A null model of the mouse whole-neocortex micro-connectome

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Motivation: Connectomics takes place in two separate worlds: Micro-connectomics, studying connections between individual neurons, but at comparatively small scales; and macro-connectomics, studying connections at large scales, but only between regions of hundreds of neurons.

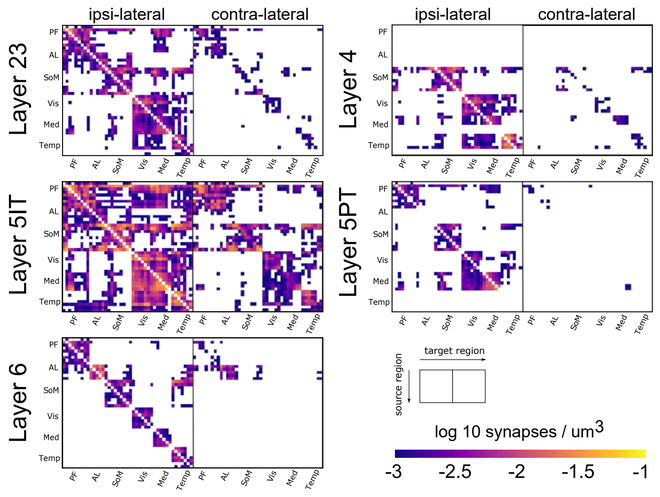
We take a first step towards consolidating the two approaches. We start by considering the micro-connectivity implied by the macro-connectivity models, that of unstructured region-to-region connections, then apply a number of additional biological constraints:

- Projections have a certain layer profile of synapse density in the target region
- Projections implement a topographical mapping between regions
- Individual neurons innervate only a subset of the regions targeted by their source region.

We then find that these simple constraints lead to highly nonrandom micro-connectivity between regions.

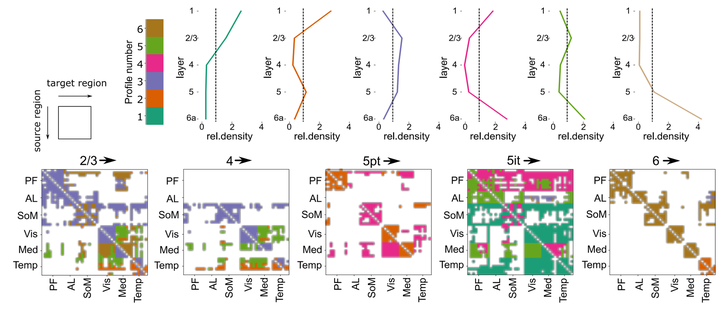
Strengths of individual projections

We start with macro- or meso-scale connectomics. Harris et al., 2018 report the strengths of projections between regions in the Allen Common Coordinate Framework. They provide strengths for five different projection classes. We convert the reported strengths to average synapse densities in terms of synapses um-3 using a predicted total number of synapses (88 billion, Schuz & Palm, 1989).



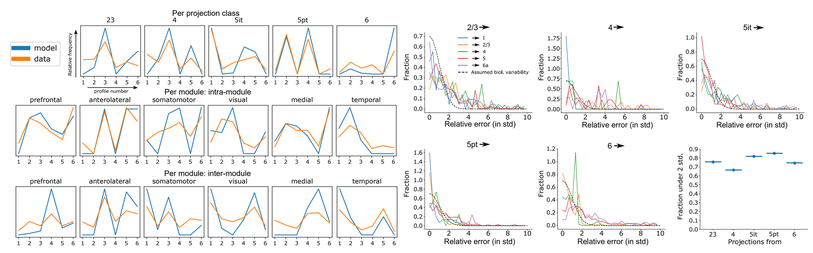
Layer profiles of synapse densities

We predict and apply layer profiles of synapse density in the target region based on data from Harris et al., 2018



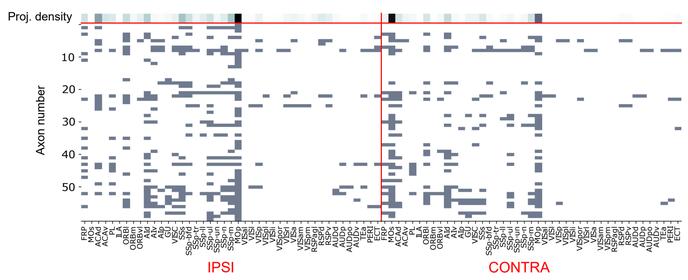
Validation of layer profiles

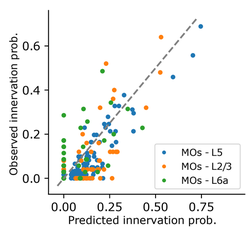
We validate the prevalence of profiles and the resulting densities against raw data of the volumetric connectome model of Knox et al., 2018



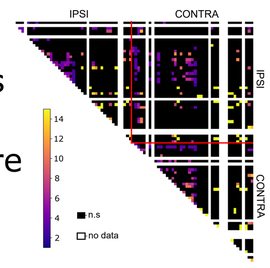
Region innervation profiles of individual axons

Which combination of regions is innervated by individual axons?
Analyze innervation patterns of reconstructed axons from *Janelia Mouselight*

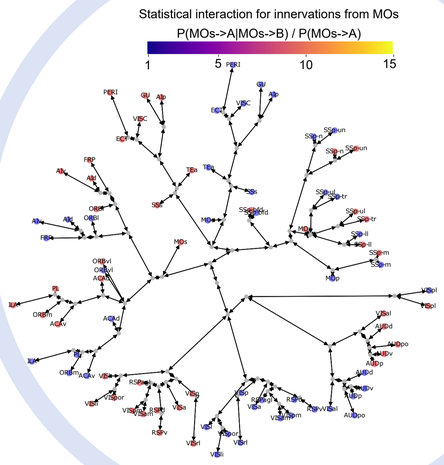




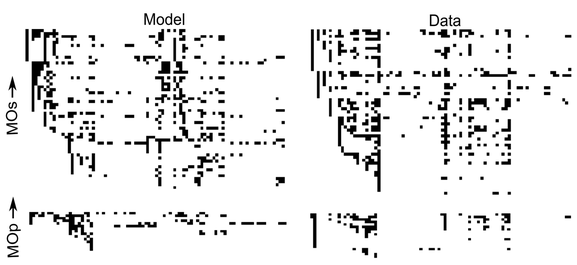
First order innervation prob. predicted from projection density



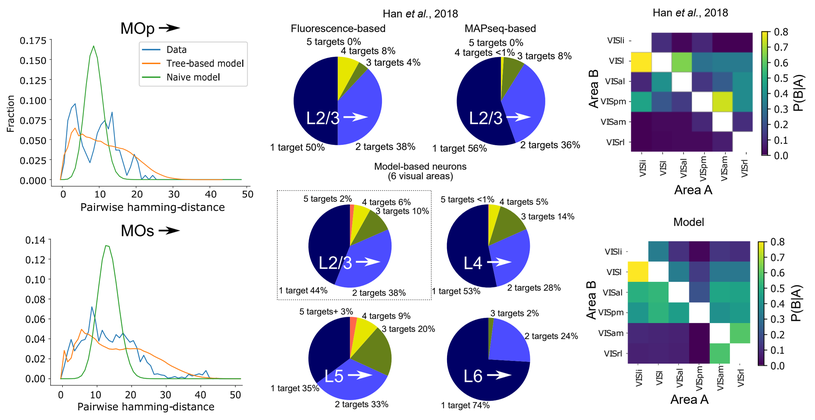
Pairs of regions tend to be innervated more often together



A tree-based model creates statistical predictions of individual region innervation profiles

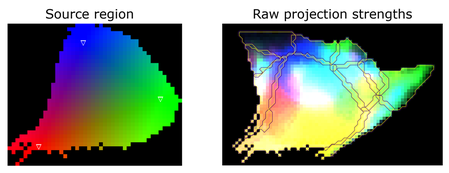


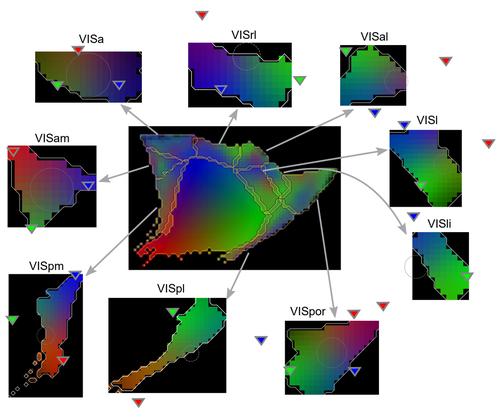
Validation of the region innervation model



Topographical mapping of projections

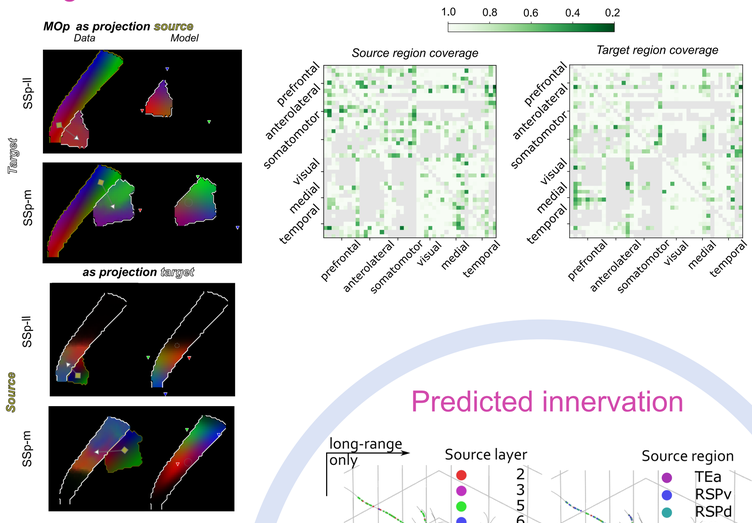
We model a topographical mapping between brain regions by defining local coordinate systems in the source and target regions.
Fit to projection data from the voxelized model of Knox et al., 2018





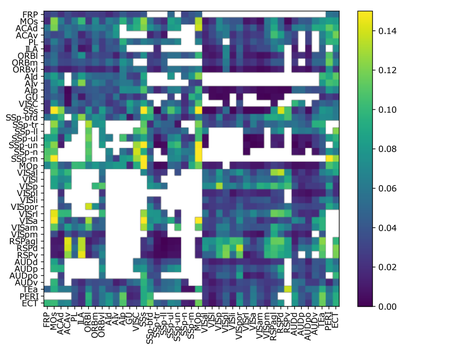
Incomplete region coverage

Not every projection completely covers both source or target region.
This is captured and quantified by the model.



Validation of the mapping

We first validate the model against the input data: How much is lost by modelling only linear mapping?



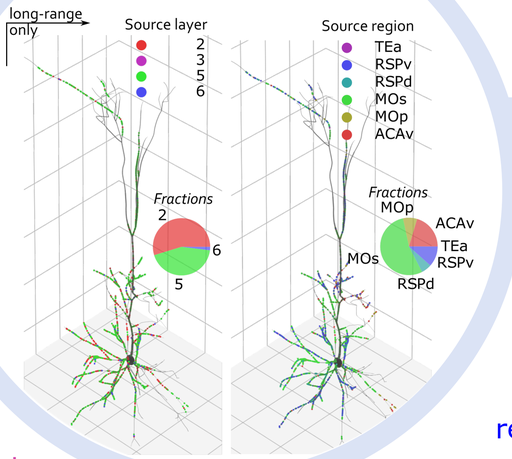
Next, we validate against the literature. This is functional, not anatomical data!

		Wang and Burkhalter (2007)	Juavinett et al. (2017)	our mapping
VISpl	*reflection?*	Yes	Yes	Yes
	rotation?	90 deg	-	90 deg
VISpor	*reflection?*	None	None	None
	rotation?	180 deg	-	180 deg
VISl	*reflection?*	Yes	Yes	Yes
	rotation?	None	-	None
VISli	*reflection?*	None	None	None
	rotation?	None	-	None
VISal	*reflection?*	None	None	None
	rotation?	180 deg	-	180 deg
VISrl	*reflection?*	Yes	Yes	Yes
	rotation?	None	-	None
VISa	*reflection?*	None	---	None
	rotation?	90 deg	-	90 deg
VISam	*reflection?*	None	None	None
	rotation?	90 deg	-	90 deg
VISpm	*reflection?*	Yes	Yes	Yes
	rotation?	None	-	None

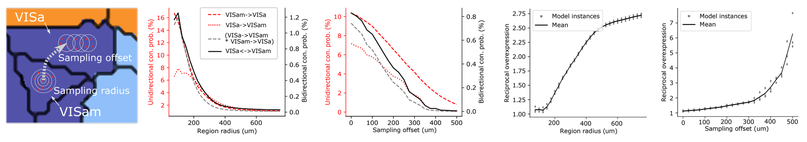
Predicted motifs and micro-connectivity

We predict the full micro-connectivity for over 10 million neurons

Predicted innervation

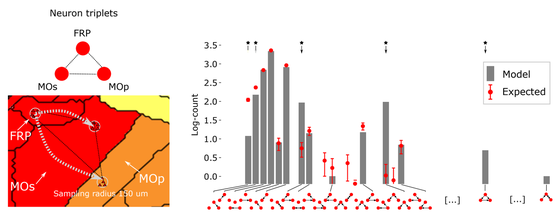


Reciprocal connectivity between regions



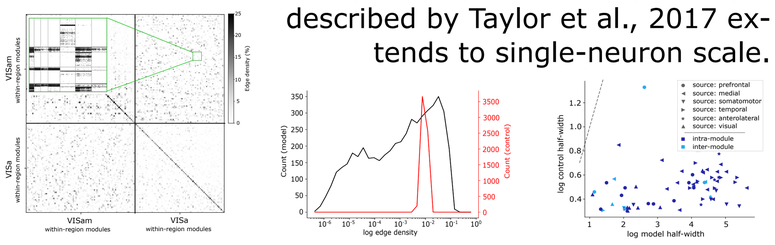
Multi-region connectivity motif counts

The model predicts over-expression of certain long-range motifs



Long-range connectivity shaped by local clusters

We predict a connectivity principle described by Taylor et al., 2017 extends to single-neuron scale.



Availability

Both the code, parameterized connectome constraints (recipe) and connectome instances are available at:

https://portal.bluebrain.epfl.ch/resources/models/mouse-projections/

References

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