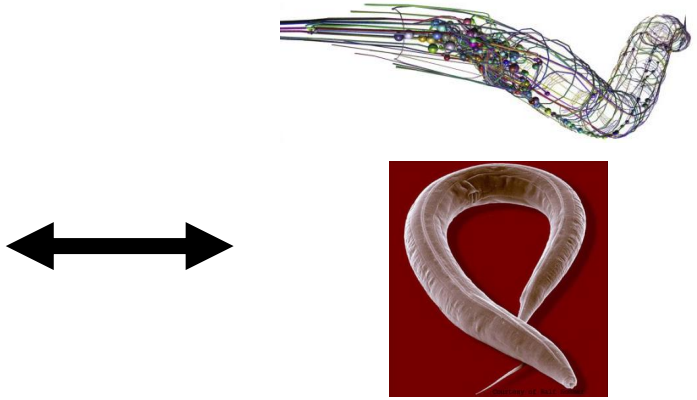
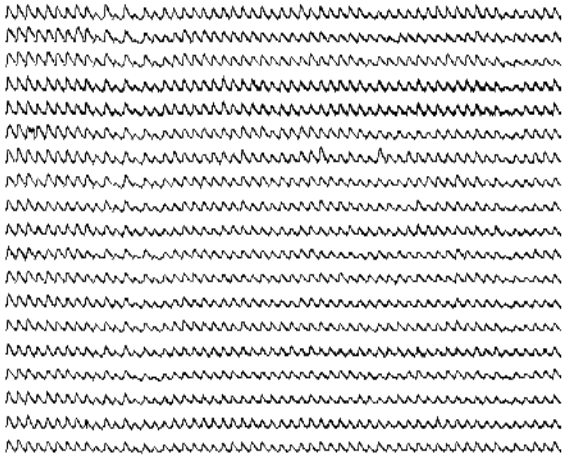


worms



BioVis in support of Neuro research

2. 19. 18

Guest Lecture: Ross Lagoy | rosslagoy@wpi.edu

Albrecht Lab | WPI Biomedical Engineering Department

Dirk Albrecht's 'Quantitative NeuroTechnology' Lab (QNTL)

1. Functional screens for modulators of neural dynamics

2. Light sheet microscopy for long-term multi-neuronal imaging with chemical and optogenetic stimulation

3. Neural signaling changes across physiological and behavioral states

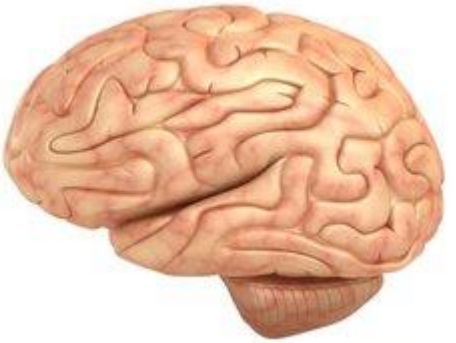
Outline: with a focus on data generation and methods for visualization

- Biological significance
  - Why? Where do the numbers come from?

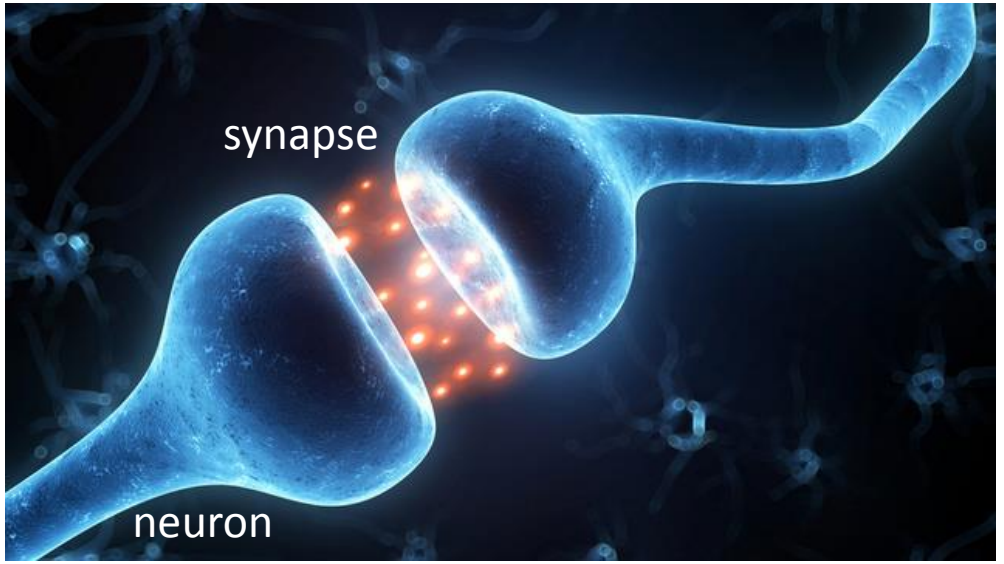
- Format(ting) of the generated data
  - What is the recorded data structure?

- Method(s) to visualize these important numbers
  - What types of plots, colors, sizes, etc.
  - What numbers are most important?
  - What do the results tell us?
  - Can the data be interactive?

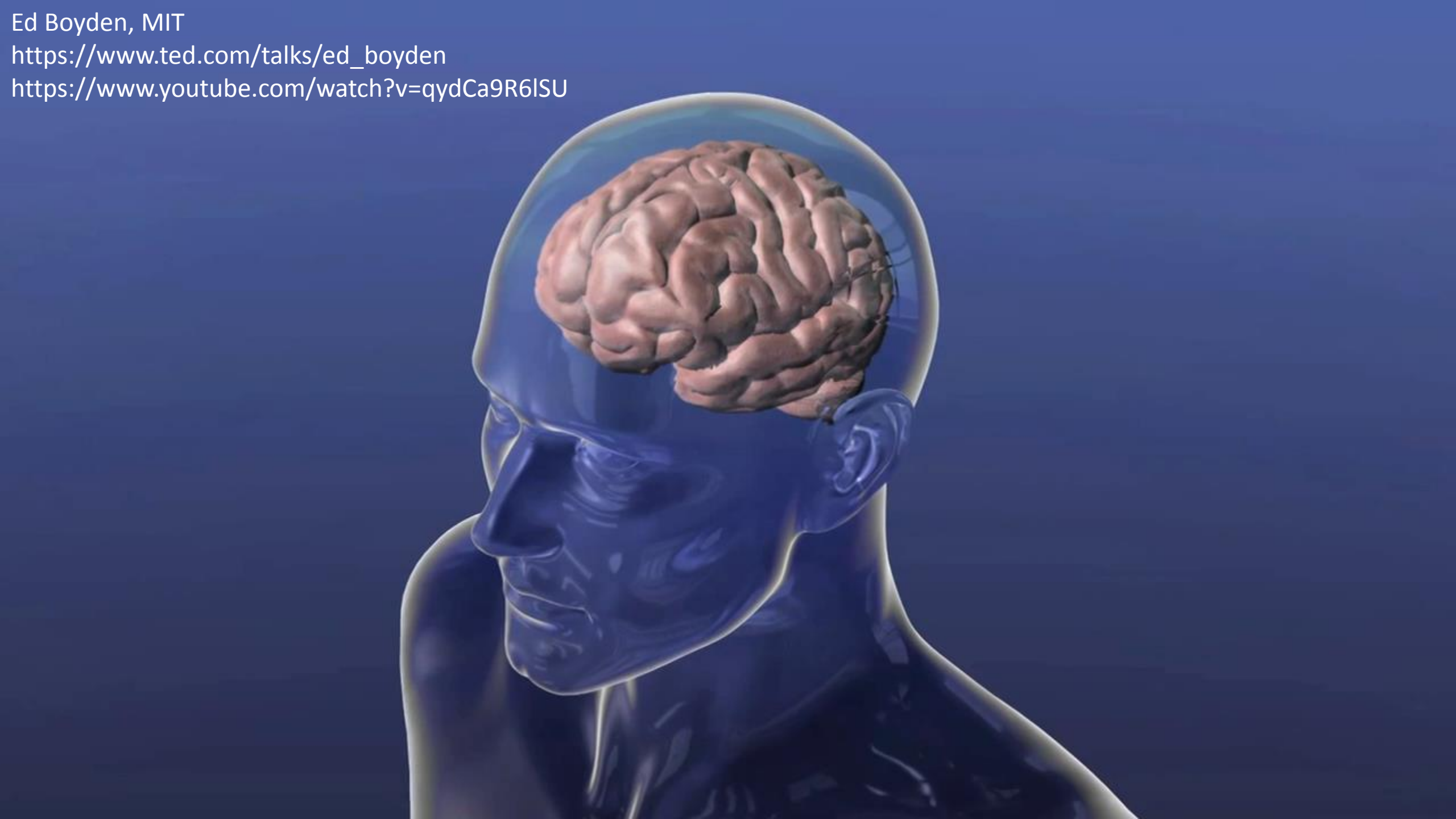
The human brain is complicated



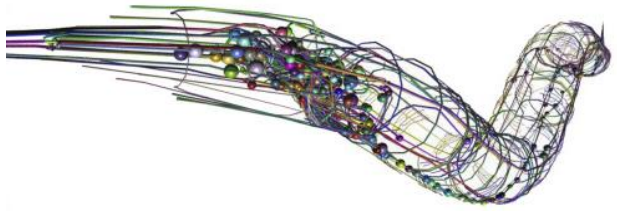
Billions of neurons
Trillions of synapses (connections between neurons)
Control of our thoughts and behavior
Affected by disease
It’s an chemical-electrical system…



Ed Boyden, MIT
https://www.ted.com/talks/ed_boyden
https://www.youtube.com/watch?v=qydCa9R6ISU



Popular model organisms to study neuroscience

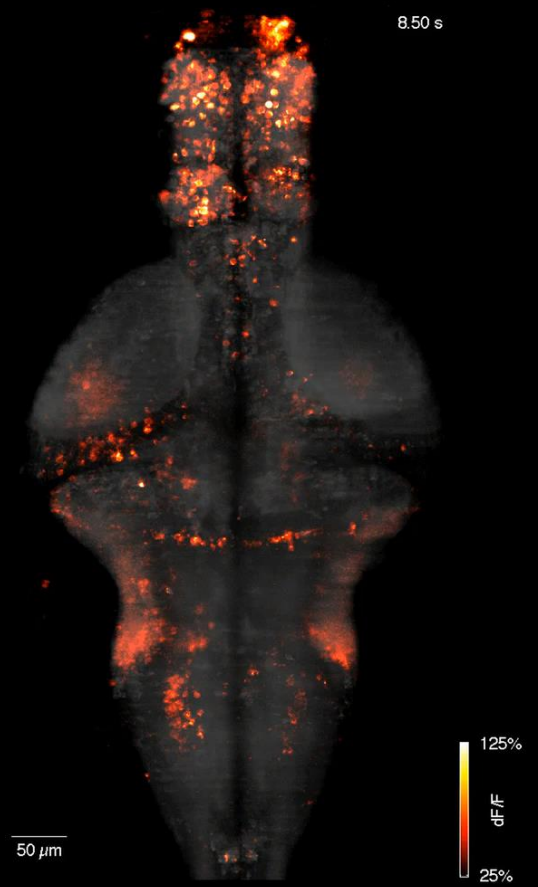


Transparent
Cheap
Lots of progeny >300
Complete connectome
Conserved genetics

Drosophila

Mice

Fluorescent calcium sensors enable monitoring neural activity in living organisms



Vladimirov, N.+ (2014) *Nature Methods*
Zebrafish

Change in fluorescence correlates to increase in calcium ion concentration

$$\uparrow \Delta F \propto \uparrow Ca^{2+} \propto \text{cellular activity}$$

Schrödel, T.+ (2013). *Nature Methods*
C. elegans

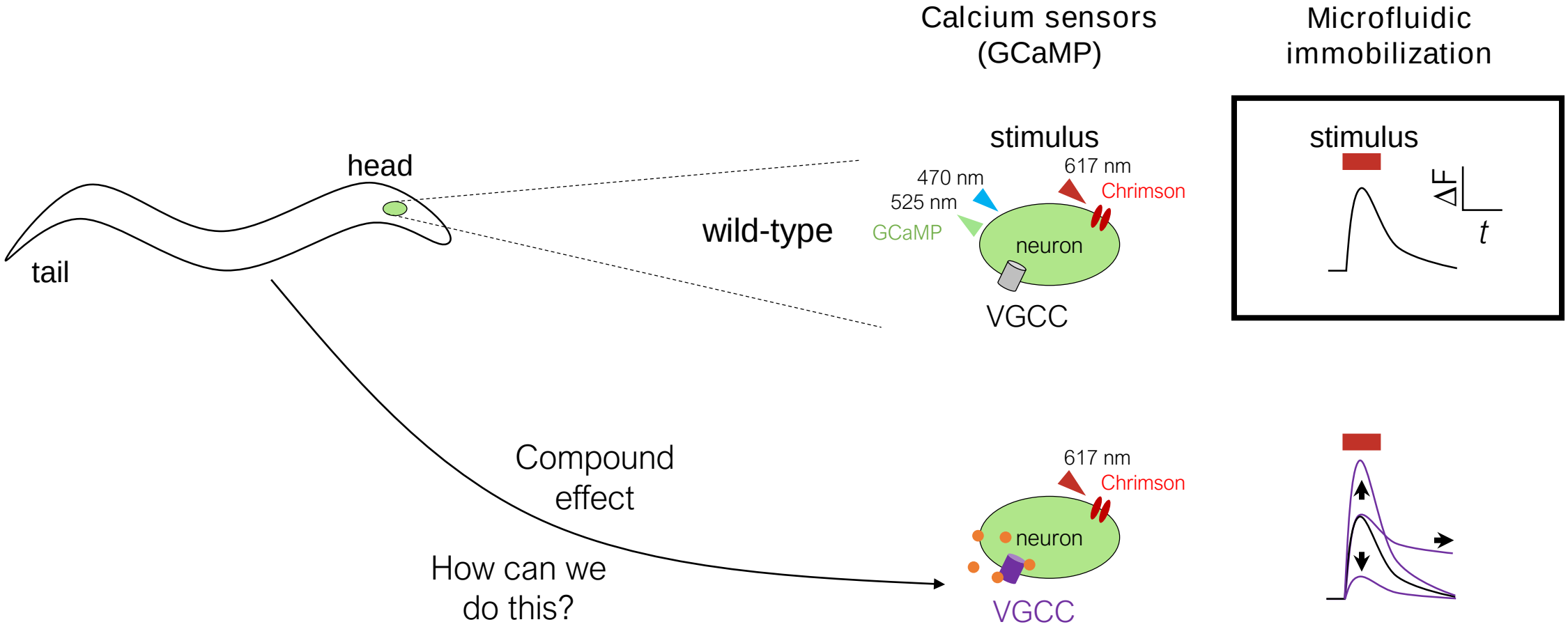
Calcium is important!

- Calcium mediates cellular activity through biological pathways
- Regulates gene expression
- Cell-cell interaction (neurotransmitter release, synaptic communication)
- Contraction in muscle cells (i.e. heart and skeletal)
- Provides a potential difference across cell membranes
- Transported through the blood stream
- Any imbalances (over/under active) can result in disease
  - Autism, epilepsy, schizophrenia, neurodegeneration (by cell death), cardiac arrhythmia, *etc.*

We can record neural activity, but how can we easily stimulate these cells?

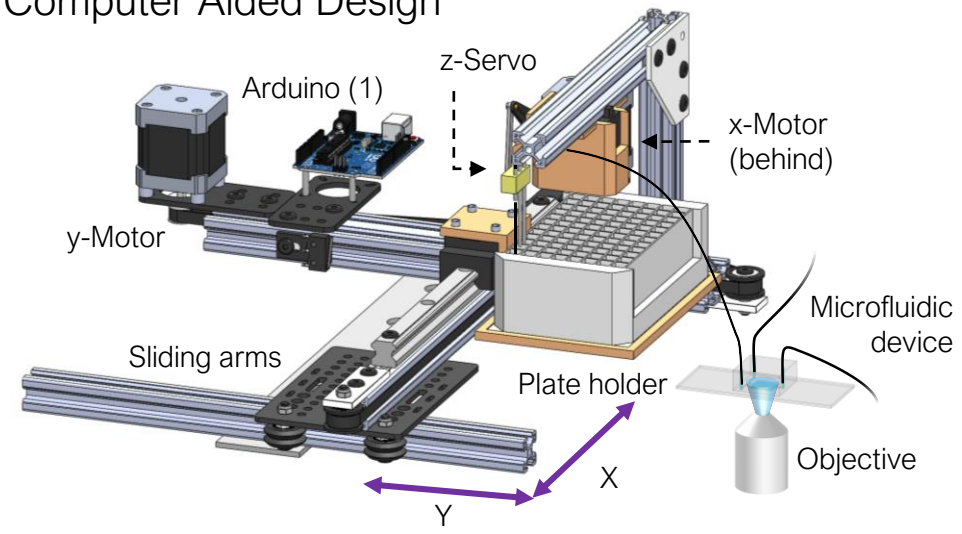
Ed Boyden, MIT
https://www.ted.com/talks/ed_boyden
https://www.youtube.com/watch?v=qydCa9R6ISU

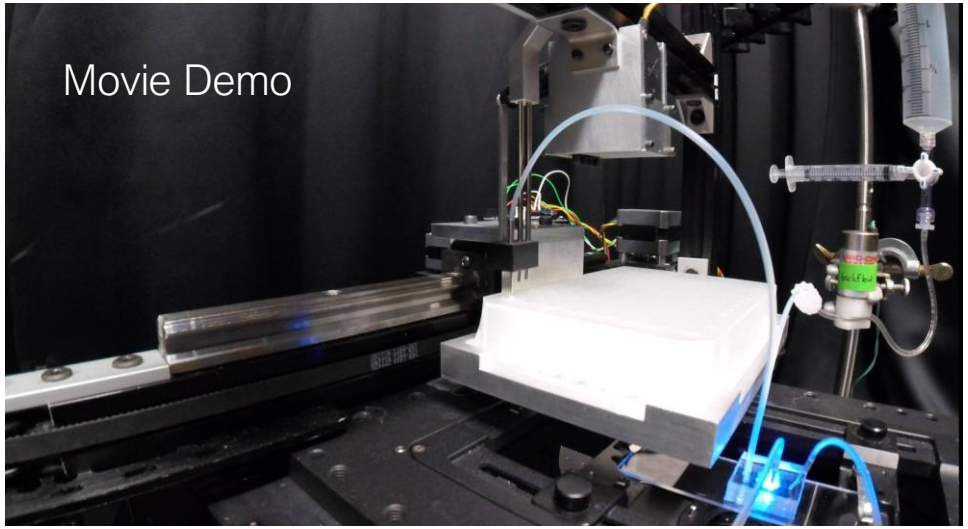
Using light to ***stimulate and record*** neural activity in *C. elegans*



A method integrating multiwell plates with microfluidic devices for automated compound screens

Computer Aided Design

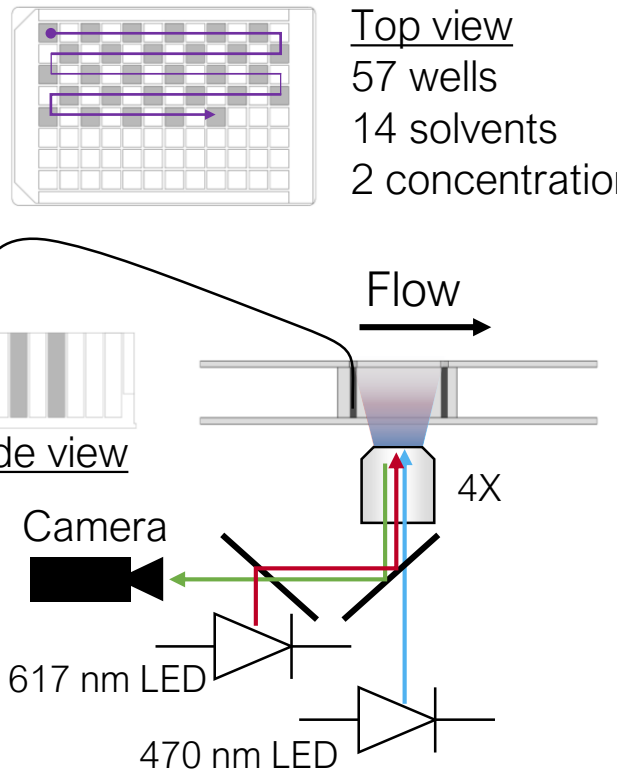




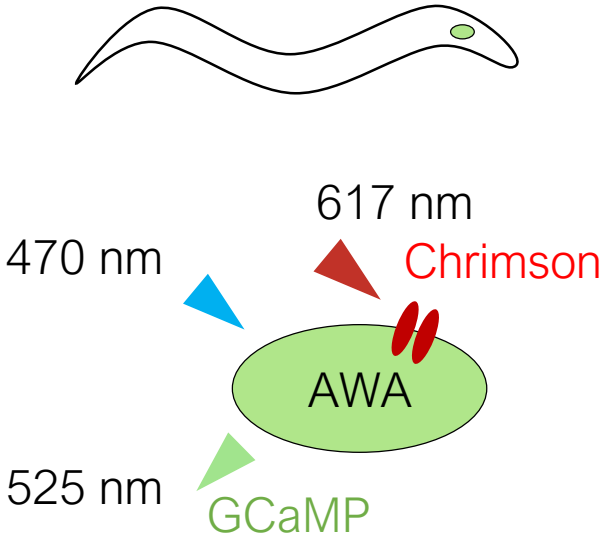
Lagoy, R.C., Albrecht, D.R. (2018) *In preparation.*
Lagoy, R.C., Albrecht, D.R. (2018) *Patent pending.*

Experiment: to identify acute modulators of calcium activity in whole-organisms

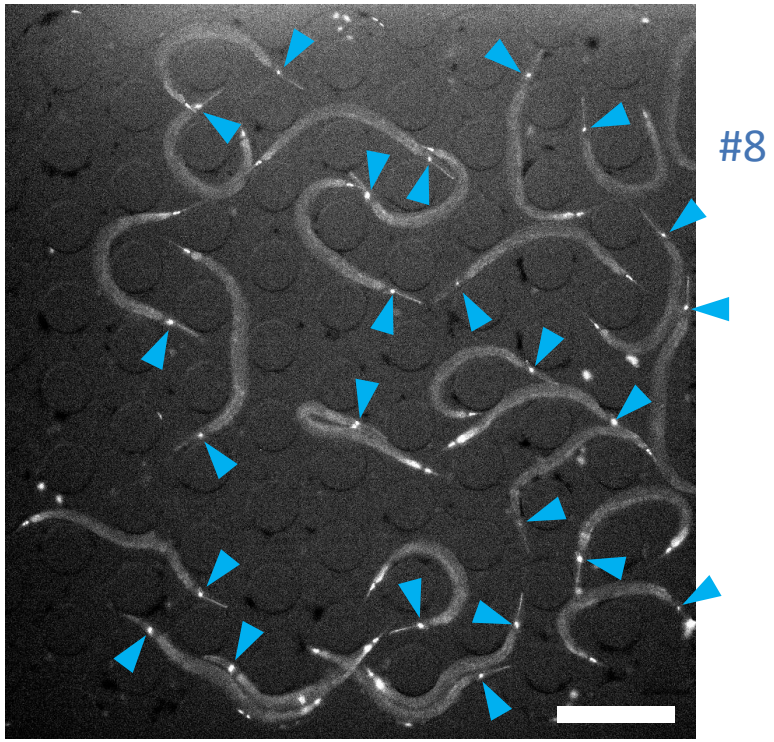
Set-up for flow of different compounds past the animals while stimulating and recording with light



Each animal co-expresses GCaMP and Chrimson in the same neuron



~20 animals immobilized for stimulation and recording of compound exposure responses



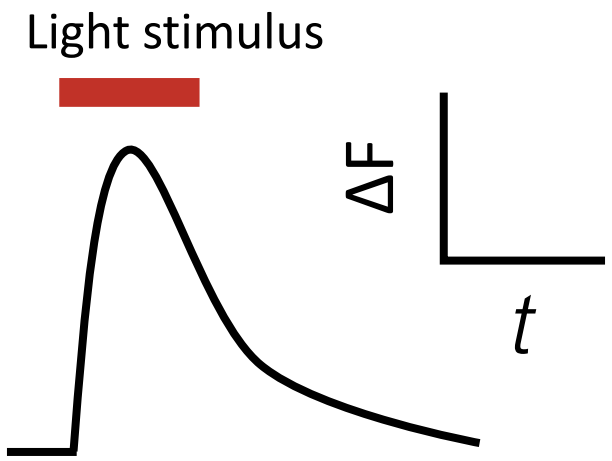
Outline: with a focus on data generation and methods for visulization

- Biological significance
  - Why? Where do the numbers come from?

- Format(ting) of the generated data
  - What is the recorded data structure?

- Method(s) to visualize these important numbers
  - What types of plots, colors, sizes, etc.
  - What numbers are most important?
  - What do the results tell us?
  - Can the data be interactive?

Data collection, type, and format of recorded individual animal neural traces



Camera/analysis output:
10 frames per second for 15 seconds
~20 animals
57 compounds (videos)

= 150 x 1140 matrix

$\Delta F/F_0$

Individual animal neuron

Frame (time)

	1	2	3	4	5
2	3440	3216	3660	1269	34
3	3619	2989	3639	1548	38
4	3295	3329	3815	1423	41
5	3875	3230	3916	1594	33
6	3909	3311	3760	1432	40
7	3504	3276	3898	1601	36
8	4255	3160	4134	1358	43
9	3681	3919	4467	1240	45
10	4316	3450	4200	1758	45
11	4673	3794	4367	1415	44
12	4623	3935	4475	1426	50
13	4973	3749	4609	1414	47

… 20 x 57 traces

⋮ 150 frames

Outline: with a focus on data generation and methods for visulization

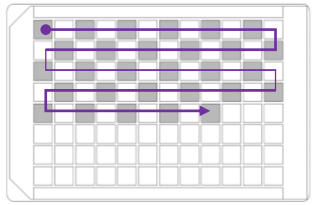
- Biological significance
  - Why? Where do the numbers come from?
- Format(ting) of the generated data
  - What is the recorded data structure?
- Method(s) to visualize these important numbers
  - What types of plots, colors, sizes, etc.
  - What numbers are most important?
  - What do the results tell us?
  - Can the data be interactive?

Experimental recap

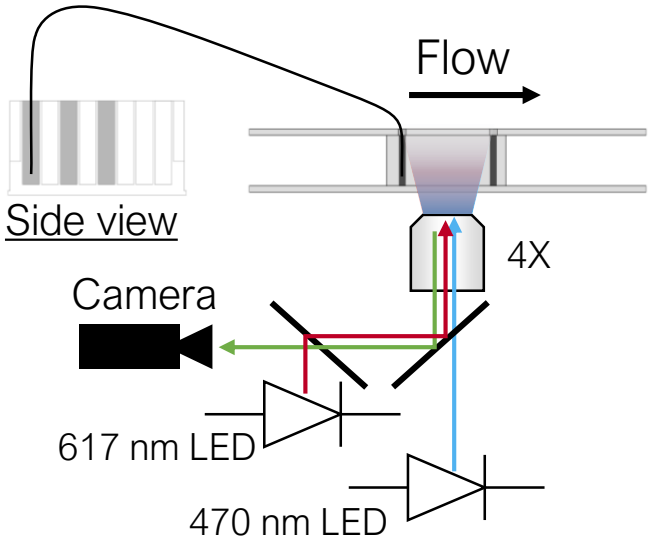
Flow 57 different compounds past the animals while stimulating and recording with light.

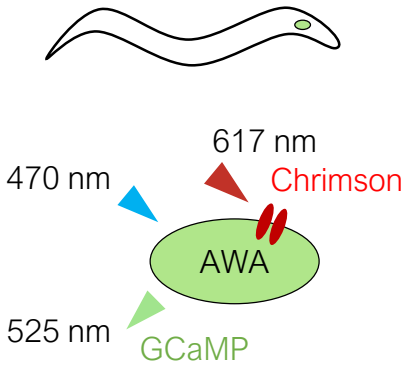
Most chemical libraries are stored in solvents such as DMSO for solubility and chemical stability, yet some show acute suppressive effects on neurons, while chronic exposure can lead to abnormal organism development.

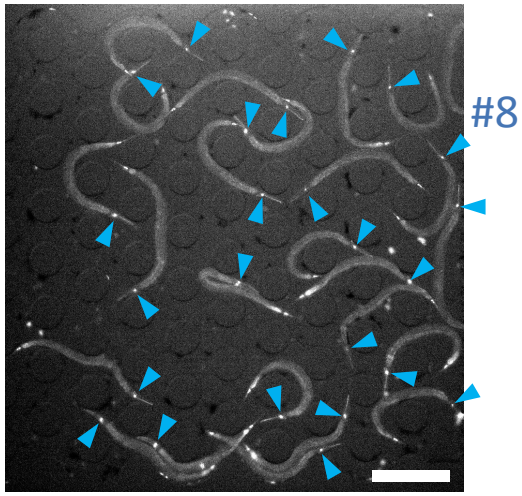
Therefore, assessment of solvent effects is important before screening commercial small-molecule libraries.



Top view
57 wells
14 solvents
2 concentrations





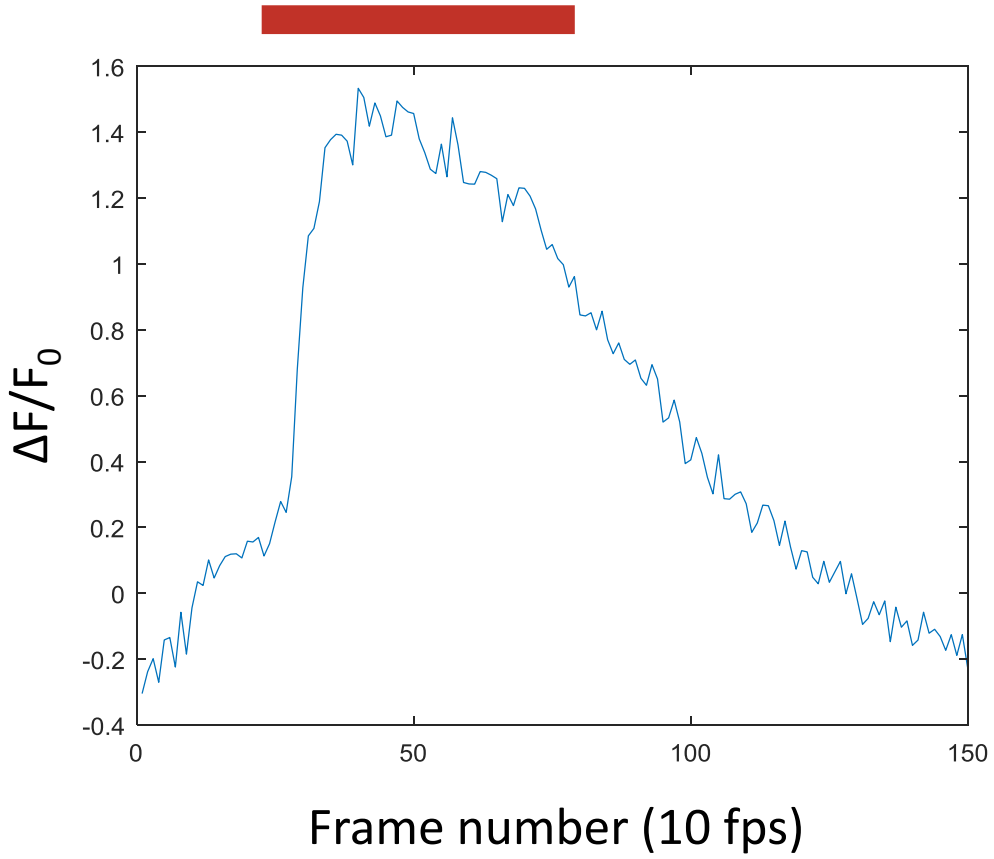


500 µm

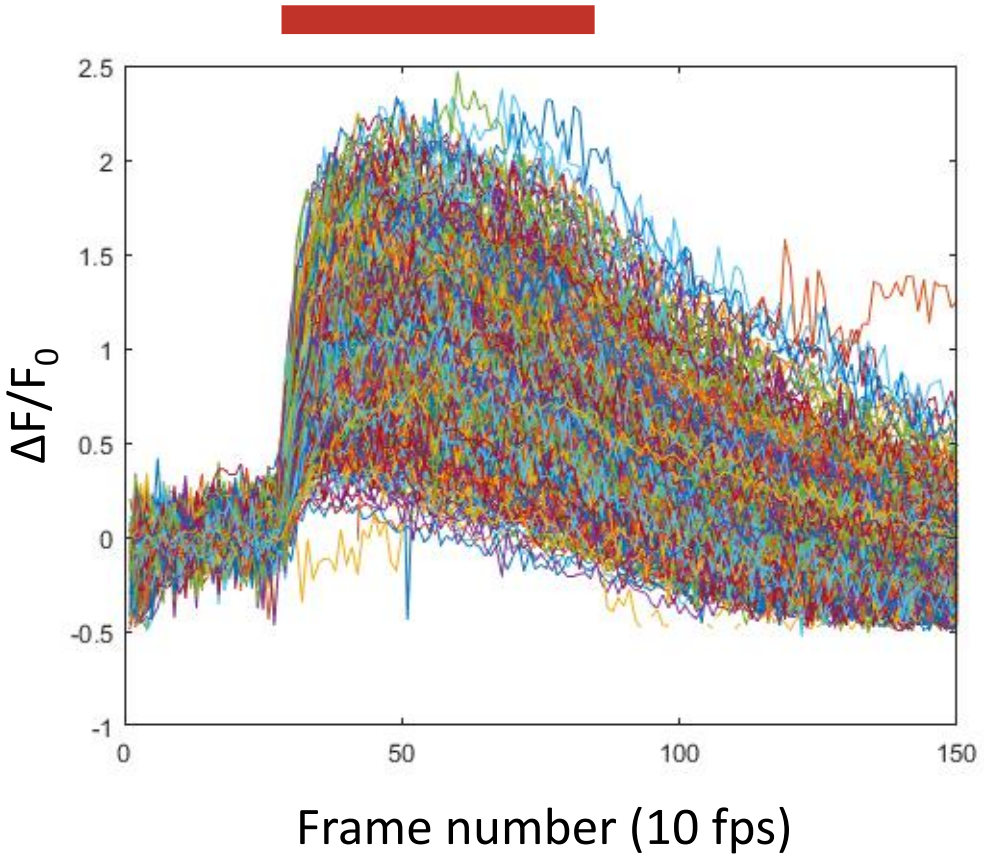
Looking at all of the neural response traces…

One animal, one exposure

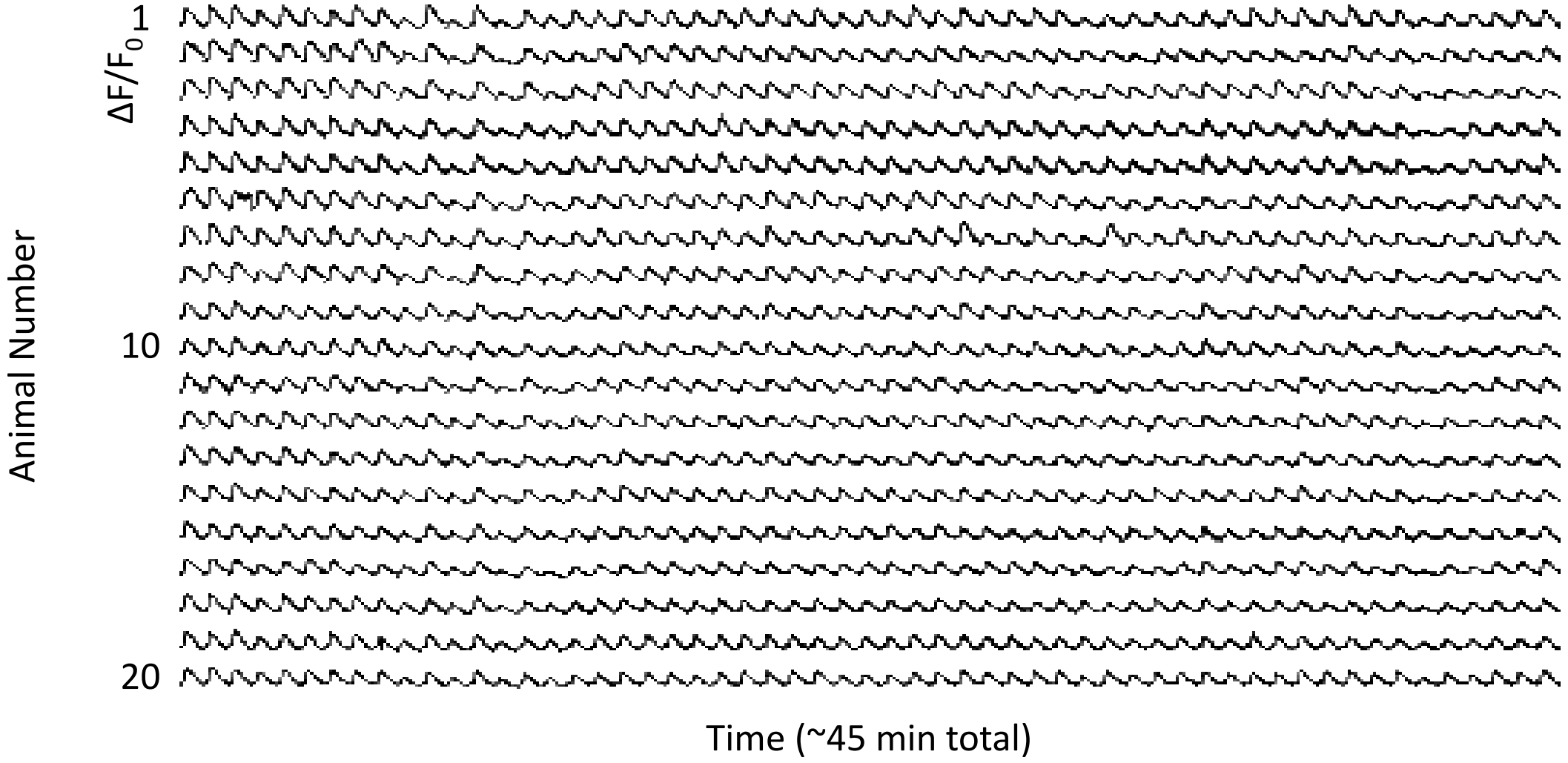
Light stimulus



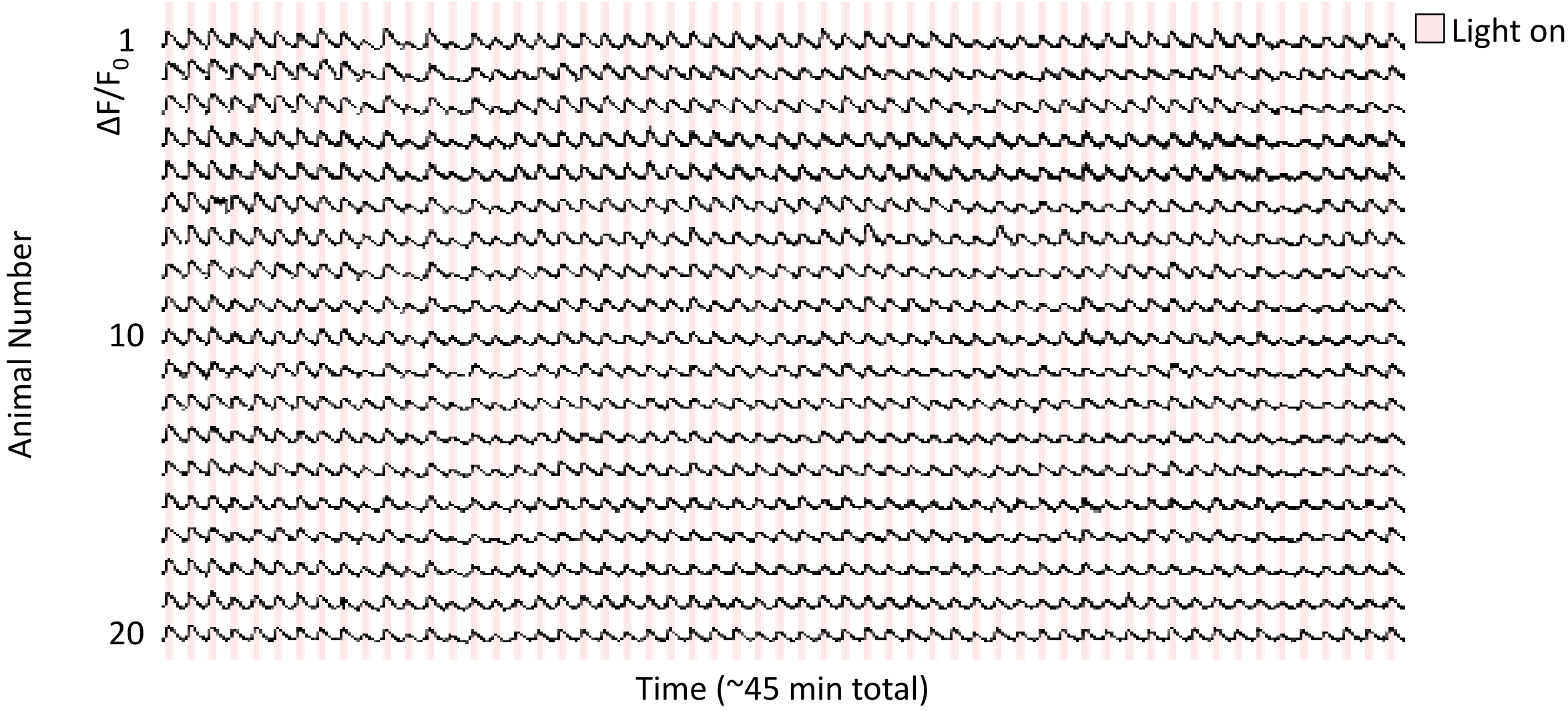
All 20 animals, all 57 exposures



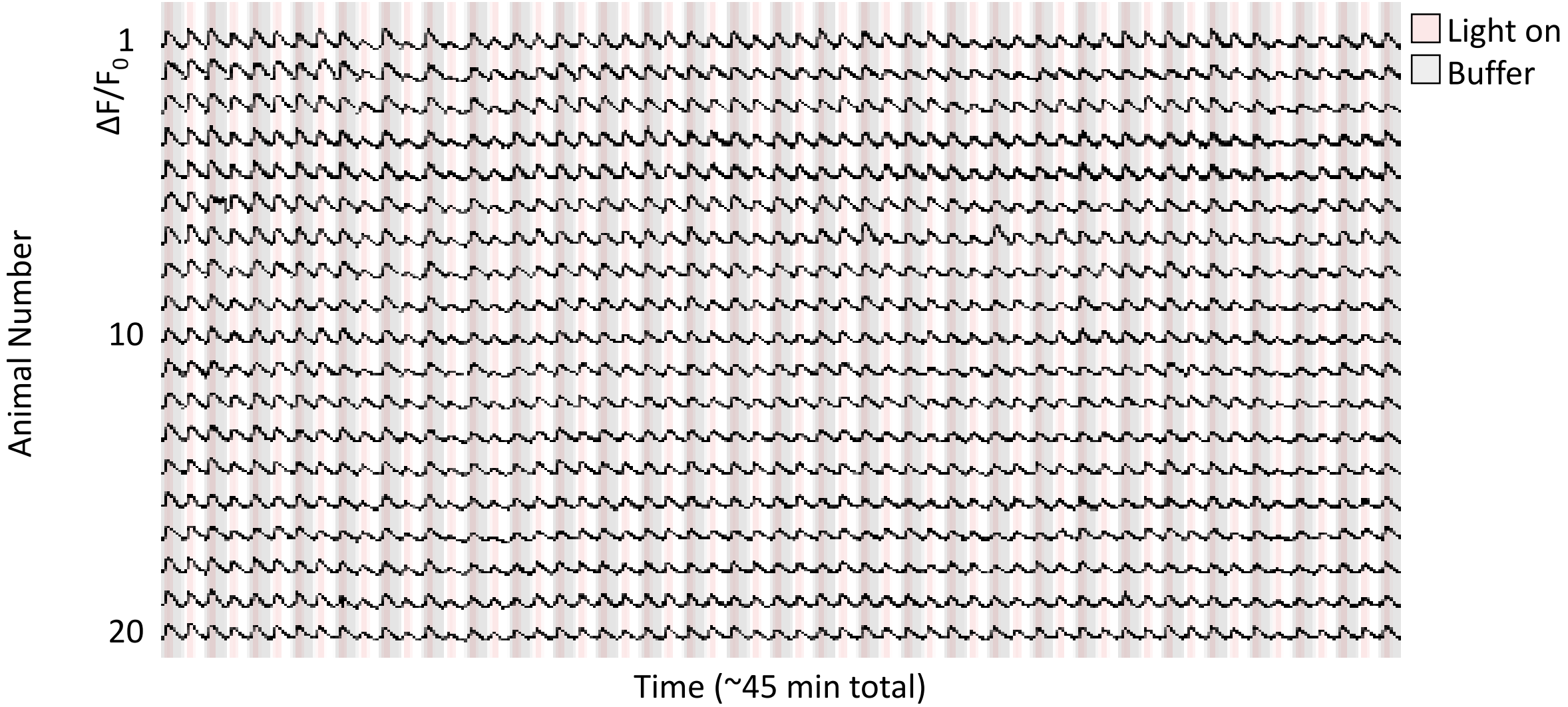
Separating and arranging the data into a matrix



Separating and arranging the data into a matrix ***with stimuli bars***

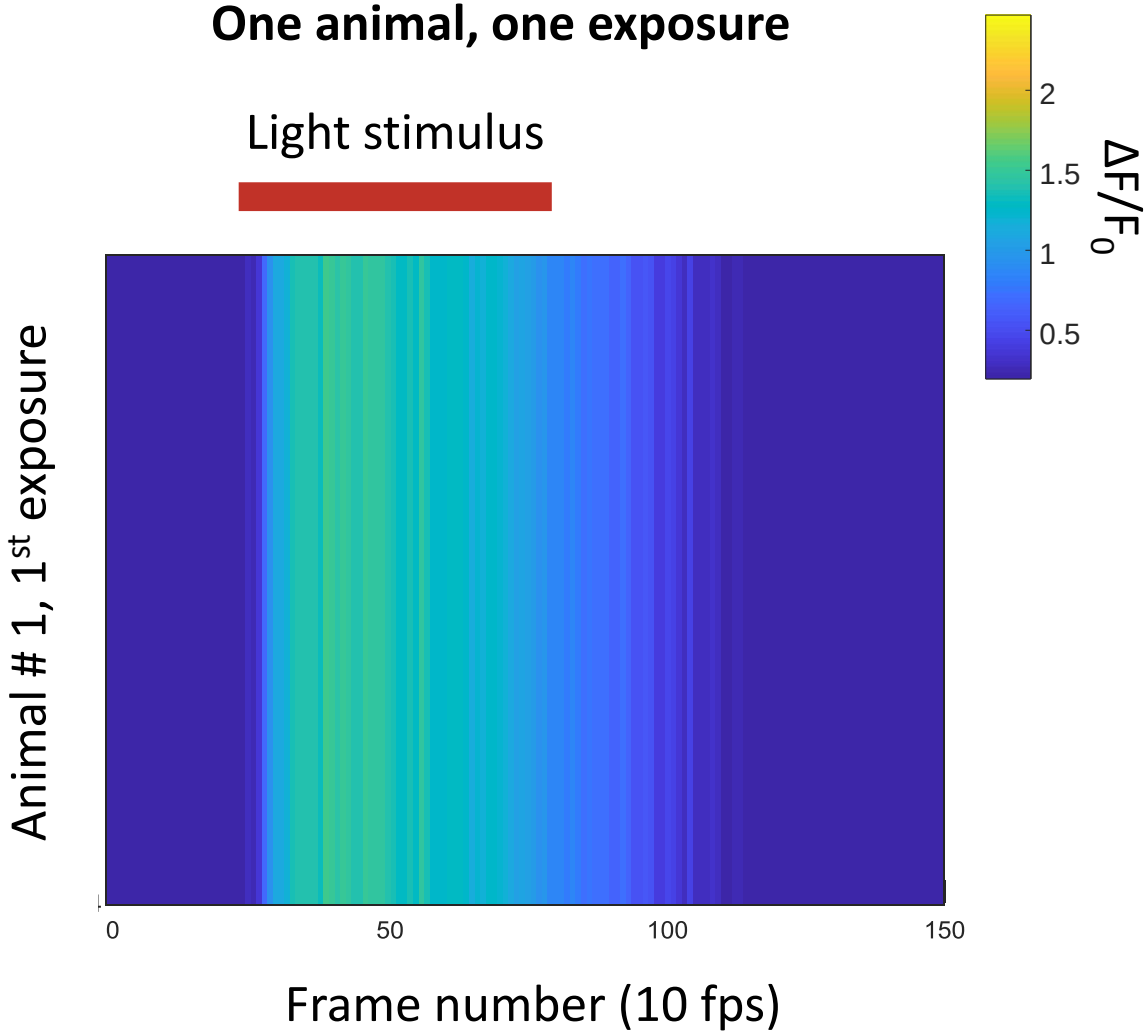


Separating and arranging the data into a matrix ***with stimuli bars and buffer wells***

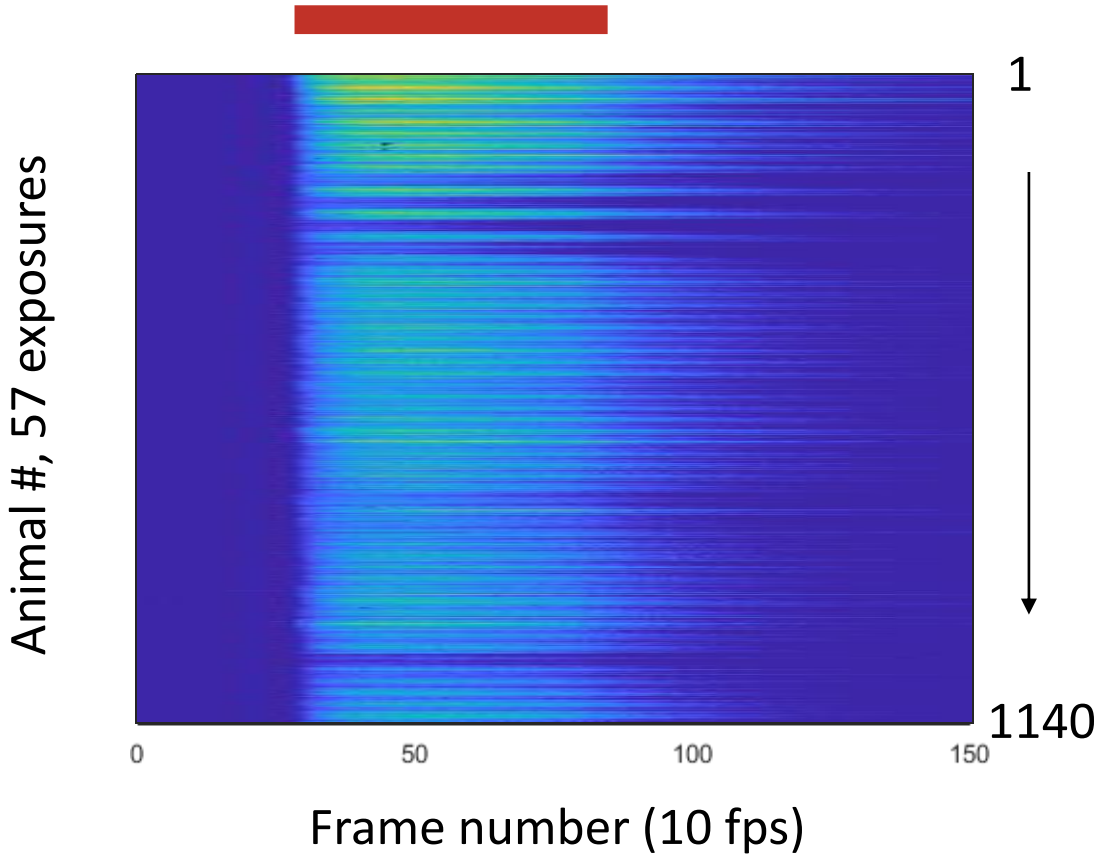


Looking at all of the neural response traces… Do heatmaps help?

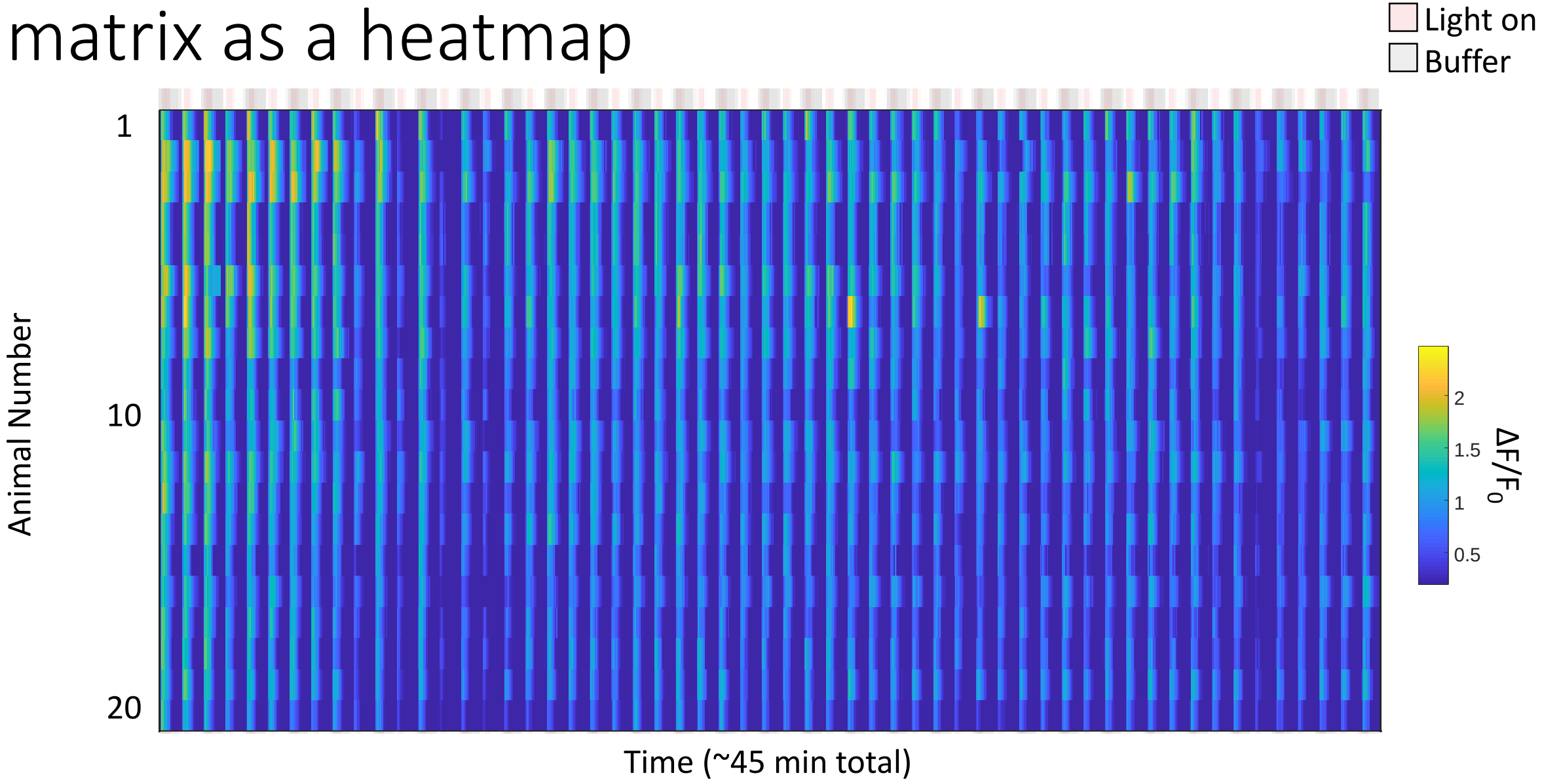
One animal, one exposure



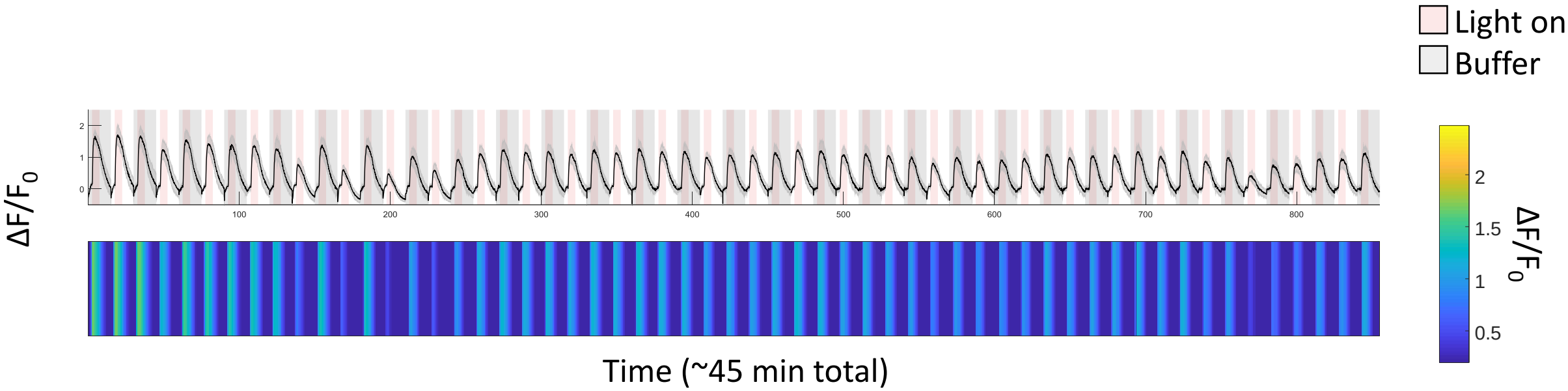
All 20 animals, all 57 exposures



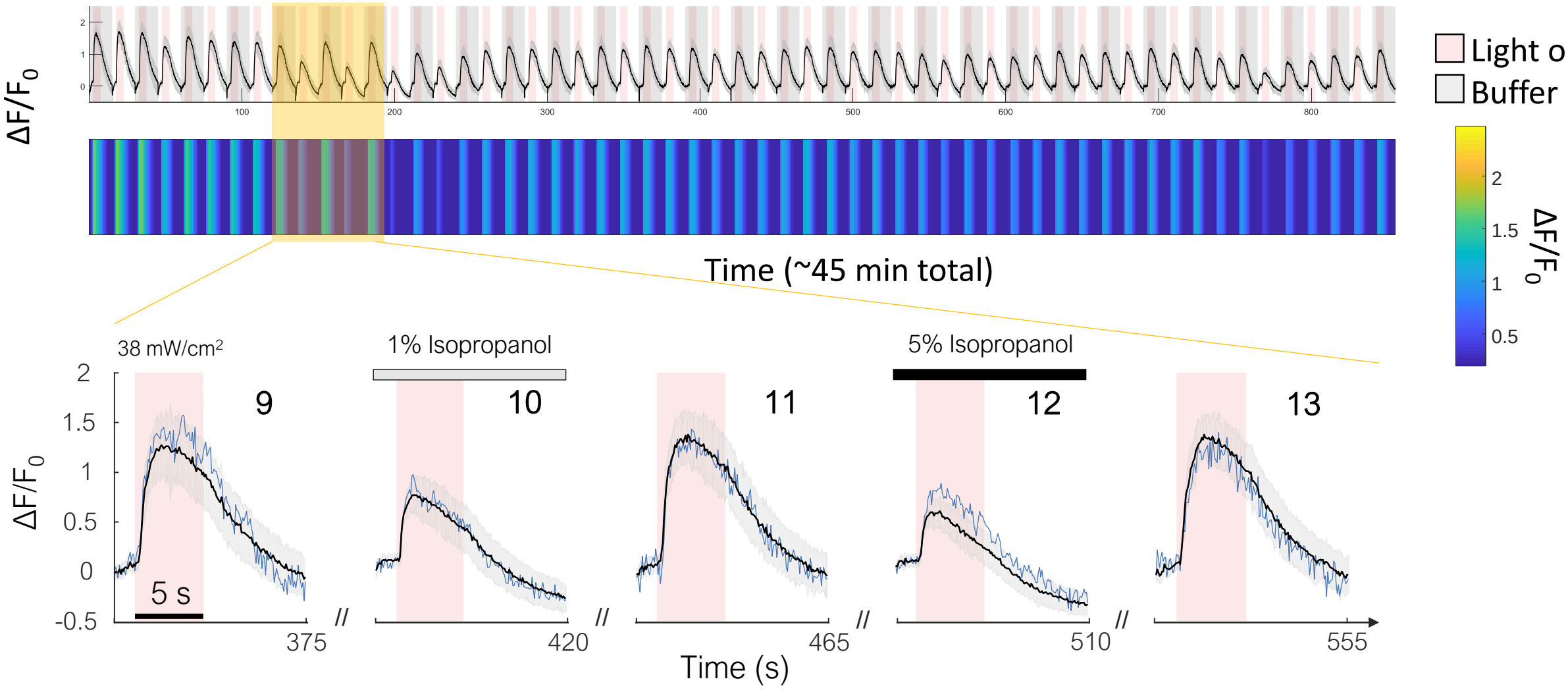
Separating and arranging the data into a matrix as a heatmap



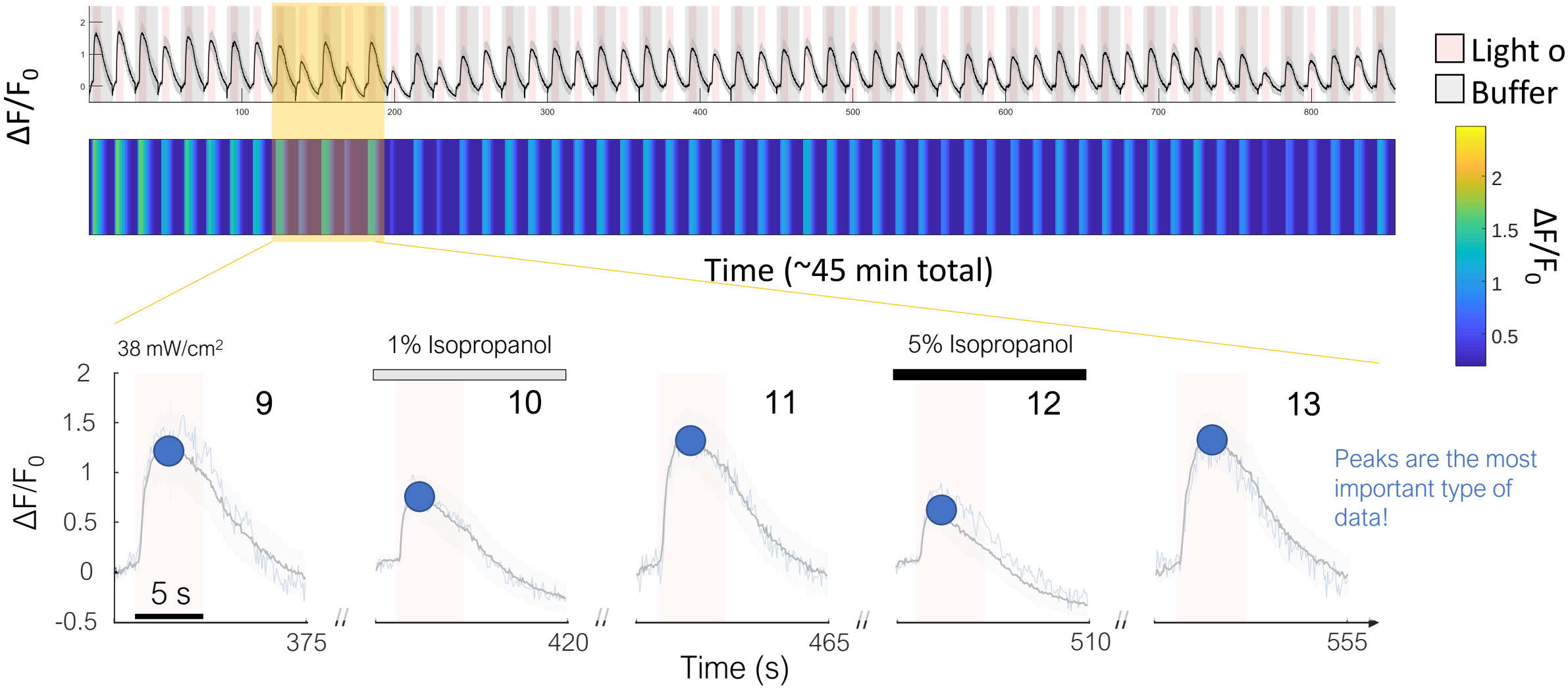
Averaging all 20 animals across all 57 exposures as a trace and heatmap



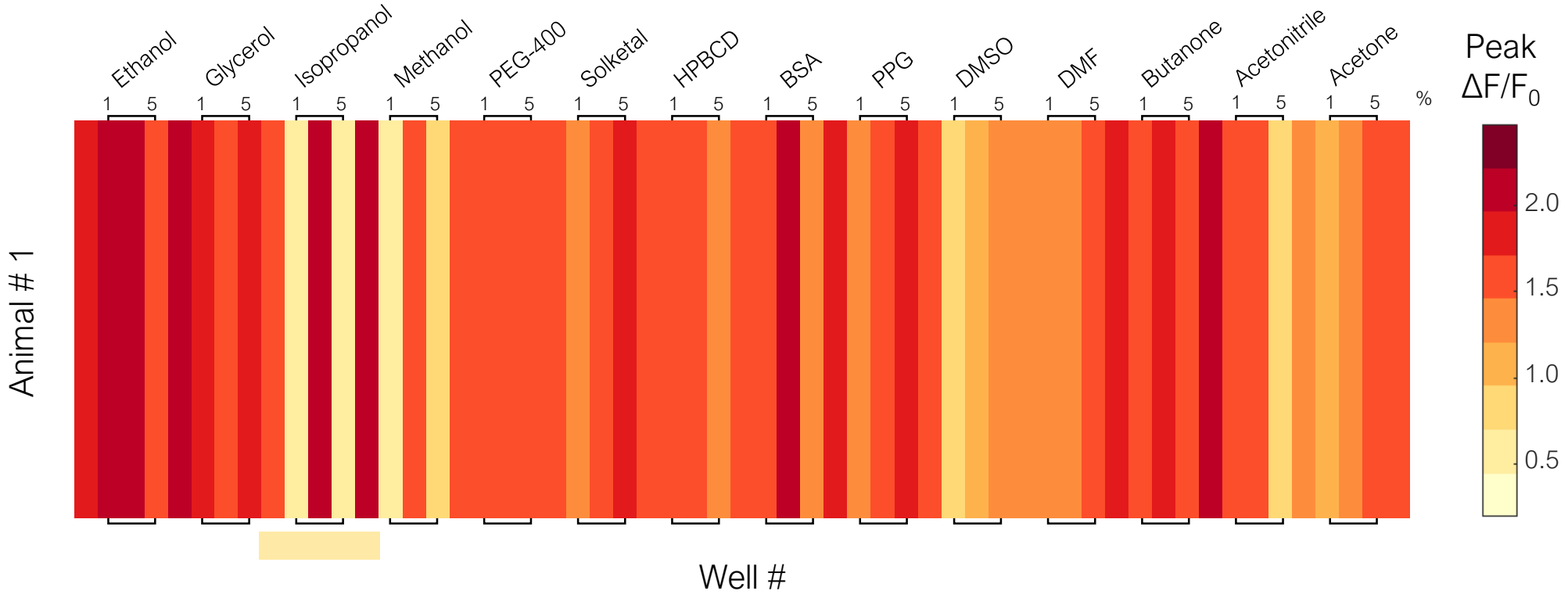
Averaging all 20 animals across all 57 exposures



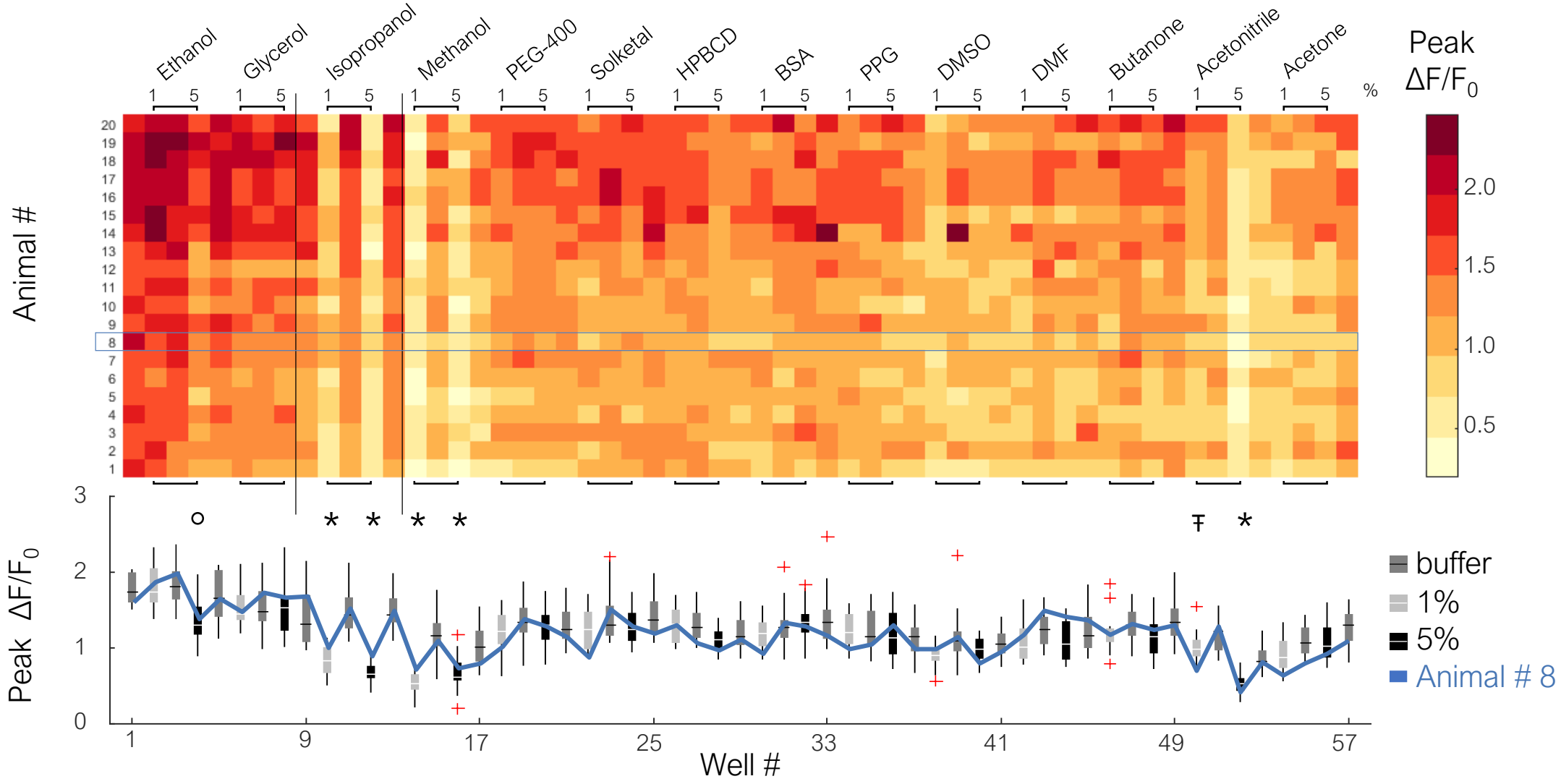
Averaging all 20 animals across all 57 exposures



A heatmap of peak neural responses from 1 animal traces and all 57 exposures



A heatmap, boxplot, and individual animal from all 1140 peak neural responses



Using d3js to visualize and interact with the data…

http://users.wpi.edu/~rosslagoy/hmv.html

What is the biological significance of this result?

- In our assay, even brief, <1 min exposures of 1% and 5% methanol, isopropanol, and acetonitrile suppressed optogenetically-activated neural activity, as did 5% ethanol.
- Since activation and neural response were in the same neurons, the observed response suppression reflects intracellular interference by these solvents.
- Although acute solvent effects were transient, these results strongly suggest that careful selection of solvents is prudent when preparing and selecting drug screen libraries for neural effects.

Are there other ways to visualize this data?

Thanks for your attention!

Any questions?

rosslagoy@wpi.edu