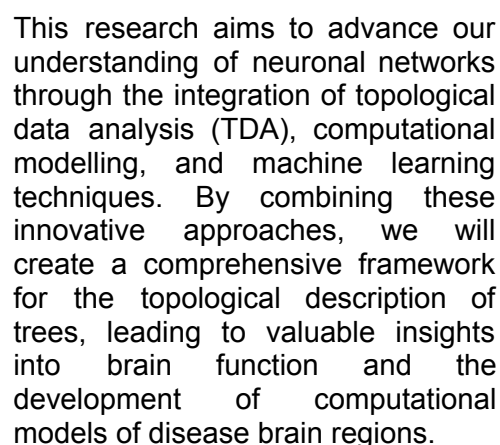


Abstract



The human brain is a complex network of billions of neurons connected by trillions of synapses. The shapes and connectivity patterns of neurons play a critical role in brain activity and are associated with various brain disorders. However, the precise mechanisms underlying the relationship between neuronal shape and network function remain elusive. We address this knowledge gap by leveraging the power of TDA, which allows us to capture and analyze the intricate topology of neuronal structures.

To achieve these objectives, we will utilize well-studied organisms such as *C. elegans* and Fruit Fly, which

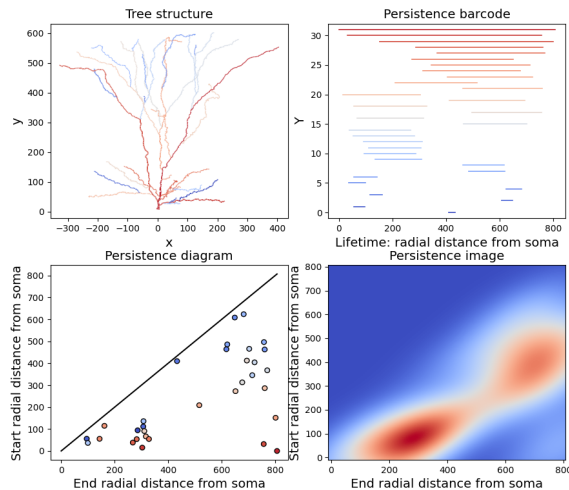
provide fully reconstructed data, to develop and validate our methodology. These organisms offer an excellent opportunity to demonstrate the efficacy of TDA in understanding brain function. Furthermore, we will employ computational modelling to simulate artificial neuronal trees and investigate the rules governing neuronal growth and network formation. This approach will enable us to generate networks with specific topological properties and shed light on the fundamental mechanisms underlying neuronal connections.

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Project 1: Topological Data Analysis

Title: Topology of Biological Trees, Networks and Point Processes

Background & Rationale:



Brain cells such as neurons, microglia, and astrocytes possess branching tree-like structures and their shape and connectivity have profound impact on brain functionality. We have developed techniques to study the topology of individual neurons based on algebraic topology (Kanari et al. 2018) and computationally generate neurons based on their topological properties (Kanari et al. 2022). In addition, through the generative models of networks, we can link the topology of single cells to the topological properties of the networks they form (Kanari et al. 2025).

The persistence barcodes generated by the tree structures of neurons (TMD) exhibit specific properties that are not observed in the persistence barcodes generated from point clouds (through Alpha, Vietoris-Rips and Cech filtrations). Namely, the barcodes of neuronal trees exhibit constraints in symmetric properties (Kanari et al. 2021. Curry et al. 2024) and defy the statistical convergence (Kapatsori and Kanari, in preparation) observed in typical persistence diagrams (Bobrowski and Skraba 2023).

Aims & Objectives:

- Develop and refine topological descriptors (e.g., persistence barcodes, tree metrics, tree filtrations) for geometric tree structures.
- Construct meaningful embeddings of trees into a metric/topological space, in order to map the “space of trees” and compare different types of tree models: biological, artificial, healthy and pathological.
- Investigate the relationship between the topology of individual trees and the topological features of the networks they form (e.g., how certain tree-shapes predispose network motifs or connectivity patterns).
- Extend tree-based topological descriptors toward the connectivity of graphs and networks.
- Develop theoretical links between combinatorial tree structures and their topological signatures.

Related Topics:

- Topological Data Analysis (TDA) for tree structures
- Computational topology of biological objects
- Topology of graphs and networks derived
- Topology of random point processes and trees

Open Questions:

1. Can we generate a meaningful embedding of trees that distinguishes biological trees from random tree models?
2. What is the relationship between the space of trees and the space of persistence barcodes (or other topological summaries)?
3. Can combinatorial enumeration be linked to topological invariants derived from persistence barcodes?
4. How can the tree-based topological frameworks be extended to study the connectivity patterns of graphs/networks?
5. What are the limits of convergence (or lack thereof) of neuronal-tree barcodes compared to standard point-cloud persistence convergence results (e.g., Bobrowski & Skraba 2023)?
6. What are the relationships between trees and polygon shapes, and can we create efficient computational algorithms to study their topological properties?

References:

1. [A Topological Representation of Branching Neuronal Morphologies](#)
2. [Computational synthesis of cortical dendritic morphologies](#)
3. [A tool for mapping microglial morphology. morphOMICs. reveals brain-region and sex-dependent phenotypes](#)
4. [From Trees to Barcodes and Back Again: Theoretical and Statistical Perspectives](#)
5. [From trees to barcodes and back again II: Combinatorial and probabilistic aspects of a topological inverse problem](#)
6. [A universal null-distribution for topological data analysis](#)
7. [Persistent homology and topological statistics of hyperuniform point clouds](#)
8. [Decomposing the Persistent Homology Transform of Star-Shaped ObjectsThe fiber of persistent homology for trees](#)
9. [Representation of molecular structures with persistent homology for machine learning applications in chemistry](#)

Project 2: Mathematics for Neuroscience

Title: Mathematical Models of Neuronal Trees and Network Structure

Background & Rationale:



The morphology of neuronal and glial cells (microglia, astrocytes) and the networks they form underlie brain function and pathologies. Despite advances in neuro-imaging and cell reconstruction, the mathematical theory for linking different computational scales is not yet well established. Building on recent progress in tree-topology and generative modelling of neurons (Kanari et al. 2018; Kanari et al. 2022; Kanari et al. 2025), this project aims to propose a rigorous mathematical framework to link the shapes of individual cells, their transcriptomics and the topological structure of their networks. Such work has potential implications for

distinguishing cell types, species, pathological states and for generating biologically realistic network models.

Aims & Objectives:

- Use topological and other mathematical descriptors to characterise and distinguish neuronal, microglial and astrocytic branching structures.
- Develop embeddings (topological/metric) that enable the classification and clustering of cell types, species, and disease states based on morphology and connectivity.
- Construct and analyse generative mathematical models for biologically realistic neuronal networks (e.g., for *Drosophila* or other accessible organisms) that reflect both the single-cell tree topology and the resultant network connectivity.
- Explore the topological link between the structure of single cells and the emergent topology of the network they inhabit.
- Develop mathematical models to explore the mechanisms of species differences, developmental changes and brain pathologies.

Related Topics:

- TDA for neuronal morphology
- TDA for microglial and astrocytic cell trees
- Mathematical modelling of neuronal networks
- Topological links between single-cell morphology and network architecture

- Cross-species and pathology-driven topological variance in brain networks

Open Questions:

1. Can we reliably distinguish species, cell-types or pathologies from the topological embedding of neuronal or glial cell trees?
2. Can we extend this discrimination to network-level topology derived from these cells (i.e., species/pathology classification via network topology)?
3. Can we propose and validate a generative mathematical model for biologically realistic neuronal networks (for example in *Drosophila*) that integrates single-cell topology and network connectivity?
4. What mathematical constraints govern the translation from branching morphology to network topology, and can these be formalised?
5. Can we use topological data analysis and machine learning to differentiate branching structures, such as vascular systems, lung branching trees?

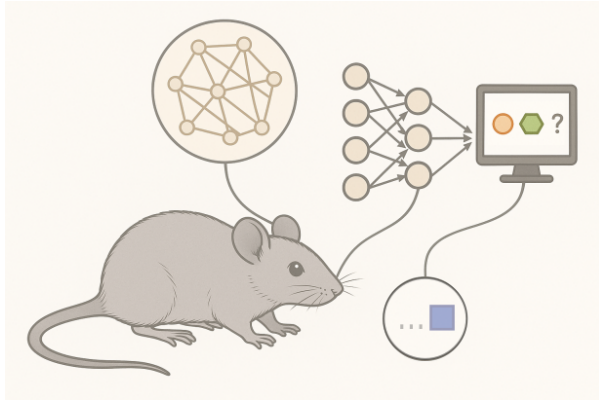
References:

1. [A Topological Representation of Branching Neuronal Morphologies](#)
2. [Computational synthesis of cortical dendritic morphologies](#)
3. [Objective Morphological Classification of Neocortical Pyramidal Cells Open Access](#)
4. [Comprehensive Morpho-Electrotonic Analysis Shows 2 Distinct Classes of L2 and L3 Pyramidal Neurons in Human Temporal Cortex Open Access](#)
5. [Of mice and men: Dendritic architecture differentiates human from mouse neuronal networks](#)
6. [Generating brain-wide connectome using synthetic axonal morphologies](#)
7. [Computational generation of long-range axonal morphologies](#)
8. [Breakdown and repair of metabolism in the aging brain](#)
9. [Modeling and simulation of neocortical micro-and mesocircuitry. Part I: Anatomy](#)
10. [Quantifying neuronal differentiation using temporal topological persistence](#)
11. [The connectome of an insect brain](#)
12. [Tuneable Digital Phantoms for Grey Matter Modelling](#)
13. [A tool for mapping microglial morphology, morphOMICs, reveals brain-region and sex-dependent phenotypes](#)
14. [Multiscale topology characterizes dynamic tumor vascular networks](#)

Project 3: Machine Learning

Title: Learning Biological Network Representations: Classification, Clustering and Generative Models

Background & Rationale:



Machine learning (ML) offers powerful tools for representing, clustering and classifying complex high-dimensional data, including biological data, such as the shape of neurons, brain images and biological cell morphologies. By combining ML with topological descriptors, we can develop novel descriptors for the accurate and robust classification, clustering and embedding of biological objects. Moreover, biological networks exhibit high topological complexity. Leveraging those biological properties to

inform the architecture of artificial neural networks may yield advances in learning efficiency, memory capacity and design of efficient AI architectures.

Aims & Objectives:

- Develop ML workflows (classification, clustering, representation learning) for neuronal trees based on topological and geometric descriptors.
- Explore unsupervised/semi-supervised techniques (autoencoders, graph neural networks) to link transcriptomic/cellular data with morphological shape and connectivity.
- Implement and evaluate generative ML models (variational autoencoders, generative adversarial networks) for producing biologically realistic network topologies and branching structures.
- Investigate whether properties of biological networks can inform novel artificial NN architectures or learning algorithms with improved performance or robustness.
- Build biologically inspired neural networks, based on the architecture of single neurons or networks of neurons from different species and explore their learning capacity.

Related Topics:

- Classification and clustering of neurons and other brain cells
- Representation learning of branching tree structures and networks
- Generative modelling of biological inspired networks
- Transfer of biological network topological principles to artificial neural networks
- Topological Deep Learning

Open Questions:

1. Can we design a learning mechanism that generates biologically realistic neuronal or network topologies?
2. To what extent can ML approximate biological networks (fly, mouse, human) from limited training data?
3. Can properties of biological networks (such as branching diversity, topological richness) be transferred to machine learning architectures to enhance their learning efficiency, robustness or generalisation?
4. How can we improve classification and clustering of neuronal trees (or networks) using combined topological and ML methods, and what are the limiting factors in current methods?
5. Can we explore generative models for random and structured networks and explore what differentiates them and what is the advantage of different architectures?

References:

1. [A Topological Representation of Branching Neuronal Morphologies](#)
 2. [Computational synthesis of cortical dendritic morphologies](#)
 3. [Neuron morphological physicality and variability define the non-random structure of connectivity](#)
 4. [Deep learning for classifying neuronal morphologies: combining topological data analysis and graph neural networks](#)
 5. [A synaptic learning rule for exploiting nonlinear dendritic computation](#)
 6. [Single cortical neurons as deep artificial neural networks](#)
 7. [Biologically inspired neural network layer with homeostatic regulation and adaptive repair mechanisms](#)
 8. [Toward universal cell embeddings: integrating single-cell RNA-seq datasets across species with SATURN](#)
 9. [A quantitative spatial atlas of transcriptomic, morphological, and electrophysiological cell type densities in the mouse brain](#)
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Notes for Students:

- Each of these three tracks is designed to be feasible within a 3- to 4-year full-time PhD programme (or equivalent).
- Candidates should expect to engage with mathematics (particularly algebraic and computational topology), computational modelling, data analysis, and where applicable machine learning frameworks.
- A strong candidate will have prior experience (or strong interest) in one or more of the intersecting domains: topology, neuroscience (cellular/neural morphology), machine learning/data science.
- Working collaboratively across these topics is highly encouraged.
- This structure provides flexibility: a candidate might focus primarily on one track, or integrate two or three tracks depending on their skills and interests.