● Collecting Aligned Activity & Connectomic Data
  Example: Mouse Vibrissal Touch Barrel Cortex

● Exploiting Coherence to Reduce Dimensionality
  Example: \textit{C. elegans} Motor Control Sequence

● Spatially & Temporally Distributed Circuit Motifs
  Example: Localized Persistent Homology

● Modeling Cortical Layers with Deep Networks
  Example: Primary Visual Cortex in Primates
Collecting Activity & Connectomic Data
## Worms, Flies, Mice and Monkeys

<table>
<thead>
<tr>
<th>Data Types:</th>
<th>EM structural; 2PE functional; IR behavioral; AT genomic[^1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annotations:</td>
<td>3D microcircuit reconstruction; sparse, weighted adjacency matrix</td>
</tr>
<tr>
<td></td>
<td>boundary I/O: sensory / motor; afferent / efferent; axonal / dendritic</td>
</tr>
<tr>
<td></td>
<td>neuron morphological types; synaptic coordinates &amp; connection types</td>
</tr>
<tr>
<td></td>
<td>dense GECI and GEVI fluorescence time series; neuron-indexed rasters[^2]</td>
</tr>
<tr>
<td></td>
<td>directed clique-complex structure summarizing local circuit motifs</td>
</tr>
<tr>
<td></td>
<td>barcode summary representation of persistent-homography evolution</td>
</tr>
<tr>
<td>Organisms:</td>
<td>species name — common name — target task — target volume</td>
</tr>
<tr>
<td>Experiments:</td>
<td><em>C. elegans</em> — nematode — forward / backward motions — whole organism</td>
</tr>
<tr>
<td></td>
<td><em>D. melanogaster</em> — fruit fly — threat detection — medulla of optic lobe</td>
</tr>
<tr>
<td></td>
<td><em>M. musculus</em> — house mouse — vibrissal touch — somatosensory (barrel) cortex</td>
</tr>
<tr>
<td></td>
<td><em>M. mutatta</em> — rhesus macaque — various — whole retina, prefrontal cortex</td>
</tr>
</tbody>
</table>

[^1]: Biological microscopy technology: electron microscopy (EM), two-photon-excitation (2PE), infrared (IR), array tomography (AT)

[^2]: Fluorescent physiological probes: genetically-encoded voltage indicator (GEVI), genetically-encoded calcium indicator (GECI)
Recording from mm$^3$ Mouse Somatosensory Cortex

Correlated Activity as a Computational Primitive

- ... variance in firing rates across neurons is correlated\(^1\)
- ... correlated synaptic input drives current fluctuations\(^2\)
- ... modulated coherence as core computational primitive\(^3\)


- ... lot of garbage in components and still it performs well\(^4\)
- ... first 2-3 principal components account for Ca\(^{2+}\) rasters\(^5\)
- ... system phase-portraits lie on low-dimensional manifolds\(^6\)


1. Single-cell-resolution Ca\textsuperscript{2+} 2PE imaging of immobilized worms:

2. Refactor Ca\textsuperscript{2+} rasters as the derivative $\Delta F/F_0$ and normalize:

3. PCA and select PCs accounting for $\geq 60\%$ of the variance:

4. Temporal PCs as weighted sum of refactored time series:

5. Cluster temporal PCs grouping highly correlated neurons:

6. Ca\textsuperscript{2+} imaging unconstrained worms with IR behavior tracking.

7. Identify transitions and segment time-series vectors by hand.

8. Bundle repeated behavior traces and construct phase portrait:
Functional Decomposition from Correlated Activity

Spatiotemporal Segmentation of Correlated Neural Activity:

- Compute the neuron distance matrix $D$ from connectomic reconstruction;
- Compute the correlation matrix $C$ for all neuron Ca$^{2+}$ time-series vectors;
- Cluster these vectors, creating $M$ vertex subsets $\{V_m \subset V : 0 \leq m < M\}$;
- Persistent homology identifies localized circuits of correlated neurons;
Mammalian Neocortex has Complex Structure
Deep Multiple Layer Recurrent Neural Networks

Deep Multiple Layer Recurrent Neural Networks

Defining Morphological and Functional Boundaries

**Dynamical System Modeling with Artificial Neural Networks:**

- Partition tissue into blocks by cutting planes or morphological homogeneity;
- Clean the block interfaces by reassigning block-boundary-spanning neurons;
- Train a multi-layer artificial neural network one block / layer at a time;
- Substitute layer functional types: max pooling, divisive normalization, etc;
# Deeper Still: Modeling Distinctive Network Motifs


![Diagram of network motifs](image)

<table>
<thead>
<tr>
<th>Brain Network</th>
<th>ID</th>
<th>Real</th>
<th>Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Cortex</td>
<td>13</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Macaque Visual Cortex</td>
<td>9</td>
<td>410</td>
<td>121.55 (21.03) z = 13.79</td>
</tr>
<tr>
<td>Macaque Cortex</td>
<td>9</td>
<td>1833</td>
<td>223.66 (34.99) z = 46.22</td>
</tr>
<tr>
<td>Cat Cortex</td>
<td>9</td>
<td>1217</td>
<td>472.33 (52.85) z = 14.16</td>
</tr>
<tr>
<td><em>C. elegans</em></td>
<td>4</td>
<td>2999</td>
<td>1067.03 (121.52) z = 15.98</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3415</td>
<td>1164.31 (134.71) z = 16.79</td>
</tr>
</tbody>
</table>
A simplicial complex is built from points, edges, triangular faces, etc.

0-simplex 1-simplex 2-simplex 3-simplex (solid) example of a simplicial complex

Homology counts components, holes, voids, etc.

hole void (contains faces but empty interior) Homology of a simplicial complex is computable via linear algebra.

Matthew Wright, Introduction to Persistent Homology. 2015.
The Ordered $n$-simplices of a Directed Graph

6 0-simplices \{1, 2, 3, 4, 5, 6\}
8 1-simplices \{12, 13, 23, ..., 56\}
1 2-simplices \{123\}
0 3-simplices \{\}

Directed Clique Complex of a Microcircuit

(a) Directed graph with vertices 1, 2, 3, 4, 5, 6, 7, and edges connecting them.

(b) Directed graph with vertices 1, 2, 3, 4, 5, 6, 7, 12, 13, 23, 24, 34, 35, 45, 56, 57, 67, 123, 234, 345, 567, and edges connecting them.

Example:

Record the barcode:

Matthew Wright, Introduction to Persistent Homology. 2015.
Example:

Record the barcode:

Matthew Wright, Introduction to Persistent Homology. 2015.
Example:

Short bars represent noise.

Long bars represent features.

Record the barcode:

Matthew Wright, Introduction to Persistent Homology. 2015.
Persistent Homology: Microcircuit Dynamics

Circuit Motifs: Spatial and Temporal Locality

Multi-Scale Spatial and Temporal Circuit-Motif Dynamics:

- For $0 \leq t < T$, construct a transmission-response\textsuperscript{1} adjacency matrix $A(t)$;
- Compute directed-clique\textsuperscript{2} complex $K(t)$ for each graph: $\{A(t): 0 \leq t < T \}$;
- For each $t$ compute subgraphs/complexes restricted to $V_m$ for $0 \leq m < M$;
- Compute topological invariants, e.g., $\{\beta_1, \beta_2, ... \}$ for all $T \times M$ complexes;

[1] [2] See the supplementary material at the end of this document for a formal definition.
Mining Neural Recordings for Computational Motifs

Distinctive Signatures for Recognizing Ongoing Computations:

- Activity Motifs — highly-correlated variance in neural spiking activity;
- Circuit Motifs — persistent task-relevant patterns of neural connectivity;

Temporal and Spatial Locality Across a Wide Range of Scales:

- fMRI hemodynamics, electroencephalography, diffusion anisotropy;
- Cortical rhythms: δ: 0.5-4 Hz, τ: 4-7 Hz, α: 8-13 Hz, β: 13-30 Hz;
- Diffuse neuromodulation, dopaminergic bursting and tonic modes, etc;
Supplementary Material
Here is the definition of a transmission-response matrix given in Dlotko et al [3]: After a systematic analysis to determine the appropriate time bin size and conditions for probable spike transmission from one neuron to another, we divided the activity of the microcircuit into 5 ms time bins for 1 second after the initial stimulation and recorded for each $0 \leq t < T$ a functional connectivity matrix $A(t)$ for the times between $5t$ ms and $5(t + 1)$ ms. The $(j, k)$-coefficient of the binary matrix $A(t)$ is 1 if and only if the following three conditions are satisfied, where $s_{ji}$ denotes the time of the $i$-th spike of neuron $j$:

1. The $(j, k)$-coefficient of the structural matrix is 1, i.e., there is connection from the $j$th neuron to the $k$th neuron.

2. There is some $i$ such that $5t$ ms $\leq s_{ji} < 5(t + 1)$ ms, i.e., the $j$th neuron spikes in the $n$-th time bin.

3. There is some $l$ such that $0$ ms $\leq s_{kl} - s_{ji} < 7.5$ ms, i.e., the $k$th neuron spikes within 7.5 ms after the $j$th neuron.

We call the matrices $A(t)$ transmission-response matrices, as it is reasonable to assume that the spiking of neuron $k$ is influenced by the spiking of neuron $j$ under conditions (1)–(3) above.

Borrowing the definition from [6], an abstract simplicial complex \( K \) is defined as a set \( K_0 \) of vertices and sets \( K_n \) of lists \( \sigma = (x_0,\ldots,x_n) \) of elements of \( K_0 \) (called \( n \)-simplices), for \( n \geq 1 \), with the property that, if \( \sigma = (x_0,\ldots,x_n) \) belongs to \( K_n \), then any sublist \( (x_{i_0},\ldots,x_{i_k}) \) of \( \sigma \) belongs to \( K_k \). The sublists of \( \sigma \) are called faces.

We consider a finite directed weighted graph \( G = (V,E) \) with vertex set \( V \) and edge set \( E \) with no self-loops and no double edges, and denote with \( N \) the cardinality of \( V \). Associated to \( G \), we can construct its (directed) clique complex \( K(G) \), which is the simplicial complex given by \( K(G)_0 = V \) and

\[
K(G)_n = \{(v_0,\ldots,v_n) : (v_i,v_j) \in E \text{ for all } i < j \} \text{ for } n \geq 1.
\]

In other words, an \( n \)-simplex contained in \( K(G)_n \) is a directed \((n + 1)\)-clique or a completely connected directed sub-graph with \( n + 1 \) vertices. Notice that an \( n \)-simplex is thought of as an object of dimension \( n \) and consists of \( n + 1 \) vertices. By definition, a directed clique (or a simplex in our complex) is a fully-connected directed sub-network: this means that the nodes are ordered and there is one source and one sink in the sub-network, and the presence of the directed clique in the network means that the former is connected to the latter in all the possible ways within the sub-network.