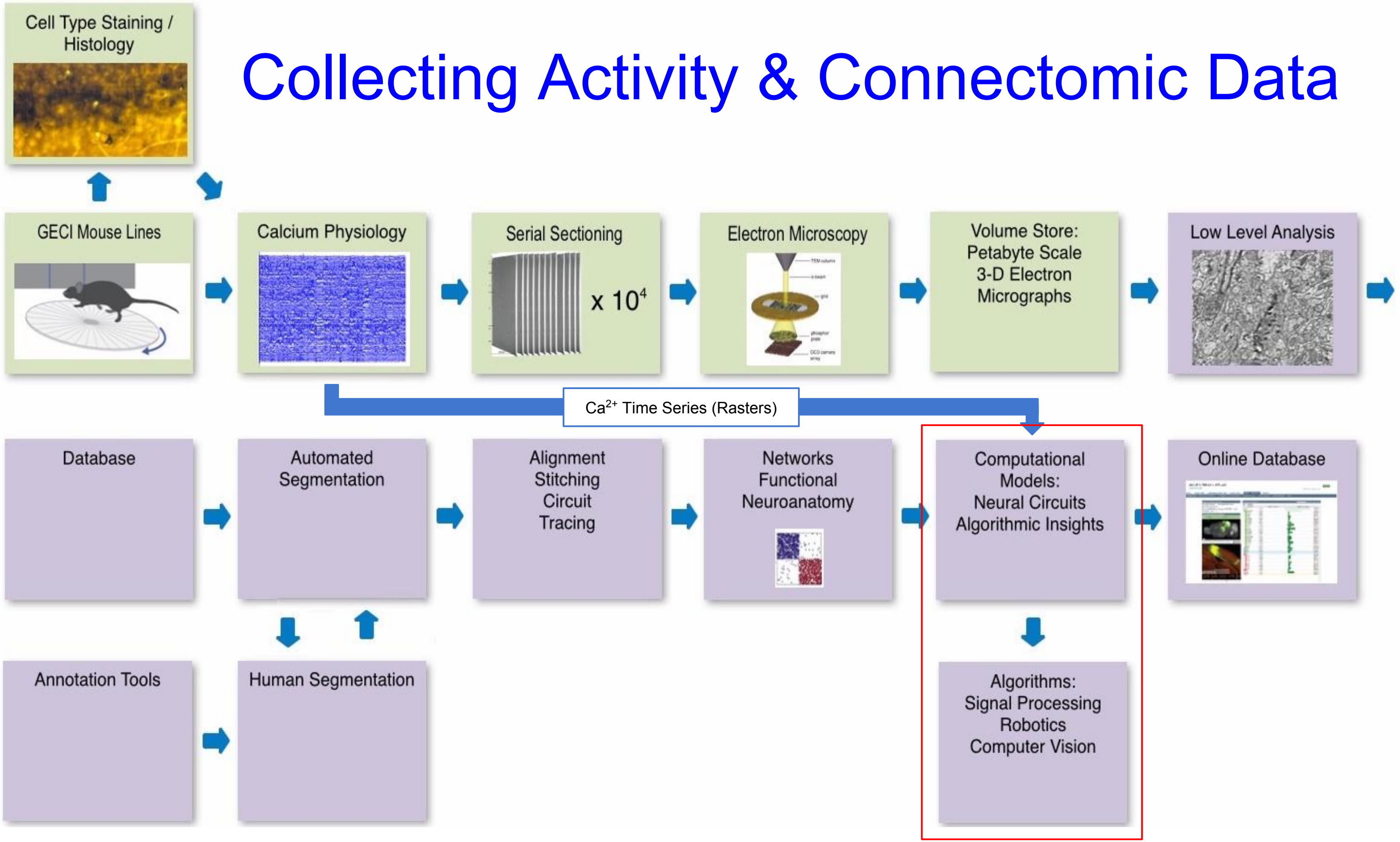
- Collecting Aligned Activity & Connectomic Data
  Example: Mouse Vibrissal Touch Barrel Cortex
- Exploiting Coherence to Reduce Dimensionality
  Example: *C. elegans* Motor Control Sequence
- Spatially & Temporally Distributed Circuit Motifs
  Example: Localized Persistent Homology
- Modeling Cortical Layers with Deep Networks
  Example: Primary Visual Cortex in Primates

Collecting Activity & Connectomic Data



Christof Koch. Project MindScope. In *Frontiers in Computational Neuroscience, 2012 Bernstein Conference*, number 33. 2012.

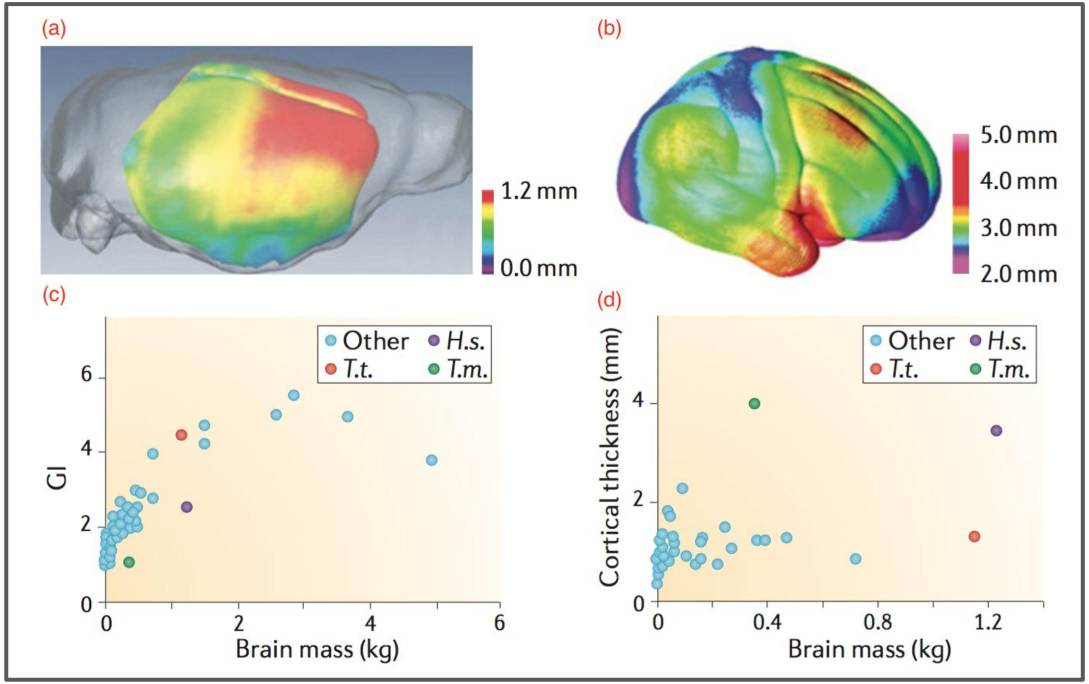
Worms, Flies, Mice and Monkeys

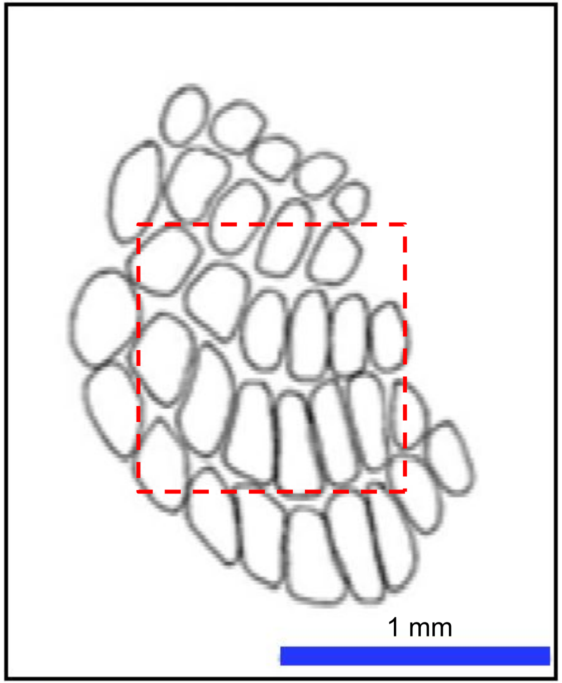
Data Types:	EM structural; 2PE functional; IR behavioral; AT genomic[1]
Annotations:	3D microcircuit reconstruction; sparse, weighted adjacency matrix
	boundary I/O: sensory / motor; afferent / efferent; axonal / dendritic
	neuron morphological types; synaptic coordinates & connection types
	dense GECI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

[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)

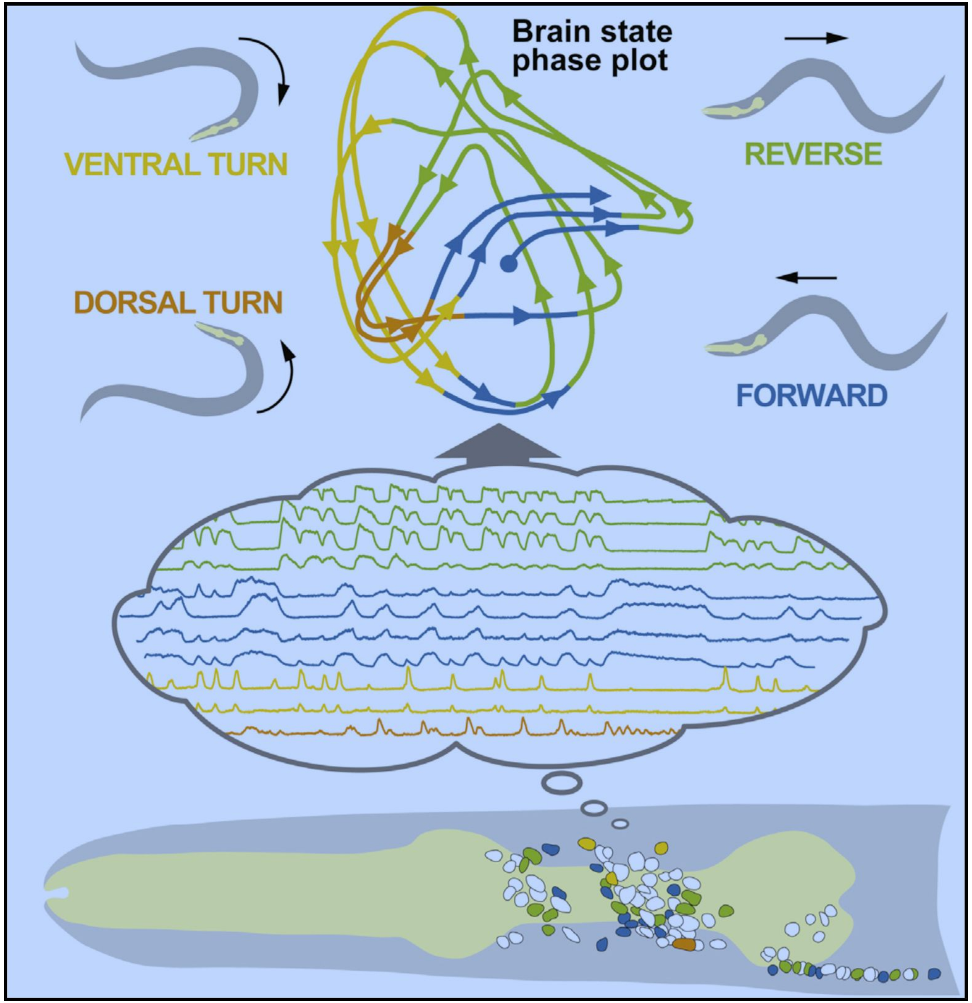
Recording from mm^3 Mouse Somatosensory Cortex





Tao Sun & Robert Hevner. Growth and folding of mammalian cerebral cortex: molecules to malformations. *Nature Reviews Neuroscience*, 15:217-232, 2014.

C. elegans Motor Control



Saul Kato, …, Manuel Zimmer. Global brain dynamics embed the motor command sequence of *caenorhabditis elegans*. *Cell*, 163:656-669, 2015.

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]

[1] S. Panzeri, S. R. Schultz, A. Treves, & E. T. Rolls. Correlations and encoding information in the nervous system. *Royal Society B: Biological Sciences*, 266(1423):1001-1012, 1999.

[2] E. Salinas & T. Sejnowski. Impact of correlated synaptic input on output firing rate and variability in simple neuronal models. *The Journal of Neuroscience*, 20(16):6193-6209, 2000.

[3] X. J. Wang. Neurophysiological and computational principles of the cortical rhythms in cognition. *Physiological Reviews*, 90(3):1195-1268, 2010.

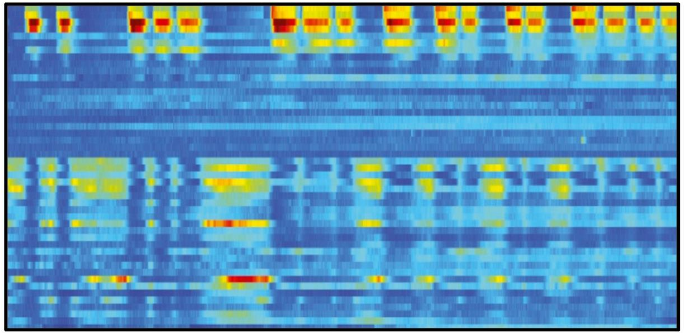
- ... lot of garbage in components and still it performs well[4]
- ... first 2-3 principal components account for Ca^2+ rasters[5]
- ... system phase-portraits lie on low-dimensional manifolds[6]

[4] Carver Mead. Neural hardware for vision. *Engineering & Science*, 1:2-7, 1987.

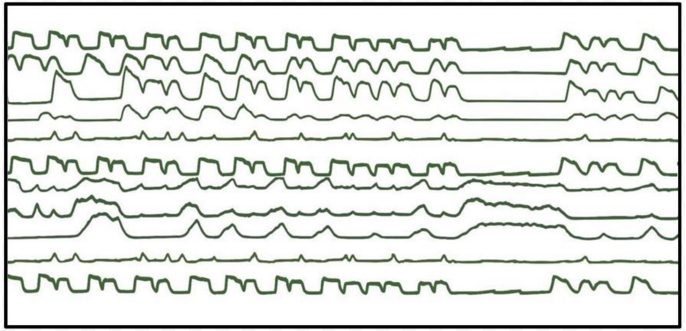
[5] S. Kato, H. S. Kaplan, T. Schrödel, S. Skora, …, E. Yemini, S. Lockery, M. Zimmer. Global brain dynamics embed the motor command sequence of *C. elegans*. *Cell*, 163:656-669, 2015.

[6] V. Mante, D. Sussillo, K, V. Shenoy, and & W. T. Newsome. Context-dependent computation by recurrent dynamics in prefrontal cortex. *Nature*, 503:78-84, 2013.

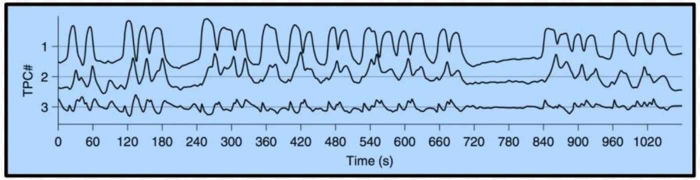
1. Single-cell-resolution Ca^{2+} 2PE imaging of immobilized worms:



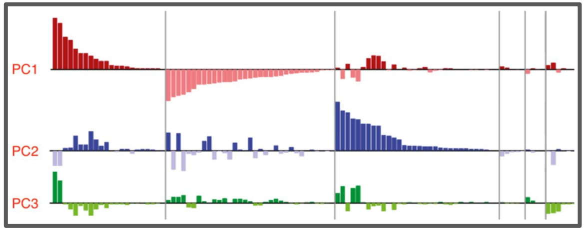
2. Refactor Ca^{2+} rasters as the derivative $\Delta F/F_0$ and normalize:



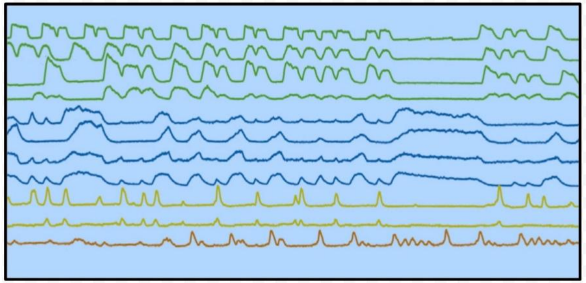
3. PCA and select PCs accounting for ≥ 60% of the variance:



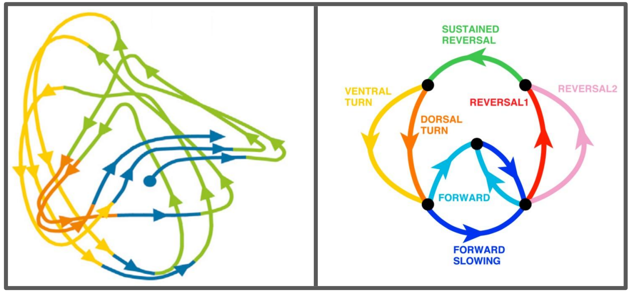
4. Temporal PCs as weighted sum of refactored time series:



5. Cluster temporal PCs grouping highly correlated neurons:



6. Ca^{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:

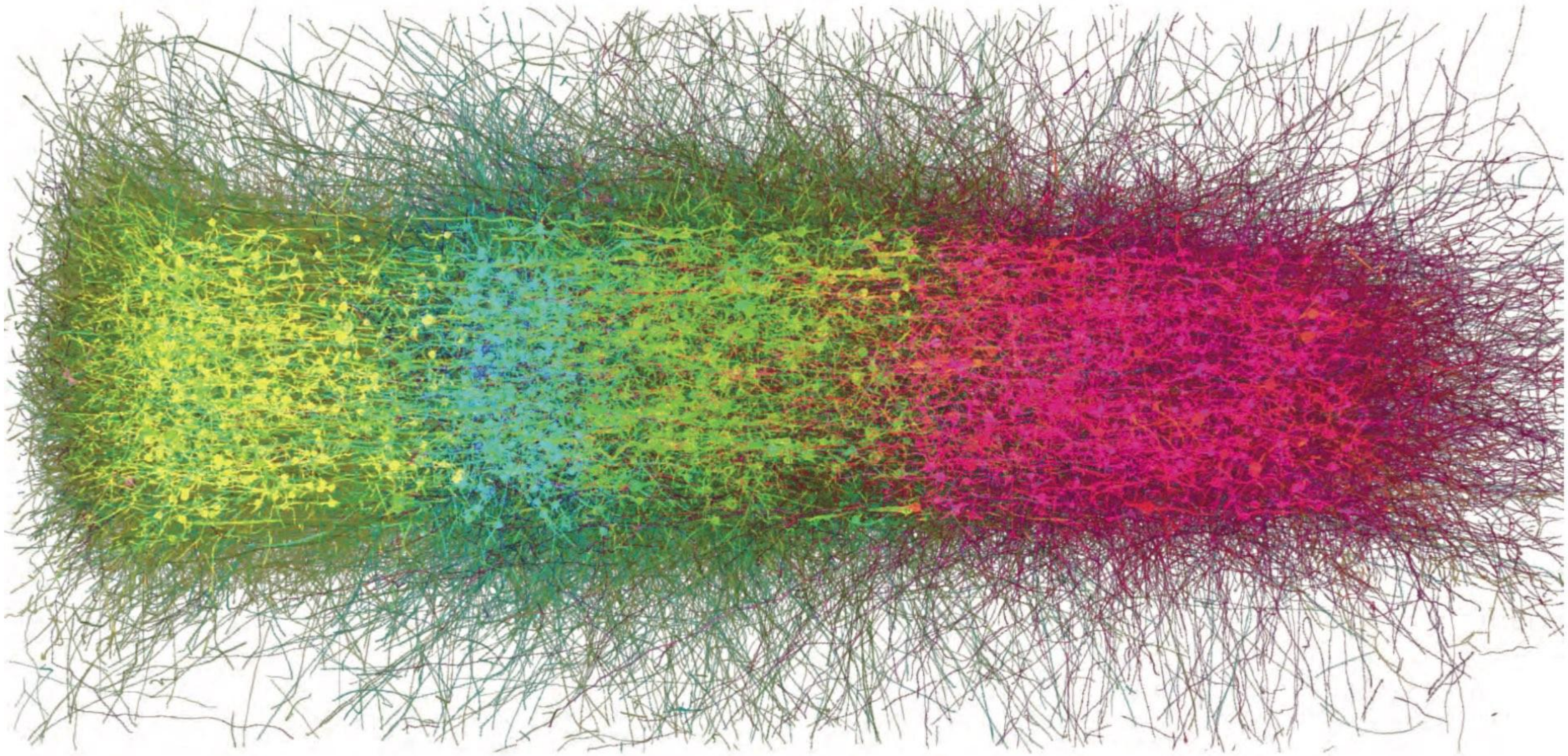


Functional Decomposition from Correlated Activity

Spatiotemporal Segmentation of Correlated Neural Activity:

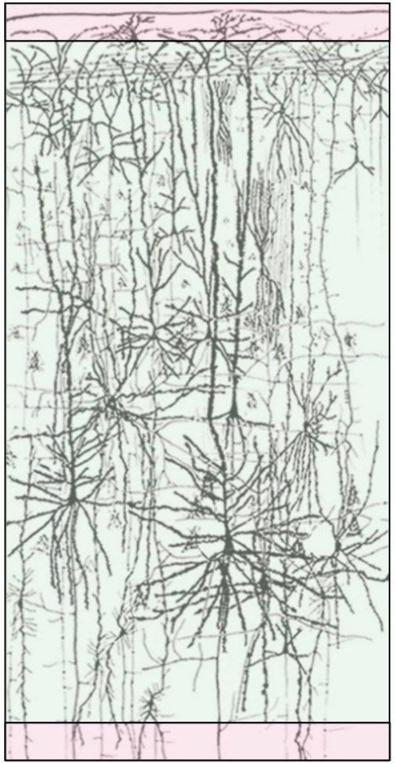
- Compute the neuron distance matrix D from connectomic reconstruction;
- Compute the correlation matrix C for all neuron Ca^{2+} time-series vectors;
- Cluster these vectors, creating M vertex subsets $\{V_m \subset V : 0 \leq m < M\}$;
- Persistent homology identifies localized circuits of correlated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

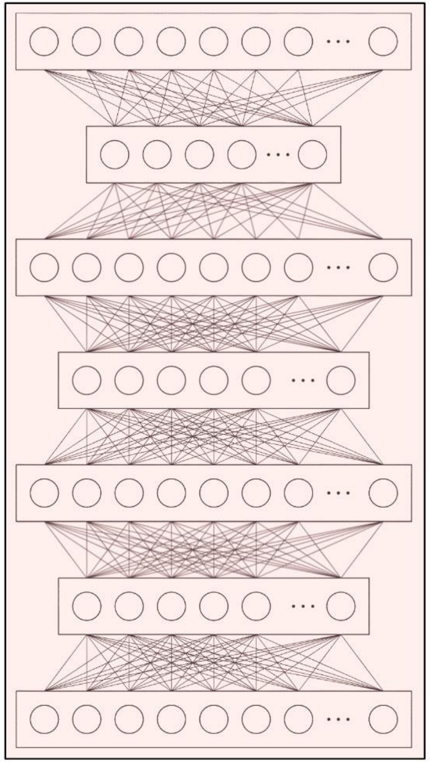
Mammalian Neocortex has Complex Structure



Henry Markram, …, Sean L. Hill, Idan Segev, Felix Schürmann. Reconstruction and simulation of neocortical microcircuitry. *Cell*, 163:456-492, 2015.

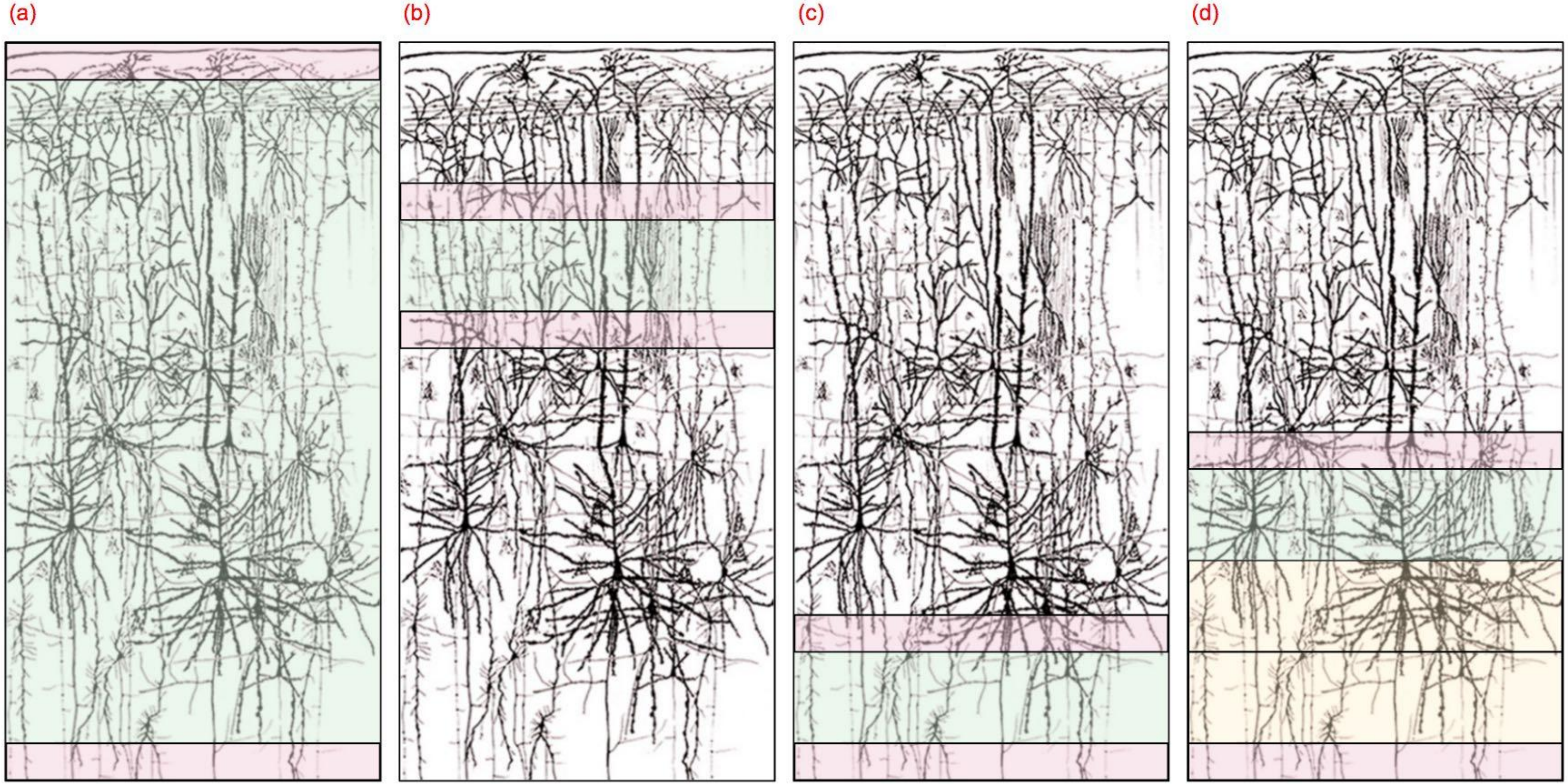
Deep Multiple Layer Recurrent Neural Networks





David Sussillo & Omri Barak. Low-dimensional dynamics in high-dimensional recurrent neural networks. *Neural Computation*, 25(3):626-649, 2013.

Deep Multiple Layer Recurrent Neural Networks



David Sussillo & Omri Barak. Low-dimensional dynamics in high-dimensional recurrent neural networks. *Neural Computation*, 25(3):626-649, 2013.

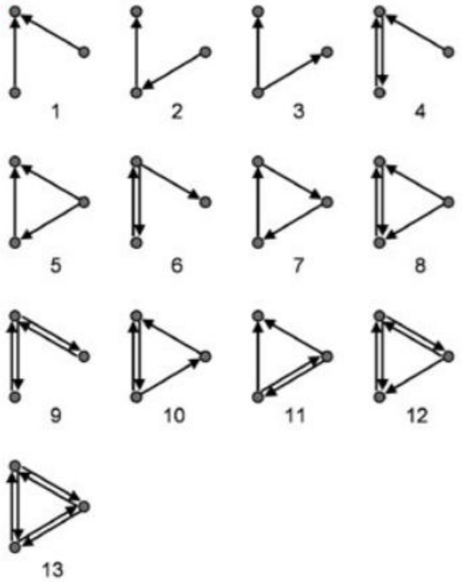
Defining Morphological and Functional Boundaries

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

(a)



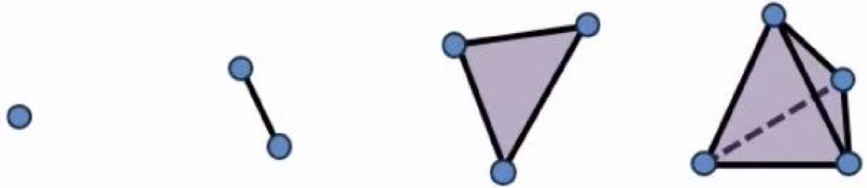
(b)

Brain Network	ID	Real	Random
Human Cortex	13	N/A	N/A
Macaque Visual Cortex	9	410	121.55 (21.03) $z = 13.79$
Macaque Cortex	9	1833	223.66 (34.99) $z = 46.22$
Cat Cortex	9	1217	472.33 (52.85) $z = 14.16$
C. elegans	4	2999	1067.03 (121.52) $z = 15.98$
	6	3415	1164.31 (134.71) $z = 16.79$

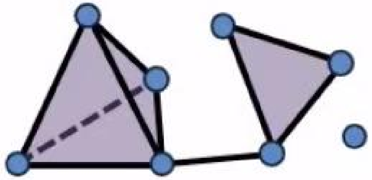
Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., Alon, U. Network Motifs: Building Blocks of Complex Networks. *Science* 298, 824-827, 2002.

Marcus Kaiser. A tutorial in connectome analysis: Topological and spatial features of brain networks. *Columbia Research Repository*, arXiv:1105.4705, 2011.

A **simplicial complex** is built from points, edges, triangular faces, etc.

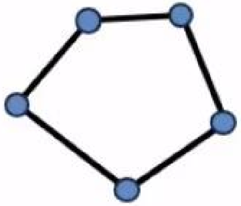


0-simplex 1-simplex 2-simplex 3-simplex (solid)

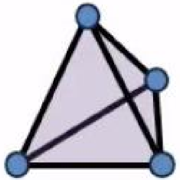


example of a simplicial complex

Homology counts components, holes, voids, etc.



hole



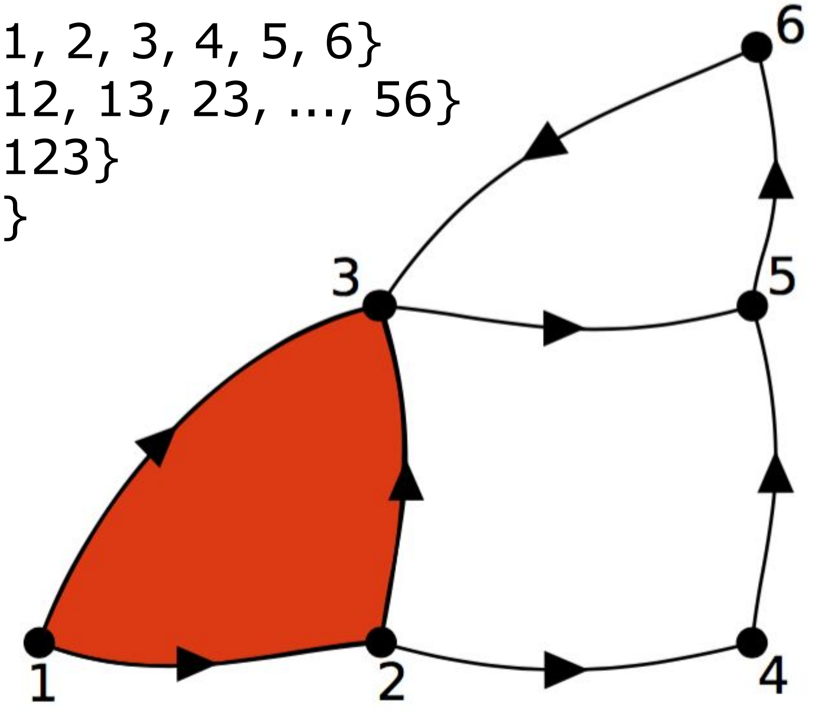
void (contains faces but empty interior)

Homology of a simplicial complex is computable via linear algebra.

Matthew Wright, Introduction to Persistent Homology. 2015.

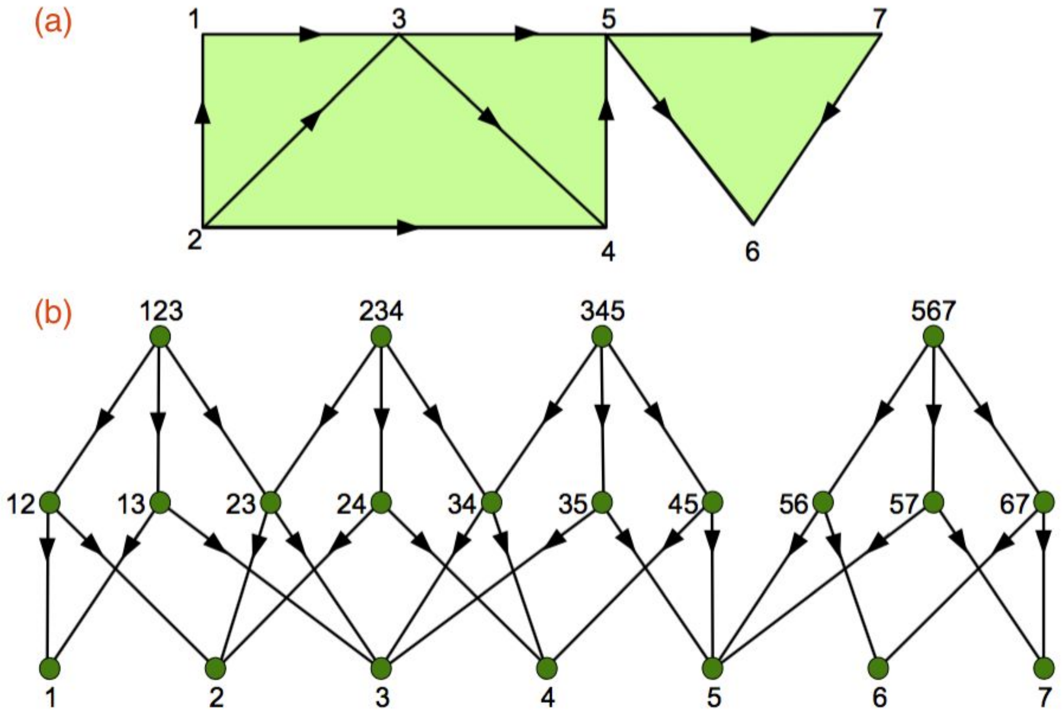
The Ordered *n*-simplices of a Directed Graph

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



Alessandro E. P. Villa Paolo Masulli. The topology of the directed clique complex as a network invariant. *CoRR*, arXiv:1510.00660, 2015.

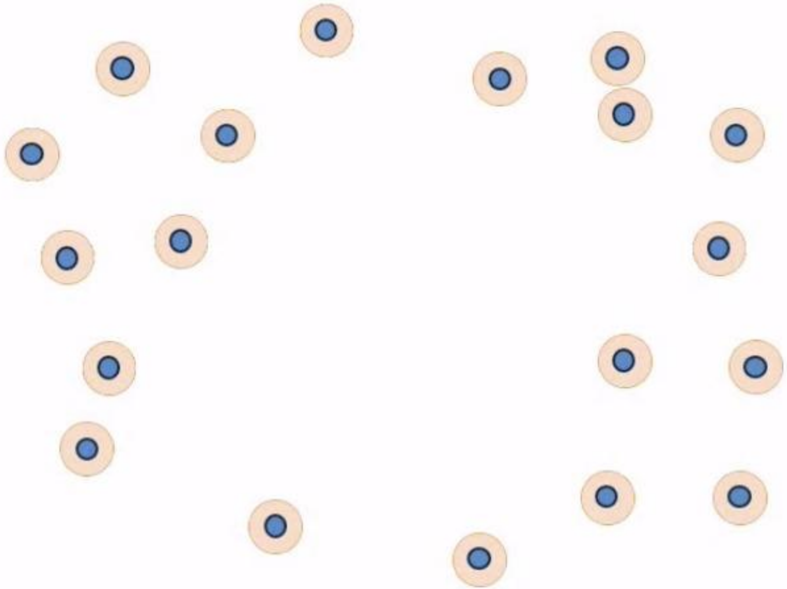
Directed Clique Complex of a Microcircuit



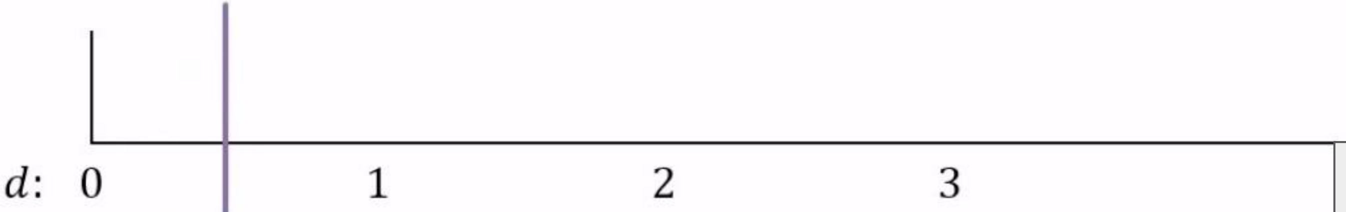
Pawel Dlotko, …, Henry Markram. Topological analysis of the connectome of digital reconstructions of neural microcircuits. *CoRR*, arXiv:1601.01580, 2016.

Persistent Homology

Example:



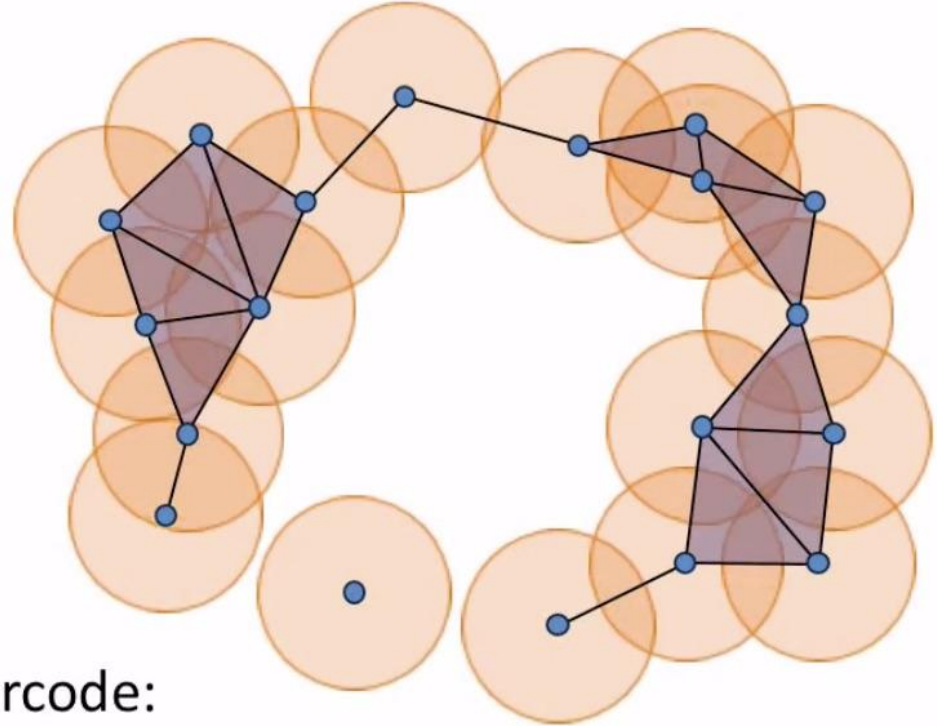
Record the barcode:



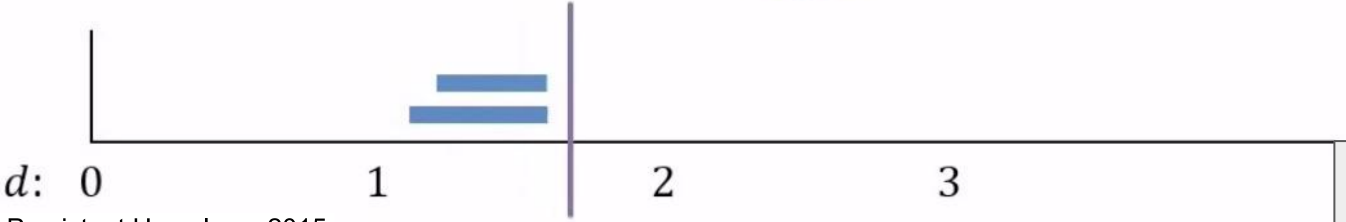
Matthew Wright, Introduction to Persistent Homology. 2015.

Persistent Homology

Example:

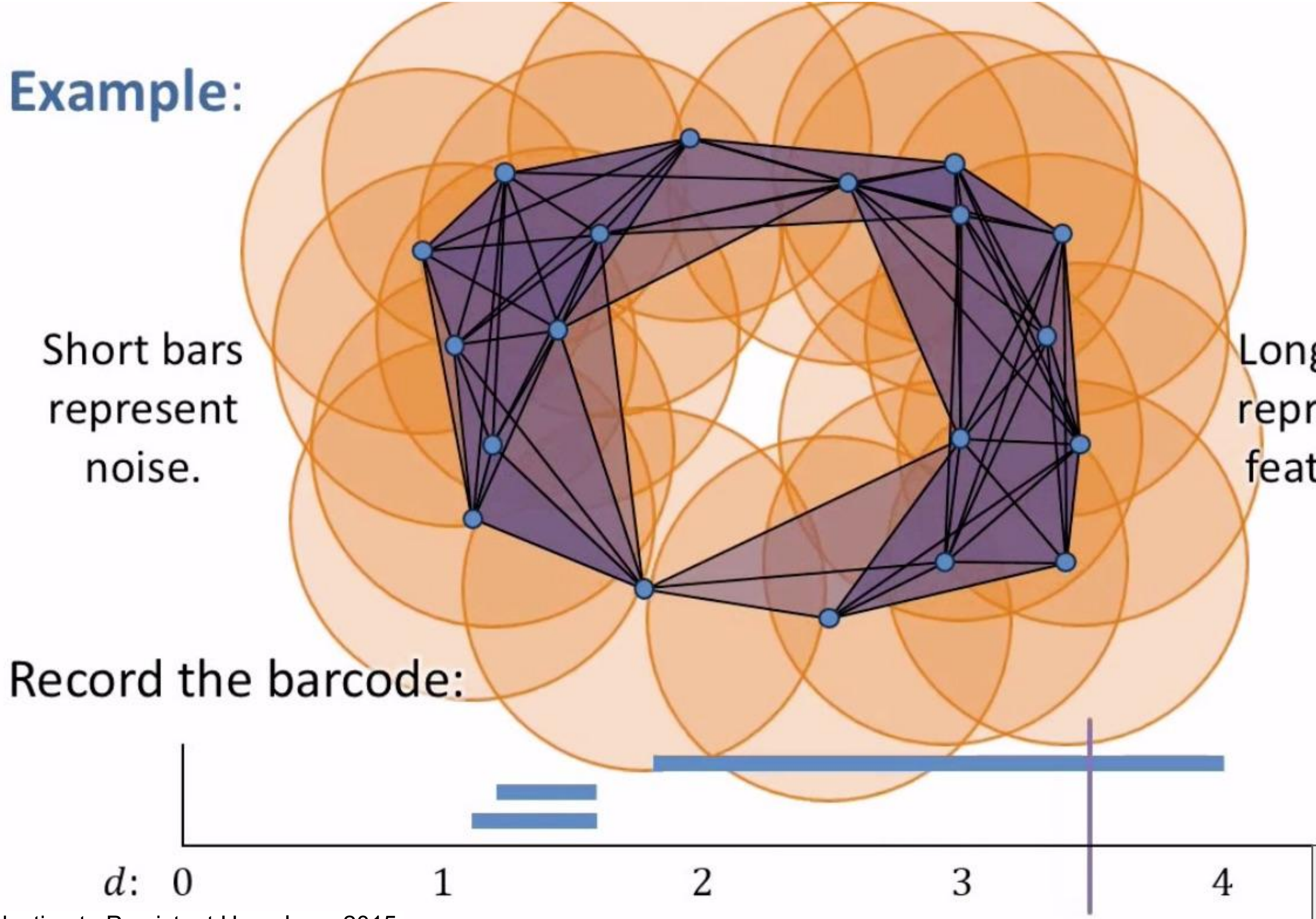


Record the barcode:



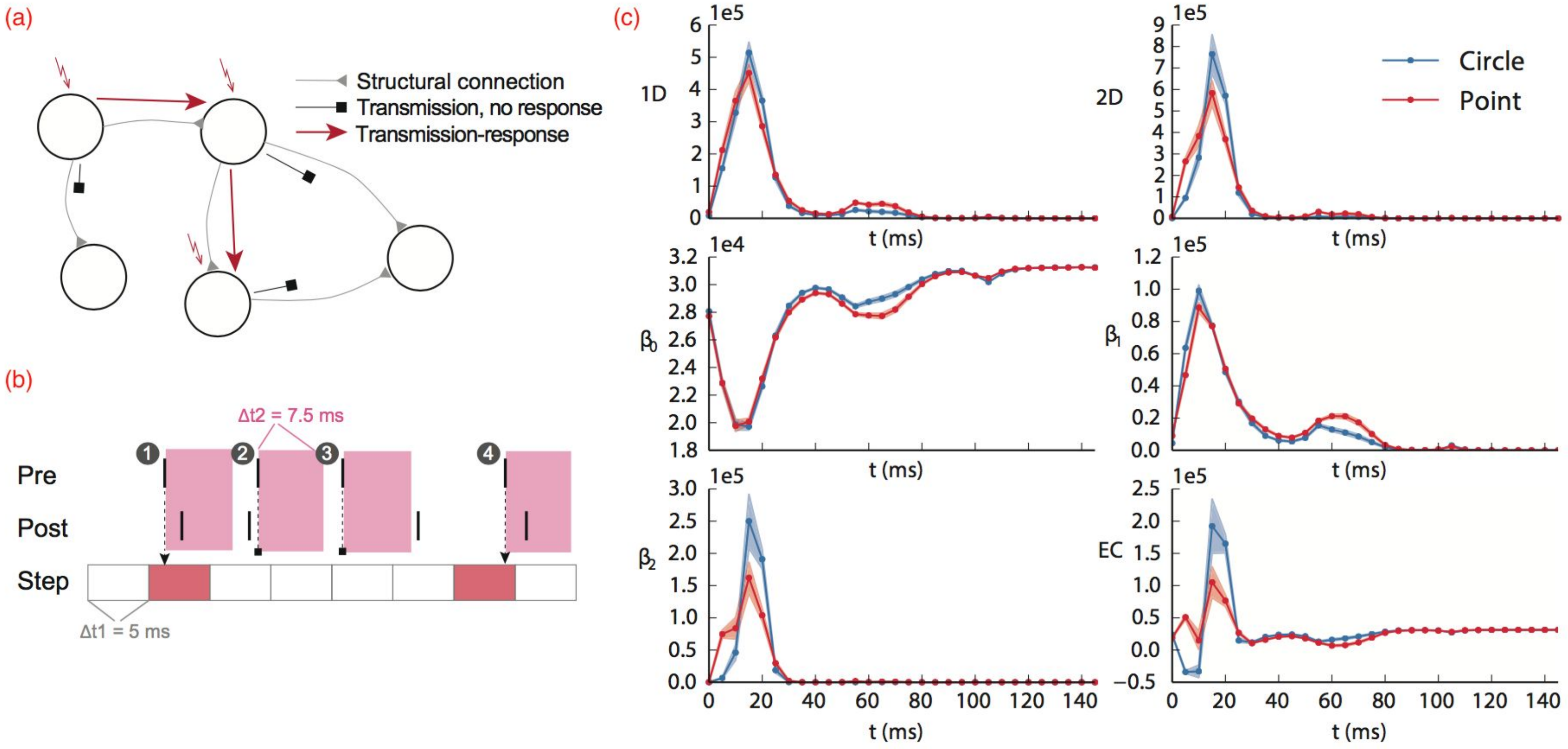
Matthew Wright, Introduction to Persistent Homology. 2015.

Persistent Homology



Matthew Wright, Introduction to Persistent Homology. 2015.

Persistent Homology: Microcircuit Dynamics



Pawel Dlotko, …, Henry Markram. Topological analysis of the connectome of digital reconstructions of neural microcircuits. *CoRR*, arXiv:1601.01580, 2016.

Circuit Motifs: Spatial and Temporal Locality

Multi-Scale Spatial and Temporal Circuit-Motif Dynamics:

- For $0 \leq t < T$, construct a *transmission-response*[1] adjacency matrix $A(t)$;
- Compute *directed-clique*[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 toplogical invariants, e.g., $\{\beta_1, \beta_2, \ldots\}$ 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

[1] 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 jth neuron to the kth neuron.
2. There is some i such that $5t \text{ ms} \leq s_{ji} < 5(t+1)$ ms, i.e., the jth neuron spikes in the n-th time bin.
3. There is some l such that $0 \text{ ms} < s_{kl} - s_{ji} < 7.5$ ms, i.e., the kth neuron spikes within 7.5 ms after the jth 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.

[3] Pawel Dlotko, …, Henry Markram. Topological analysis of the connectome of digital reconstructions of neural microcircuits. *CoRR*, arXiv:1601.01580, 2016.

[2] 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 σ belongs to K_k. The sublists of σ 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

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

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.

[6] Alessandro E. P. Villa Paolo Masulli. The topology of the directed clique complex as a network invariant. *CoRR*, arXiv:1510.00660, 2015.