

Delivering data, tools and knowledge on brain cell types, connections and activity

March 30, 2017

Lydia Ng
Sr. Director, Technology

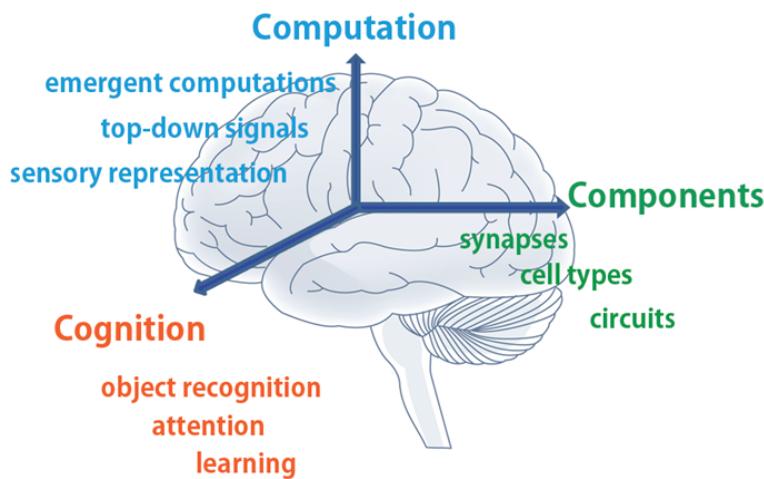


Allen Institute for Brain Science

Mission:

To accelerate the understanding of how the human brain works in health and disease.

Using a big science approach, we generate useful public resources, drive technological and analytical advances, and discover fundamental brain properties through integration of experiments, modeling, and theory.

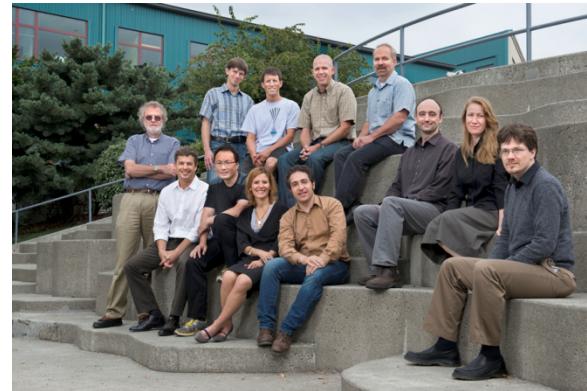


- **What are the parts?**
 - Genes, proteins, synapses, cells, functional areas
- **How are the parts connected?**
 - Synapses, neurotransmitters, circuits, relay centers
- **How do the parts receive, store, and respond to information?**
 - Circuit function, neural codes; behavior
- **What goes wrong in disease?**
 - Mechanism, pathways, interventions



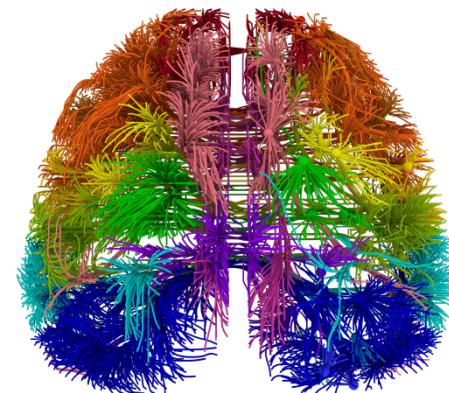
Allen Institute Guiding Principles

Team Science: Multi-disciplinary teams working towards common goal



Big Science: Clear goals or milestones for large-scale projects

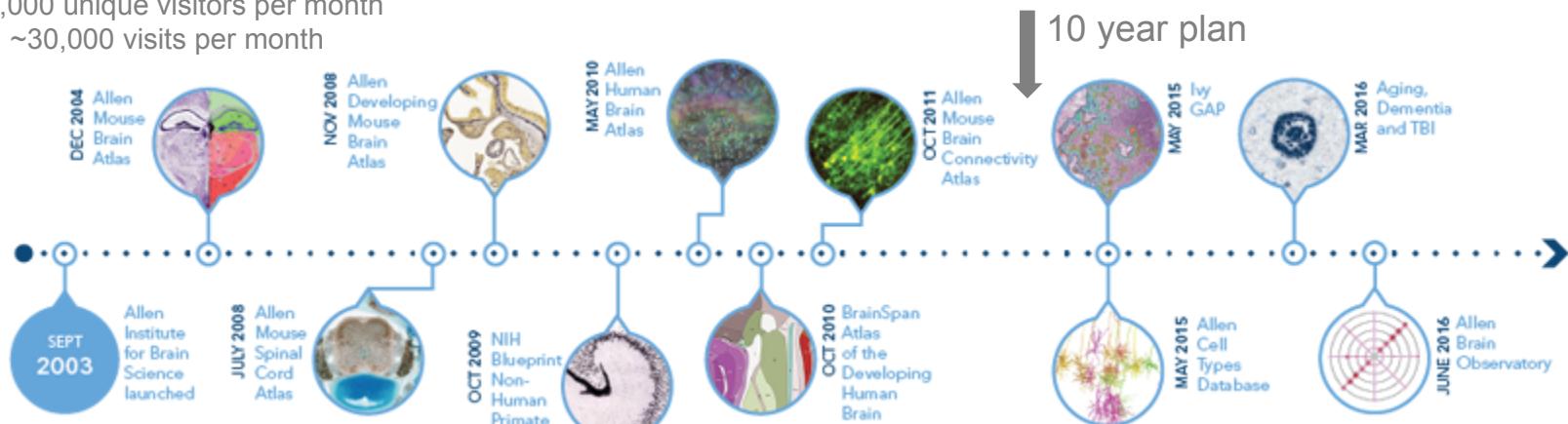
Open Science: All of our data, knowledge and tools are publicly available on brain-map.org.



Allen Institute for Brain Science Resources

~13,000 unique visitors per month

~30,000 visits per month



Data

Gene Expression

Connectivity

Single Cell
Characterization

Visual
Coding

Physiology

Transcriptomics
Morphology

Visual
Behavior

Specimen

Mouse

NHP

Human

Brain

Spinal Cord

Cells

Development

Disease



Making a resource: from data to insight

Data Generation

Data Processing

Data Integration

Data Presentation

Data Access

Community Usage

Large scale data generation using standard operating procedure (SOP) to ensure quality and uniformity

Experimental design optimized for automated downstream processing

Collect additional metadata and channel to enable integration and data interoperability



The purpose of computing is insight, not numbers - Richard Hamming

Making a resource: from data to insight

Data Generation

Data Processing

Data Integration

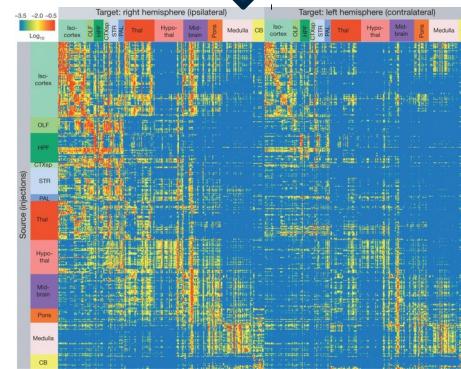
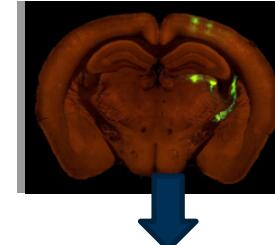
Data Presentation

Data Access

Community Usage

Processing and annotation of data to extract quantitative features for analysis

Systematic application of standardized informatics pipeline to work at scale



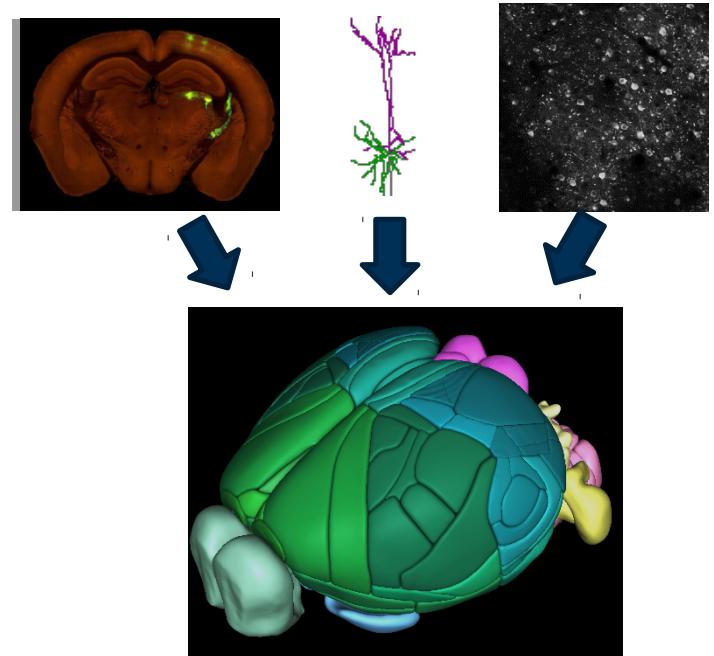
The purpose of computing is insight, not numbers - Richard Hamming

Making a resource: from data to insight

Data Generation Data Processing **Data Integration** Data Presentation Data Access Community Usage

Enable computational comparison and interoperability of datasets within and across resources

- Unified database with common metadata
- Common coordinate framework
- Common mouse line across resources
- Standard file format (NWB)



The purpose of computing is insight, not numbers - Richard Hamming

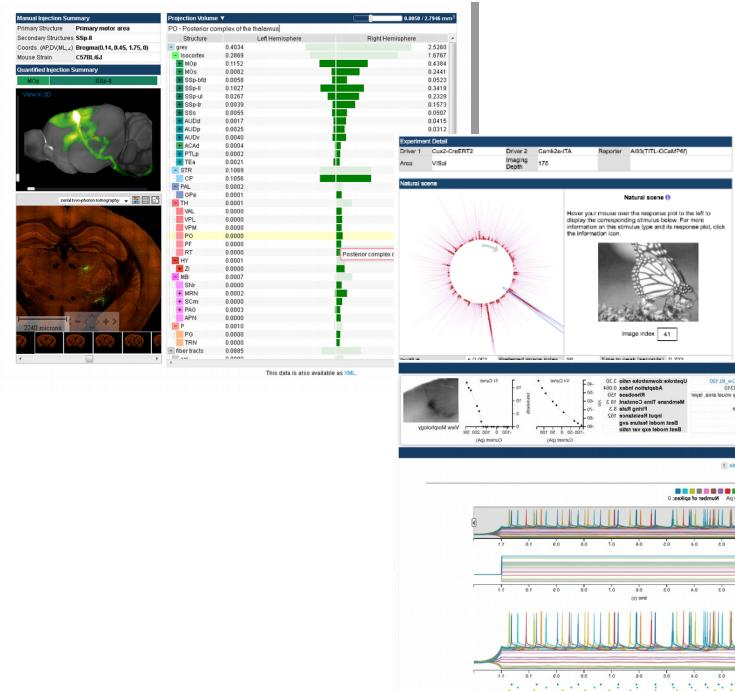
Making a resource: from data to insight

Data Presentation

Online browsing to provide insight into data content and meaning

Summary views to capture key biological features of data

Search, browse and explore data of interest



The purpose of computing is insight, not numbers - Richard Hamming

Making a resource: from data to insight

Data Generation

Data Processing

Data Integration

Data Presentation

Data Access

Community

Data access through application programming interface (API)

Software library of functions and scripts to get started on data analysis (SDK)

The data_set variable is an NWBdataset instance, which has some methods we can use to access the injected current stimulus waveform and the voltage response waveform for all experimental sweeps. Let's pull one sweep out and plot it.

```
In [2]: #matplotlib inline
import numpy as np
import matplotlib.pyplot as plt

sweep_number = 30
sweep_data = data_set.get_sweep(sweep_number)

index_range = sweep_data["index"]
i = sweep_data["stimulus"][0:i]
v = sweep_data["response"][0:i]
i *= 1e12 # to pA
v *= 1e3 # to mV

sampling_rate = sweep_data["sar"]
t = np.arange(0, len(v)) * (1./sampling_rate)

plt.style.use('ggplot')
fig, axes = plt.subplots(2, 1, sharex=True, sharey=False)
axes[0].plot(i, v, color='black')
axes[1].plot(i, v, color='gray')
axes[0].set_ylabel("mV")
axes[1].set_ylabel("pA")
axes[1].set_xlabel("seconds")
plt.show()
```

ALLEN BRAIN ATLAS
SOFTWARE DEVELOPMENT KIT

CONTENTS

- Install Guide
- Data Resources
 - Brain Observatory
 - Cell Types
 - Mouse Connectivity
 - API Access
- Models
 - Generalized LIF
 - Biophysical
- Examples
- Source Documentation
 - allensdk.api package
 - allensdk.brain_observatory package
 - allensdk.config package
 - allensdk.core package
 - allensdk.ephys package
 - allensdk.model package
 - allensdk.morphology package
- Github Profile

WELCOME TO THE ALLEN SDK

The Allen Software Development Kit houses source code for reading and processing Allen Brain Atlas data. The Allen SDK focuses on the Allen Brain Observatory, Cell Types Database, and Mouse Brain Connectivity Atlas.

ALLEN BRAIN OBSERVATORY

The Allen Brain Observatory is a data resource for understanding sensory processing in the mouse visual cortex. The study systematically measures visual responses in multiple cortical areas and layers using two-photon calcium imaging of GCaMP-labeled neurons targeted using Cre driver lines. Response characteristics include orientation tuning, spatial and temporal frequency tuning, temporal dynamics, and spatial receptive field structure.

The mean fluorescence traces for all segmented cells are available in the Neurodata Without Borders file format ([NWB files](#)). These files contain raw data describing the visual responses of individual cells for stimulus-specific tuning analysis. The Allen SDK provides code to:

- download and organize experiment data according to cortical area, imaging depth, and Cre line
- remove the contribution of neuropil signal from fluorescence traces
- access (or compute) dF/F traces based on the neuropil-corrected traces
- perform stimulus-specific tuning analysis (e.g.: drifting grating direction tuning)

ALLEN CELL TYPES DATABASE

The Allen Cell Types Database contains electrophysiological and morphological characterizations of individual neurons in the mouse primary visual cortex. The Allen SDK provides Python code for accessing electrophysiology measurements ([NWB files](#)) for all neurons and morphological reconstructions ([SWC files](#)) for a subset of neurons.

The Database also contains two classes of models fit to this data set: biophysical models produced using the NEURON simulator and generalized leaky integrate and fire models (GLIFs) produced using custom Python code provided with this toolkit.

The Allen SDK provides sample code demonstrating how to download neuronal model parameters from the Allen Brain Atlas API and run your own simulations using stimuli from the Allen Cell Types Database or custom current injections:

- Biophysical Models
- Generalized LIF Models

ALLEN MOUSE BRAIN CONNECTIVITY ATLAS

The Allen Mouse Brain Connectivity Atlas is a high-resolution map of neural connections in the mouse brain. Built on an array of transgenic mice genetically engineered to target specific cell types, the Atlas comprises a unique compendium of projections from selected neuronal populations throughout the brain. The primary data of the Atlas consists of high-resolution images of axonal projections spanning different anatomic regions of the mouse brain. The data is available at [alleninstitute.org](#).

The purpose of computing is insight, not numbers - Richard Hamming

Making a resource: from data to insight

Data Generation

Data Processing

Data Integration

Data Presentation

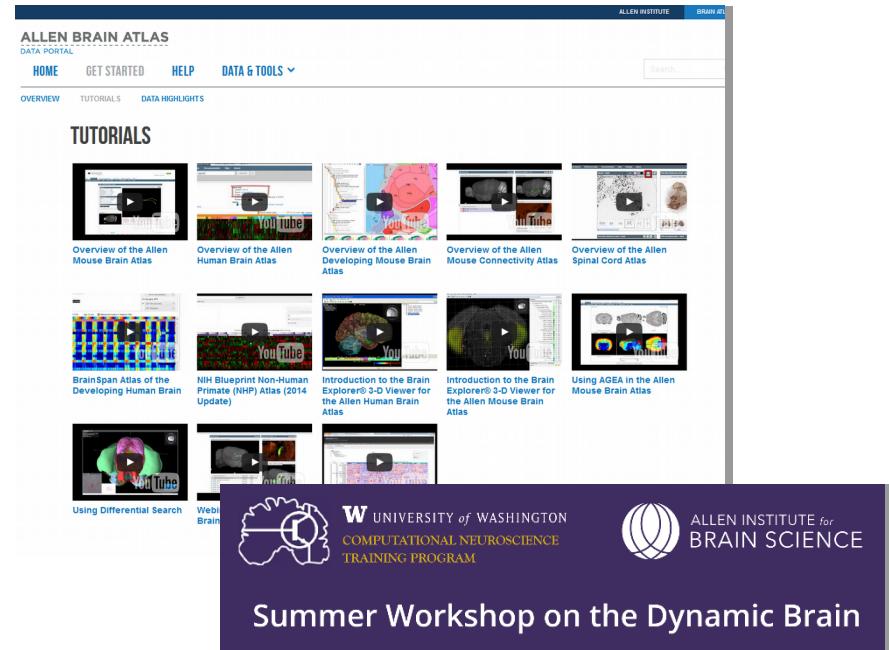
Data Access

Community Usage

User training and tutorial

Collaboration

Summer workshop on the dynamic brain



The purpose of computing is insight, not numbers - Richard Hamming

Allen Brain Atlas: Data Portal

<http://brain-map.org>

The screenshot shows the main navigation bar with links for HOME, GET STARTED, HELP, DATA & TOOLS, and a search bar. Below the navigation is a section titled "SCIENCE VIGNETTES" featuring a brain map with colored dots. To the right is a "DATA & TOOLS" section with four sub-sections: "CELL TYPES" (neuron tracing), "BRAIN OBSERVATORY" (activity heatmap), "MOUSE CONNECTIVITY" (brain map), and "DEVELOPING HUMAN BRAIN" (brain map). Further down are sections for "WHAT'S NEW" (Latest Data Release June 9, 2016, Events & Training), "ALLEN INSTITUTE PUBLICATIONS" (list of publications), "TUTORIALS" (list of video resources), and footer links for "SEND US A MESSAGE", social media, and legal information.

Web: online browse and search
API: data download
SDK: tutorial and use cases

<http://alleninstitute.github.io/AllenSDK/>

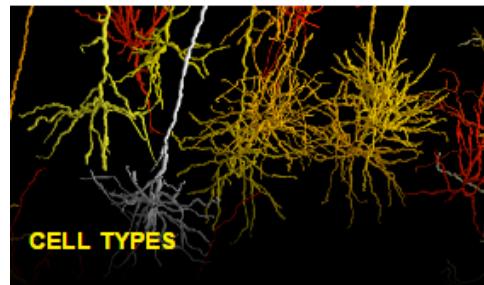
Allen Mouse Brain Connectivity Atlas



Axonal projection from selected neuronal populations

Mesoscale Connectome

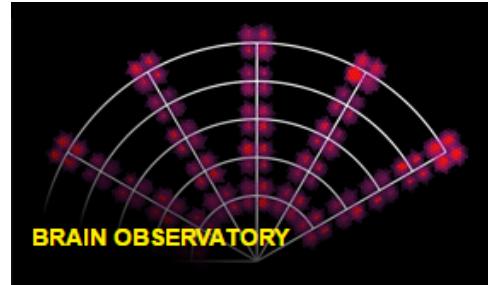
Allen Cell Types Database



Multimodal characterization of single cells

Cell Types Taxonomy

Allen Brain Observatory

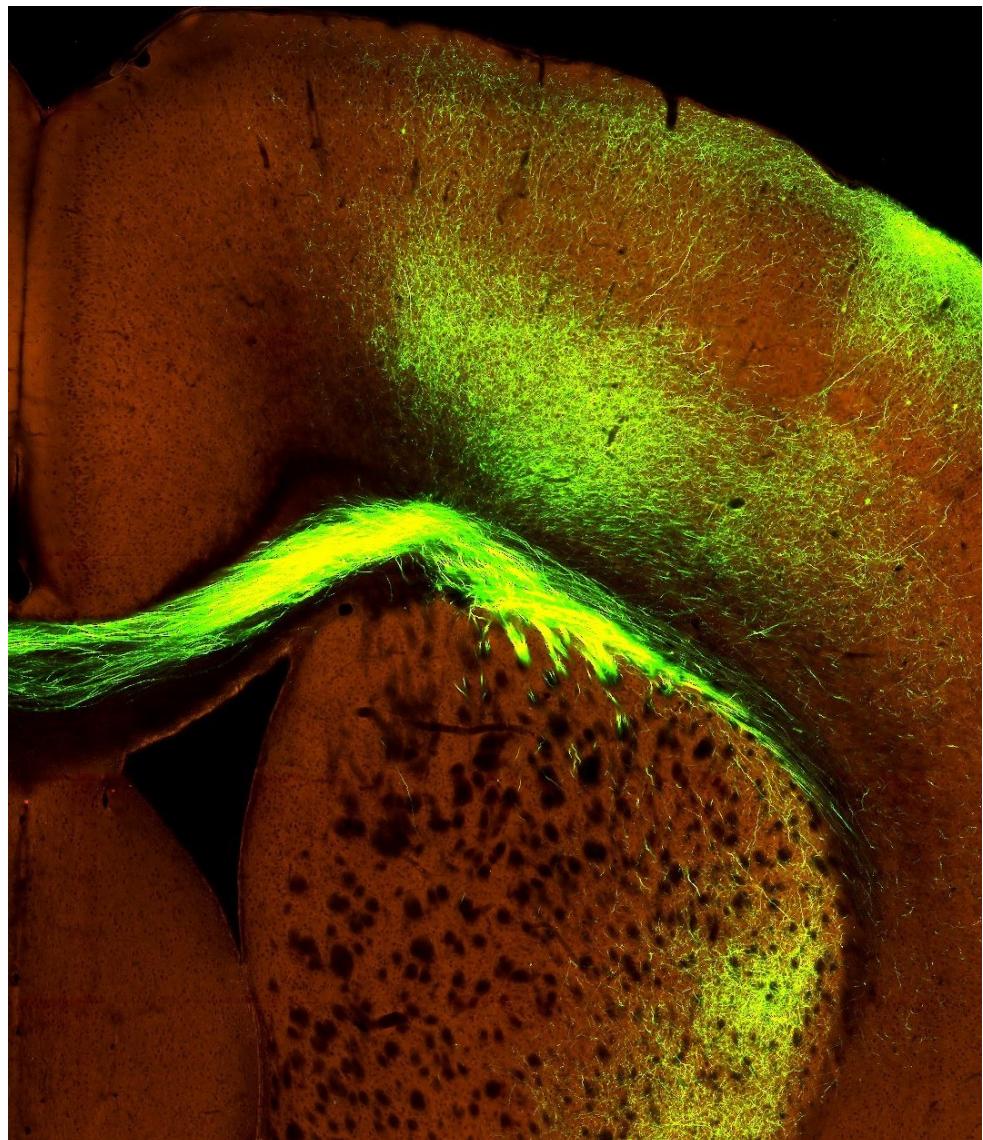
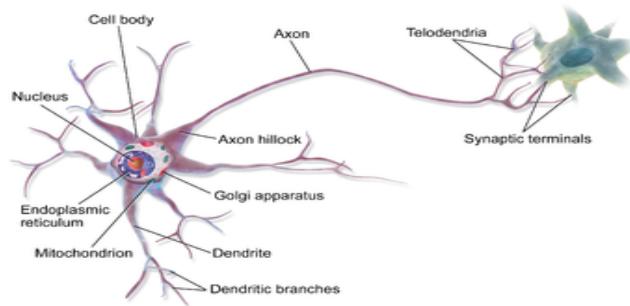
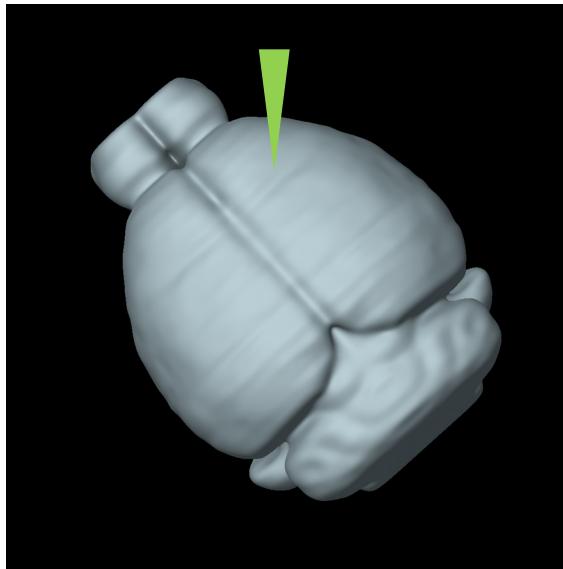


Physiological activity of cells in awake behaving mouse

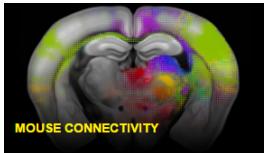
Visual Coding
Visual Behavior



ALLEN Mouse Brain Connectivity Atlas

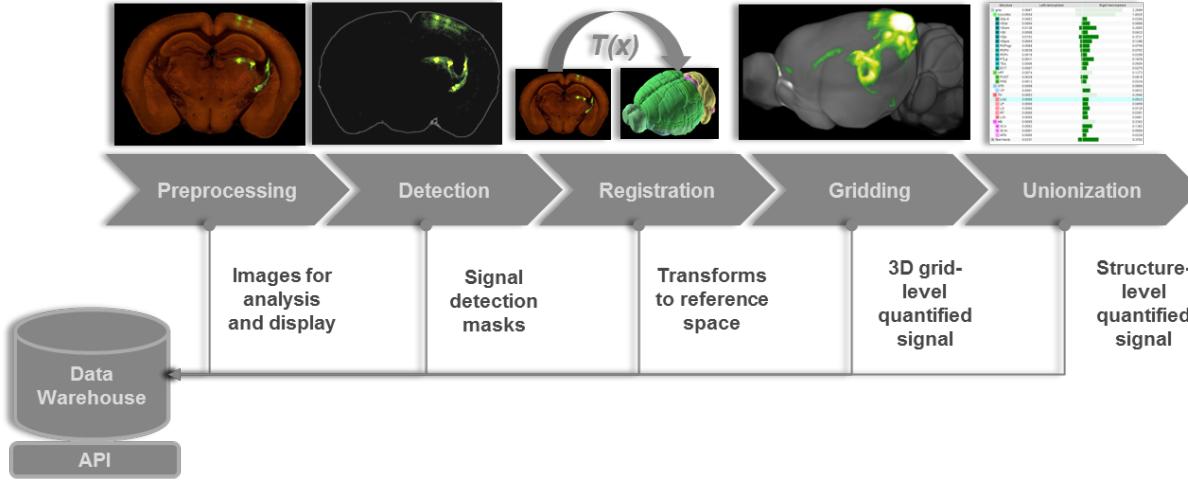
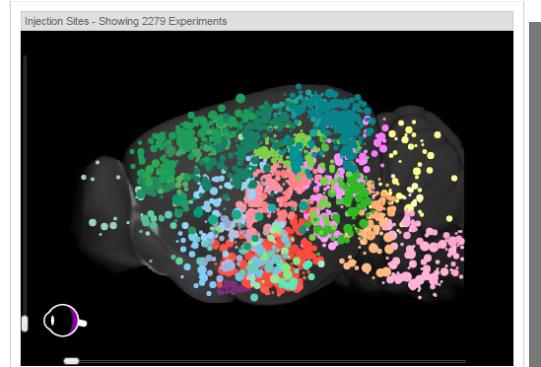
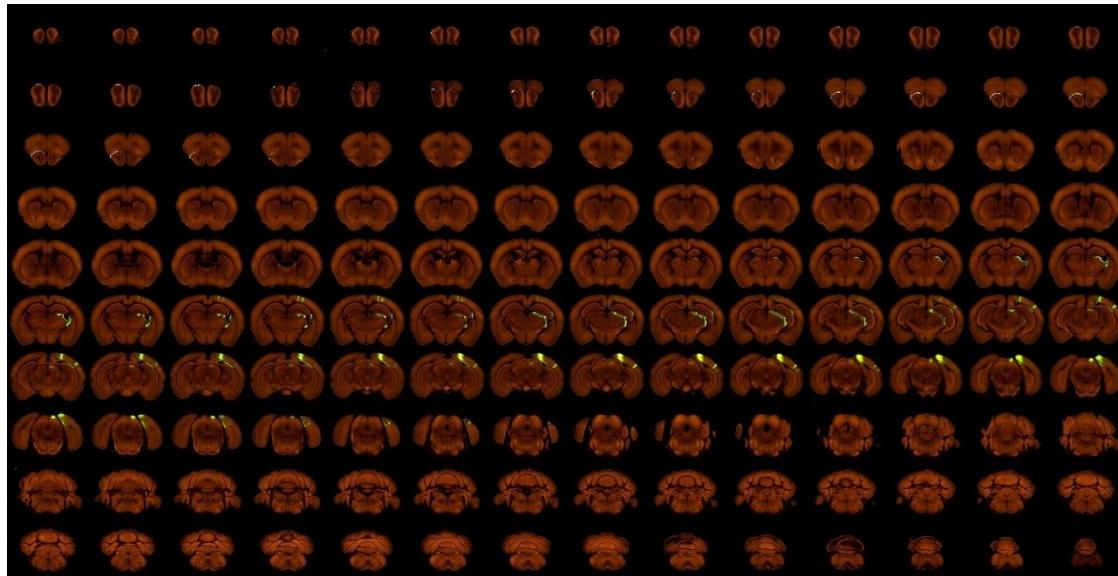


0.35 μ m pixels



Allen Mouse Connectivity Atlas

<http://connectivity.brain-map.org>



Allen Mouse Common Coordinate Framework

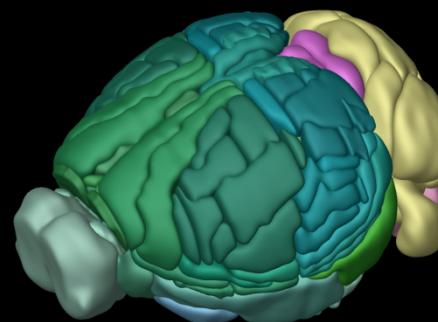
Version 1
(2005)

Version 2
(2011)

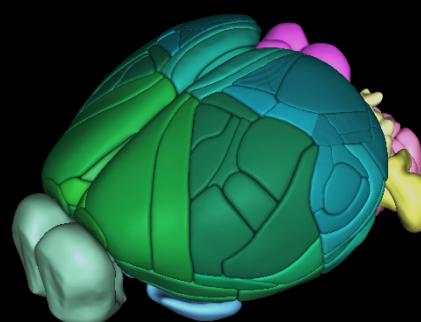
Version 3
(2015, 2016)



Single specimen
One-sided annotation
~200 structures

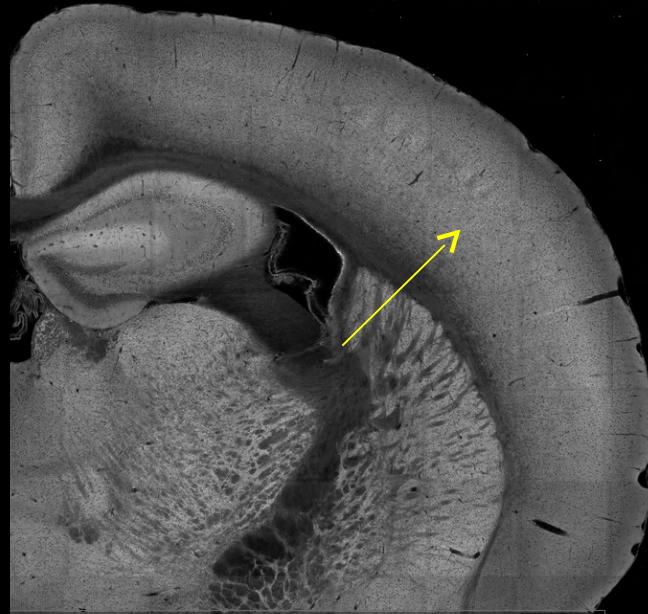


Symmetric
Double-sided annotation
860 structures



Shape and intensity average
of 1675 specimens
200+ newly drawn structures

Average Template: Construction

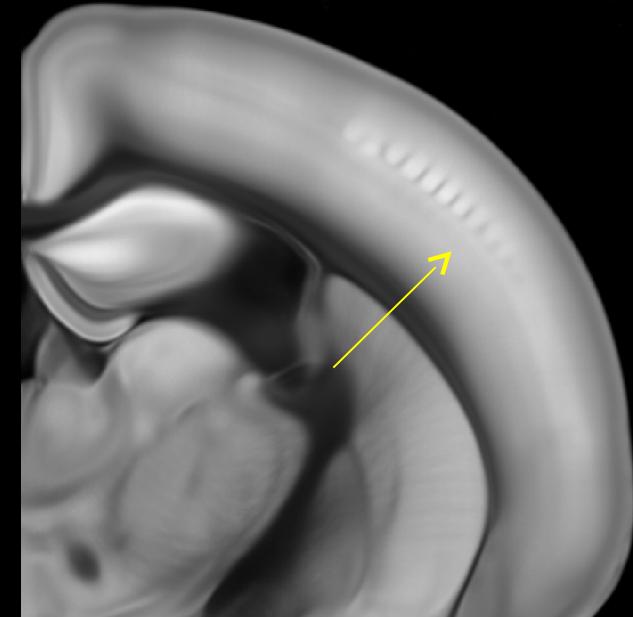


Single Specimen

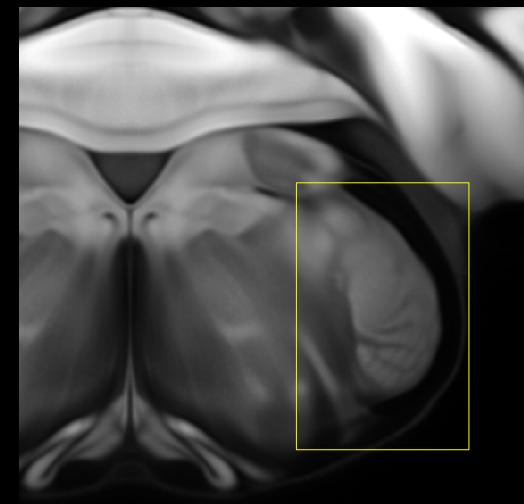
Specimen
Images

Iteration N
Template

Registration
and Warp



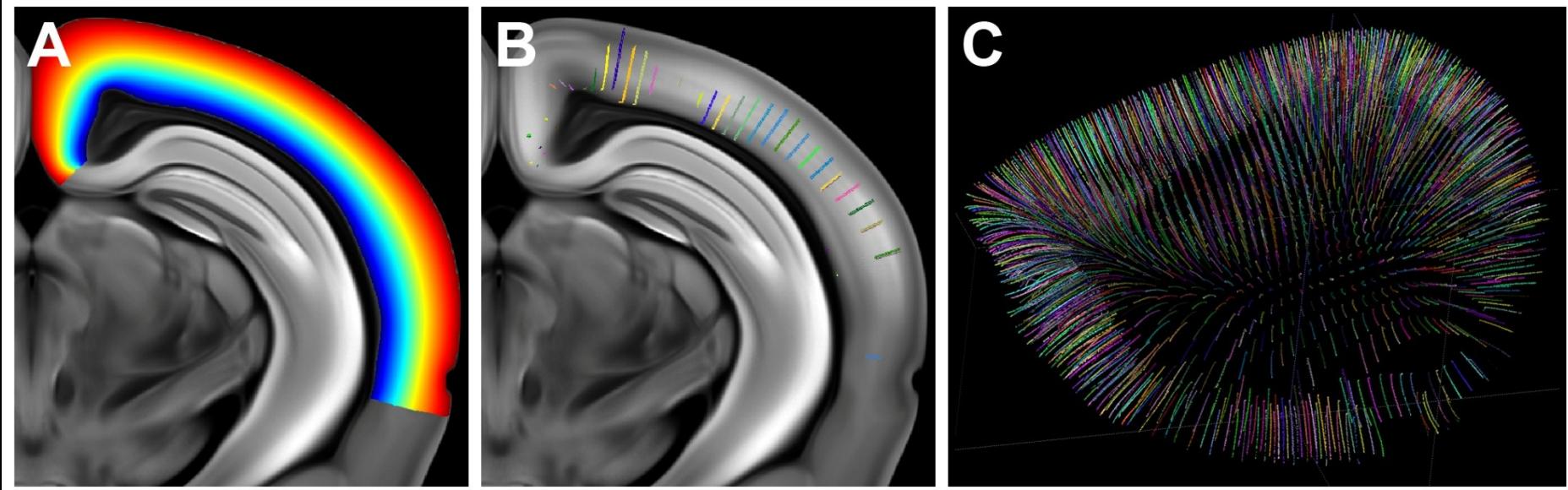
Average



Shape and Intensity Average
1675 Specimens



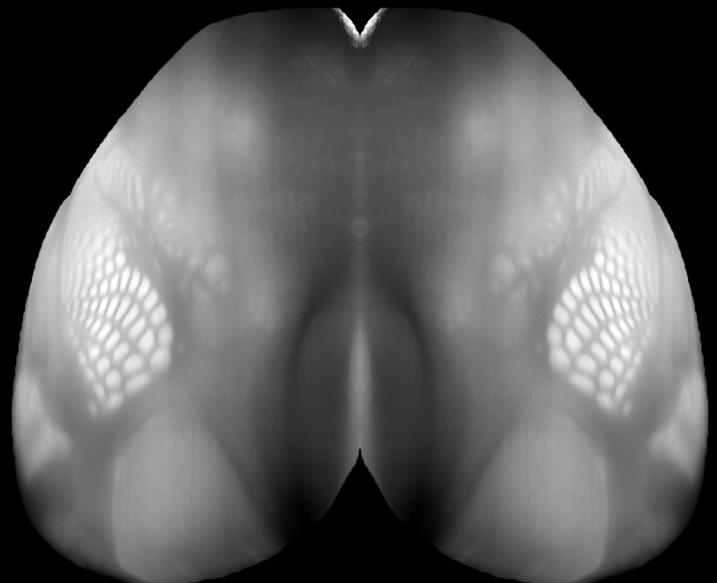
Cortical Coordinates



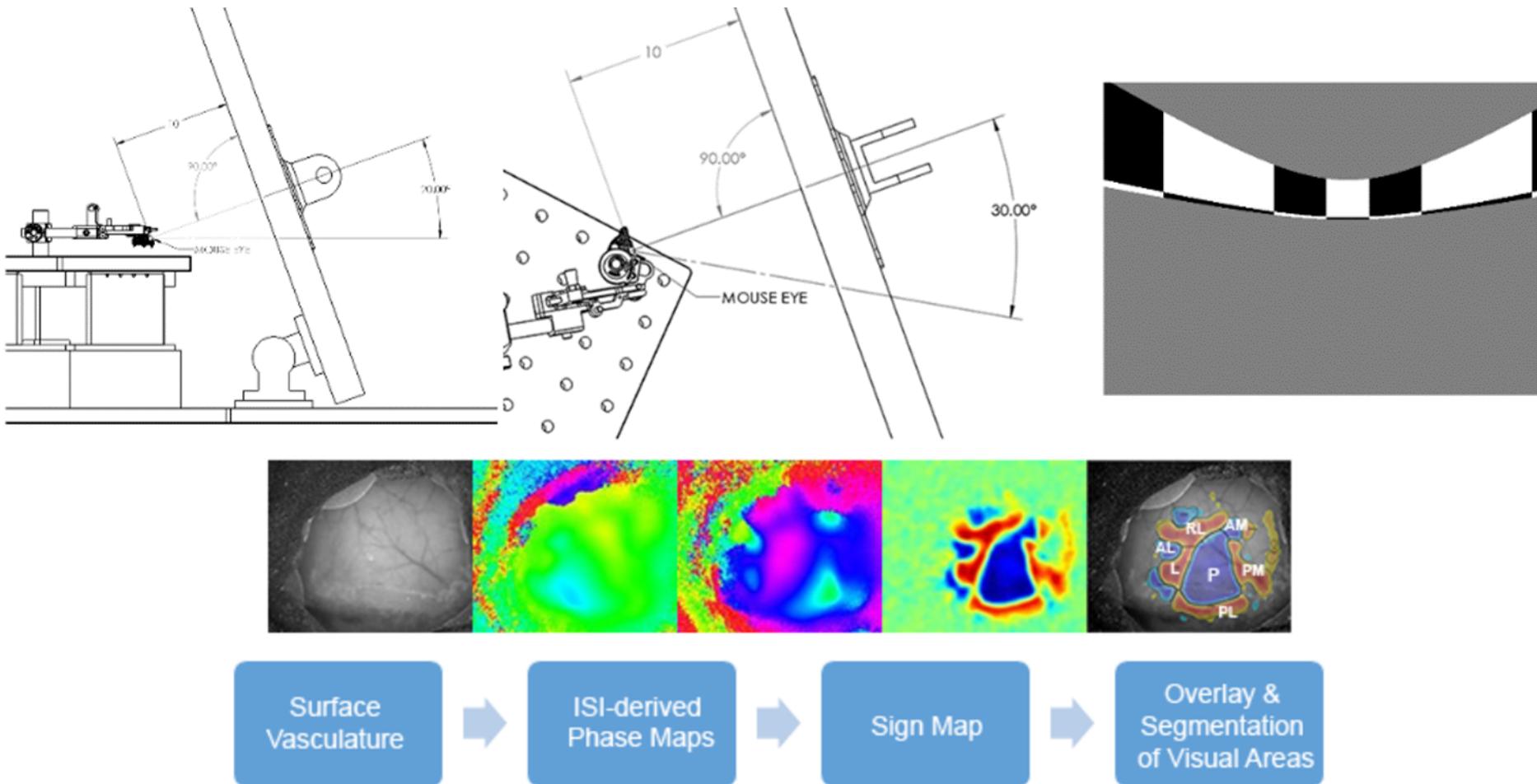
A curved cortical coordinate system for integrating information at different cortical depths

Use Laplace's equation to generate equi-potential surfaces. Streamlines are shortest path through equi-potential field.

Maximum density projection along streamlines



Integrating functional information: Mapping visual areas by intrinsic signal imaging (ISI)



- Stereotaxic injections can also be targeted to functionally known areas



Cortical Flat maps: Projection

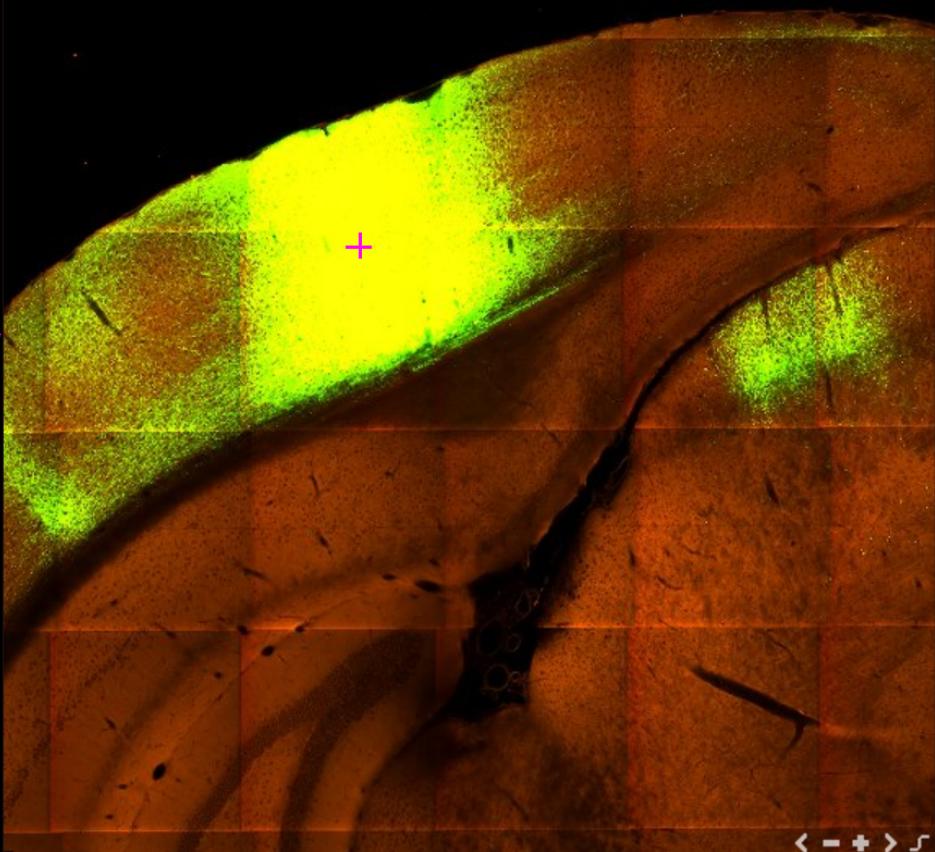
Experiment: 500836840

Primary Injection Structure: Primary visual area

Mouse Line: Emx1-IRES-Cre

Position: 8757 1182 2998

Mapped Area: Primary visual area, layer 4



Projection Density Intrinsic imaging sign map Structures

◀ - + ▶ ↕

Cortical Flat maps: ISI sign map

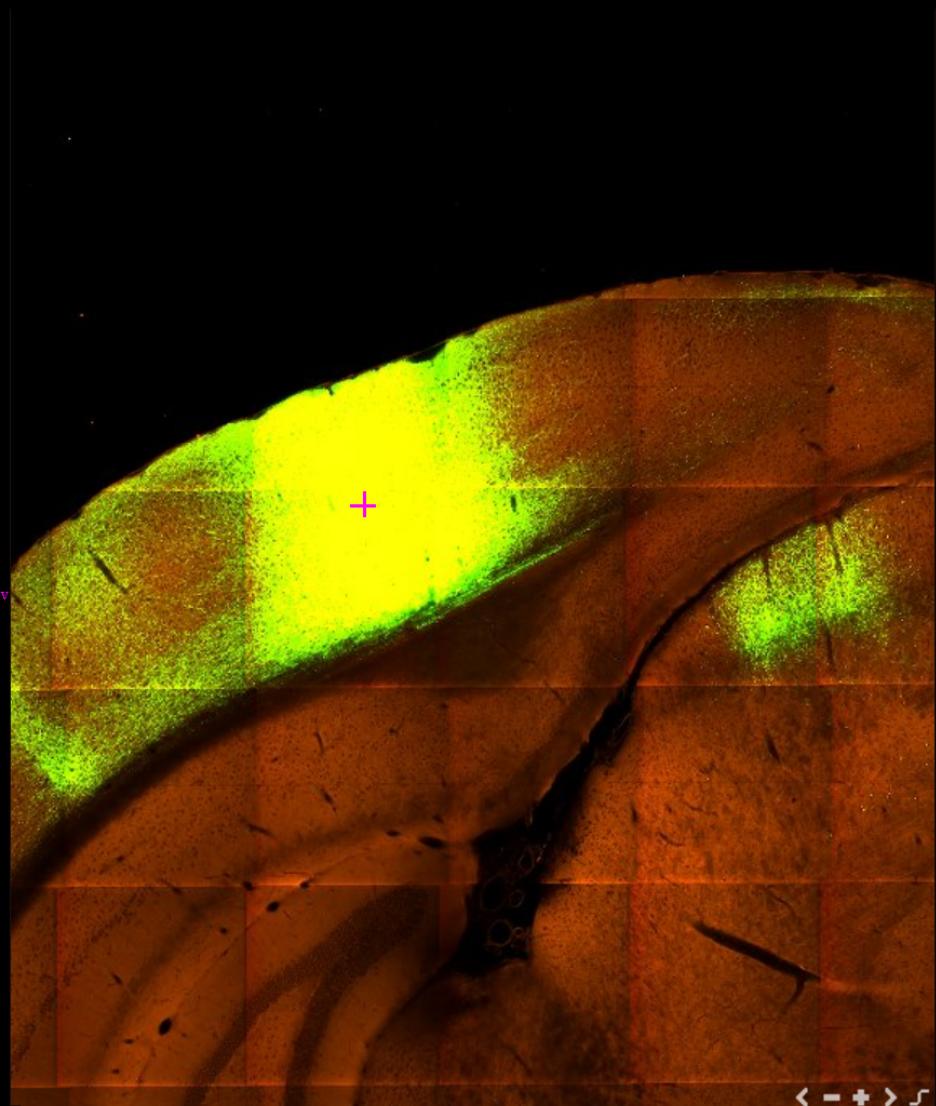
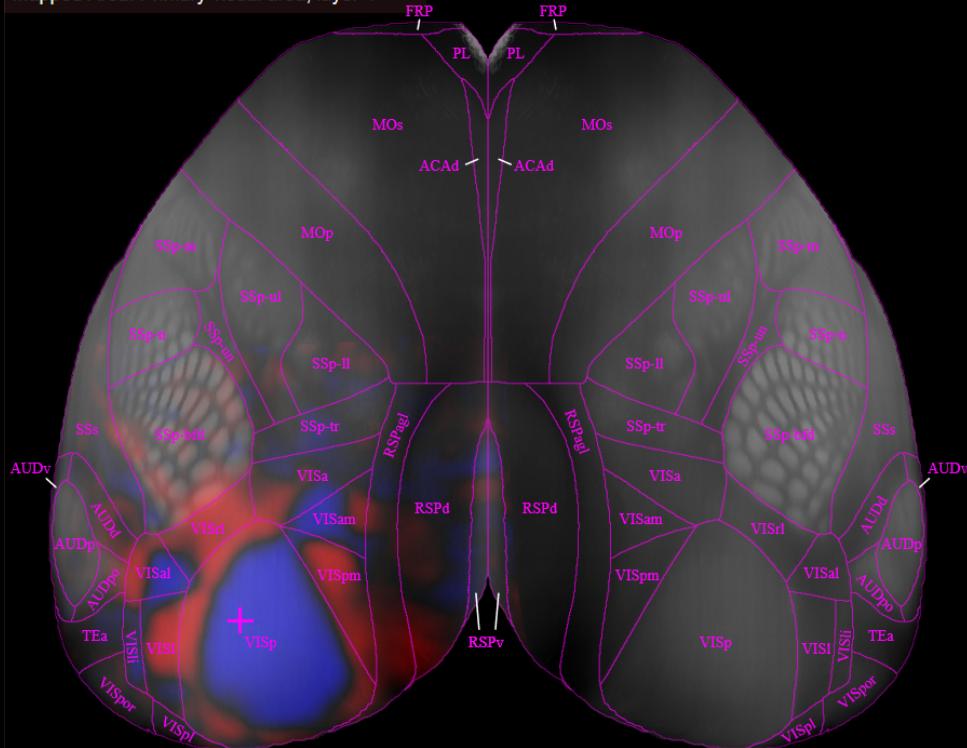
Experiment: 500836840

Primary Injection Structure: Primary visual area

Mouse Line: Emx1-IRES-Cre

Position: 8757 1182 2998

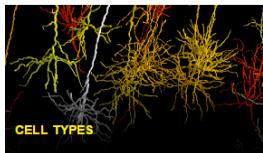
Mapped Area: Primary visual area, layer 4



■ Projection Density Intrinsic imaging sign map Structures

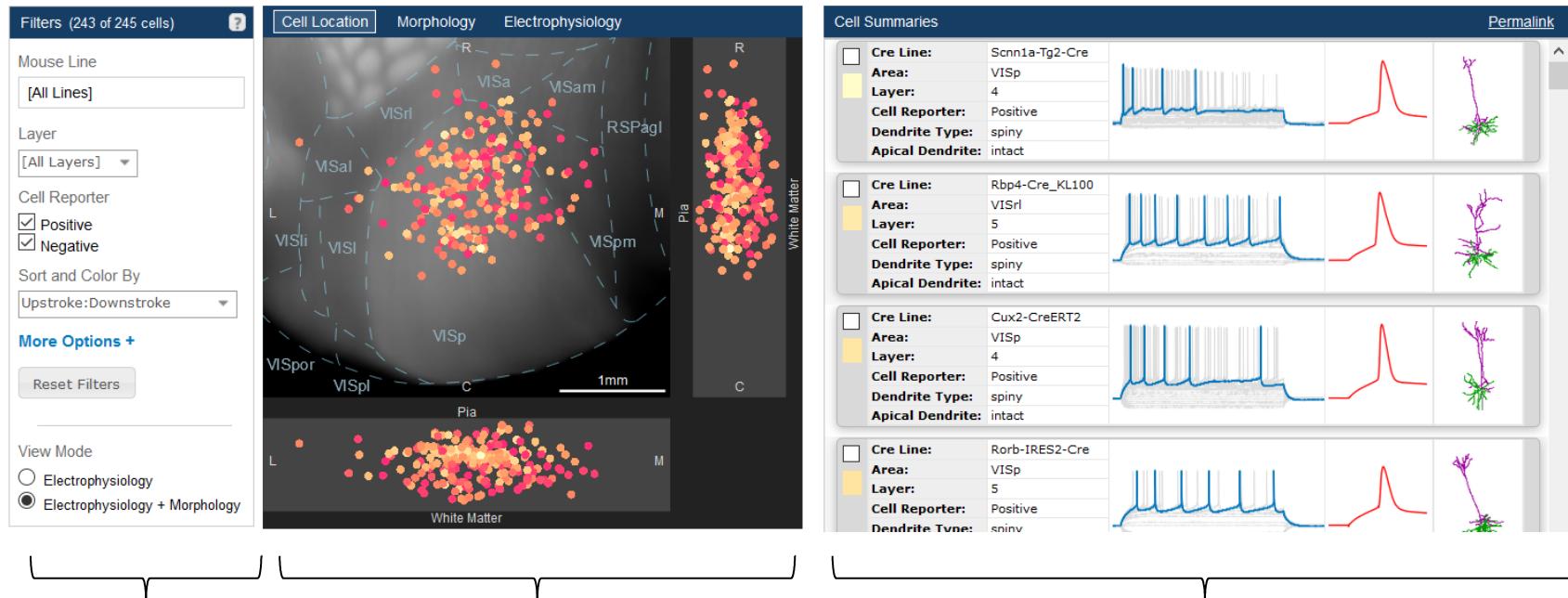
◀ ▶ ↺ ↻





Allen Cell Types Database

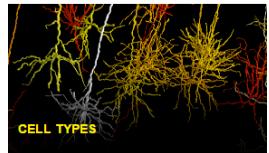
<http://celltypes.brain-map.org>



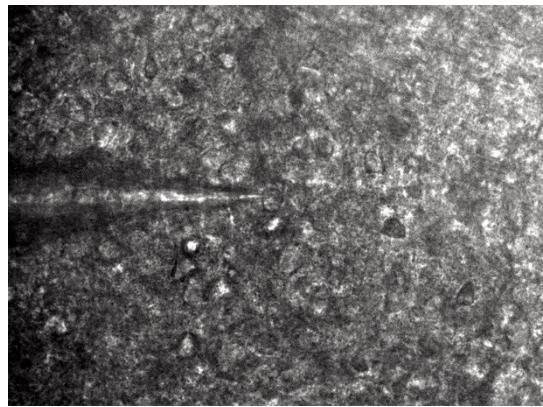
Search and
Filter Options

Cell Positions in Common
Coordinate Framework

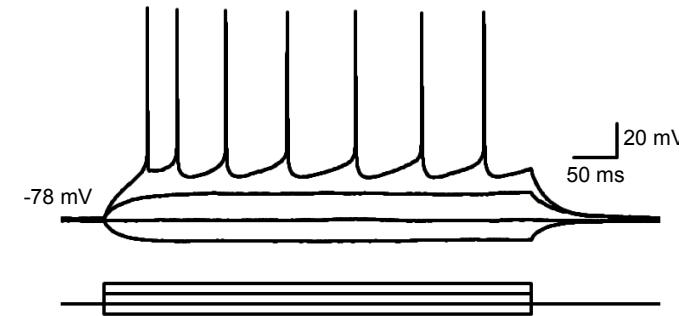
Summary of Cell
Characteristics
(Click for additional details)



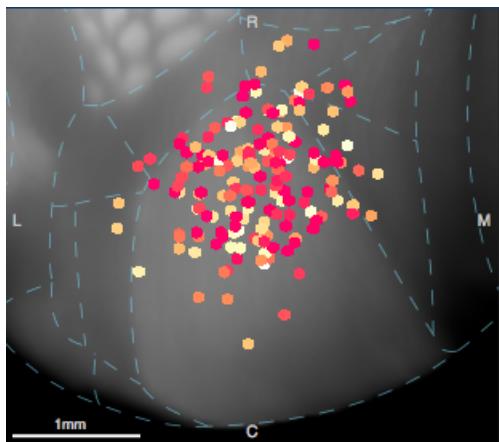
Data Processing Pipeline



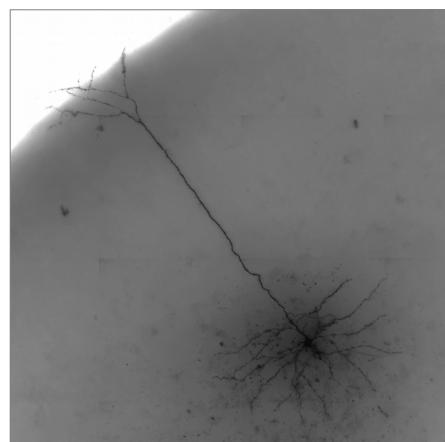
1. Record from Cre-labeled cell in slices



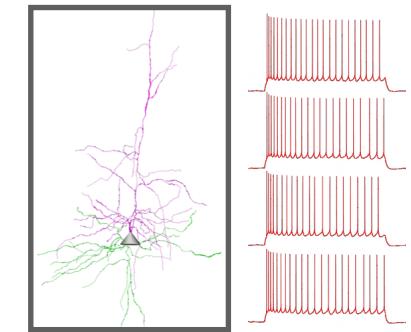
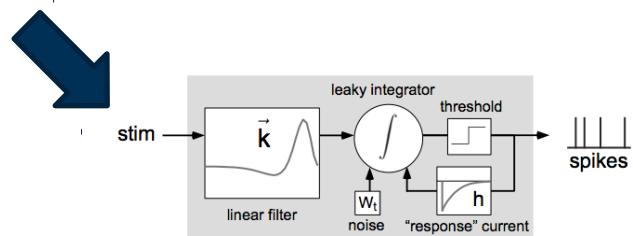
2. Collect standardized electrophysiology data and calculate relevant features



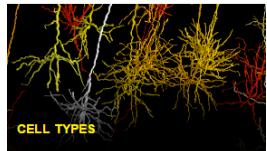
3. Place cell in CCF



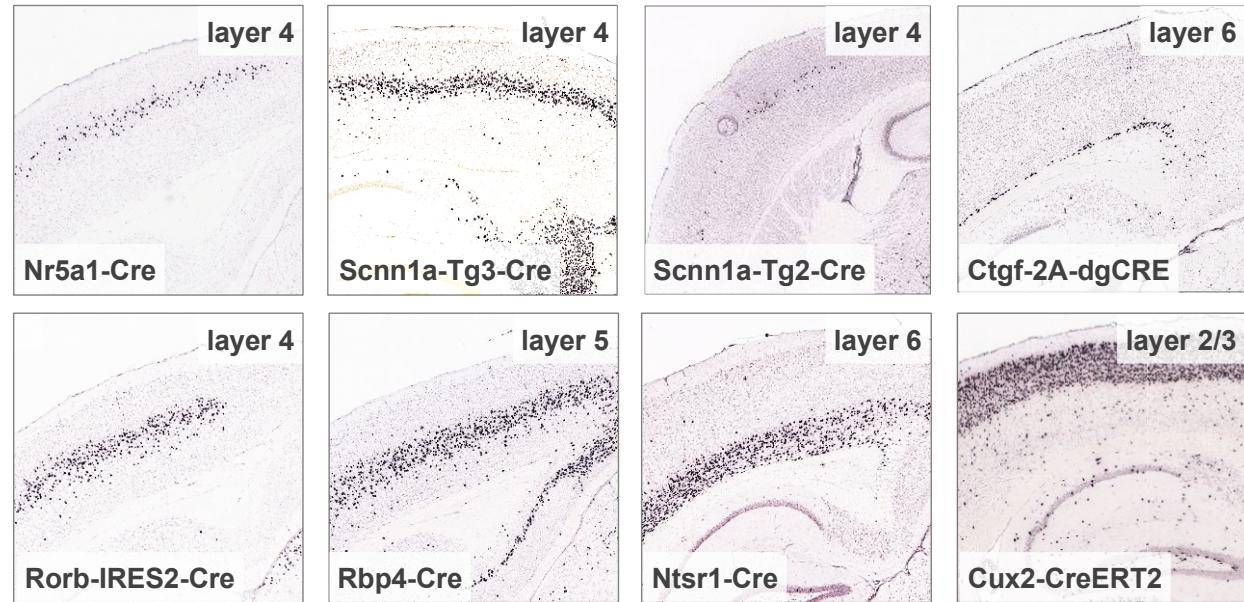
4. Fill, stain, and reconstruct morphology
0.1 μ m pixels



5. Build single-cell models

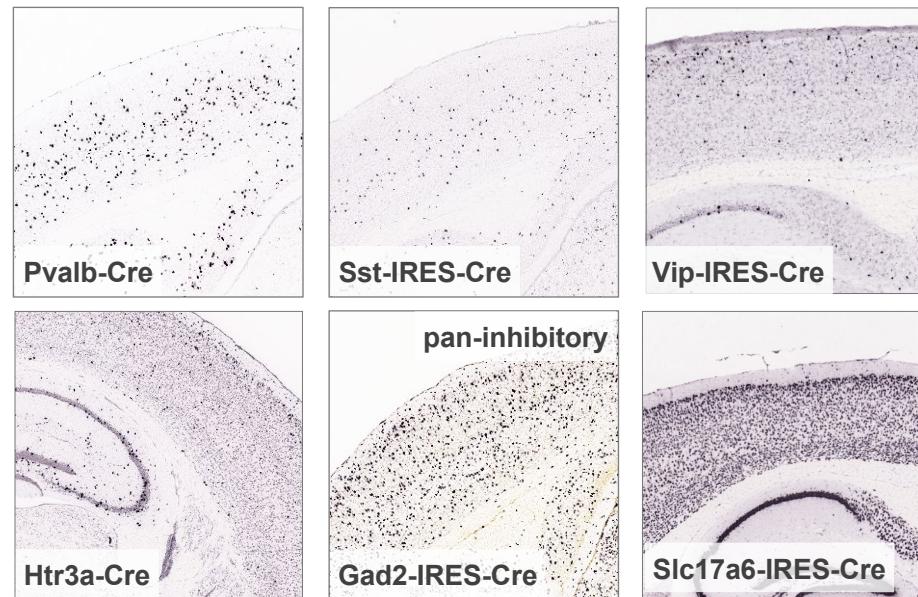


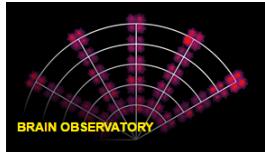
Excitatory neurons



Genetic Markers via Cre Lines

Inhibitory neurons

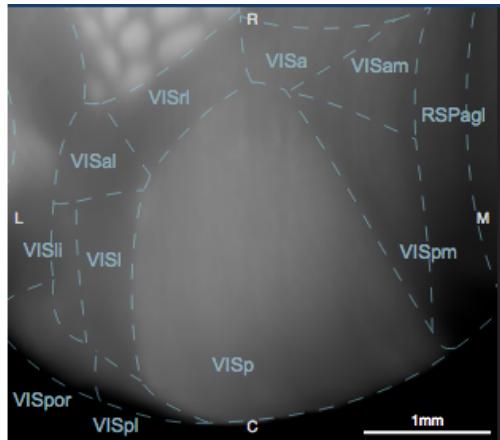




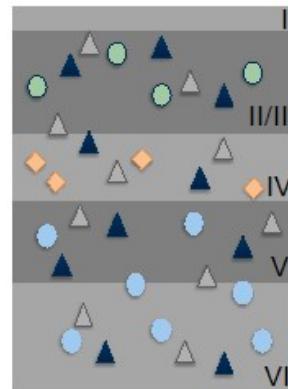
ALLEN Brain Observatory: Visual Coding

<http://observatory.brain-map.org/visualcoding>

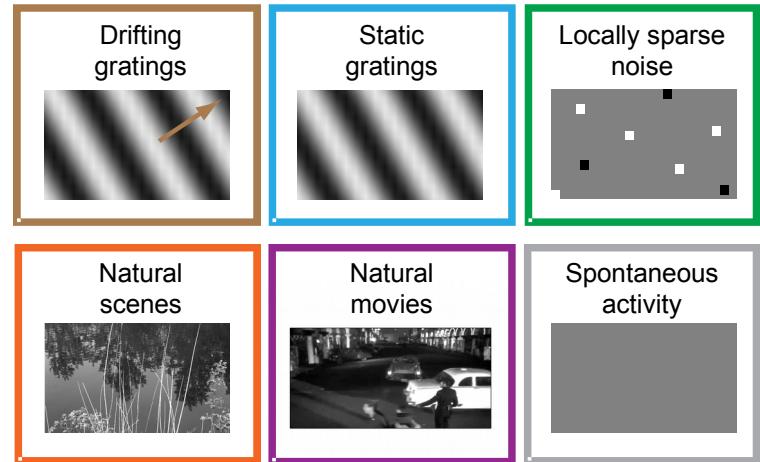
Cortical Visual Areas



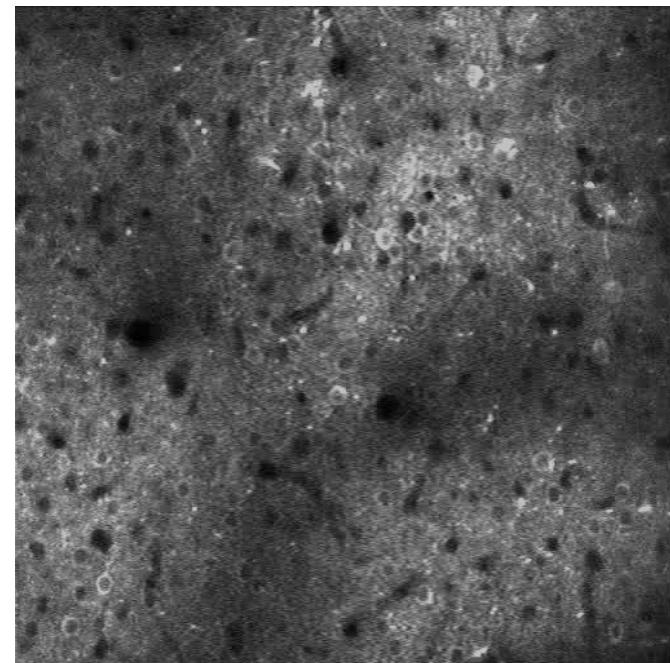
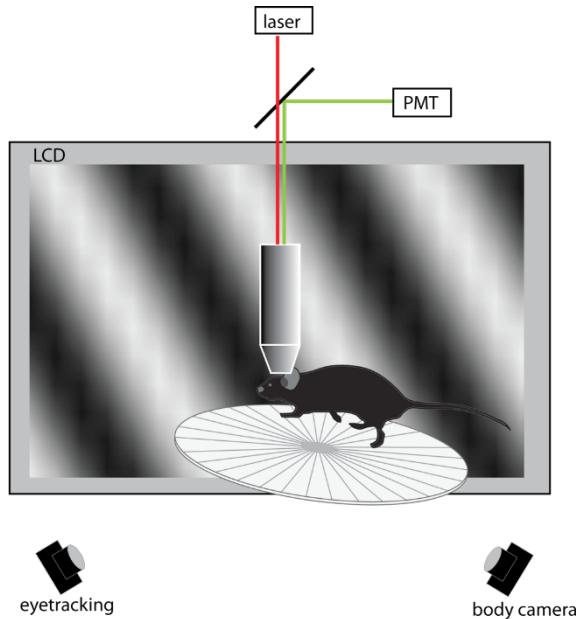
Cortical Layers
Cre Lines



Visual Stimuli



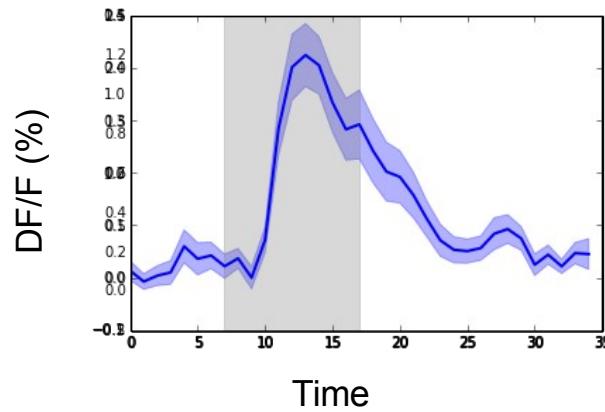
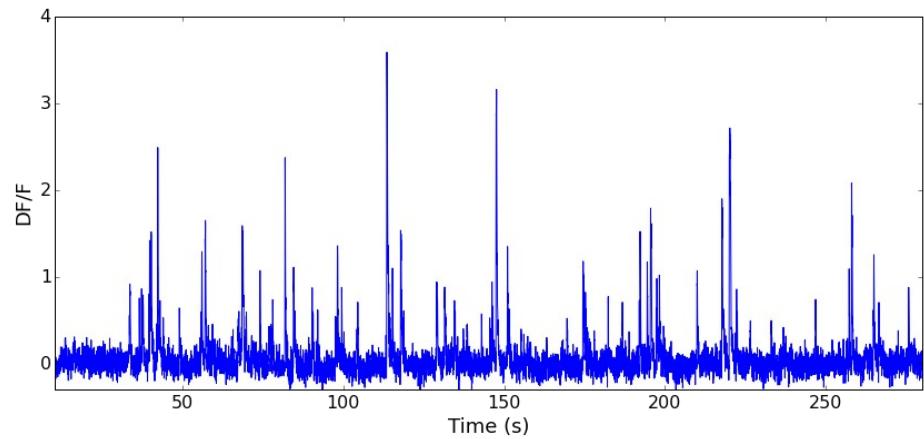
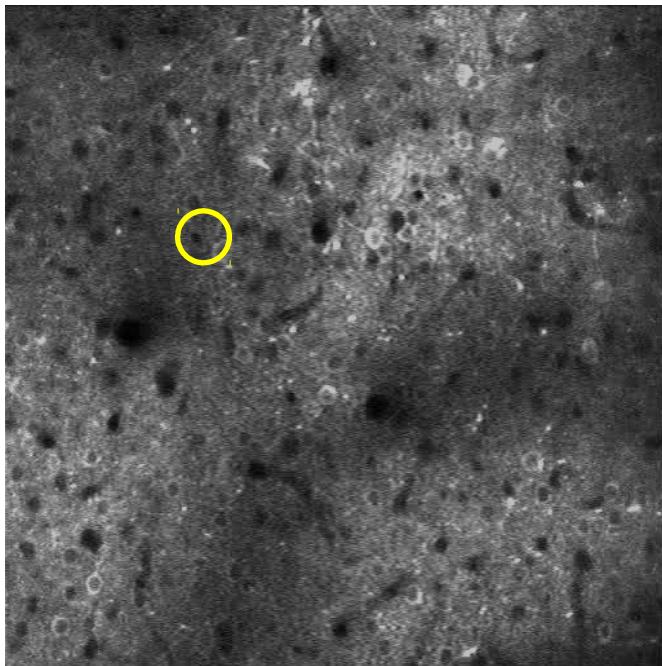
Two-photon imaging of visual responses in mouse cortex

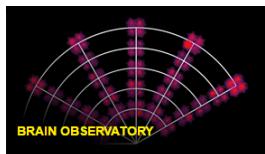


512 x 512 pixels
400 x 400 μm

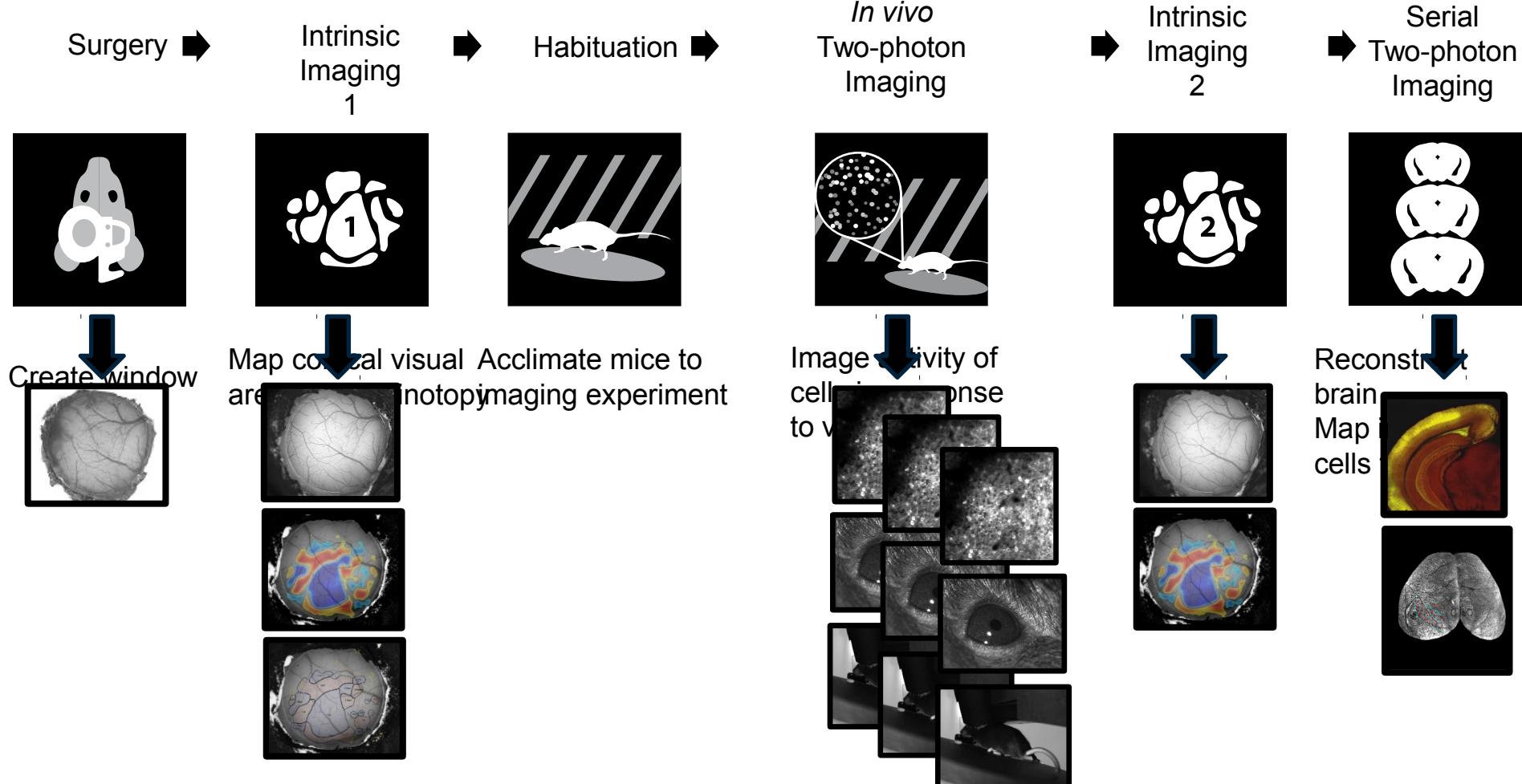


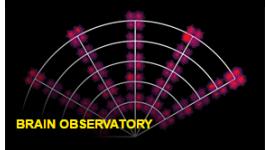
Visual responses of individual cells



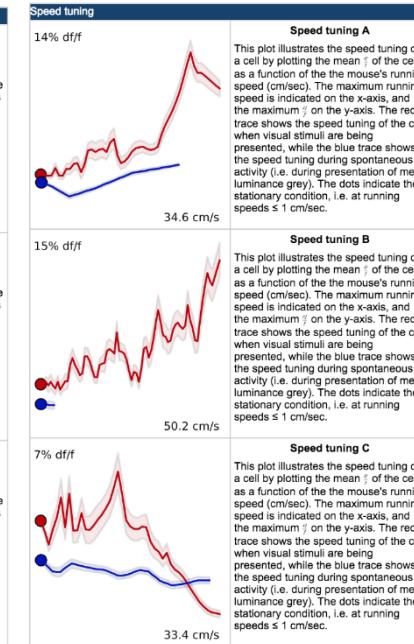
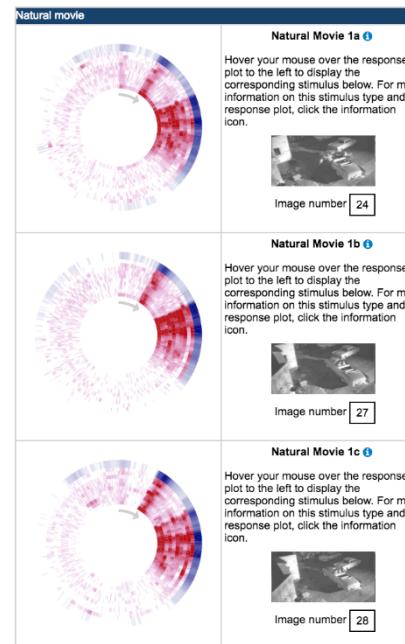
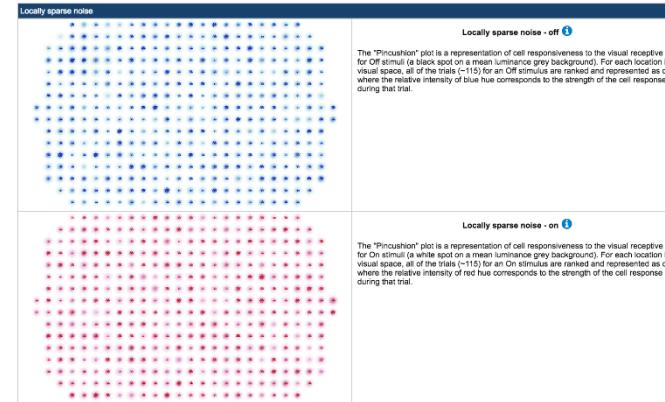
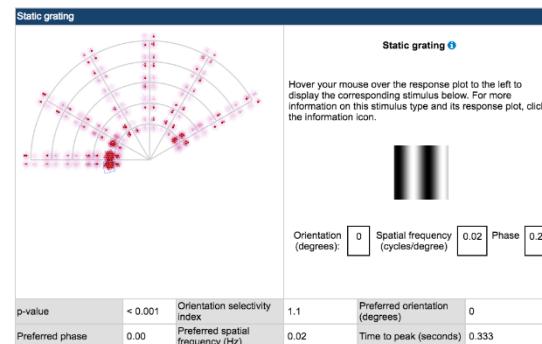
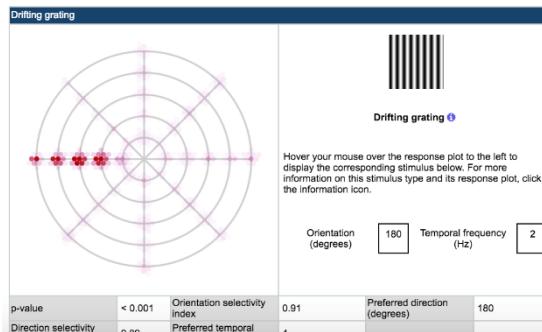
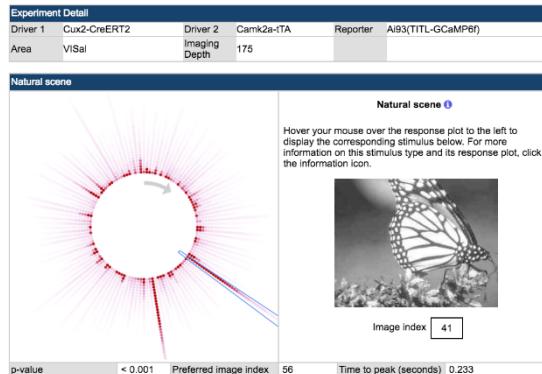


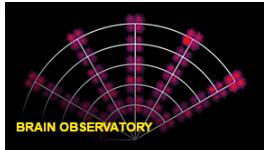
Data Production





Dynamic Visualization of Cell Tuning





Data from each experiment session contained in a NWB file

Max projection

ROI masks

Raw fluorescence for each ROI

Surrounding neuropil trace and r value

$\Delta F/F$ for each ROI

Stimulus table

Stimulus template

Mouse's running speed

Motion correction (x & y pixels)

Meta data (cre line, visual area, imaging depth, experiment container, mouse ID, age, sex, etc)

Brain Observatory

This notebook documents some classes and functions in the AllenSDK that help manipulate files and data structures in the Allen Brain Observatory. The main entry point in the `BrainObservatoryCache` class. This class is responsible for downloading any requested data or metadata on request and storing it in well known locations.

Download this file in ipynb format [here](#).

Experiment Containers

The experiment container describes a set of experiments. It has a number of functions for figuring out what experiments

```
In [1]: from allenSDK.core.brain_observatory_ca import pprint

# This class uses a 'manifest' to keep
# All downloaded files will be stored in
# this file. If 'manifest_file' is a relative
# path, it will be saved relative to your working directory.
boc = BrainObservatoryCache(manifest_file='manifest.json')

# Download a list of all targeted areas
targeted_structures = boc.get_all_targeted_structures()
print("all targeted structures: " + str(targeted_structures))

all targeted structures: ['VISal', 'u'V
```



```
In [2]: # Download experiment containers for V1
visp_ecs = boc.get_experiment_container('V1')
print("all V1Sp experiment containers: " + str(visp_ecs))

all V1Sp experiment containers: 25
```



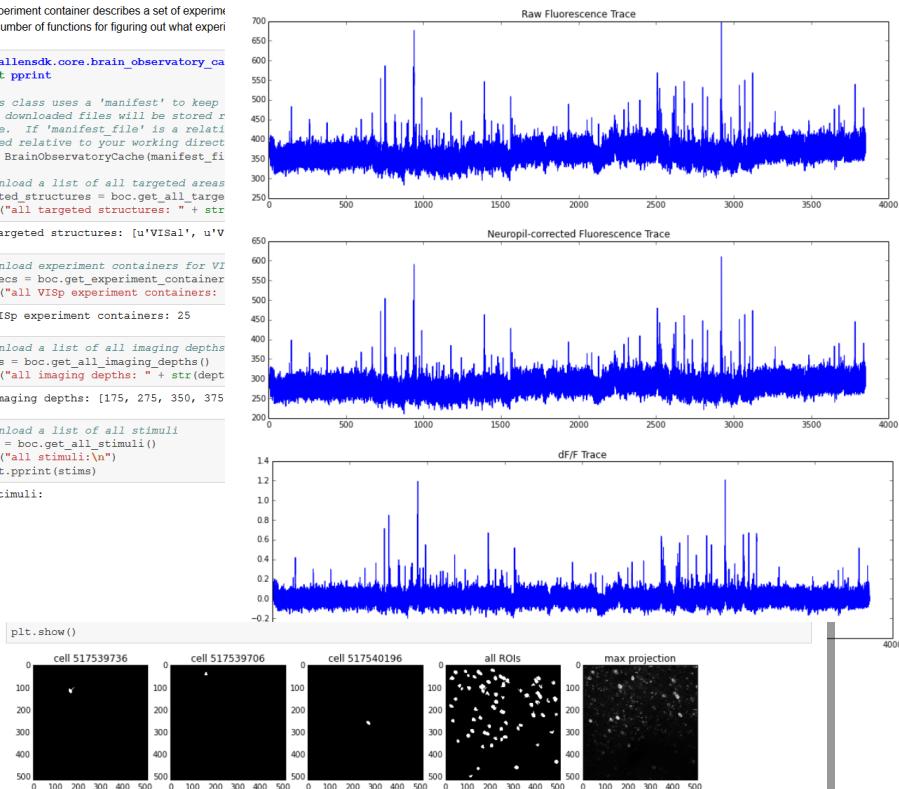
```
In [3]: # Download a list of all imaging depths
depths = boc.get_all_imaging_depths()
print("all imaging depths: " + str(depths))

all imaging depths: [175, 275, 350, 375]
```



```
In [4]: # Download a list of all stimuli
stimuli = boc.get_all_stimuli()
print("all stimuli: " + str(stimuli))
pprint.pprint(stimuli)

all stimuli:
```





THANK YOU

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