Blue Brain Project

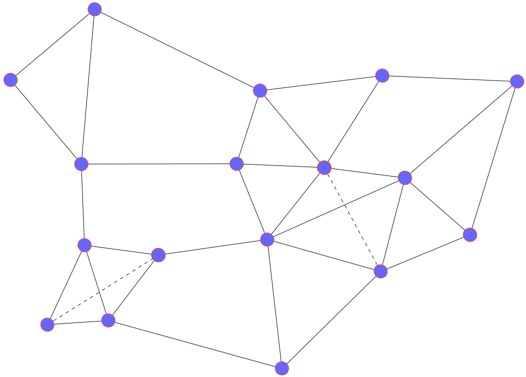
- An intricate and biologically accurate digital reconstruction of the neocortical column of a 14 days old rat.
- Each microcircuit consists of roughly $3 \cdot 10^4$ neurons of 55 distinct morphological types and approximately 8×10^6 connections between neurons.

The Blue Brain Project

- The reconstruction allows recovering an abundance of information. For example:
  - the full adjacency matrix: Every modelled neuron has a number $A = (a_{i,j})$, with $a_{i,j} = 1$ if the axon ofneuron i is connected to the dendrite of neuron j.
  - the strength of each connection: How many synapses; distance between somas.
  - the type and spatial position of each individual neuron.
  - full spiking data for each neuron under varying electrical and chemical conditions.
- This gives rise to directed graphs (potentially weighted, and time dependent).
- Graphs give rise to topological objects.

Recall: The Flag Complex

The flag complex of a graph is the maximal abstract simplicial complex containing the graph as its 1-skeleton.



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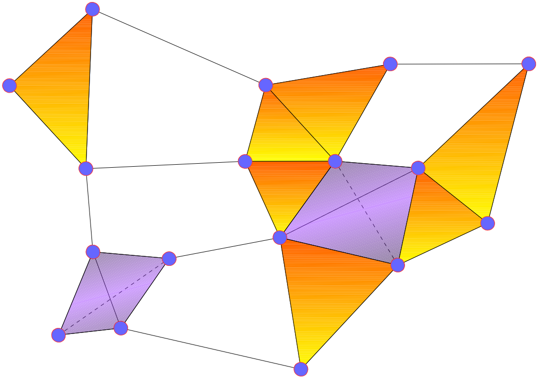


Seven 2-simplices and two 3-simplices.

Recall: Abstract ordered simplicial complexes and the directed flag complex of a directed graph

An abstract *ordered* simplicial complex is a collection $\mathcal{S}$ of finite *ordered* sets, such that

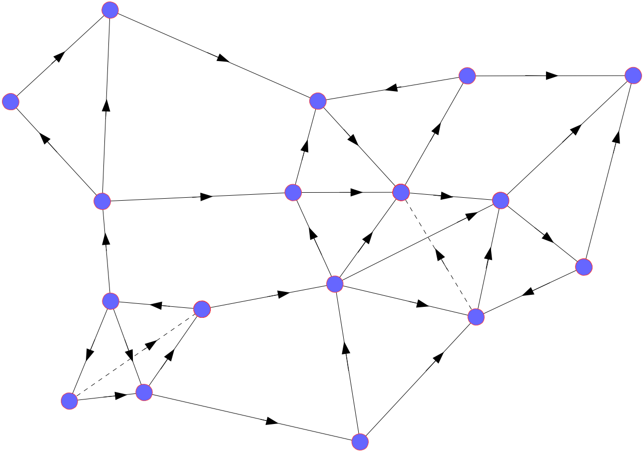
$$\sigma \in \mathcal{S} \implies \tau \in \mathcal{S}, \qquad \forall \tau \subset \sigma.$$

The subsets $\sigma \in \mathcal{S}$ are called the simplices of $\mathcal{S}$.

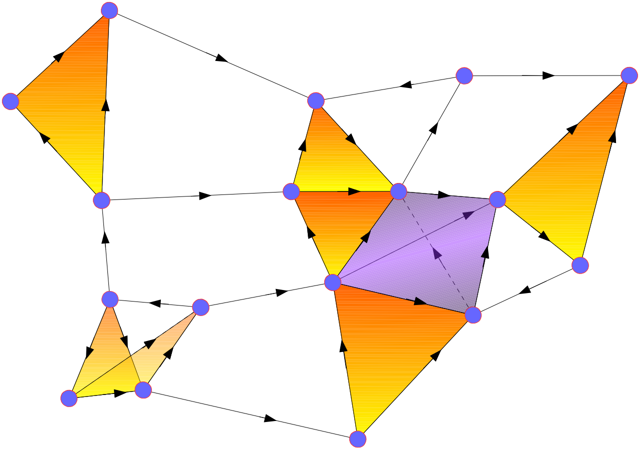
- A *digraph* $\mathcal{G}$ is a pair (V, E) where V is the set of vertices and $E \subseteq V \times V$ is the set of directed edges.
- The *directed* flag complex of a digraph $\mathcal{G}$ is the abstract ordered simplicial complex $S = S(\mathcal{G})$, whose n-simplices are ordered $(n+1)$-tuples of vertices

$$S_n = \{(v_0, v_1, \dots, v_n) \mid (v_i, v_j) \in E, \ \forall 0 \leq i < j \leq n\}$$

Recall: Digraphs and the directed flag complex



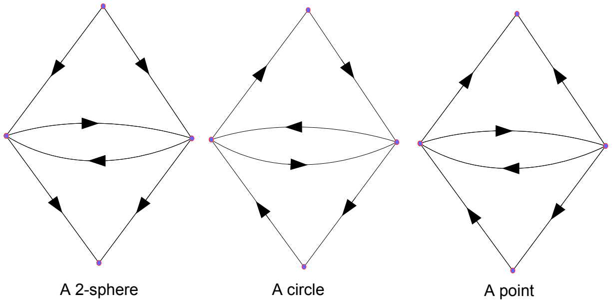
Recall: Digraphs and the directed flag complex



Seven 2-simplices, but not the same as before and only one 3-simplex.

Recall: Reciprocal connections

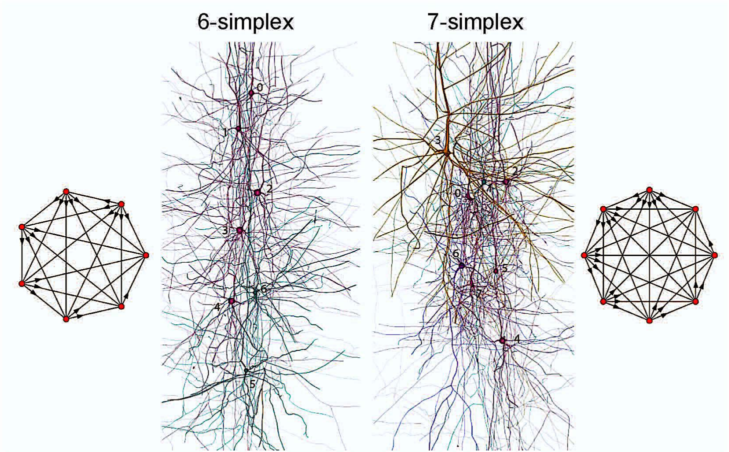
A digraph arising from a neural system may have reciprocal connections. Hence the complex defined intuitively as in the picture above may not be an abstract simplicial complex. The following three (different!) digraphs give rise to directed flag complexes of different homotopy type:



The ordinary flag complex of any of these graphs will not see the difference among them.

Analysis of the Blue Brain Project Reconstruction:
A first surprise

There are directed simplices in the Blue Brain microcircuit of dimension up to 7.



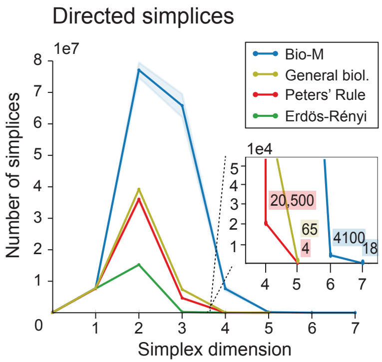
Analysis of the Blue Brain Project Reconstruction

Topological Analysis of Structure

At our disposal 42 reconstructed microcircuits based on the cortex of 5 individual rats. Adjacency matrices for each microcircuit - average size 31,000 with average connectivity of 0.8%. In addition we generated:

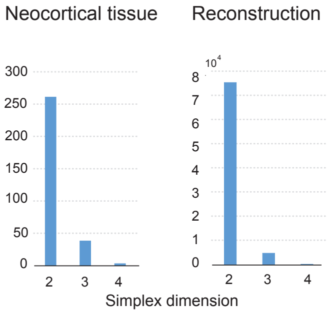
- Erdős-Rényi random connectivity matrices with the same size and average connectivity as the reconstruction.
- Two sets of controlled randomisations of an average microcircuit, preserving distance-dependent connection probability across **i)** all pairs of layers, and **ii)** all pair of morphological types, but otherwise random.
- A set of controlled randomisations of an average microcircuit according to Peter's rule: Connect two neurons if they contain arbors with distance at most $3\mu m$, and then prune uniformly until the required average connectivity is obtained.

Distribution of simplices



For each of the connectivity matrices we computed the directed flag complex. The complexes resulting from the Blue Brain reconstruction show dramatically different behaviour from the randomised matrices.

How realistic is this? A biological verification

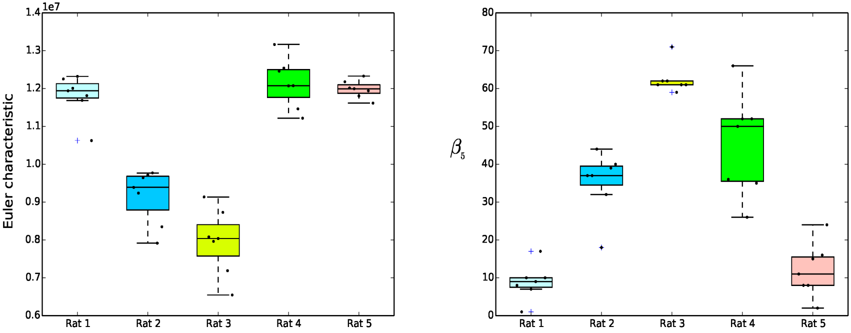


Left: Number of directed simplices of various dimensions found in 55 in-vitro patch-clamp experiments sampling groups of pyramidal cells in layer 5. Right: Number of simplices of various dimensions found in 100,000 in-silico experiments mimicking the patch-clamp procedure.

(mod-2) Homology

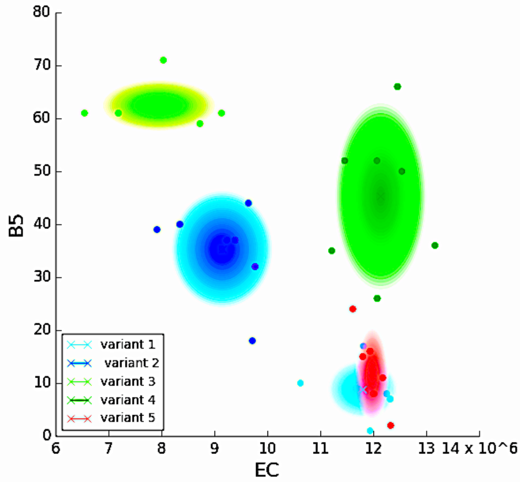
- Homology is used as a measure of topological complexity arising from the connectivity graph. However computing the homology of a flag complex of a graph with $\sim 3 \cdot 10^4$ vertices and $\sim 8 \cdot 10^6$ edges is hard even if the complex is random.
- In our complex there are roughly $8 \cdot 10^7$ 2-simplices and $6.5 \cdot 10^7$ 3-simplices. The computation crushes on memory.
- If X is a complex, let $X_{(n)} \subseteq X$ denote the n-coskeleton of X, i.e., the subcomplex obtained by taking all simplices in X of dimension $\geq n$, and all their faces.
- The inclusion induces an isomorphism on homology in dimensions $\geq n$.
- The top non-vanishing homology in our (42) samples is in dimension 5.

Euler characteristic and $H_5(-;\mathbb{F}_2)$



- On the left, the Euler characteristic of the complex of each individual reconstruction, sorted by the animal that gave rise to the data. On the right the same with respect to β_5.
- Taken individually, each of these parameters seem rather meaningless.

Euler characteristic and (mod 2) homology



Is there any biological significance/interpretation of this distinction among animals?

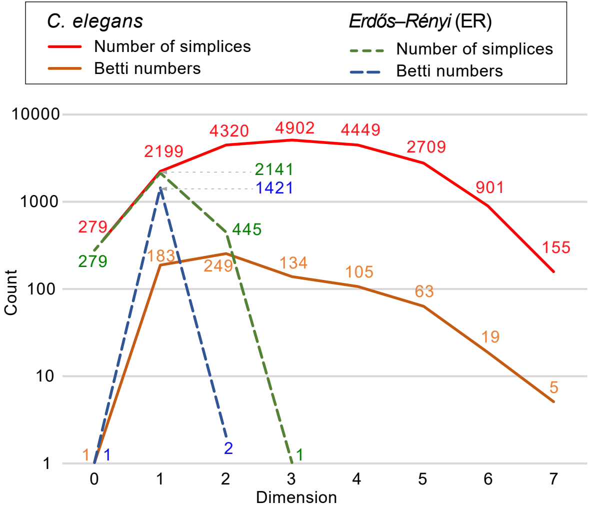
Wait!!!

We are applying our techniques to a digital reconstruction. Accurate as it may be, it is not the “real thing”.

How about a little sanity check?

Remember Mr. Caenorhabditis Elegans?
It’s the one biological brain we really understand.

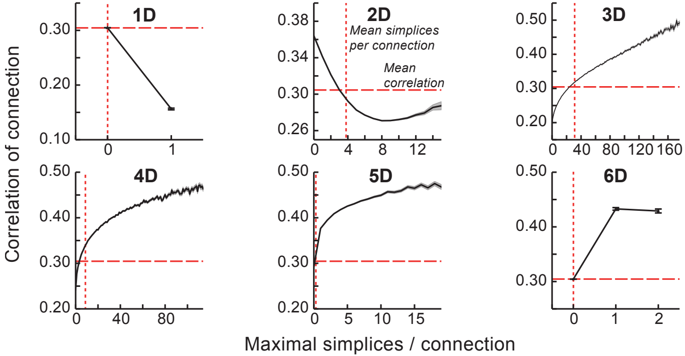
The topology of c-elegans's brain



OK, so both a rat and a c-elegans have nontrivial brains, topologically speaking, BUT:

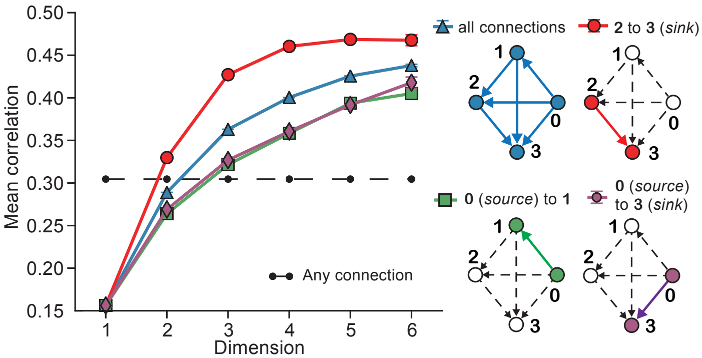
- Is it reasonable to expect the brain "know" algebraic topology?
- Do neurons in a simplex "fire together"?
- Is activity of neurons in a simplex better correlated compared to other constellations?
- Are directed cliques more or less prevalent from arbitrary (undirected) cliques?
- What role is played by directionality of the simplices? Is there a notable difference between the functionality of directed cliques compared to arbitrary ones?

Connections belonging to high dimensional simplices are better correlated



Mean correlation coefficients for connected pairs of neurons against the number of maximal simplices the edge between them belongs to, dimension by dimension.

Correlation depends on location within a simplex



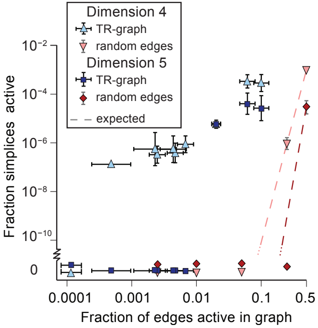
Mean correlation coefficient of pairs of neurons, given their position within a simplex and its dimension.

Neocortical Slice: Simulation of Activity

Activity: The Transmission-Response method

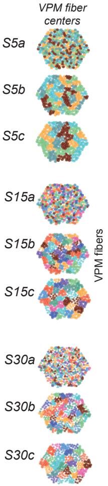
- The microcircuit is stimulated in time intervals of 50ms for a whole second. The reaction is recorded in time bins $t = 0 \dots 199$ of 5 ms each (size optimised by experimentation).
- Let A denote the structural connectivity matrix for the given microcircuit.
- In each time bin k consider the "successful transmission" connectivity matrix A^k where $A^k_{i,j} = 1$ if and only if the following three conditions are satisfied:
  - $A_{i,j} = 1$, i.e., there is a structural connection from neuron i to neuron j,
  - neuron i fired in time bin k, and
  - neuron j fired within 10ms after neuron i did (optimised by experimentation).

Transmission-Response method well suited to topological approach



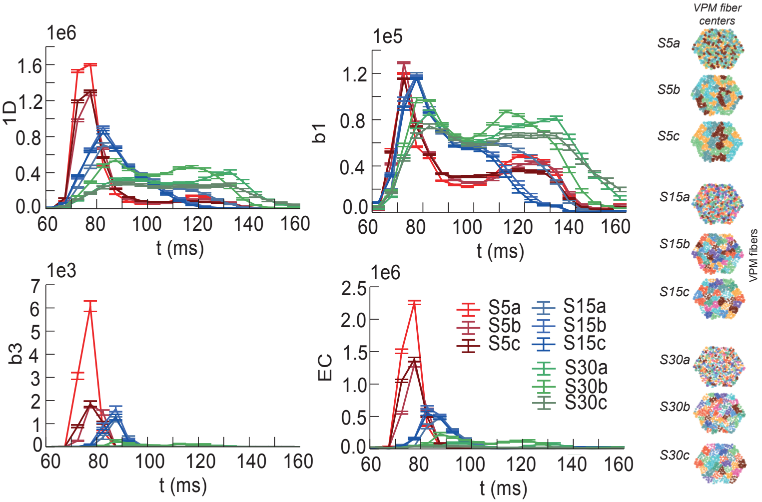
We found significantly more simplices in the TR graphs than would be expected based on the number of edges alone indicating that correlated activity becomes preferentially concentrated in directed simplices.

Some stimulation experiments



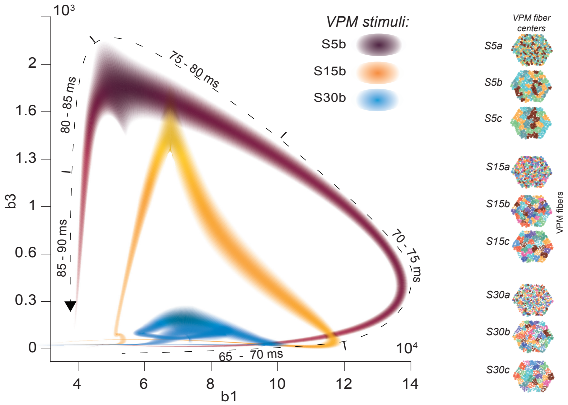
Patterns of thalamic innervation in the reconstruction. Each circle represents the center of innervation of a thalamic fiber. Each color represents a unique thalamic spike train assigned to that fiber.

Stimulation experiments



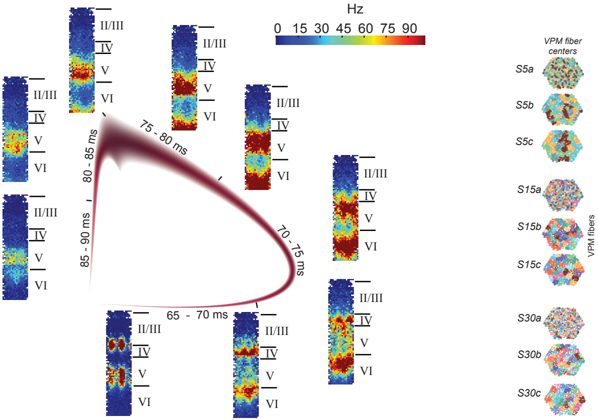
Each stimulation produces a different reaction. Similar stimulations produce “close” reactions.

Stimulation experiments



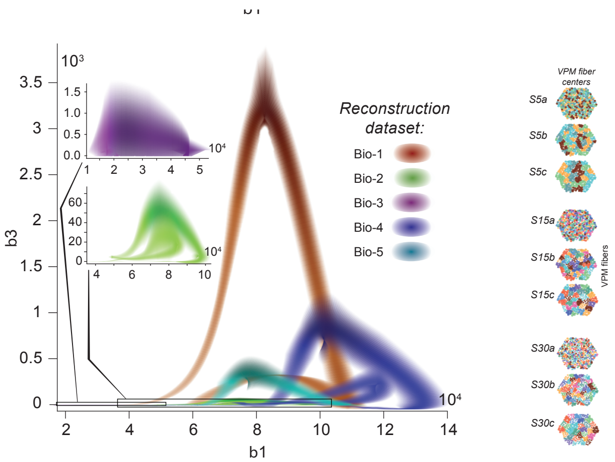
Trace of time series of β_1 against β_3: β_1 grows to a peak, then starts declining as β_3 starts growing, to its peak and then the reaction disintegrates.

Stimulation experiments



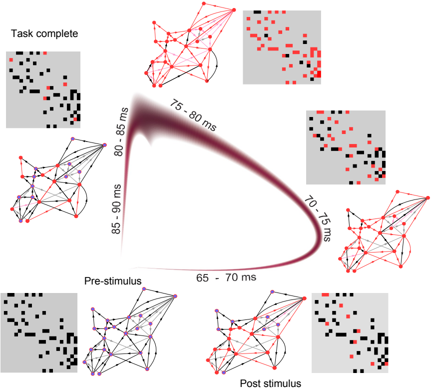
Trace for the stimuli S5b, along with the mean firing activity at different locations of the microcircuit.

Stimulation experiments



Trace of time series of β_1 against β_3, as before, but for TR graphs of Bio 1-5, in response to stimulus S15b. Reaction is stereotypical but different, possibly due to varying electro-chemical conditions.

Stimulation experiments - what is actually happening?



As the trajectory fills up, the lower dimensional cavities disappear and higher dimensional ones appear reaching a peak at completion of the task.