Amber Wu, 1 March 2022

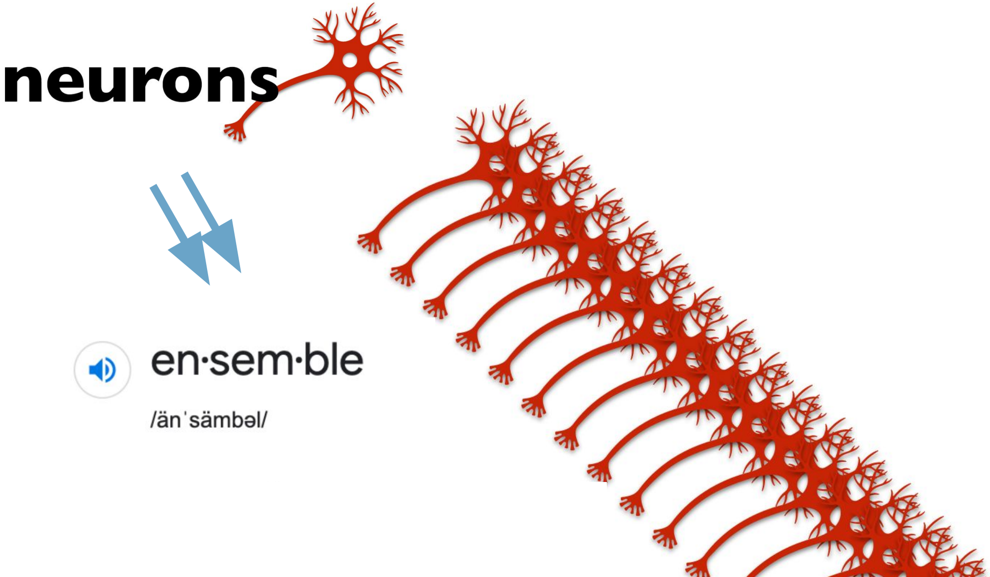
Structure and Function of
A Mouse Brain

Cliques of Neurons Bound into Cavities Provide a Missing Link between Structure and Function Michael W. Reimann et al.

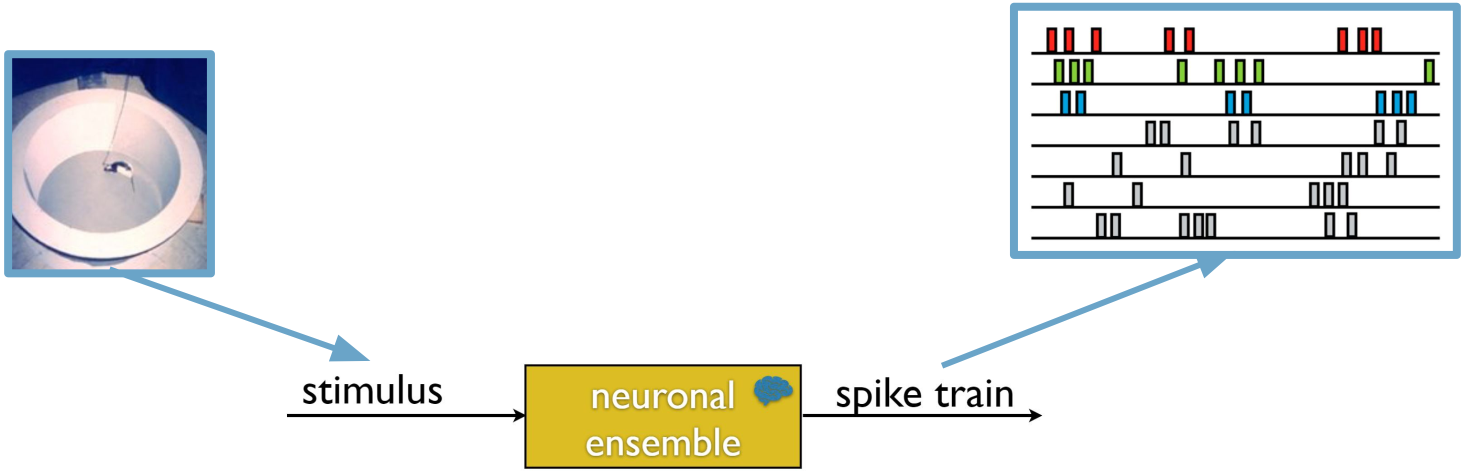
—— Blue Brain Project
12 June 2017

EPFL

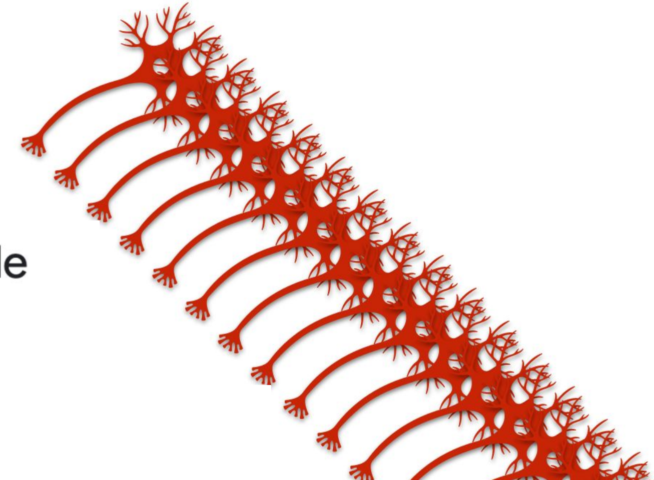
Structure & Function?



Structure & Function?



Structure & Function?

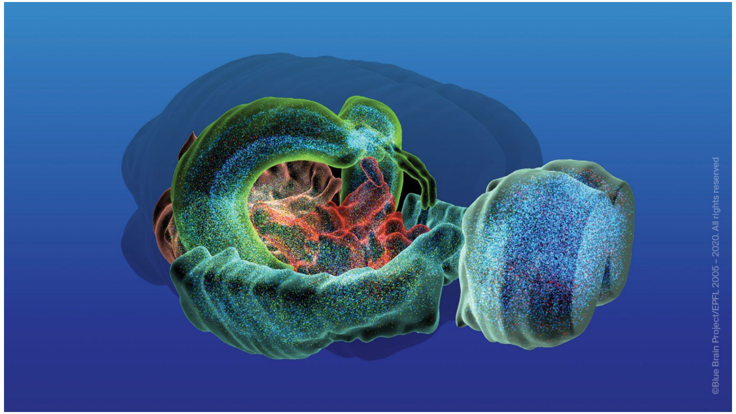


en·sem·ble

/änˈsämbəl/

Authors

Blue Brain Project



- Henry Markram (EPFL), found in 2005
- Biologically detailed digital reconstructions and simulations of the mouse brain
    - Cellular model (2005)
    - Neural cliques (2017)
    - Digital 3D brain atlas (2018)

Contents

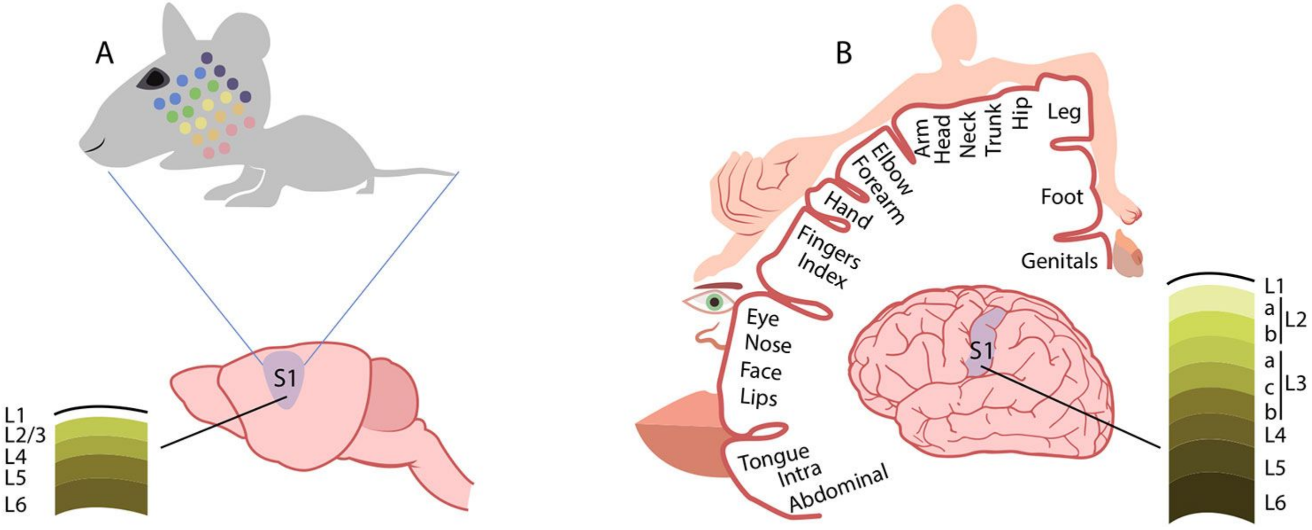
Structure (Cliques of Neurons)

- Local
    - Biological background
    - Topological Construction
        - Directed Graph
        - Simplices & Complexes
- Global

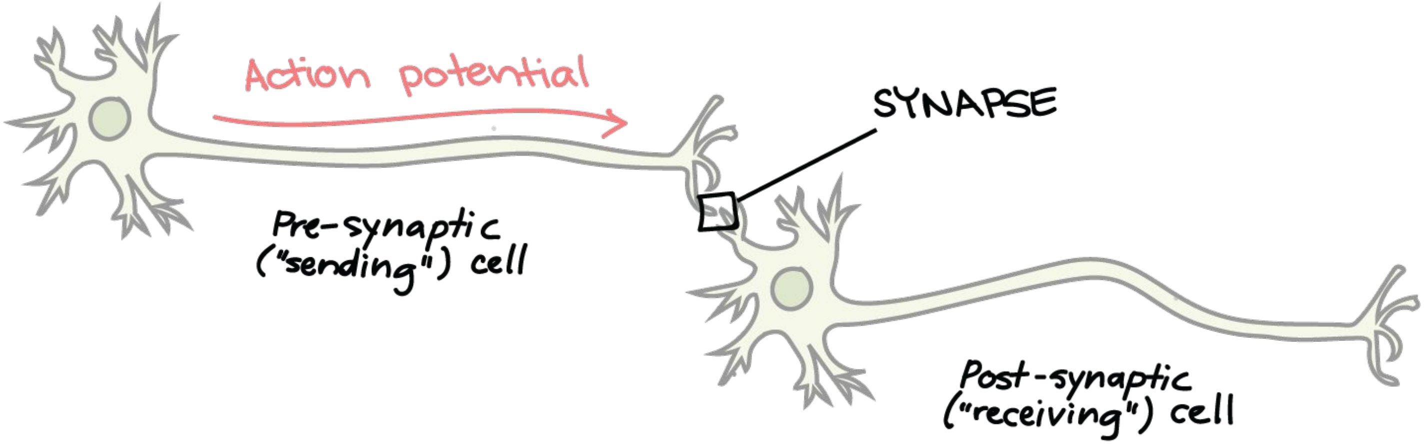
Function (Bound into Cavities)

- Local
- Global

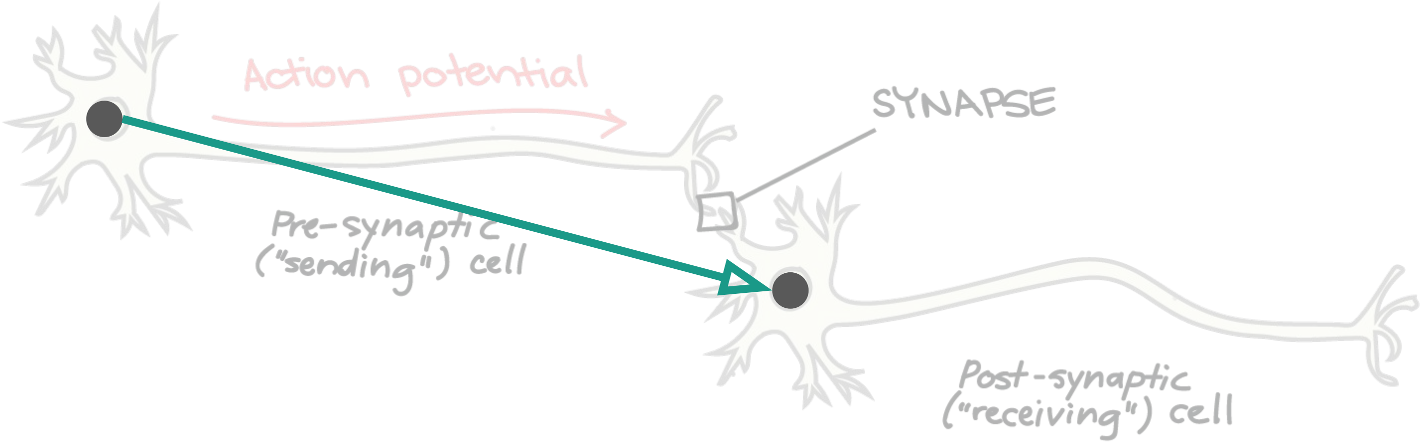
Primary Somatosensory Cortex



Neurons & Synapse



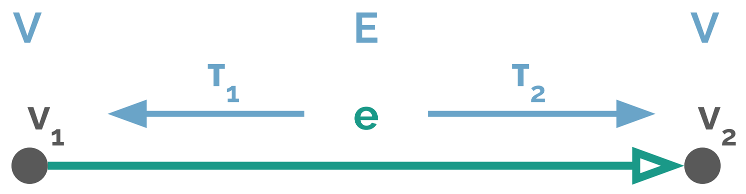
Directed Graphs



Directed Graphs $\mathcal{G}$

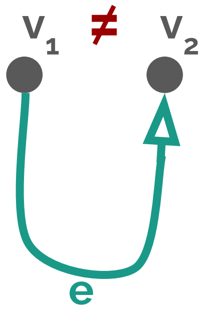
- Finite sets (V, E)
- $\tau = (\tau_1, \tau_2) : E \longrightarrow V \times V$
- $\tau_1(e) = v_1$, source vertex
- $\tau_2(e) = v_2$, target vertex

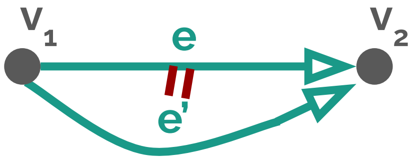
direction



Directed Graphs - function τ

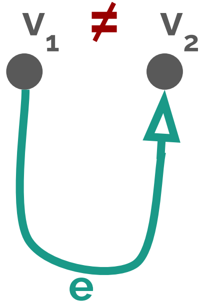
1) No self-loop
2) Injective

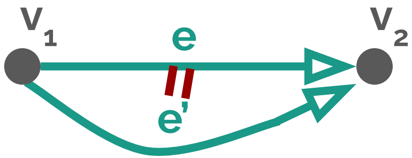




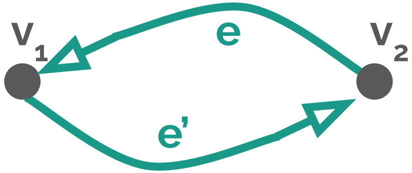
Directed Graphs - function τ

1) No self-loop
2) Injective





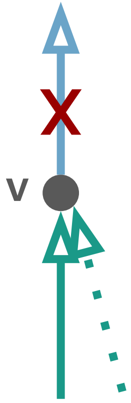
Note:

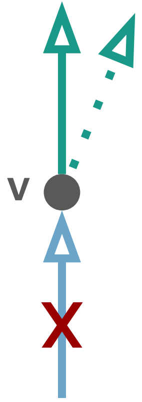


is allowed!

Directed Graphs - vertex v

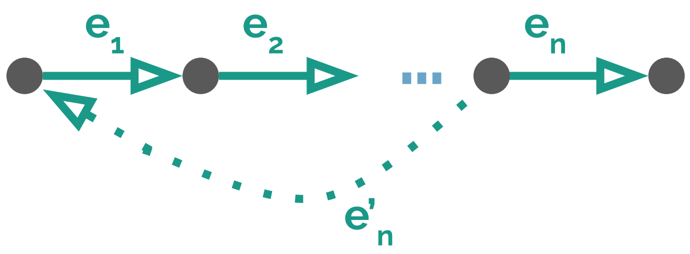
- Sink
  - if there exists no $e \in E$ such that $v = \tau_1(e)$, but there is at least one edge $e' \in E$ such that $\tau_2(e')=v$
- Source
  - if there exists no $e \in E$ such that $v = \tau_2(e)$, but there is at least one edge $e' \in E$ such that $\tau_1(e')=v$





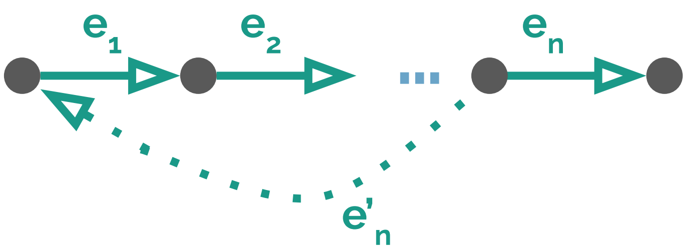
Directed Graphs - path

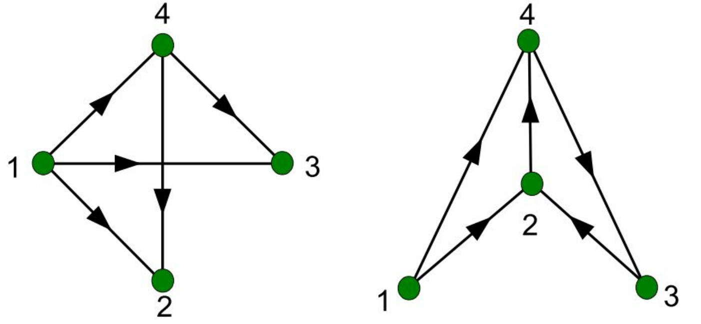
- Sequence of edges $(e_1, \ldots, e_n)$
  - $\tau_2(e_k) = \tau_1(e_{k+1})$ for all $1 \leq k < n$
- Length := n
- Oriented circle
  - $\tau_2(e_n) = \tau_1(e_1)$



Directed Graphs - path

- Sequence of edges $(e_1, \ldots, e_n)$
  - $\tau_2(e_k) = \tau_1(e_{k+1})$ for all $1 \leq k < n$
- Length := n
- Oriented circle
  - $\tau_2(e_n) = \tau_1(e_1)$
- Graph containing no oriented circle is acyclic.





Abstract directed simplex & simplicial complex

- An **abstract direct simplicial complex** is a collection $\mathcal{S}$ of finite, *ordered* sets which is closed under taking subsets.
- A **subcomplex** is a subcollection of $\mathcal{S}$ that is itself an abstract directed simplicial complex.
- Elements of $\mathcal{S}$ are called its **simplices**, denoted σ.

Abstract directed simplex & simplicial complex

- **Dimension** of σ, denoted dim(σ) := (cardinality of σ) - 1.
- σ is called an **n-simplex** if it has dimension n.
- Set of all n-simplices is denoted $\mathcal{S}_n$.

Abstract directed simplex & simplicial complex

- τ is a **face** of $\sigma = (v_0, \dots, v_n)$ if it is a subset with strictly smaller cardinality.
- **front face** $= (v_0, \dots, v_m)$, $0 < m < n$
- **back face** $= (v_m, \dots, v_n)$, $0 < m < n$
- **i-th face of σ** is the (n-1)-simplex obtained from σ by removing vertex v_{n-i}
- A simplex is **maximal** if it is not a face of any other simplex.

Abstract directed simplex & simplicial complex

Remark 1

The set of all maximal simplices of a simplicial complex determines the entire simplicial complex, since every simplex is either maximal itself or a face of a maximal simplex.

(realized) **Simplicial complex**

- **Simplicial complex** is induced from an abstract simplicial complex by geometric realization. It gives rise to a topological space.
    - 0-simplex: a point
    - 1-simplex: an edge
    - 2-simplex: a filled-in triangle
    - ...
- Simplicial complexes are realized by gluing realized simplices together by their common faces.

(realized) **Simplicial complex**

<u>**Remark 2**</u>

If for two simplices, neither of them is a face of the other, then their intersection is a proper subset, therefore a face, of both simplices.

Thus, simplicial complexes are well-defined geometric objects.

Directed flag complex of $\mathcal{G}$

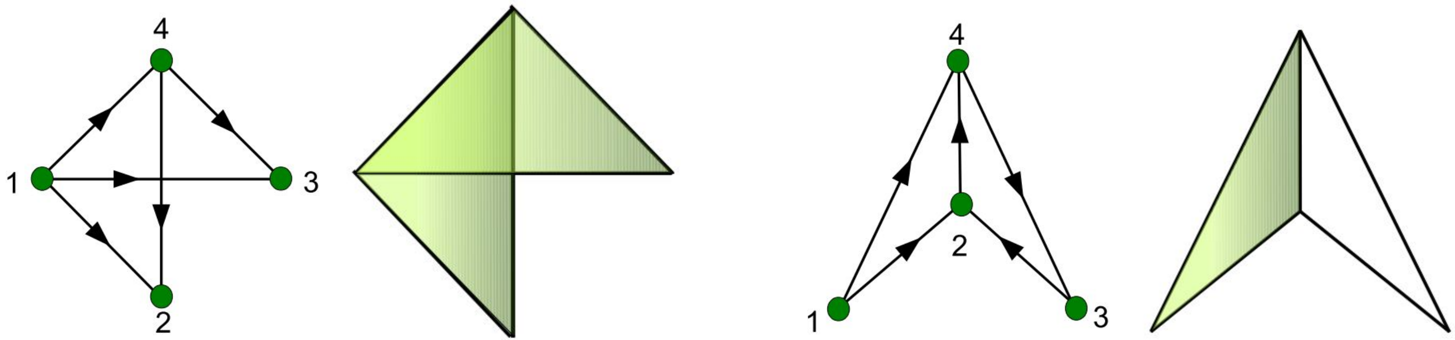
- For $\mathcal{G}$ = (V, E, τ) a directed graph, the associated directed flag complexes are defined by $\mathcal{S} = \mathcal{S}(\mathcal{G})$h that
    - $\mathcal{S}_0$ (set of all 0-simplices) = V
    - $\mathcal{S}_n$ = {(v_0, … , v_n)} such that there exists an edge directed from v_i to v_j for every $0 \leq i < j \leq n$
    - Therefore v_0 is the source and v_n is the sink of the simplex.

Directed flag complex of $\mathcal{G}$

Remark 3 (disambiguation)

An n-simplex in $\mathcal{S}$ is characterized by the (ordered) sequence $(v_0, \ldots, v_n)$, but not by the labeling of vertices. For instance (v_1, v_2, v_3) and (v_2, v_1, v_3) are **distinct** 2-simplices with the same set of vertices.

Directed flag complex of $\mathcal{G}$



Contents

Structure (Cliques of Neurons)

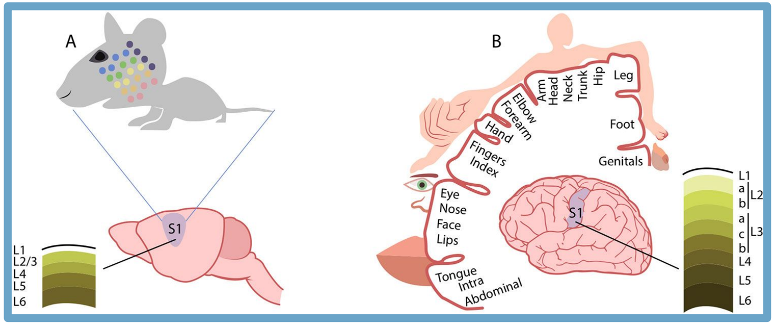
- Local
  - Biological background
  - Topological Construction
    - Directed Graph
    - Simplices & Complexes
- Global
  - Biological background
  - Simplices
    - Construction
    - Robustness check

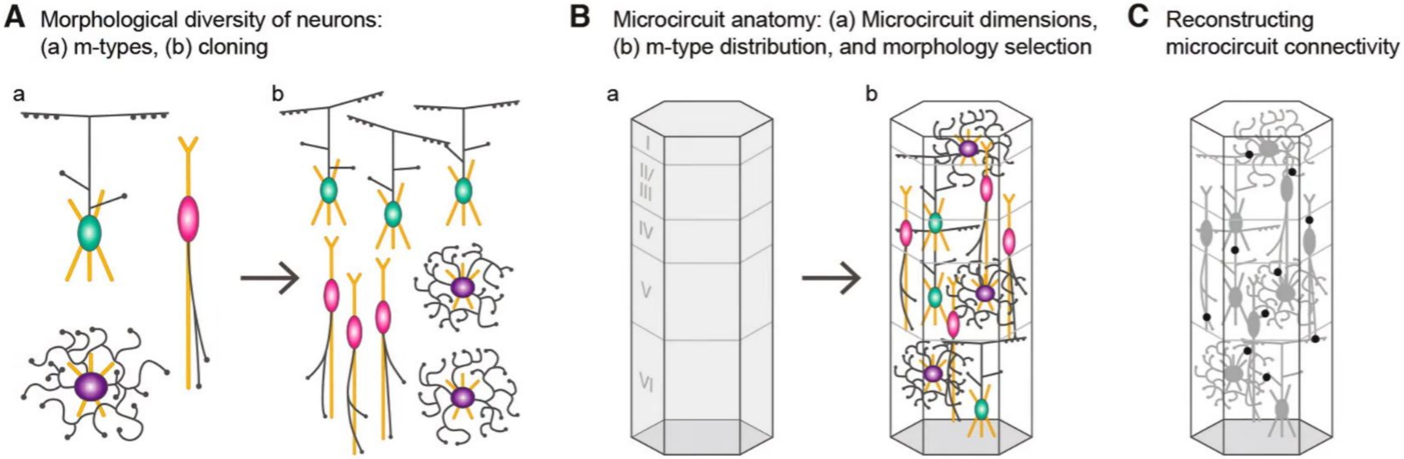
Function (Bound into Cavities)

- Local
- Global

‘Core’ Sample

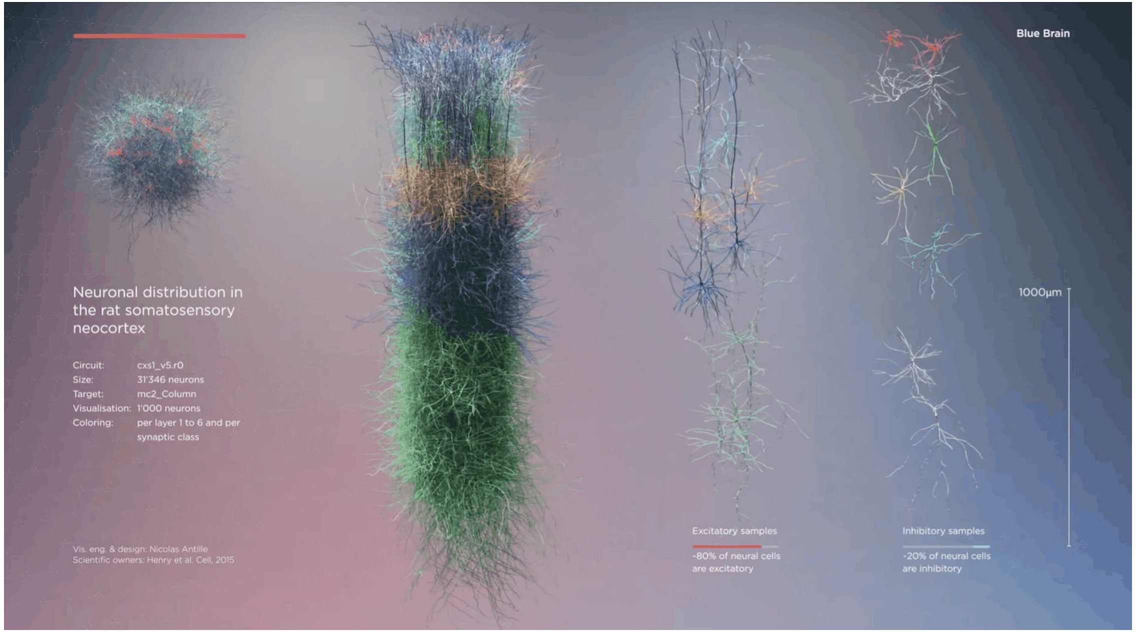
- 5 samples: 2mm high, 0.25mm radius





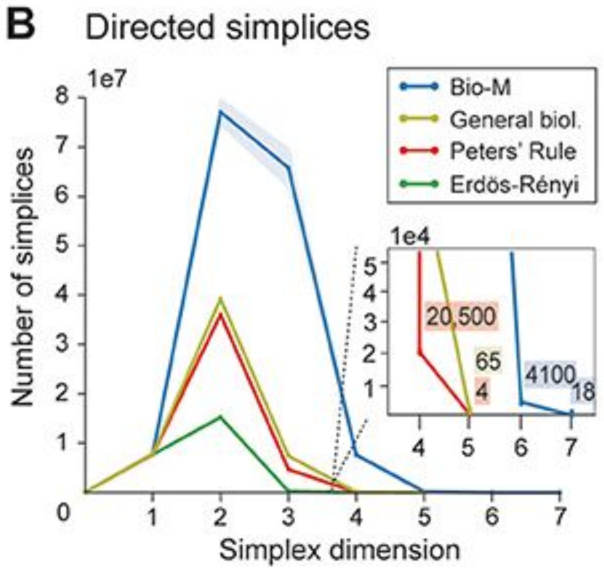
Microcircuit

- ~8 million connections (edges)
- ~31,000 neurons (vertices)



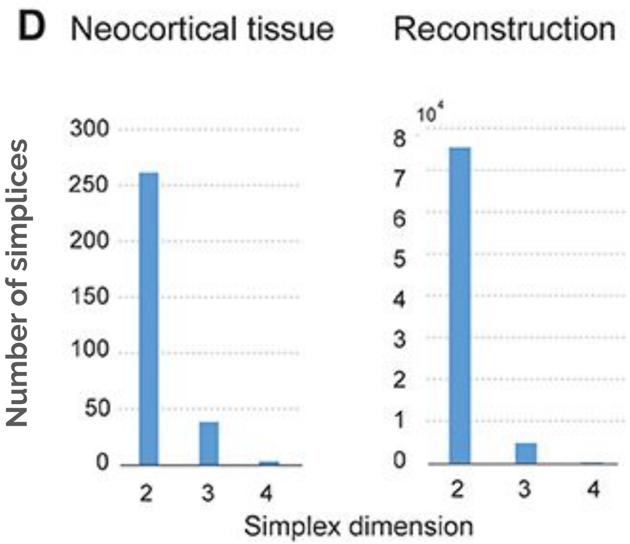
Abundance of Directed Simplices

- Mean of the 5 microcircuits based on samples from 5 mice
- Compared to circuits with the same size that
  - Preserve **distance dependance**
  - Preserve 3D **neuronal model**
  - Is connected with the same **average connection probability** (~0.8%)



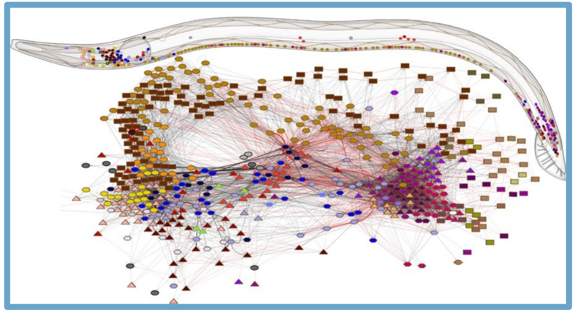
Robustness check - Observation

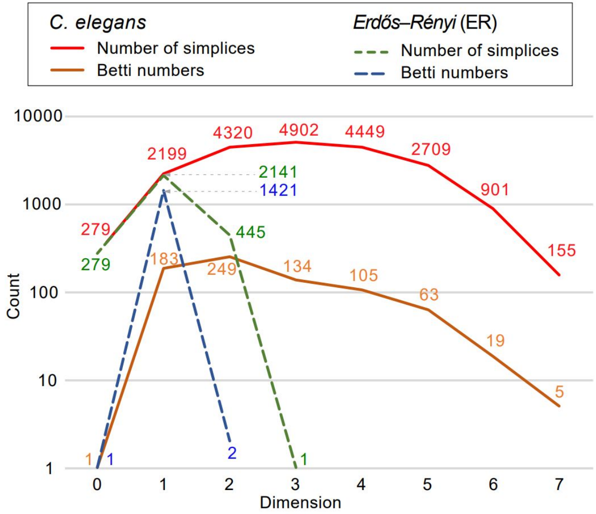
- 55 *in vitro* patch-clamp experiments
  - 6 - 12 neurons, 300 μm slices
  - same age and brain region as samples used for digital reconstruction
- *in silico* simulation
  - volume of 200 × 200 × 20 μm
  - *"repeating the same multi-neuron patch-clamp recordings"*



Robustness check - Neural network of another species

- *C. elegans* connectome
  - a free-living transparent nematode about 1 mm in length that lives in temperate soil environments





Result 1

- The **numbers of high-dimensional cliques and cavities** found in the reconstruction are far **higher than** in null models, even in those closely resembling the biology-based reconstructed microcircuit
- Their existence is **verified** in actual neocortical tissue
- **Similar structures** are found in a nervous system as phylogenetically different as that of the worm C. elegans

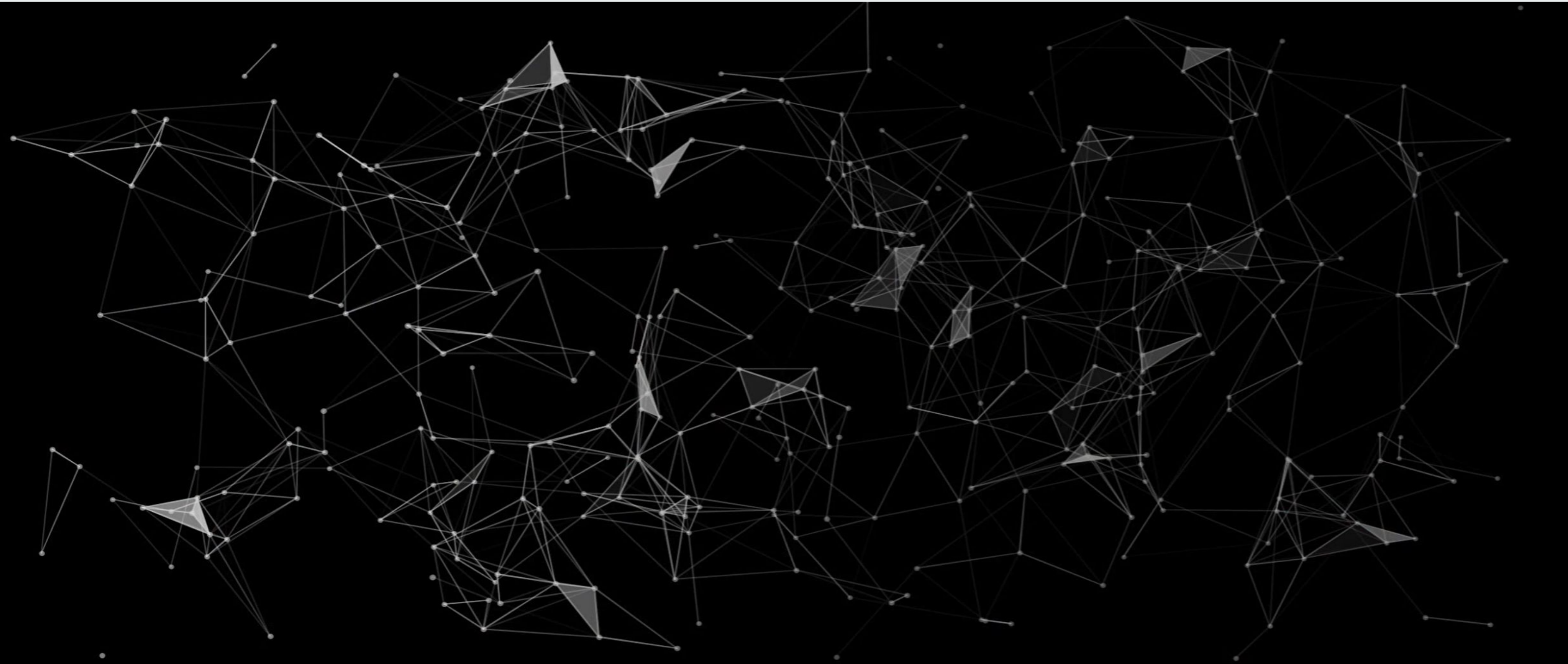
Contents

Structure (Cliques of Neurons)

- Local
  - Biological background
  - Topological Construction
    - Directed Graph
    - Simplices & Complexes
- Global
  - Biological background
  - Simplices
    - Construction
    - Robustness check
  - *Complexes: Homology?*

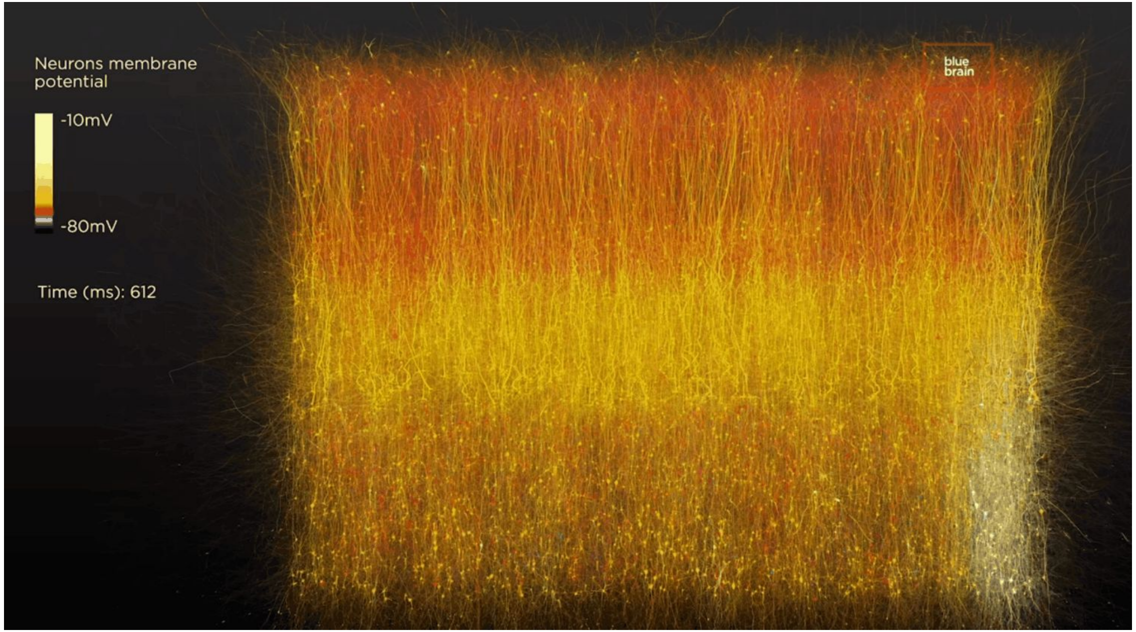
Function (Bound into Cavities)

- Local
- Global



Break…

Synaptic reaction to stimuli *(in vivo)*



Contents

Structure (Cliques of Neurons)

- Local
  - Biological background
  - Topological Construction
    - Directed Graph
    - Simplices & Complexes
- Global
  - Biological background
  - Simplices
    - Construction
    - Robustness check
  - *Complexes: Homology?*

Function (Bound into Cavities)

- Local
  - Simplices
    - Topological features
    - Spiking response
- Global

Directionality of finite directed graphs

- For each vertex v $\in \mathcal{G}$, define the **signed degree of v** to be

$$\mathrm{sd}(v) = \mathrm{Indeg}(v) - \mathrm{Outdeg}(v)\,. \qquad (1)$$

- Then, define the directionality of $\mathcal{G}$

$$\mathrm{Dr}(\mathcal{G}) = \sum_{v \in V} \mathrm{sd}(v)^2. \qquad (2)$$

Directionality of finite graphs

<u>Remark 4</u>

If $\mathcal{G}_n$ is a directed n-simplex, let $\mathcal{G}$ be any directed graph on (n+1) vertices, then

$$\mathrm{Dr}\left(\mathcal{G}\right) \leq \mathrm{Dr}\left(\mathcal{G}_n\right).$$

If additionally $\mathcal{G}$ is a fully connected directed graph without reciprocal connections (*n-simplex*), then the equality holds if and only if the two directed graphs are isomorphic to each other.

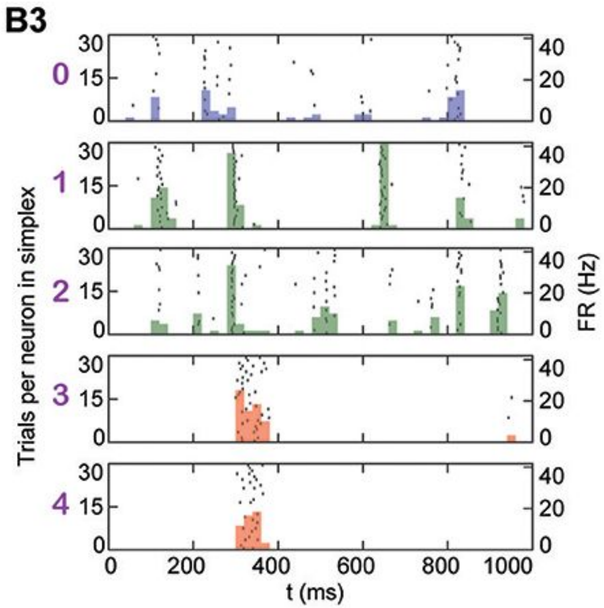
Abstract directed simplex & simplicial complex

Remark 1

The set of all maximal simplices of a simplicial complex determines the entire simplicial complex, since every simplex is either maximal itself or a face of a maximal simplex.

Average Spiking Response

- peri-stimulus time histogram (PSTH)
    - bin size: 25 ms
    - 5 seconds of thalamo-cortical input over 30 trials of a given input pattern



Spike Correlations

- Concatenating PSTH of 9 different thalamic stimuli of 5 seconds, 30 trials
- The **normalized covariance matrix** of the PSTHs of all neurons is calculated by

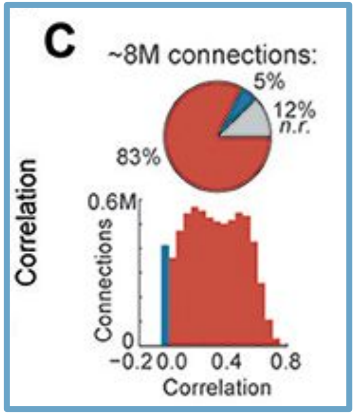
$$R_{ij} = \frac{C_{ij}}{\sqrt{C_{ii} C_{jj}}}, \qquad (9)$$

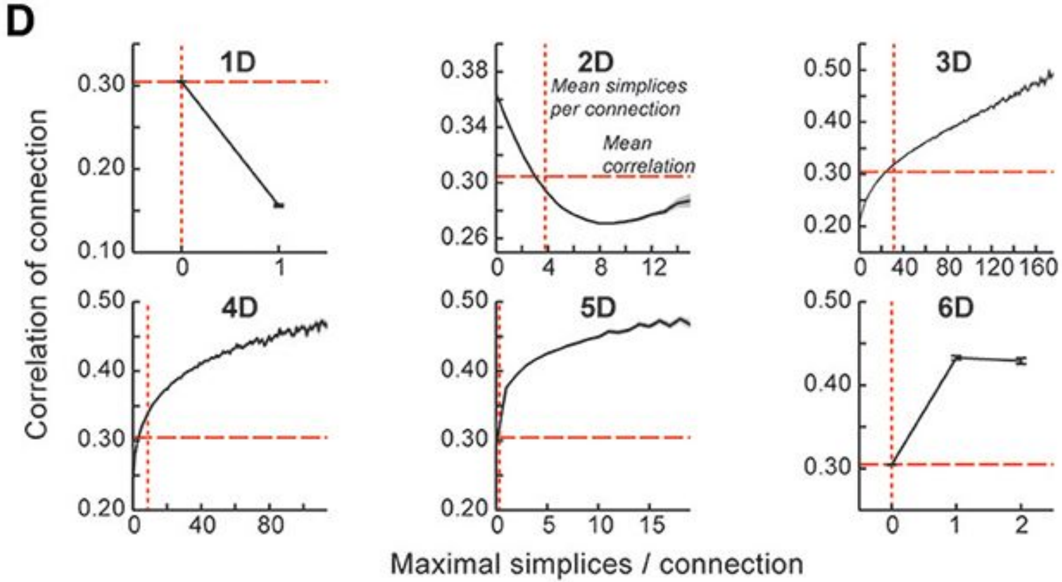
where C_{ij} is the covariance of the PSTHs of neurons i and j.

Remark 5

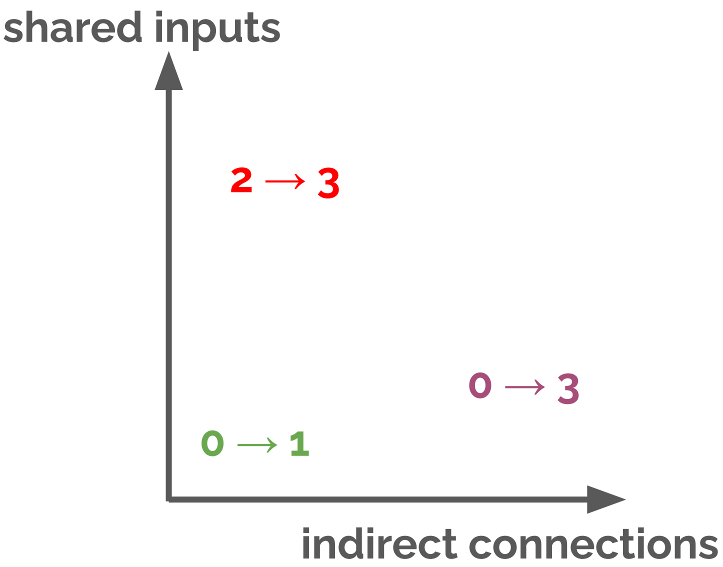
Each entry of R_{ij} refers to a particular connection in at least one maximal simplex.

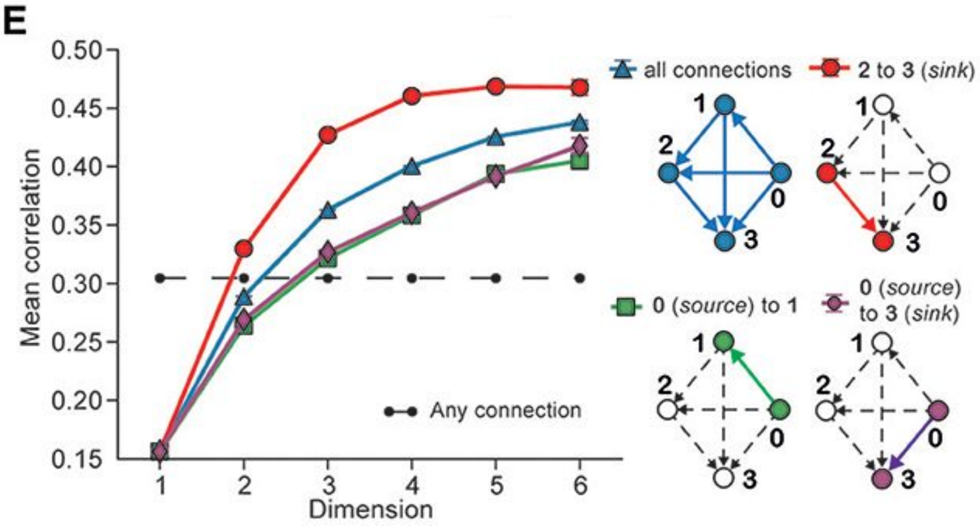
Spike Correlations





Spike Correlations - pairwise





<u>Result 2</u>

- **Spike correlation of a pair of neurons** strongly increases with the **number and dimension** of the **cliques** they belong to
- It even depends on their **specific position** in a directed clique
- Generalize the similar link for motifs built from 2-dimensional simplices found by previous studies to higher dimensions

Contents

Structure (Cliques of Neurons)

- Local
  - Biological background
  - Topological Construction
    - Directed Graph
    - Simplices & Complexes
- Global
  - Biological background
  - Simplices
    - Construction
    - Robustness check
  - *Complexes: Homology?*

Function (Bound into Cavities)

- Local
  - Simplices
    - Topological features
    - Spiking response
- Global
  - Complexes: Homology
    - Betti number & Euler characteristic
  - Filtration
    - Construction
    - Brief evaluation

Betti Number & Euler characteristic

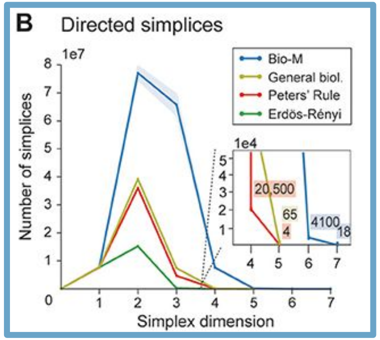
- Homology groups are computed using mod 2 coefficients, notation: $\mathbb{F}_2$ or $\mathbb{Z}/2\mathbb{Z}$
- The **n-th Betti Number** indicates the number of "n-dimensional cavities" in $\mathcal{S}$

$$\beta_n(\mathcal{S}) = \dim(H_n(\mathcal{S}))$$

- The **Euler characteristic** is defined to be

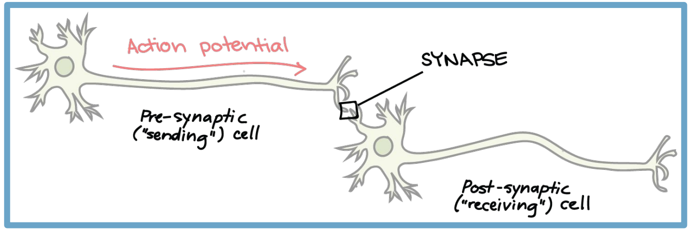
$$\chi(\mathcal{S}) = \sum_{n\geq 0}(-1)^n \beta_n(\mathcal{S}) .$$

However...



- The complexity of computing the n-th Betti numbers scales with the number of simplices in dimensions n − 1, n, and n + 1. (*Rank and nullity of matrices of dimension (n − 1) × n and n × (n + 1)*)
- Calculation of Betti numbers of dimension **above 0 and below 5** was computationally not viable.
- Euler characteristic computations imply that at least one of β_2 or β_4 must be nonzero, and it is highly likely the β_k is nonzero for all $k \leq 5$.

Transmission Response Matrices

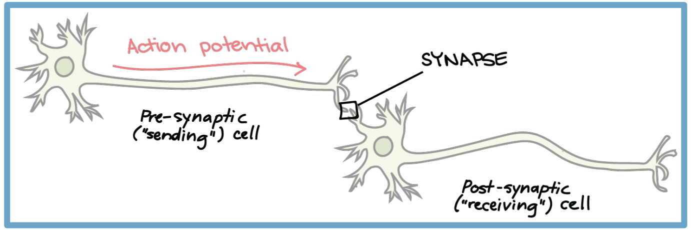


- Want to construct time series of sub-graphs with all vertices and *active* edges.
- Define the temporal sequence of **<u>transmission-response matrices</u>** associated to a simulation of neuronal activity of duration T

$$TR(\Delta t_1, \Delta t_2) := \{A(n) = A(n, \Delta t_1, \Delta t_2)\}_{n=1}^{N}, \qquad (10)$$

where n-th matrix A(n) is a binary matrix recording spiking activities within time interval $[n\cdot\Delta t_1, (n+1)\cdot\Delta t_1 + \Delta t_2]$, and where $N = T/\Delta t_1$.

Transmission Response Matrices

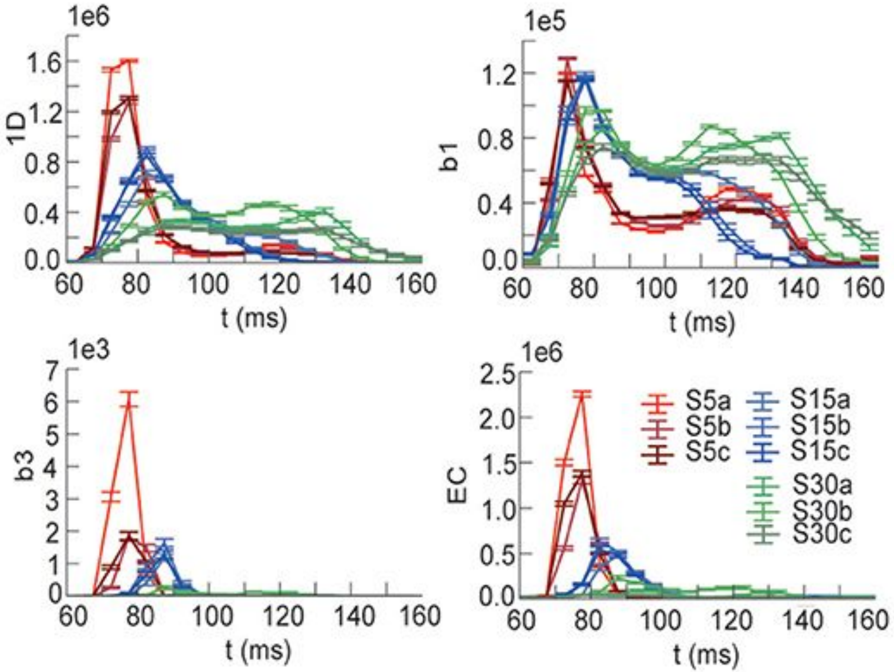


$$TR(\Delta t_1, \Delta t_2) := \{A(n) = A(n, \Delta t_1, \Delta t_2)\}_{n=1}^{N}, \qquad (10)$$

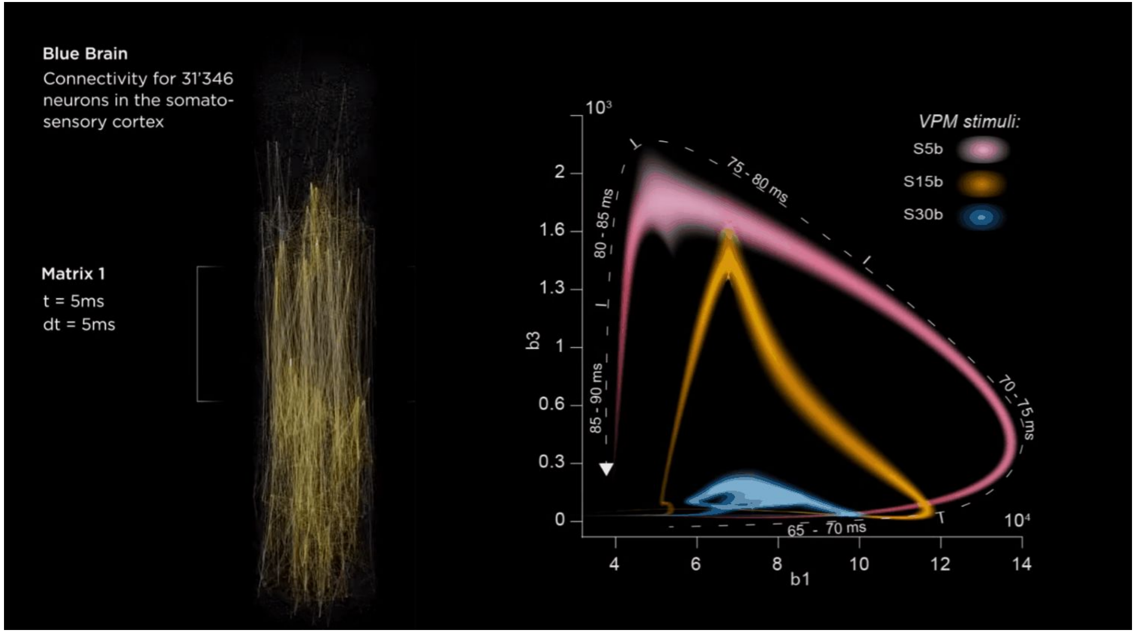
- $A(n)_{ij}$ is 1 if and only if
    - neuron j to neuron k forms a pre-post synaptic pair. (*Namely, there exists an edge between the two corresponding vertices regardless of direction.*)
    - neuron j spikes in the n-th time bin
    - neuron k spikes after neuron j, within a Δt_2 interval
- $\Delta t_1 = 5$ and $\Delta t_2 = 10$ are optimized parameter to best reflect the actual successful transmission of signals between the neurons in the microcircuit.

Bound into Cavities

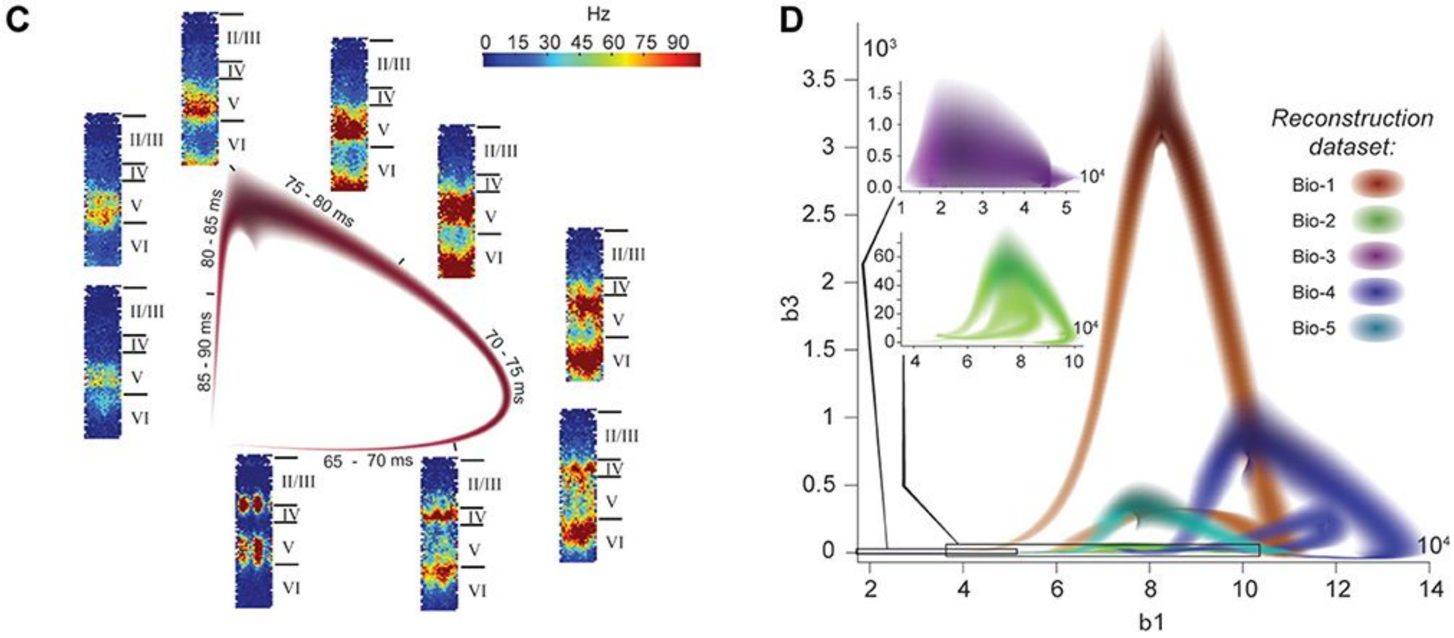
- neurons become bound into cliques and cavities by correlated activity



Bound into Cavities



Bound into Cavities



Result 3

- Applying **topological metrics** (homology) to time-series of transmission-response sub-graphs revealed **a sequence of cavity formation and disintegration** in response to stimuli, consistent across different stimuli and individual microcircuits
- The size of the trajectory was determined by the degree of synchronous input and the biological parameters of the microcircuit, while its location depended mainly on the biological parameters
- Neuronal activity is therefore organized not only within and by directed cliques, but also by highly structured relationships between directed cliques, consistent with a recent hypothesis concerning the relationship between structure and function

Contents

Structure (Cliques of Neurons)

- Local
  - Biological background
  - Topological Construction
    - Directed Graph
    - Simplices & Complexes
- Global
  - Biological background
  - Simplices
    - Construction
    - Robustness check
  - *Complexes: Homology?*

Function (Bound into Cavities)

- Local
  - Simplices
    - Topological features
    - Spiking response
- Global
  - Complexes: Homology
    - Betti number & Euler characteristic
  - Filtration
    - Construction
    - Brief evaluation

Conclusion

This study...

- provides a simple, powerful, parameter-free, and unambiguous mathematical framework for **relating the activity of a neural network to its underlying structure**, both locally (in terms of simplices) and globally (in terms of cavities formed by these simplices)
- suggests that neocortical microcircuits process information through a stereotypical progression of **clique and cavity formation and disintegration**, consistent with a recent hypothesis of common strategies for information processing across the neocortex

References

- ***Cliques of Neurons Bound into Cavities Provide a Missing Link between Structure and Function***. https://www.frontiersin.org/articles/10.3389/fncom.2017.00048/full
- *Digital Neuroscientist of the Future | Kathryn Hess Bellwald | TEDxLugano.* https://www.youtube.com/watch?v=uQKrCKy3h1E
- *Sensory Abnormalities in Autism Spectrum Disorders: A Focus on the Tactile Domain, From Genetic Mouse Models to the Clinic.* https://www.pnas.org/doi/10.1073/pnas.1803274115
- *Redundancy in synaptic connections enables neurons to learn optimally.* https://www.pnas.org/doi/10.1073/pnas.1803274115

- *Scientists discover hidden patterns of brain activity.* https://actu.epfl.ch/news/scientists-discover-hidden-patterns-of-brain-activ/
- *Blue Brain solves a century-old neuroscience problem.* https://actu.epfl.ch/news/blue-brain-solves-a-century-old-neuroscience-probl/
- *The Mind-Boggling Math That (Maybe) Mapped the Brain in 11 Dimensions.* https://www.wired.com/story/the-mind-boggling-math-that-maybe-mapped-the-brain-in-11-dimensions/
- *The human brain sees the world as an 11-dimensional multiverse.* https://nypost.com/2017/06/13/the-human-brain-sees-the-world-as-an-11-dimensional-multiverse/
- *Digital 3D atlas of a mouse brain.* https://bbp.epfl.ch/nexus/cell-atlas/