Of Mice and Men

Seminar in Mathematics, Physics & Machine Learning

IST

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EPFL
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The topology of neuron morphologies

Y. Deitcher et al, Cerebral Cortex, 2017.
L. Kanari et al, Cerebral Cortex, 2019.
A (very) brief intro to neurobiology
Rat pyramidal cells

Apical dendrites

Basal dendrites

Tuft
How to classify neuron morphologies?

VS
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.
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

B. Persistence barcode

C. Persistence diagram

D. Persistence image
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
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Morphological characterization of microglia
Of mice and men

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

CDK  AIBS  JDF  LNMC

CDK  AIBS  JDF  LNMC
Anatomical comparison

A. Neuron density decreases in human cortex
   - Mouse cortex: Neuron density in Layer 2/3
   - Human cortex: Neuron density in Layer 2/3
   - Neuron density comparison:
     - Mouse: $N_m = 81$ neurons
     - Human: $N_h = 68$ neurons

B. Average distance doubles in human cortex
   - Average neuronal distance in Layer 2/3:
     - Mouse: $<R_m> = 11 \mu m$
     - Human: $<R_h> = 19 \mu m$

C. Dendritic density preserved within cortical layers
   - Human PC dendritic density: $1240 \text{ m/ mm}^3$
   - Mouse PC dendritic density: $1340 \text{ m/ mm}^3$

D. Layer 2/3 neurons are sparser in human
   - Human IN neuron density:
     - $137 \text{ K/ mm}^3$
   - Mouse IN neuron density:
     - $25 \text{ K/ mm}^3$

E. Non-uniform scaling of distances for PC - IN
   - Non-uniform distances:
     - $D_{pc}$-pc: $11.5 \mu m$
     - $D_{pc}$-IN: $21.3 \mu m$
     - $D_{pc}$-IN: $28.5 \mu m$

Graphs showing:
- Percentage of points distribution
- Average closest neighbor distance (um)
Anatomical comparison
Anatomy and connectivity

A. Distribution of neurons within a cortex slice

B. Distribution of distances around soma

C. Increased intra-neuron distances changes connection probability

D. Size does not preserve connection probability
Topological comparison

Human neuron

Mouse neuron
Topological comparison

Topological barcode

Topological difference (500um)

Topological barcode

Radial distance from soma
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.)
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

- Dendritic density
- Dendritic complexity
- Pairwise connectivity
- Network complexity
- Neuron density
- Inter-neuron distance

- Decreases in human
- Increases in human
- Preserved
Possible functional implications?

Why has the human brain evolved to prioritize complexity of individual neurons?
Possible functional implications?

A. Increased dendritic complexity

Topological entropy

\[ E(PB) = - \sum_{i}^{N} \frac{l_i}{L} \cdot \log\left(\frac{l_i}{L}\right) \]

Chintakunta et al. (2015)
Possible functional implications?

A. Increased dendritic complexity

B. Increased memory capacity

Topological entropy

\[ E(PB) = - \sum_{i} \frac{l_i}{L} \cdot \log\left(\frac{l_i}{L}\right) \]

Chintakunta et al. (2015)

Nonlinear memory capacity

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

Poirazi and Mel (2001)
Possible functional implications?

A. Increased dendritic complexity

B. Increased memory capacity

Memory capacity of individual neurons

Simplicial complexity of the connectome

Computational power of the connectome
Thank you!