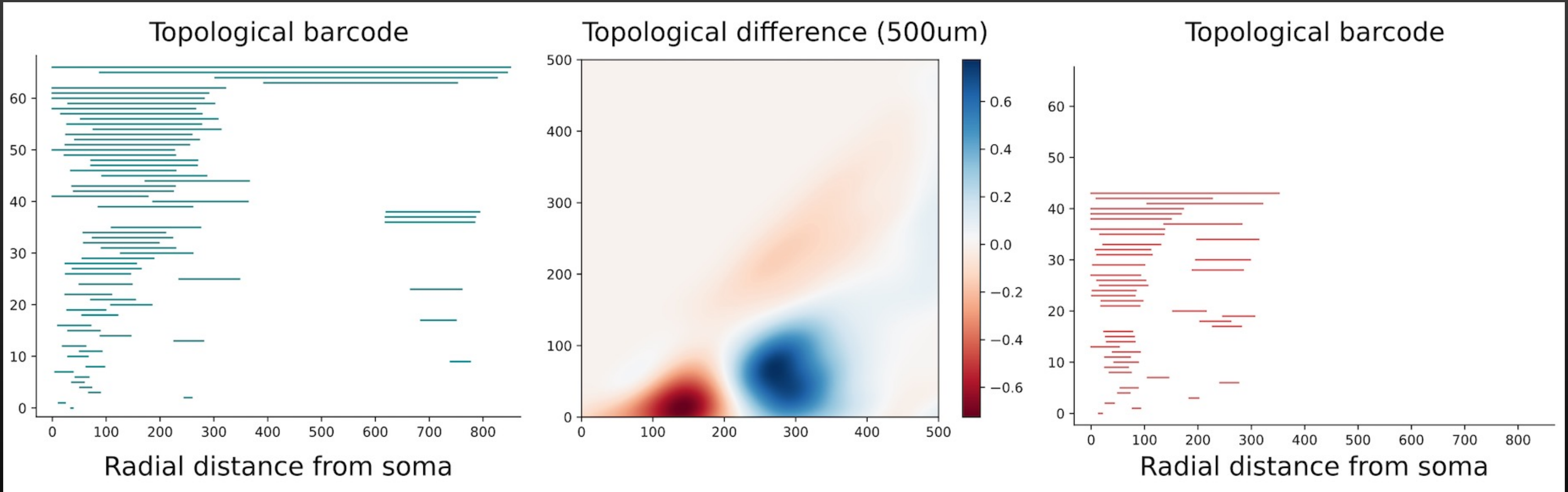


Human neuron

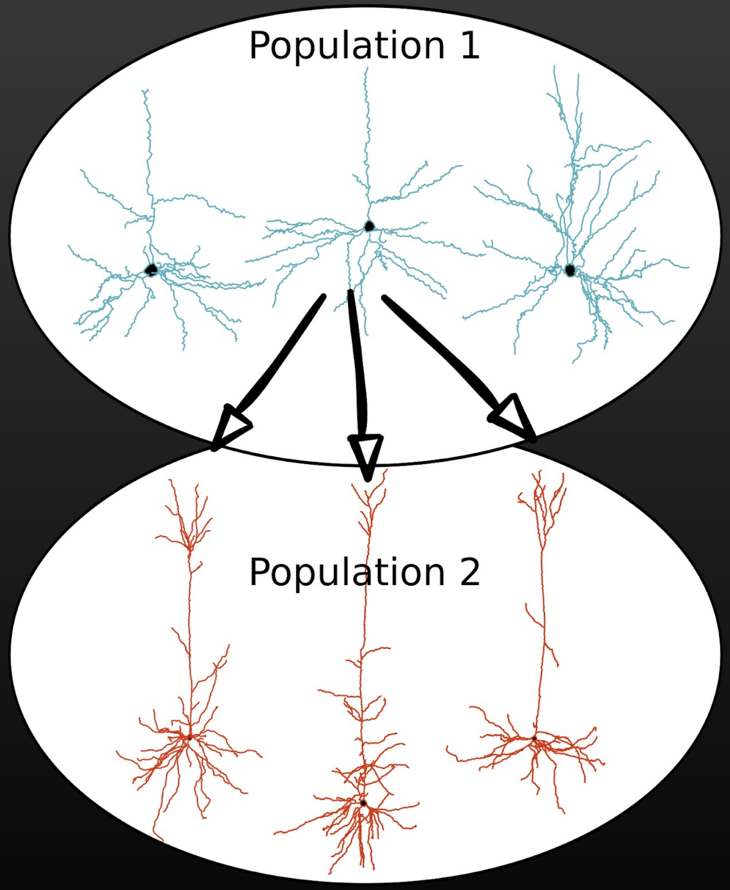


Mouse neuron

Topological comparison



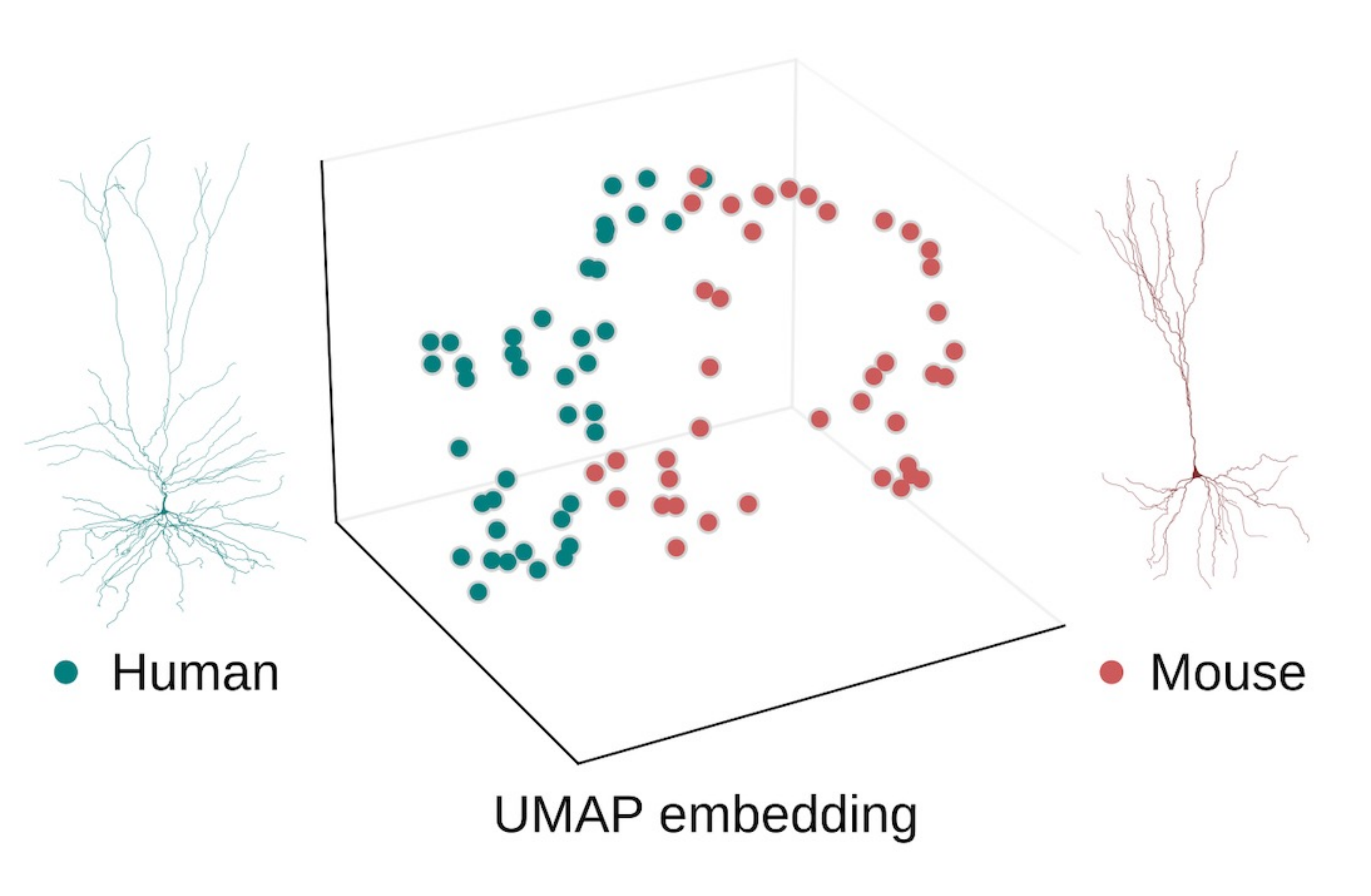
Population comparison



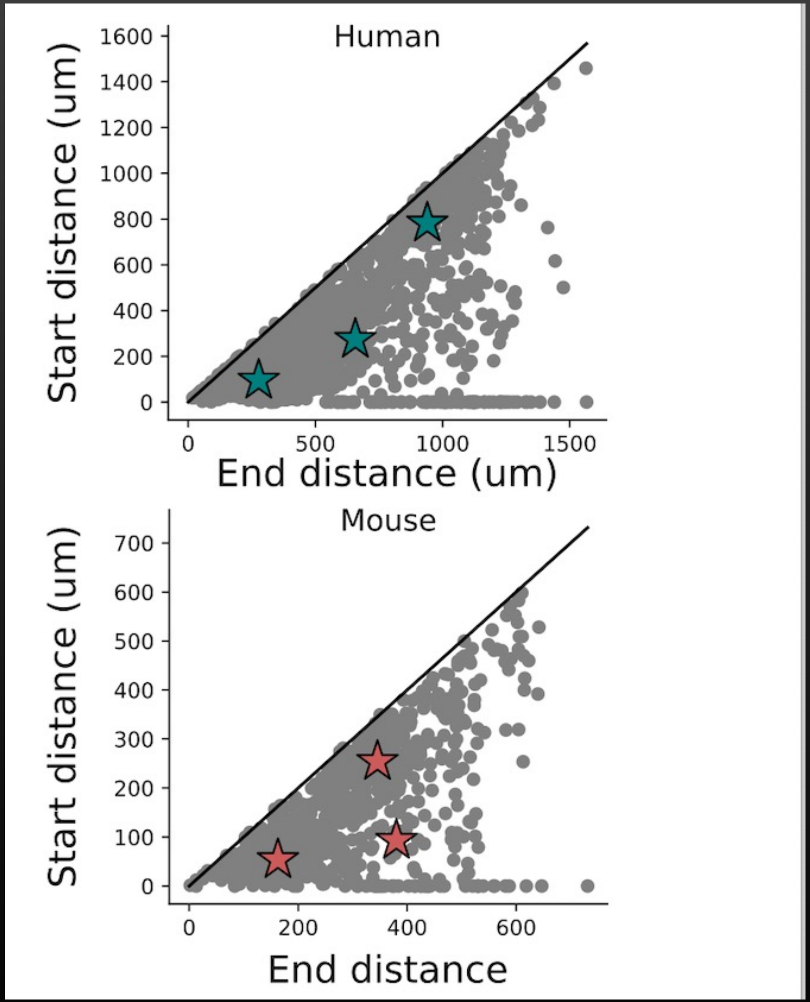
- Match neurons in the two populations with similar properties, e.g., cortical depth
- Compare important features (e.g., morphometrics, TMD) of matched neurons

Topology distinguishes mouse and human populations

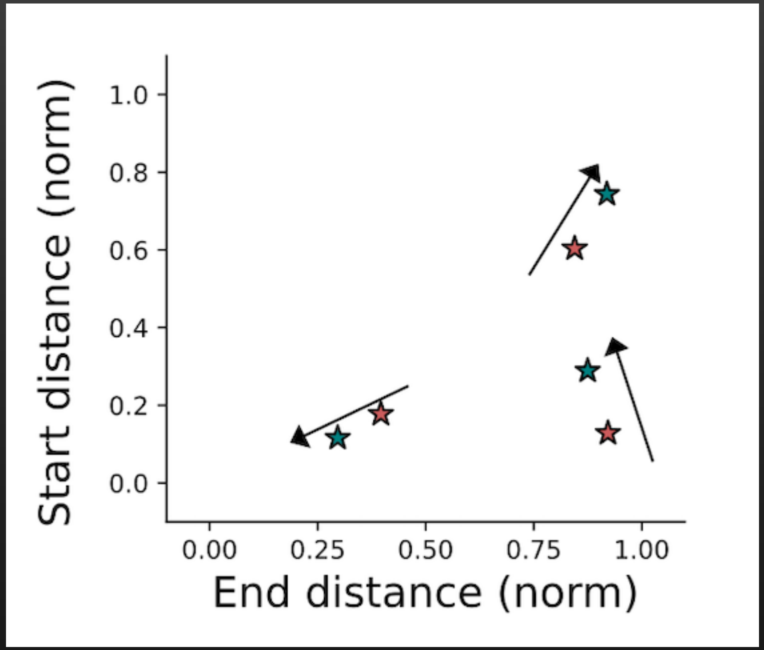
(Human neurons rescaled to enable comparison.)



The insufficiency of rescaling



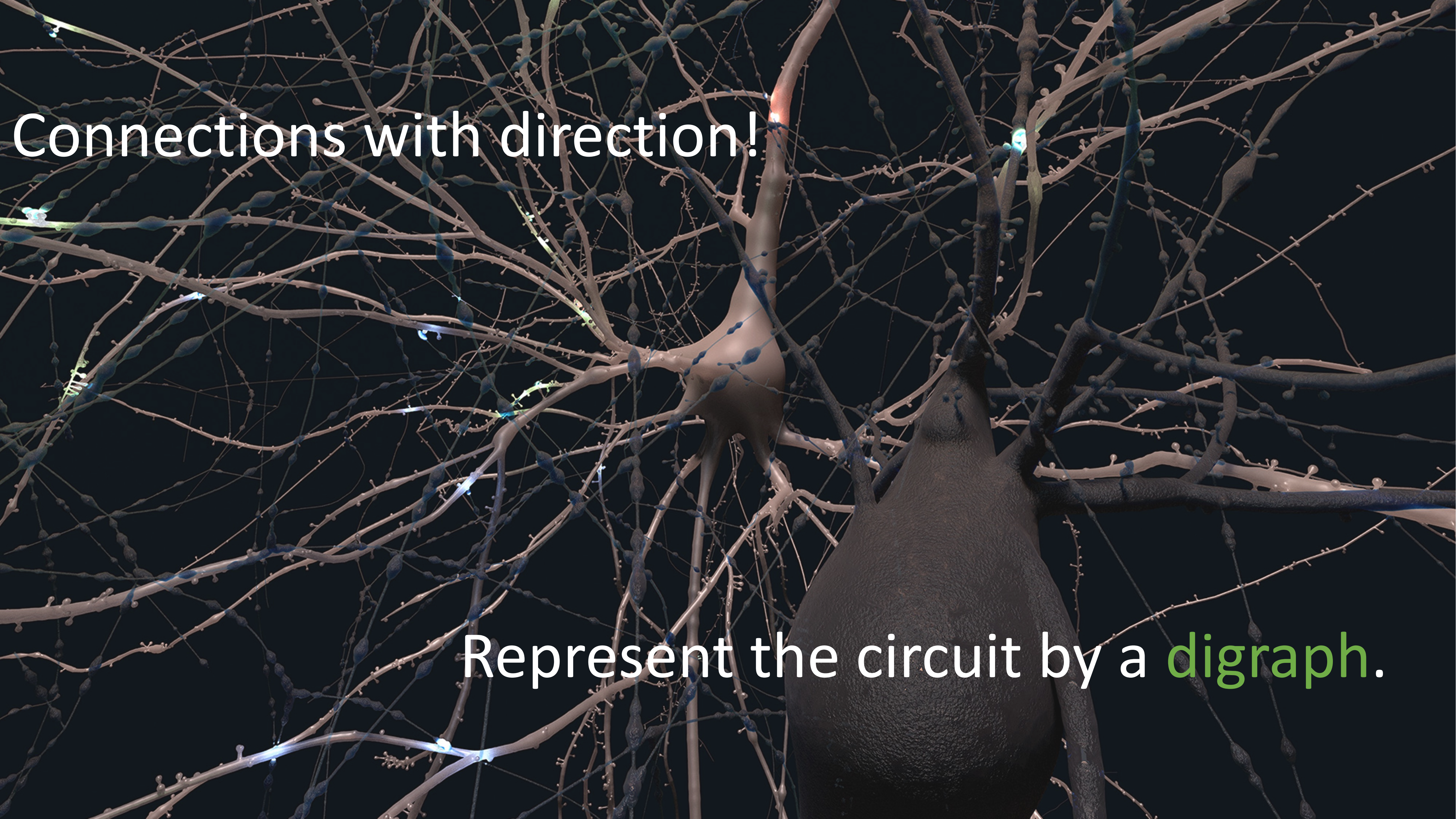
Population persistence diagrams



Optimal transformation of the Gaussian kernels

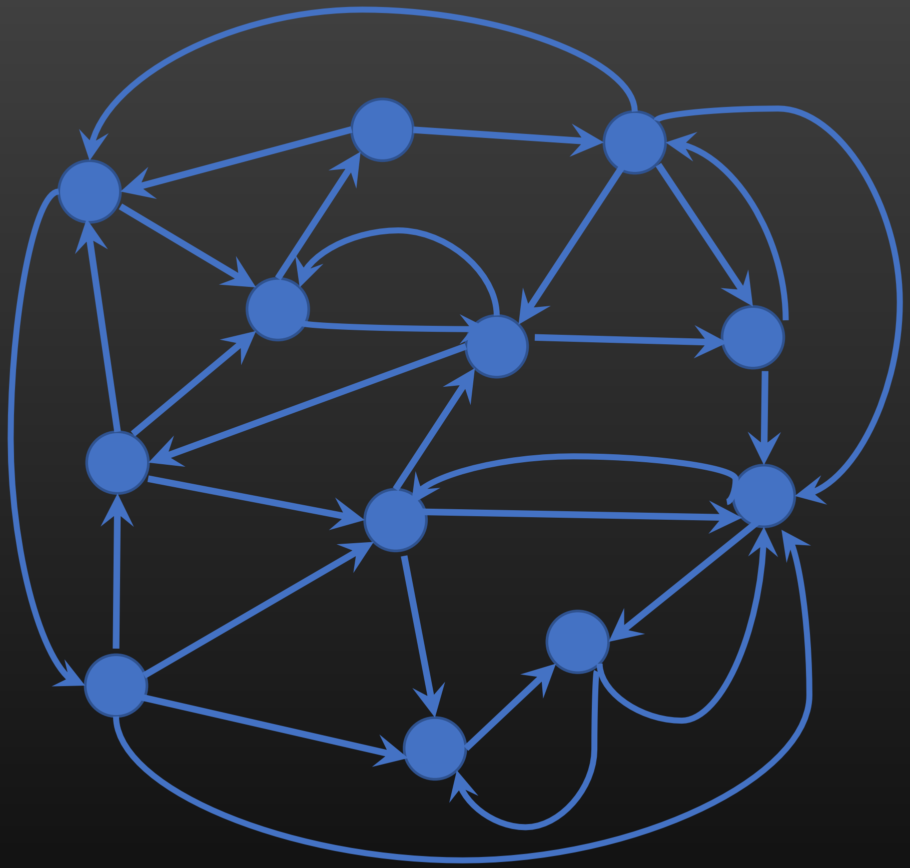
ii) Comparison of networks

Connections with direction!



Connections with direction!

Represent the circuit by a digraph.



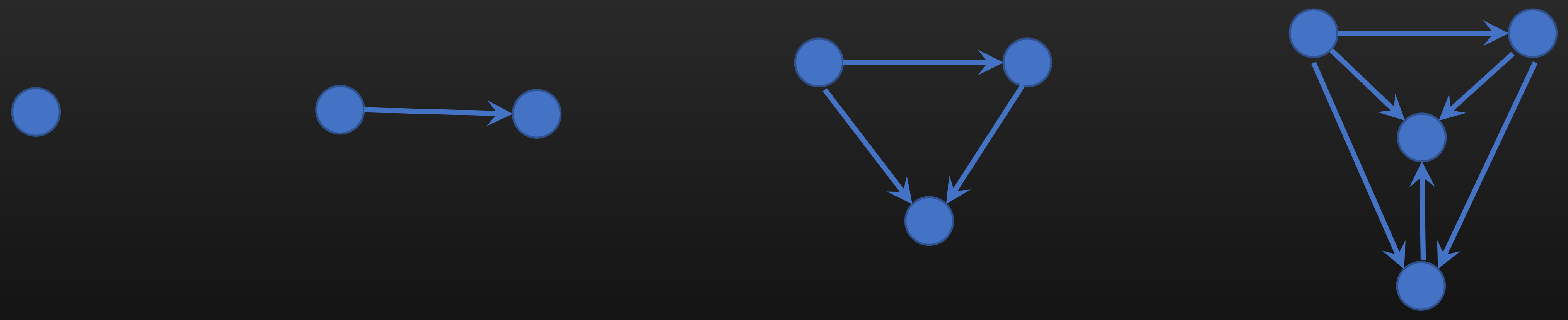
How to analyze and characterize the structure of a complex digraph?

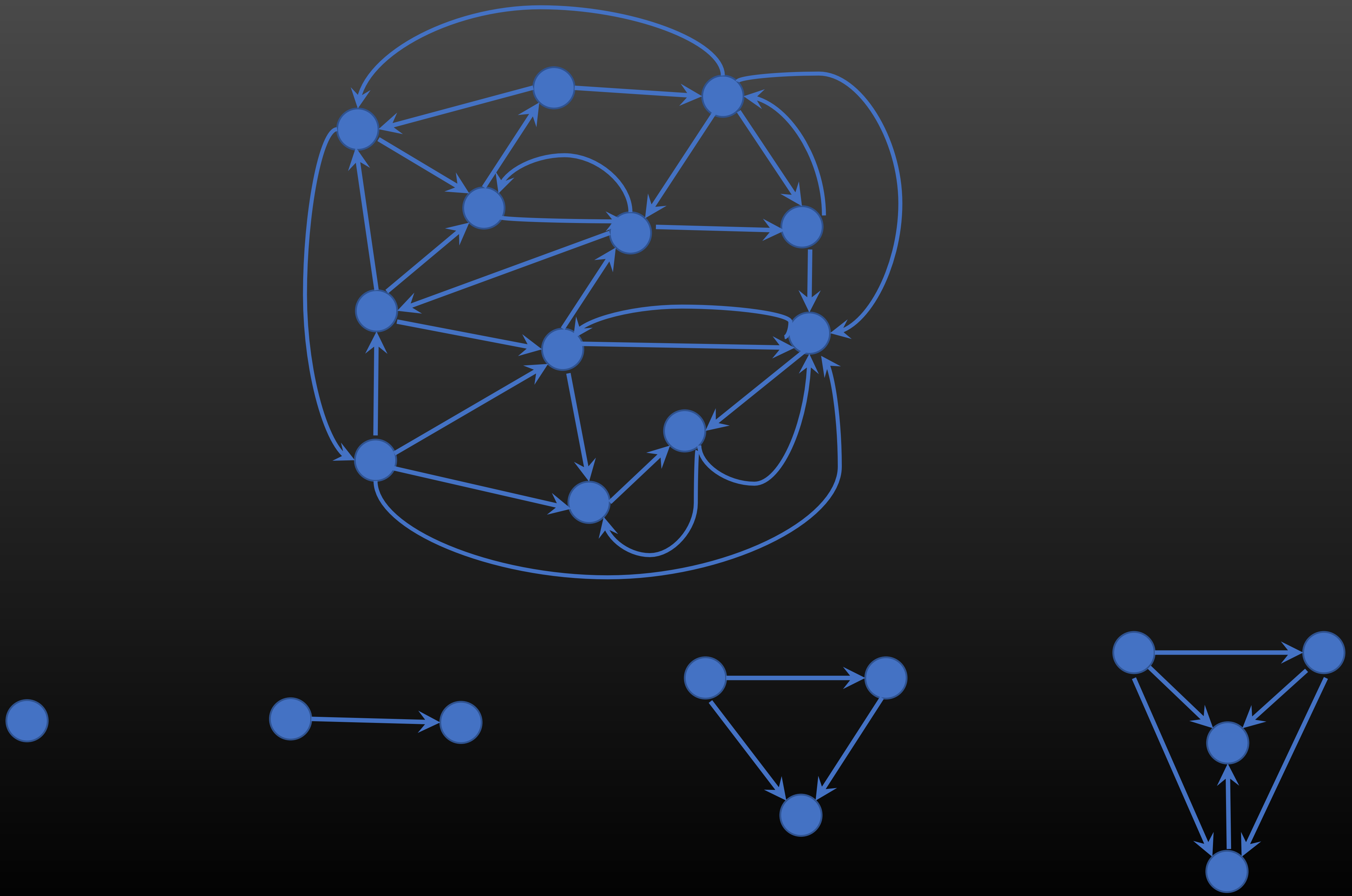
Topological network analysis

- For each type of network (undirected/directed/weighted…), choose an appropriate family of significant subnetworks (e.g., motifs, graphlets) to study.
- The numbers of different types of significant subnetworks in a given network provide important local information about the network.
- Quantify how the significant subnetworks overlap in the network to obtain important global information.

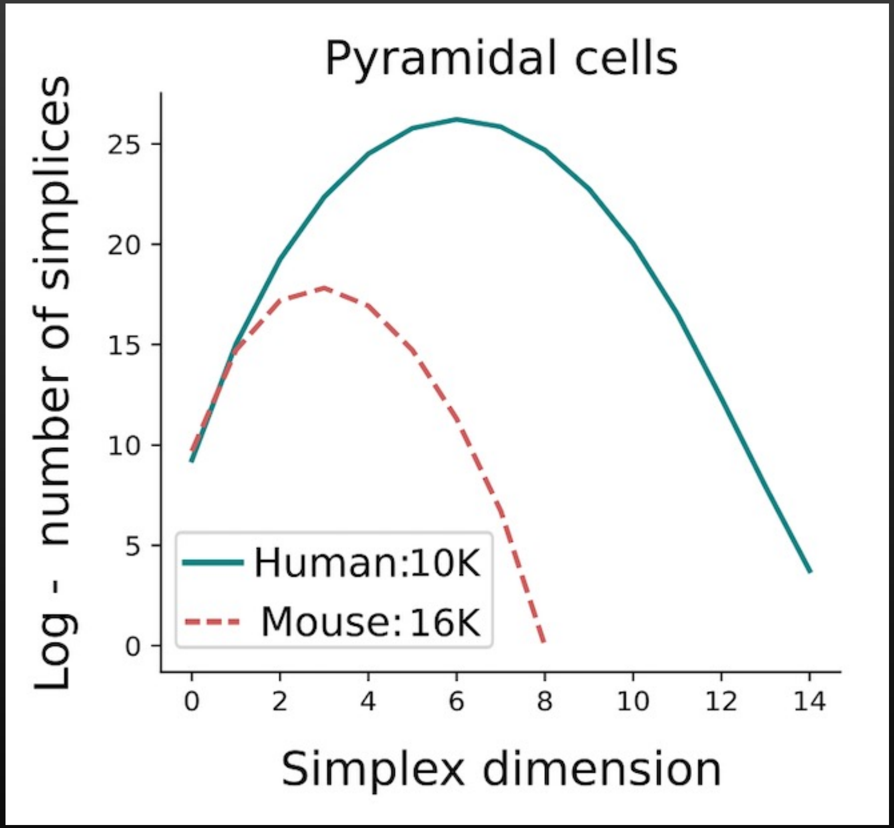
Topological network analysis

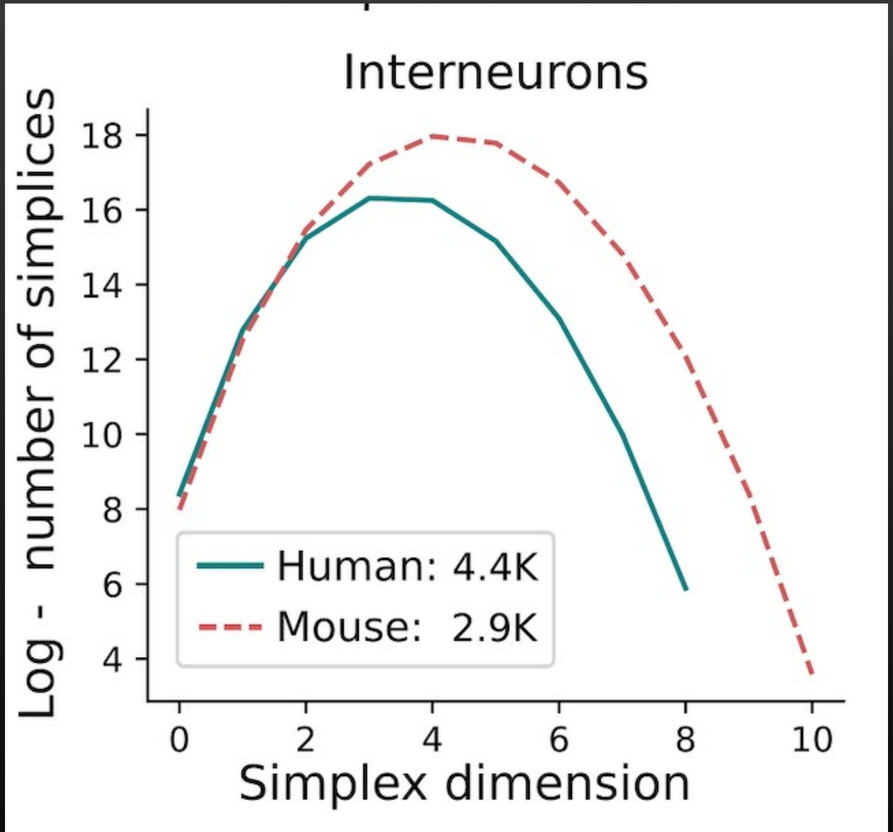
Let $\mathcal{G}$ be a directed graph. A directed *n*-simplex of $\mathcal{G}$ is a complete, acyclic subgraph on *n+1* vertices of $\mathcal{G}$.





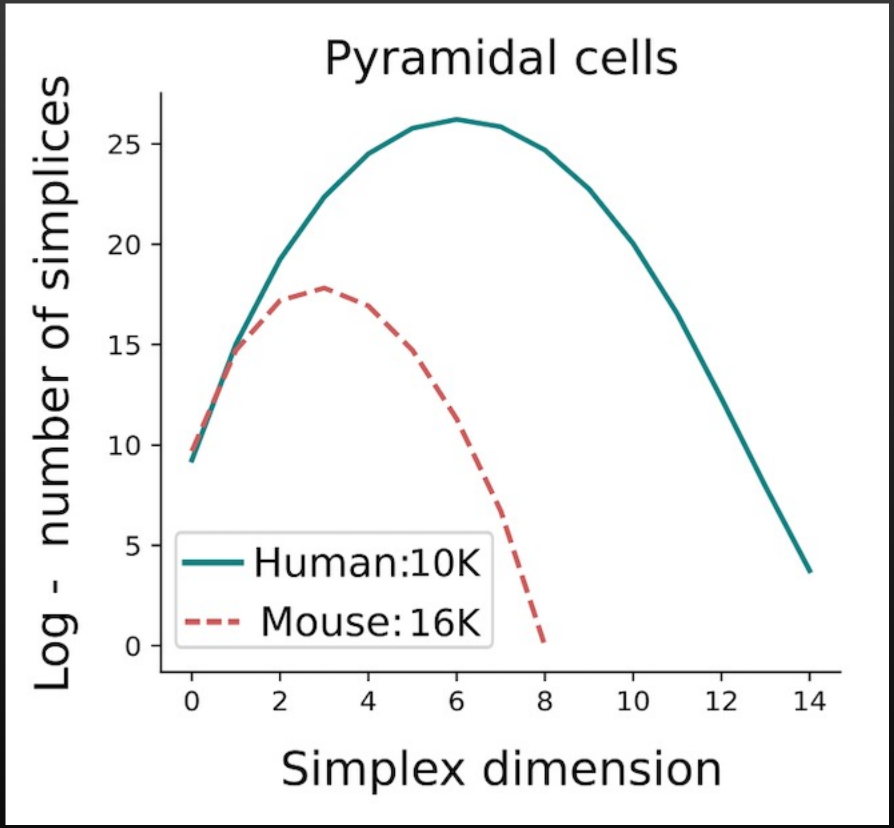
Simplicial comparison of connectomes





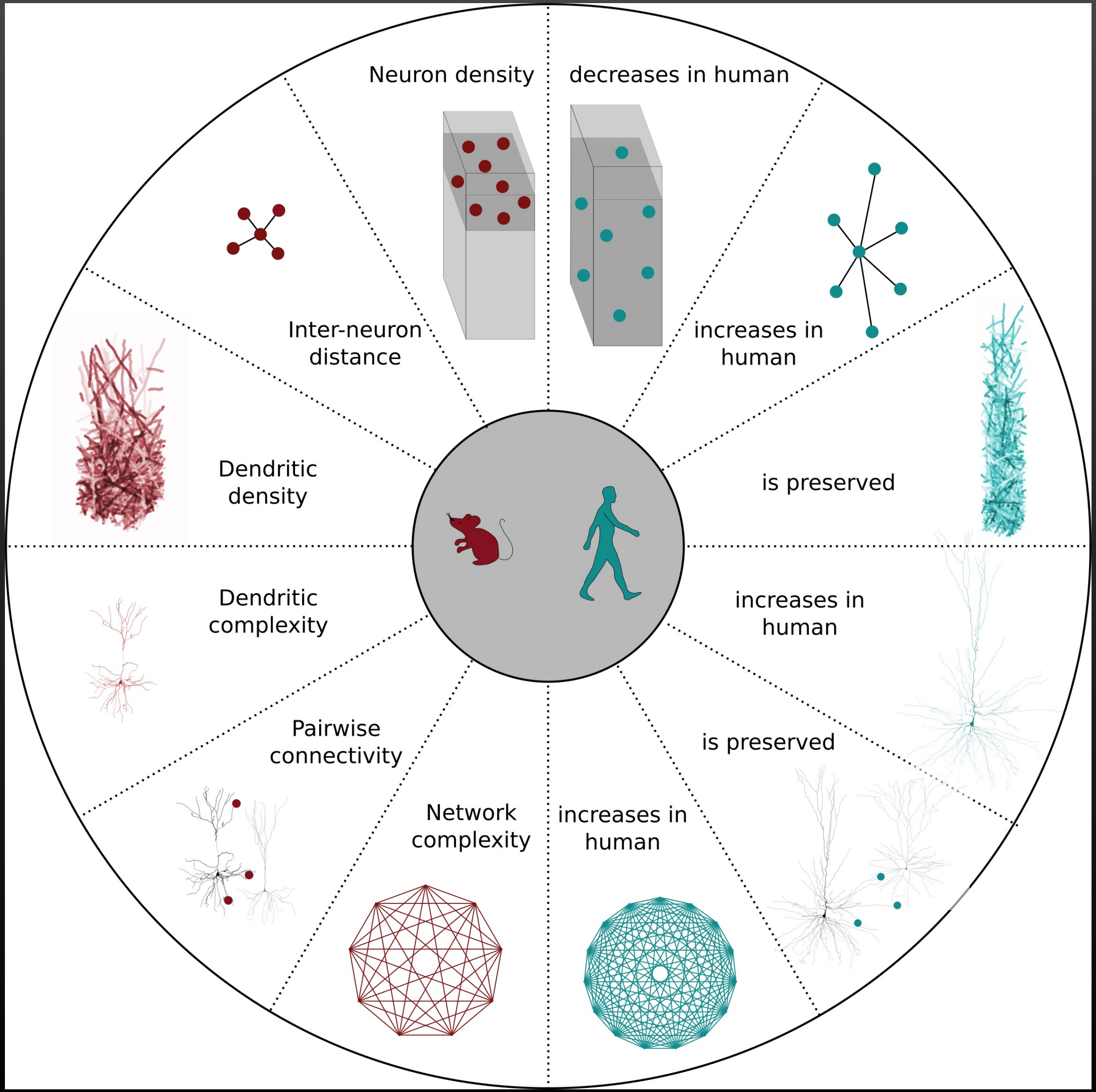
(Reconstructed volumes of 1mm x 1mm x layer thickness, supposing that 50% of appositions give rise to synapses.)

Simplicial comparison of connectomes



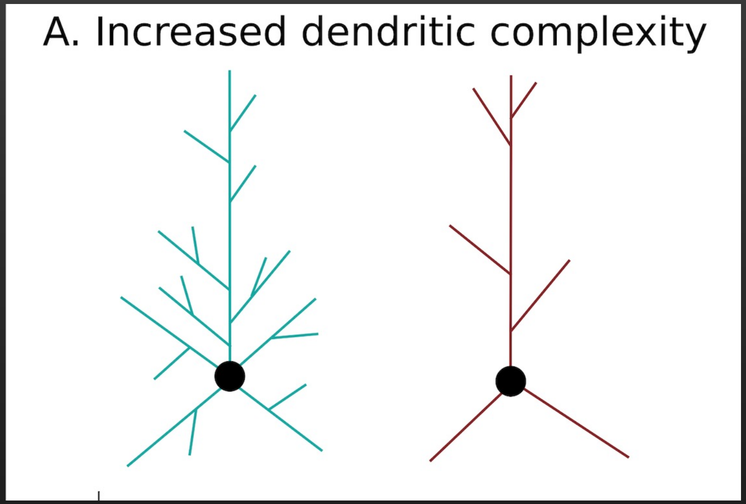
Conclusion: The greater complexity of the branching structure of human pyramidal dendrites more than compensates for the lower neuron density in human cortex, leading to substantially more complex network structure.

Summary



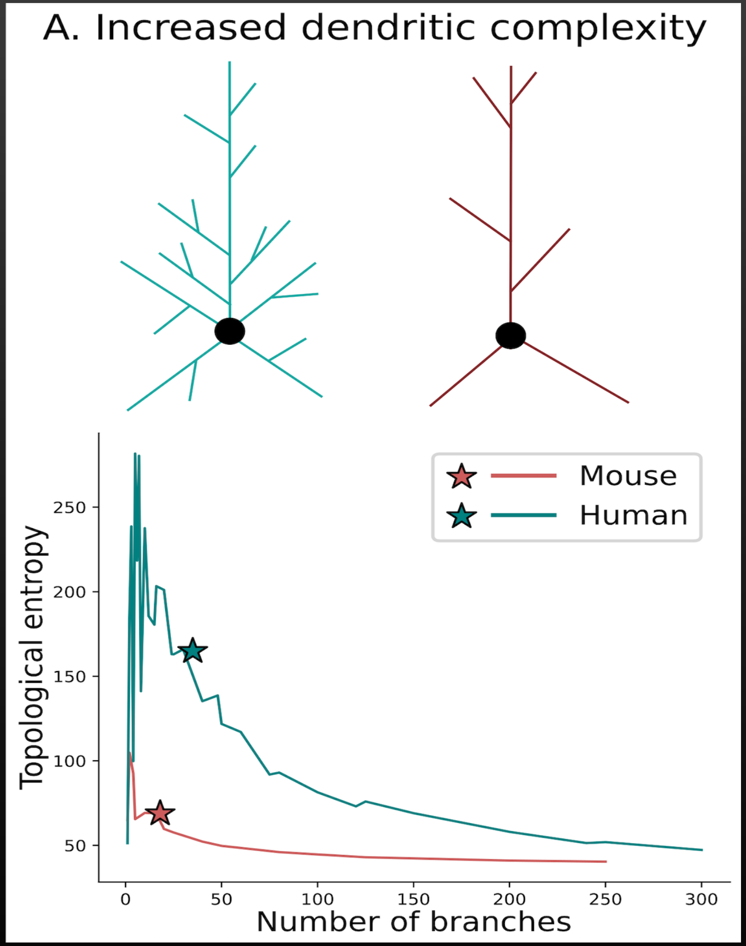
Neuron density
decreases in human
Inter-neuron distance
increases in human
Dendritic density
is preserved
Dendritic complexity
increases in human
Pairwise connectivity
is preserved
Network complexity
increases in human

Possible functional implications?



Why has the human brain evolved to prioritze complexity of individual neurons?

Possible functional implications?

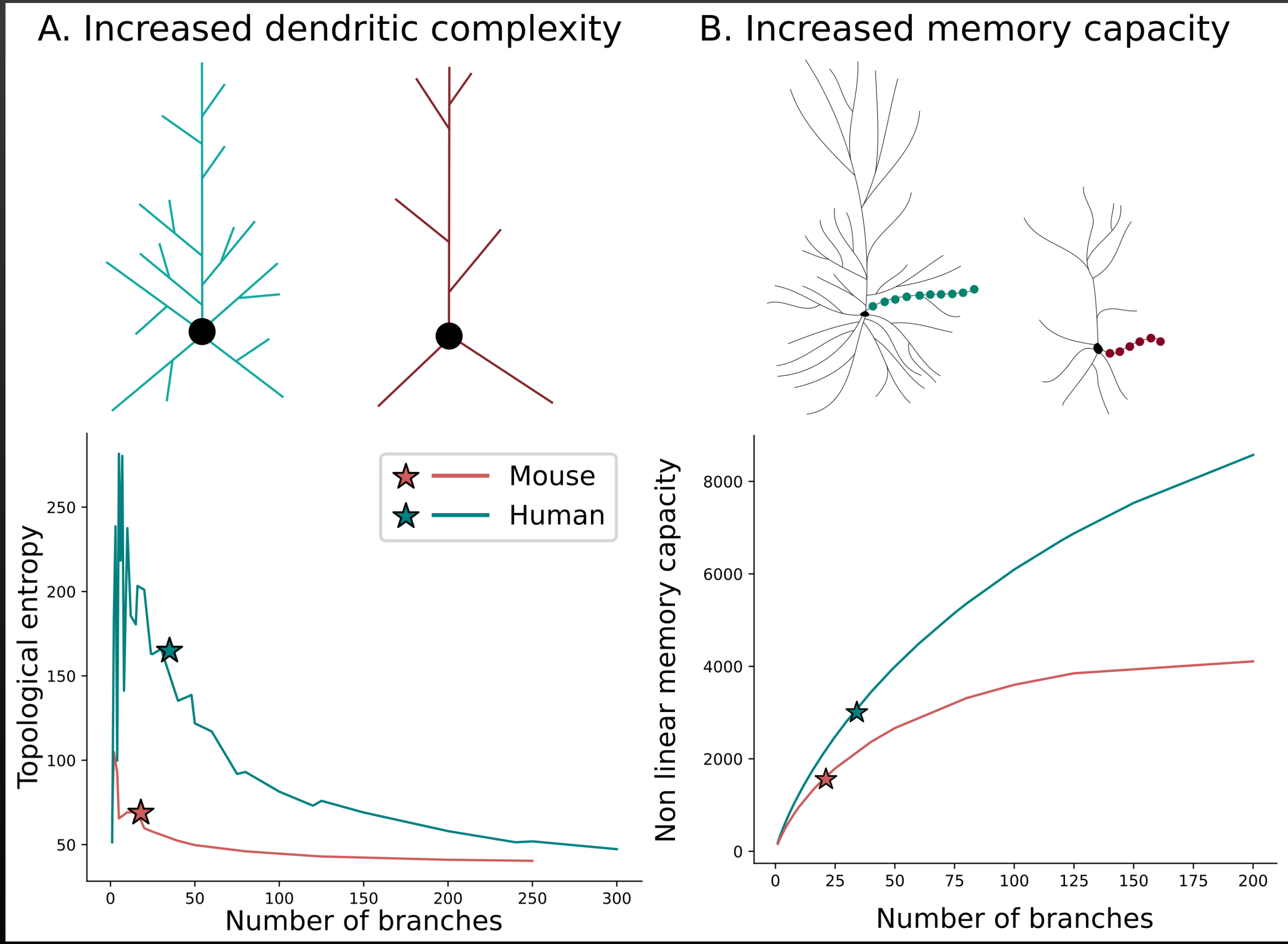


Topological entropy

$$E(PB) = -\sum_{i}^{N} \frac{l_i}{L} \cdot log(\frac{l_i}{L})$$

Chintakunta et al. (2015)

Possible functional implications?



Topological entropy

$$E(PB) = -\sum_{i}^{N} \frac{l_i}{L} \cdot log(\frac{l_i}{L})$$

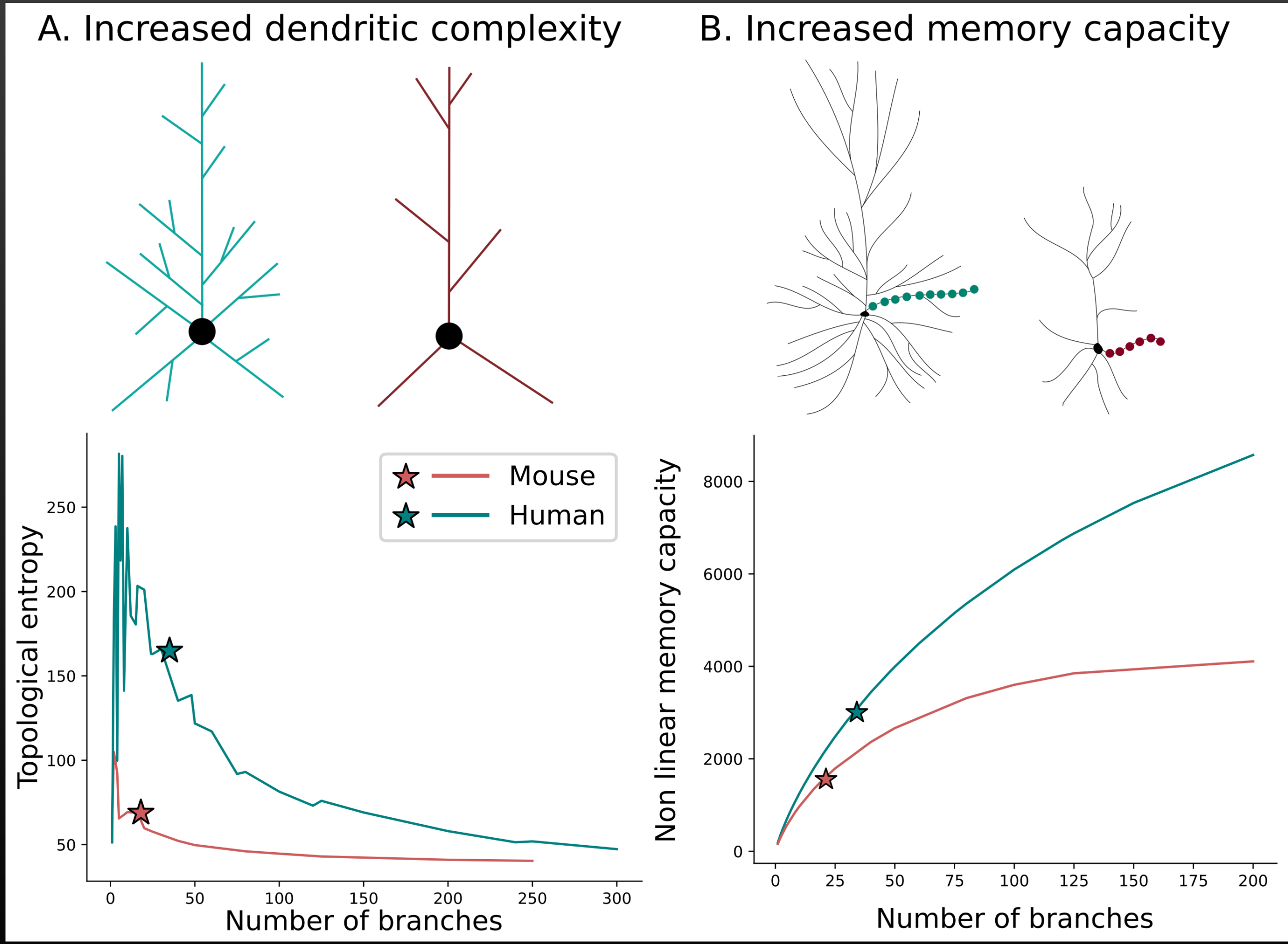
Chintakunta et al. (2015)

Nonlinear memory capacity

$$C_N = 2log_2\left(\binom{\binom{k+d-1}{k} + m - 1}{m}\right)$$

Poirazi and Mel (2001)

Possible functional implications?



Memory capacity of individual neurons

+

Simplicial complexity of the connectome

?

Computational power of the connectome


Thank you!