

Teaching Neurons—Functional Programming of Human Stem- Cell Derived Neuronal Networks with External Cues

Derrick Lin

Michael Vu

February 5th, 2024



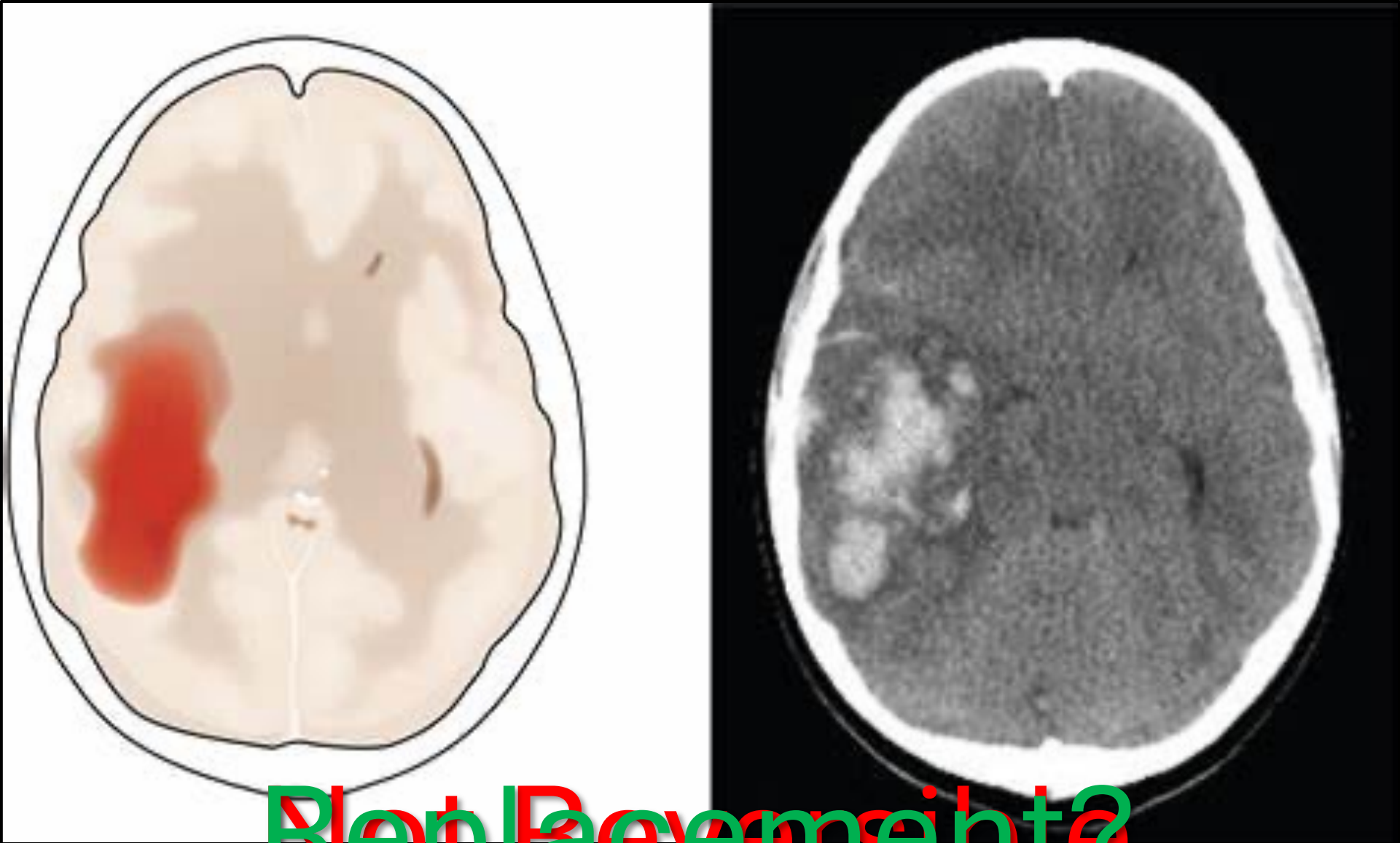
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STEM CELL RESEARCH CENTER
UNIVERSITY of CALIFORNIA • IRVINE



**Department of
Biomedical
Engineering**

Approvals

- This project received approval from the Human Stem Cell Research Oversight (HSCRO) committee at UCI.



Reversible?

Current State of Clinical Neurorestorative Therapies

- Stem-cell based therapies are a promising approach to many neurological diseases...

Clinical Trial > [Lancet Neurol](#). 2017 May;16(5):360-368. doi: 10.1016/S1474-4422(17)30046-7.

Epub 2017 Mar 17.

Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial

David C Hess¹, Lawrence R Wechsler², Wayne M Clark³, Sean I Savitz⁴, Gary A Ford⁵, David Chiu⁶, Dileep R Yavagal⁷, Ken Uchino⁸, David S Liebeskind⁹, Alexander P Auchus¹⁰, Souvik Sen¹¹, Cathy A Sila¹², Jeffrey D Vest¹³, Robert W Mays¹⁴

Clinical Trial > [J Neurol Neurosurg Psychiatry](#). 2020 Apr;91(4):396-401.

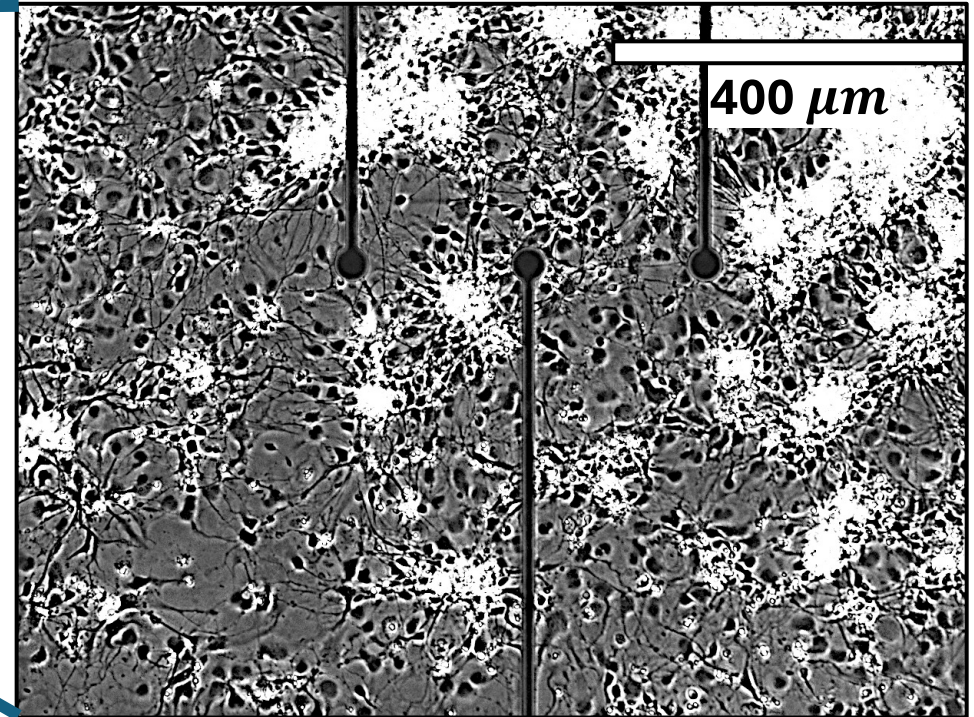
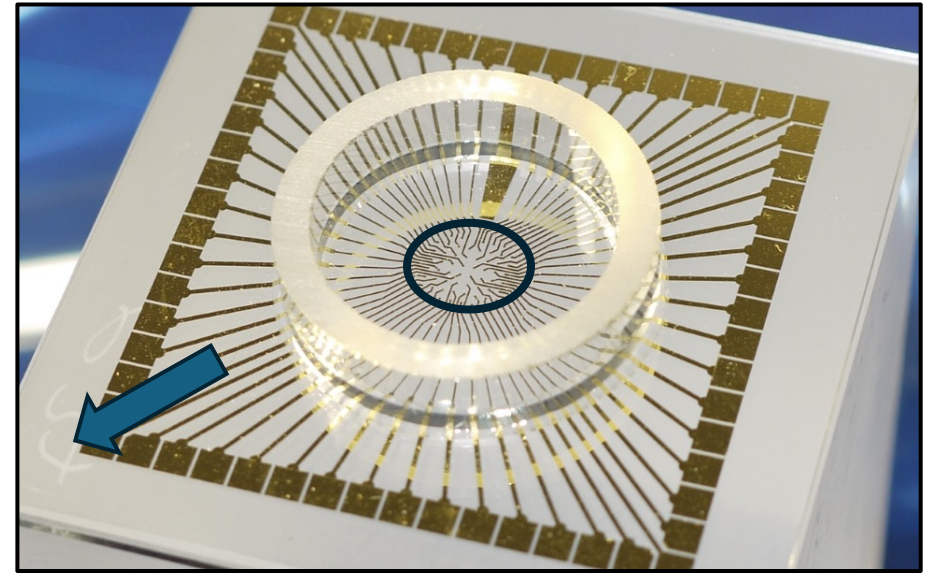
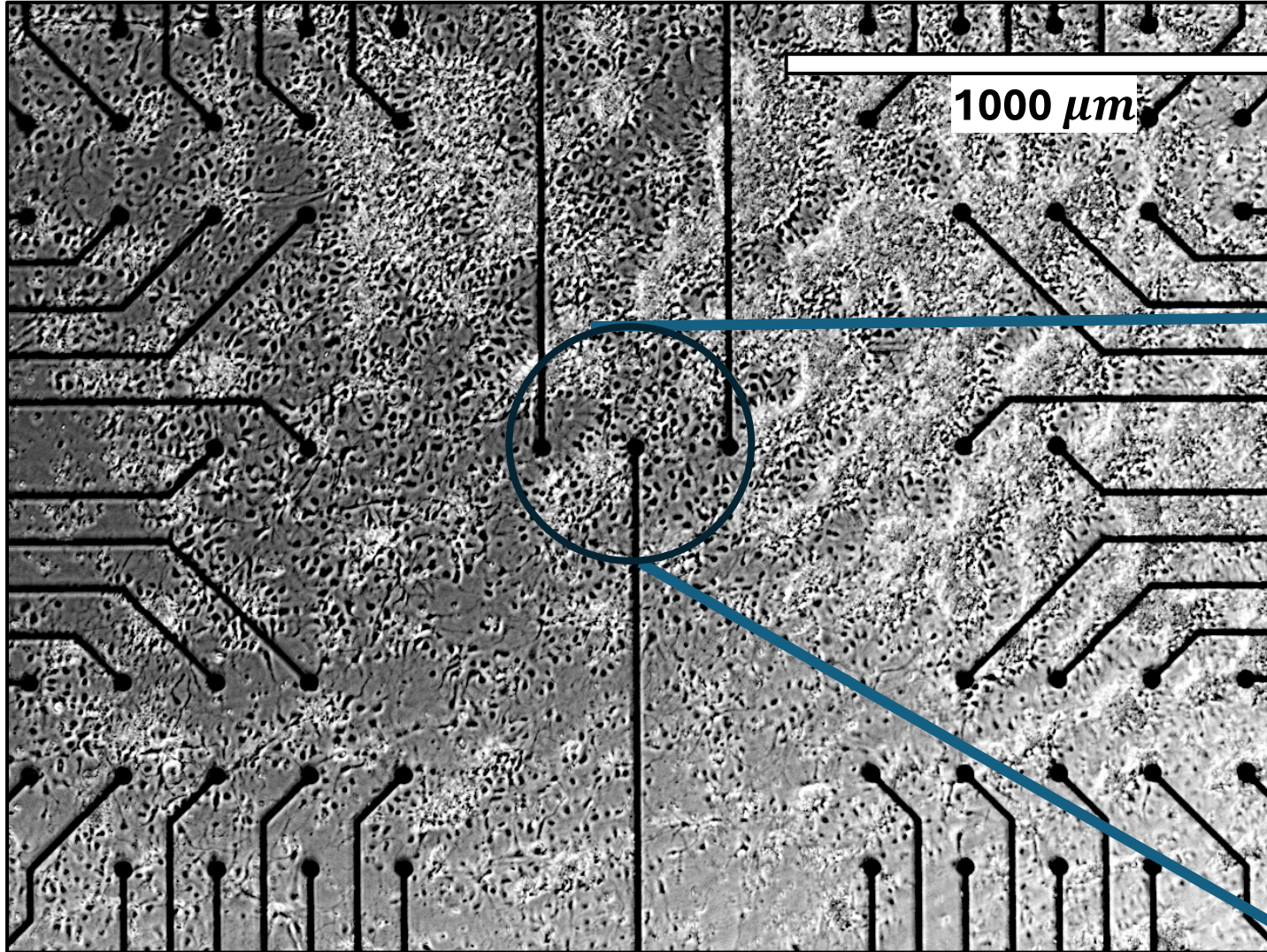
doi: 10.1136/jnnp-2019-322515. Epub 2020 Feb 10.

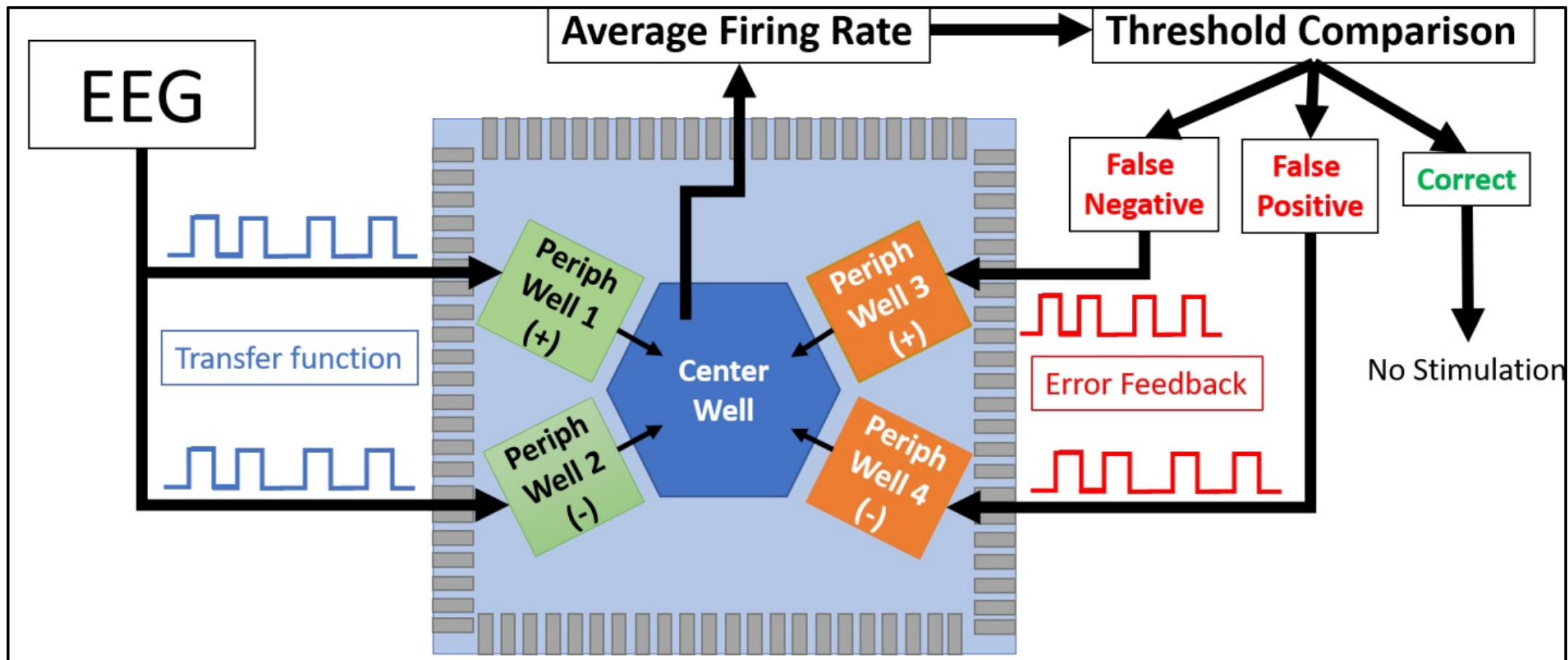
Intracerebral implantation of human neural stem cells and motor recovery after stroke: multicentre prospective single-arm study (PISCES-2)

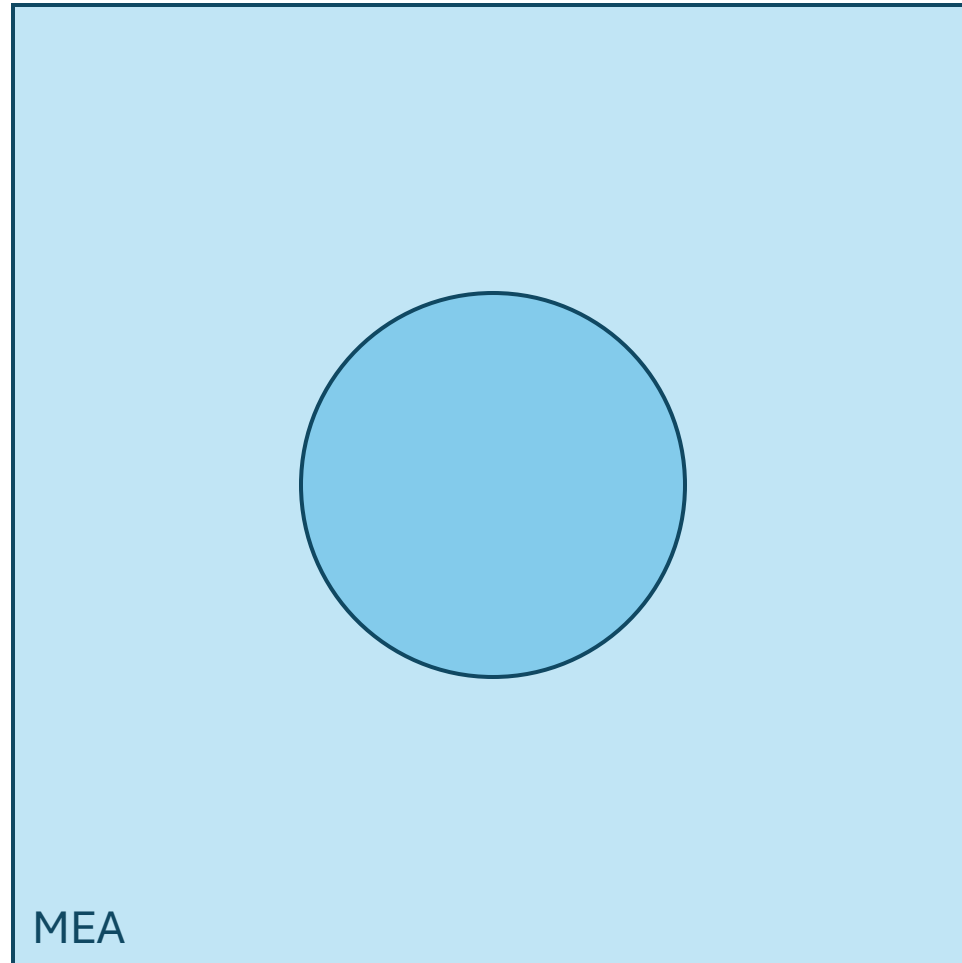
Keith W Muir¹, Diederik Bulters², Mark Willmot³, Nikola Sprigg⁴, Anand Dixit⁵, Nick Ward^{6 7}, Pippa Tyrrell⁸, Arshad Majid⁹, Laurence Dunn¹⁰, Philip Bath⁴, Julian Howell¹¹, Paul Stroemer¹¹, Kenneth Pollock¹¹, John Sinden¹¹

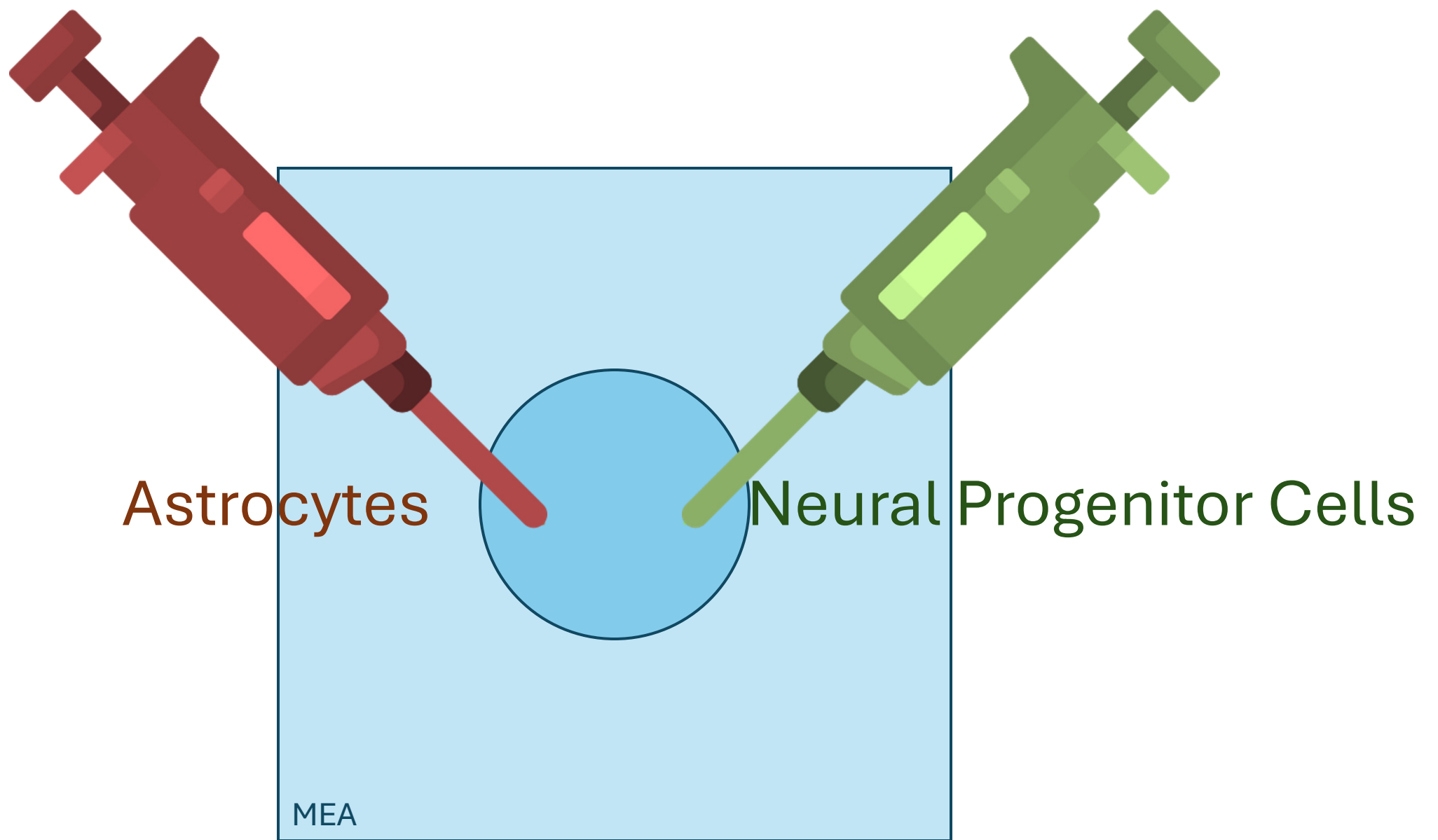
Not necessarily neurorestorative! Maybe need functional cues?

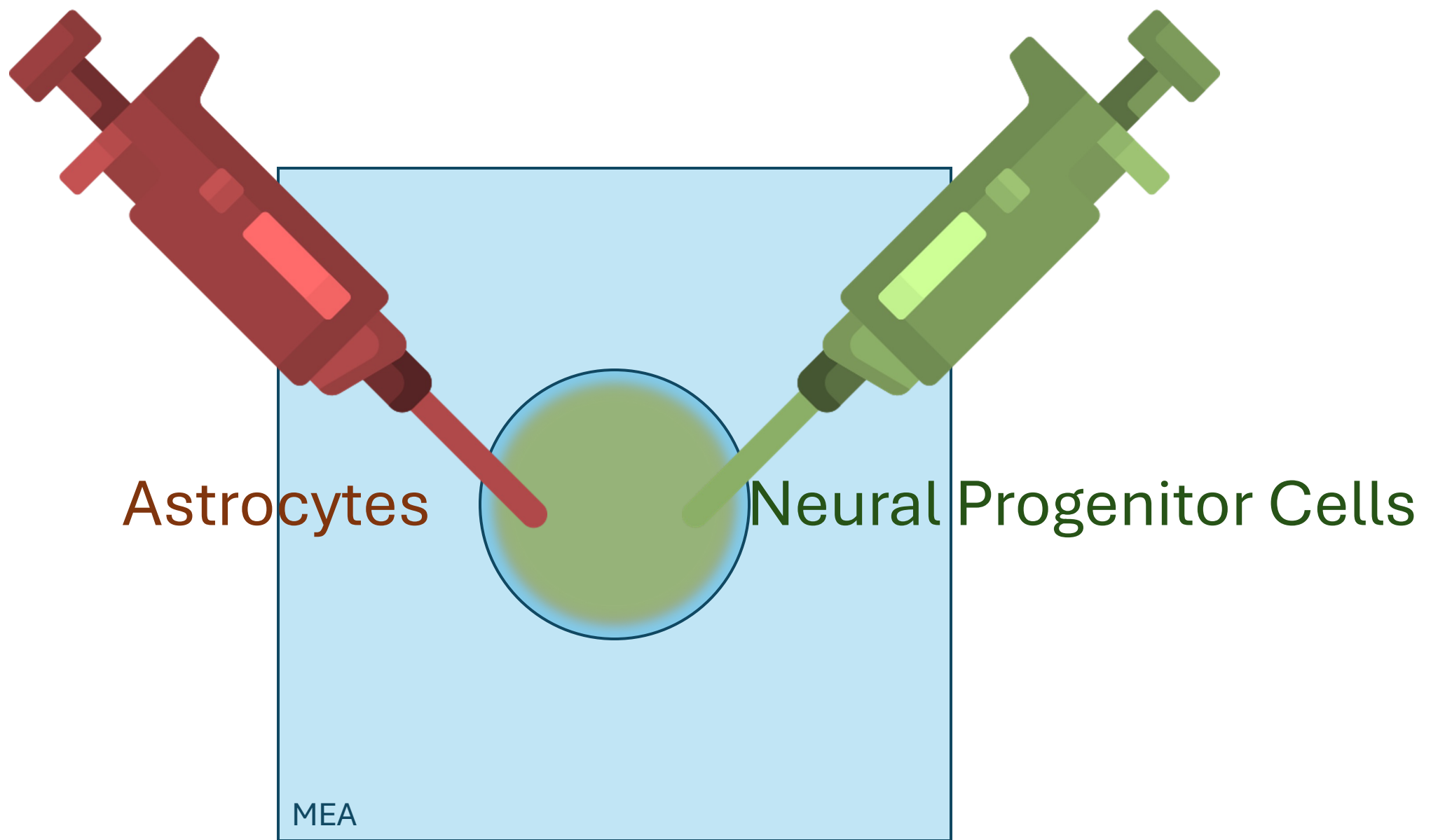
Microelectrode Arrays

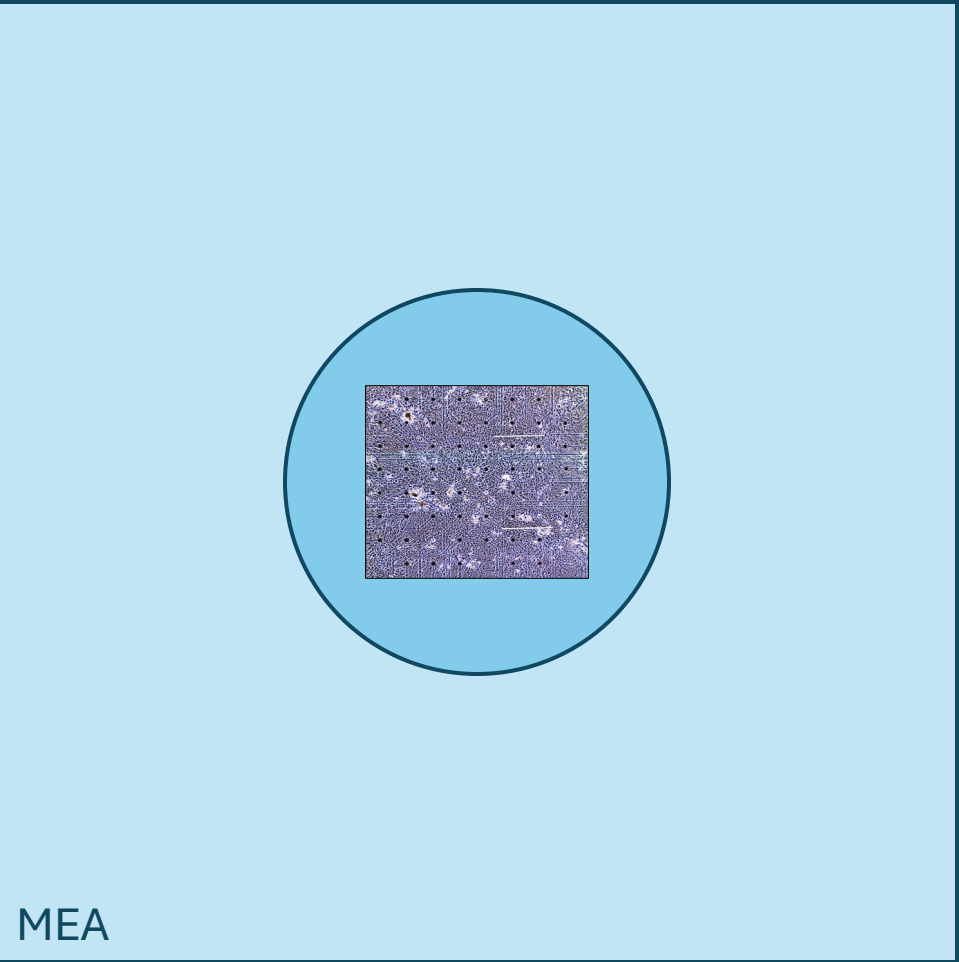


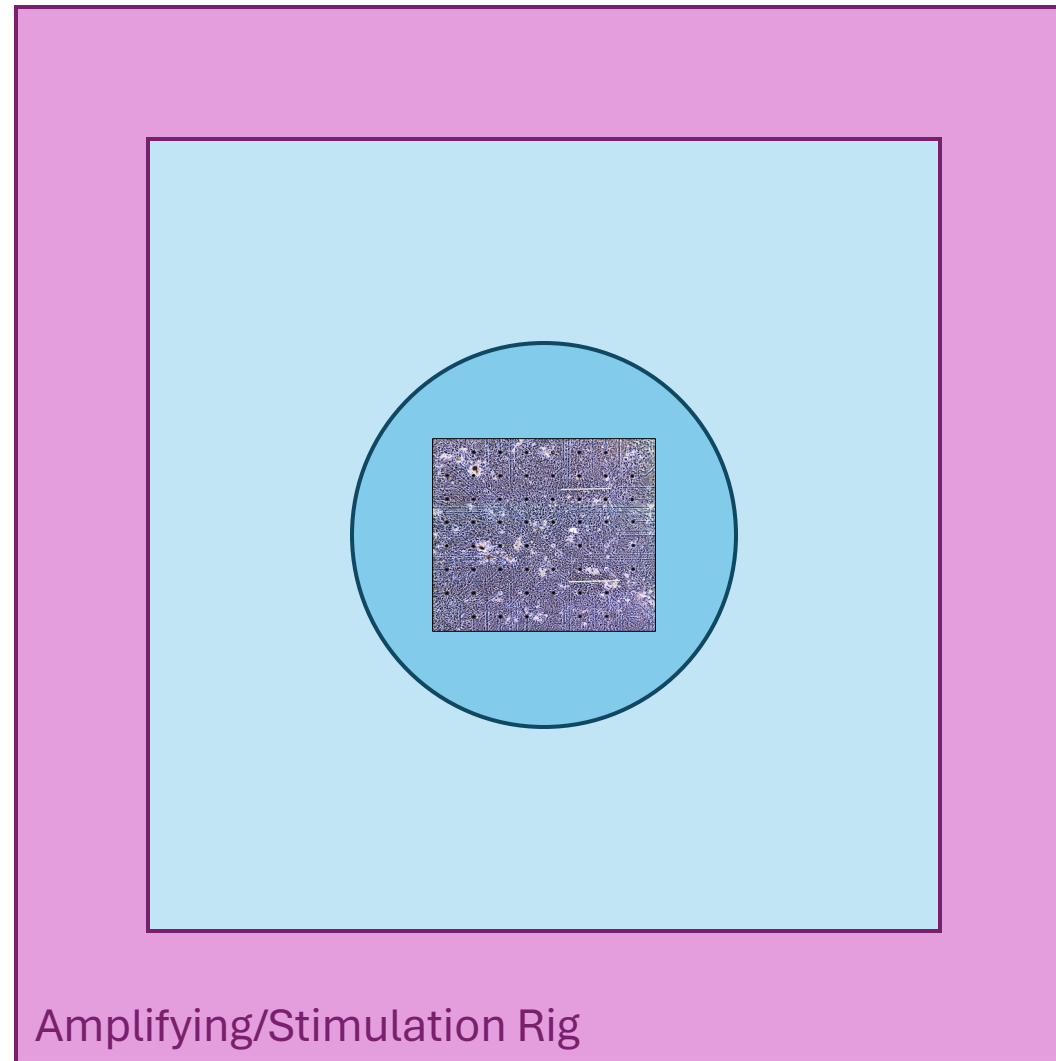




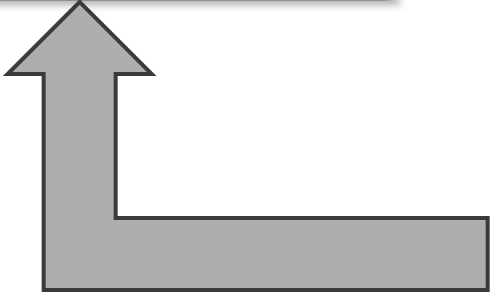




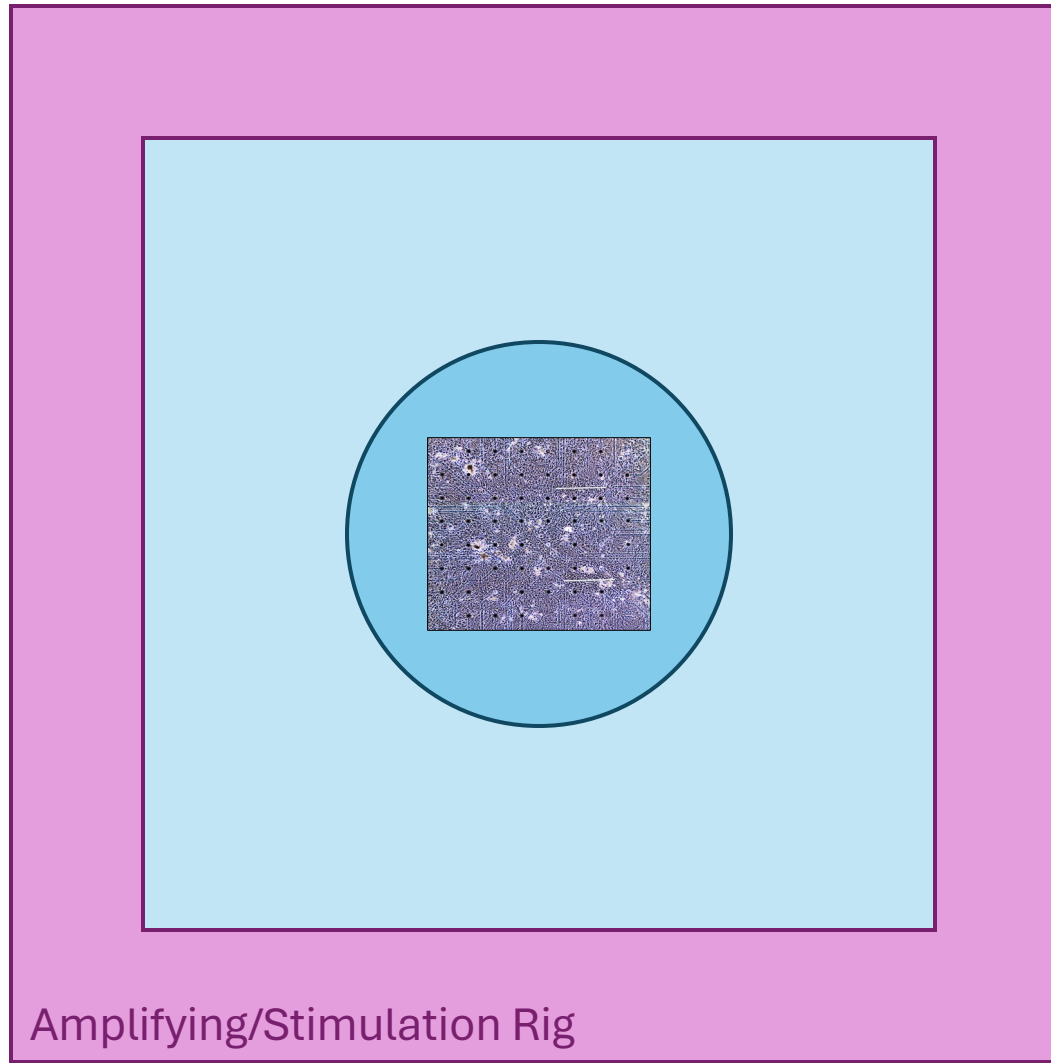


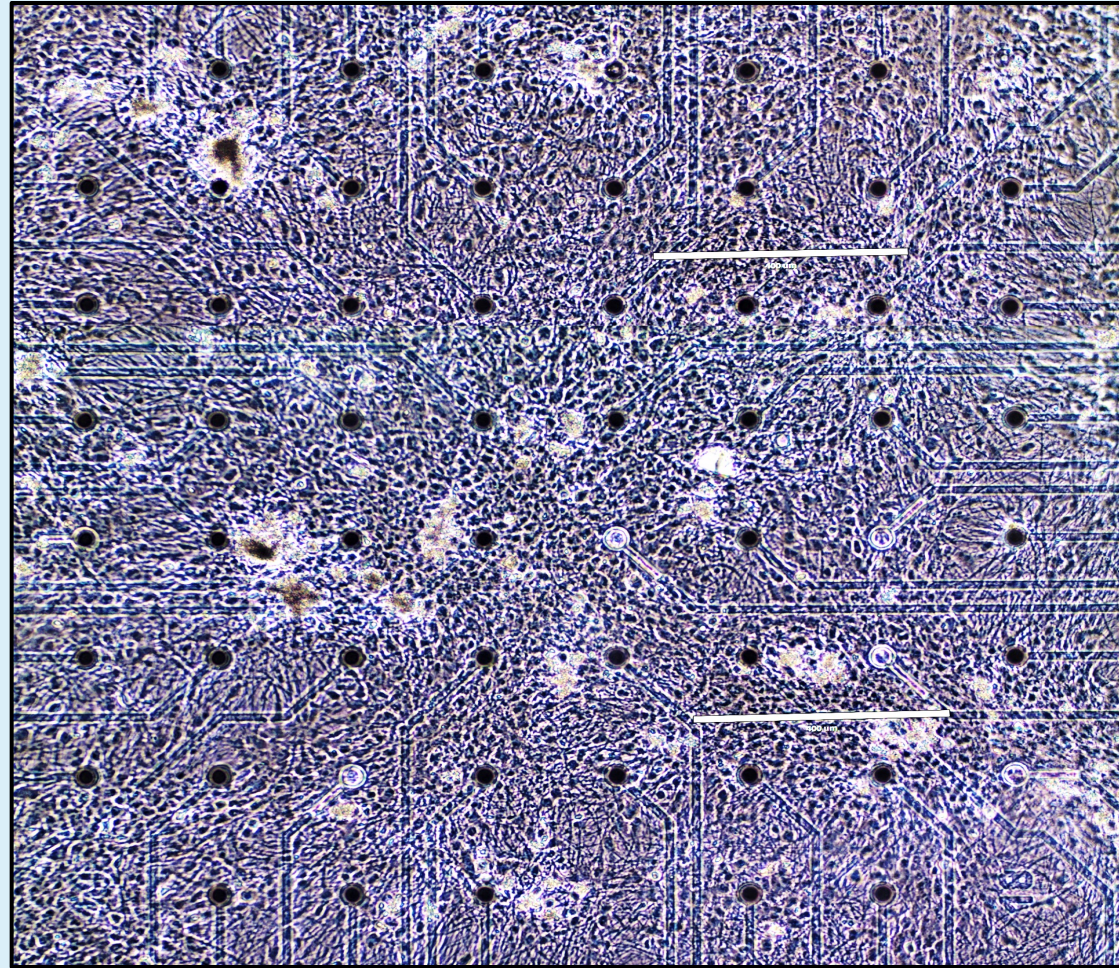


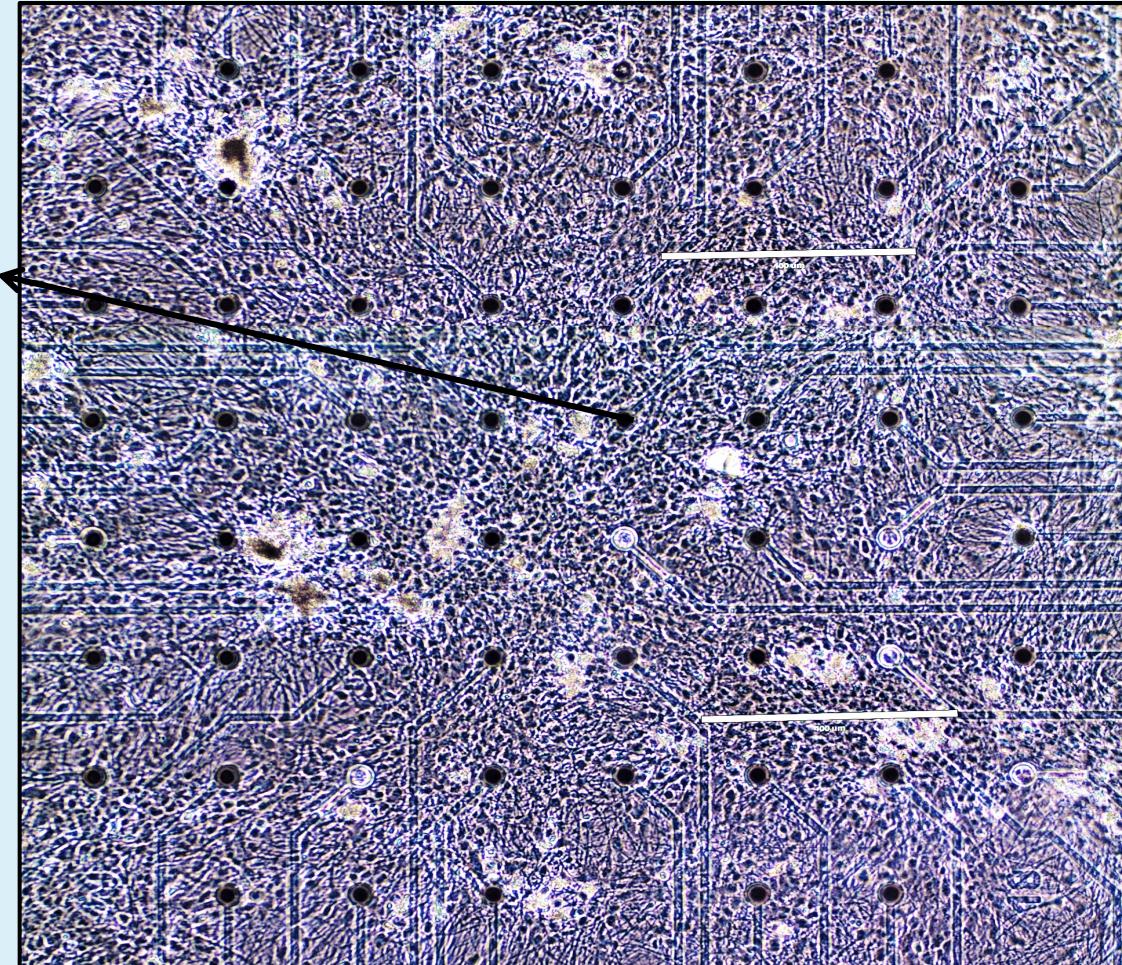
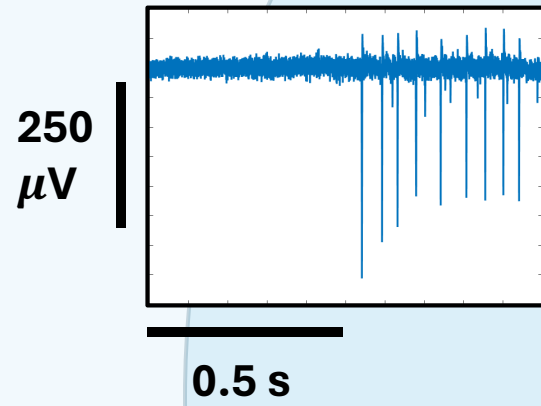
Stimulation

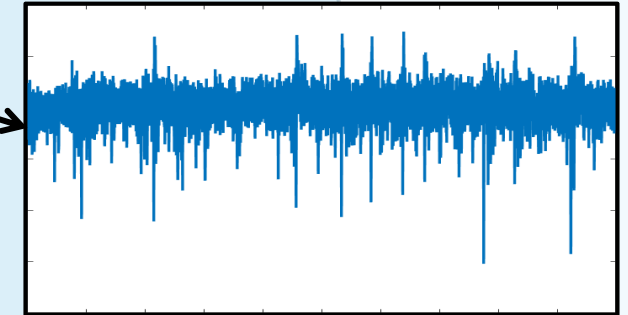
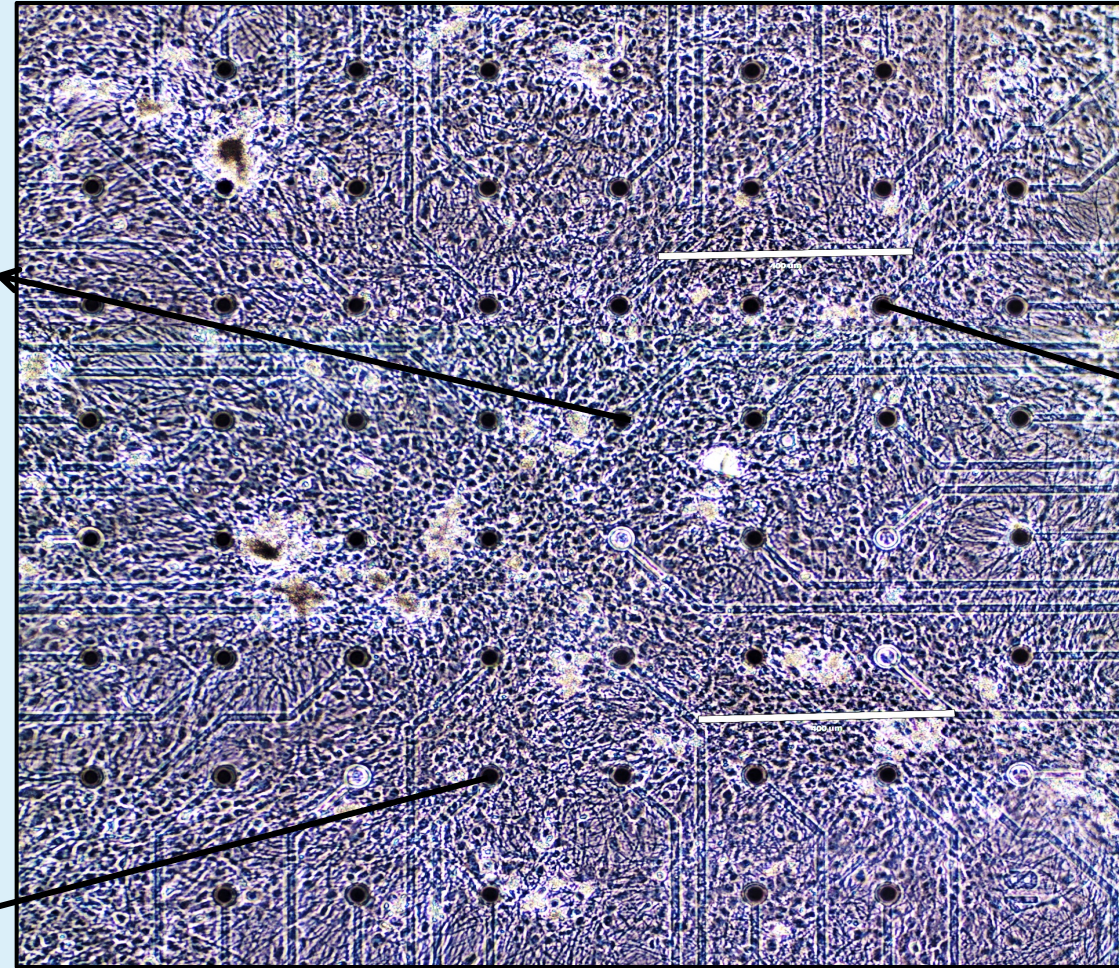
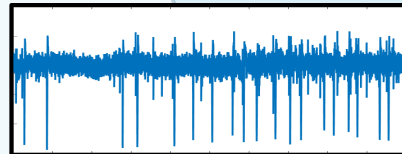
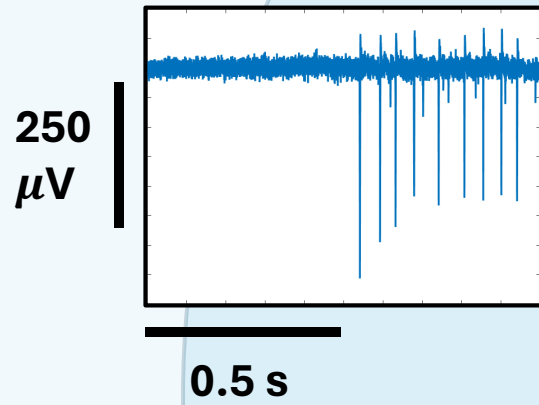


Recording

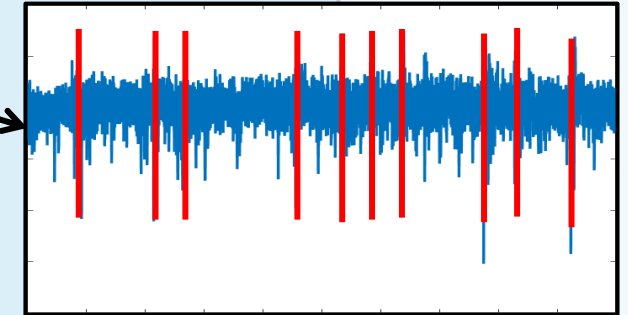
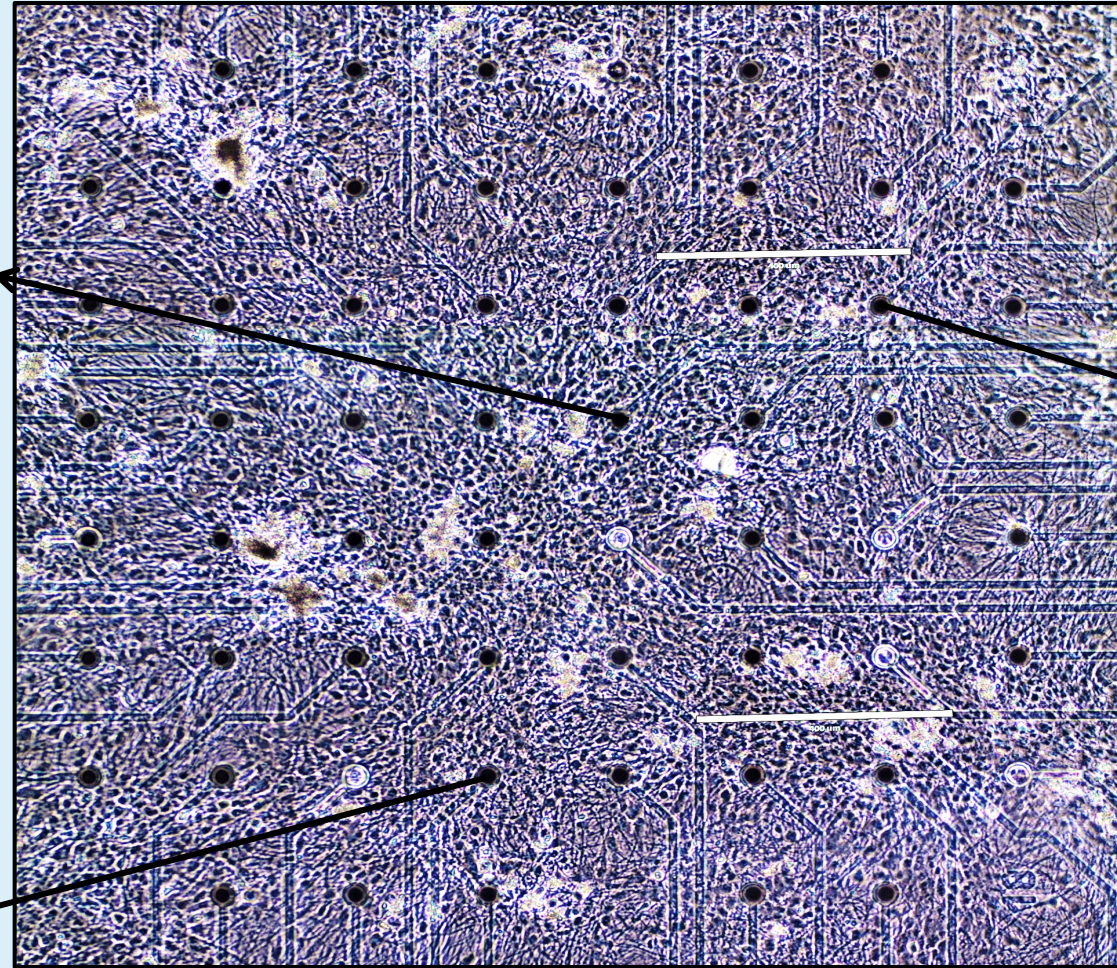
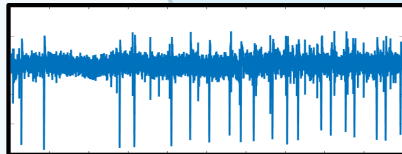
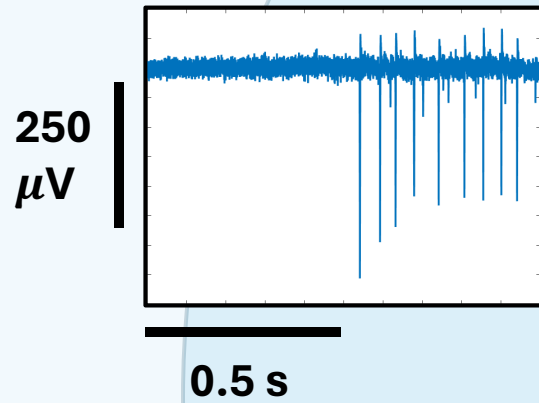








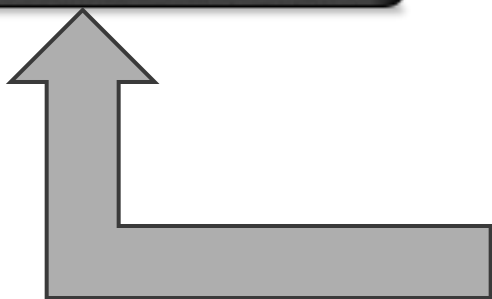
*spontaneous action potentials
(APs) observed at multiple
electrodes*



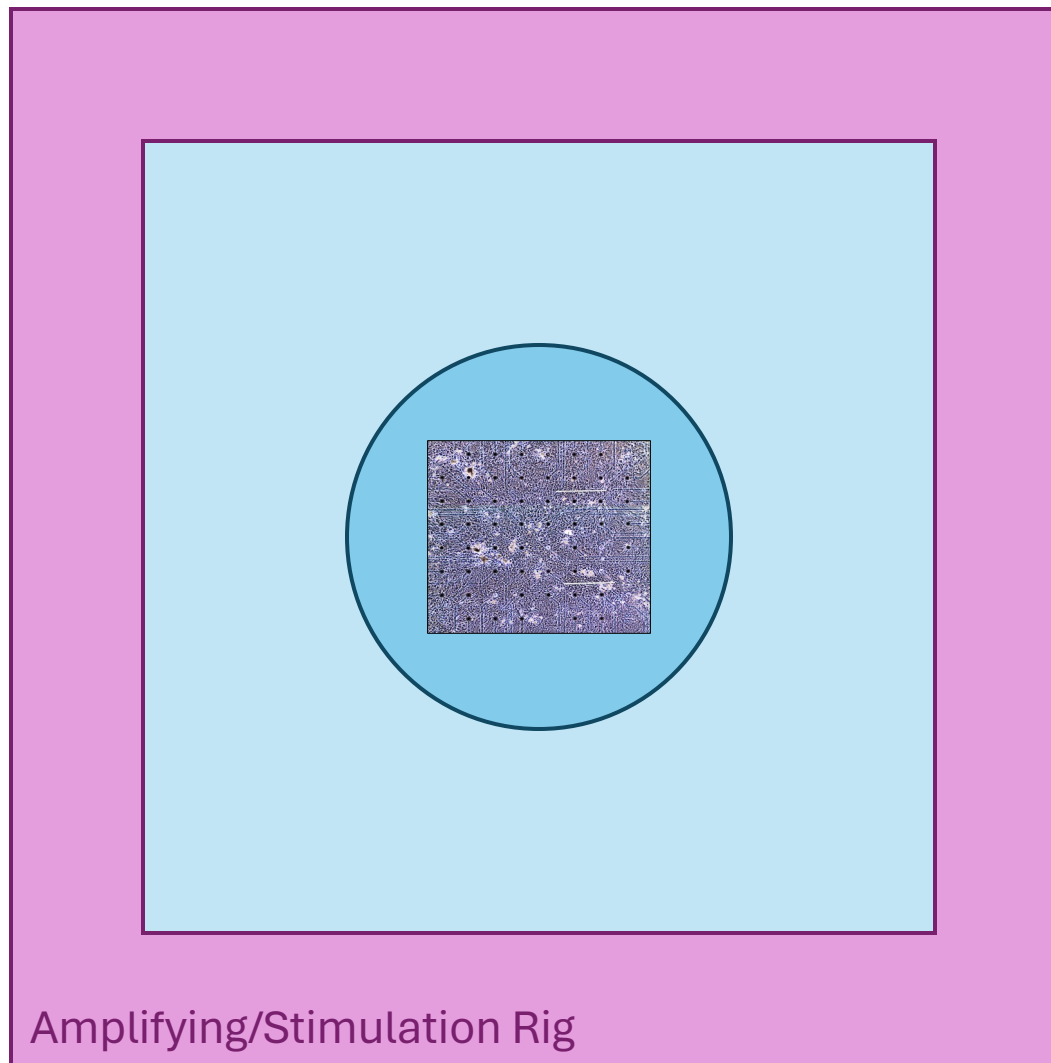
Applying spike detection, we can generate raster plots

*spontaneous action potentials
(APs) observed at multiple
electrodes*

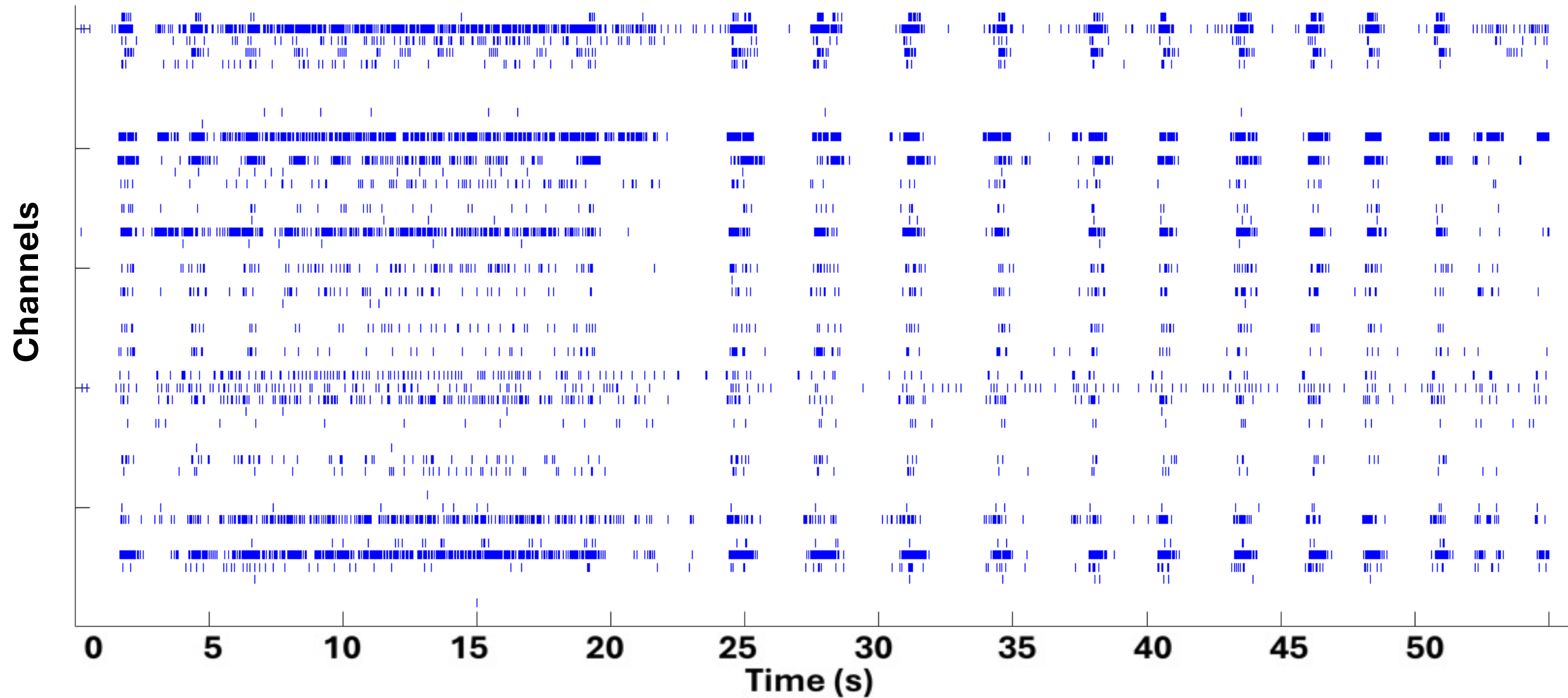
Stimulation



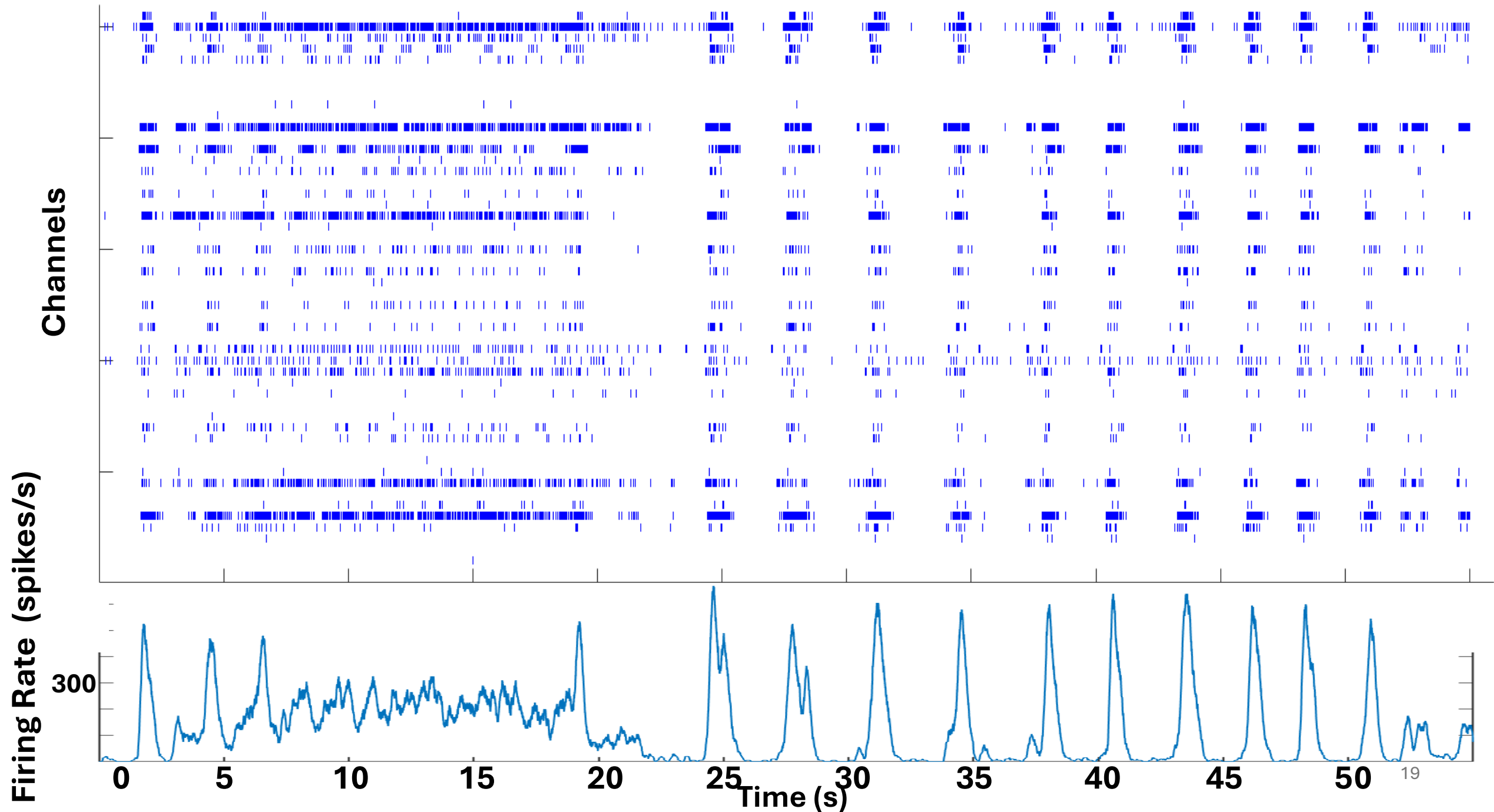
Recording



MEA Raster Plot at 71 DIV



MEA Raster Plot at 71 DIV

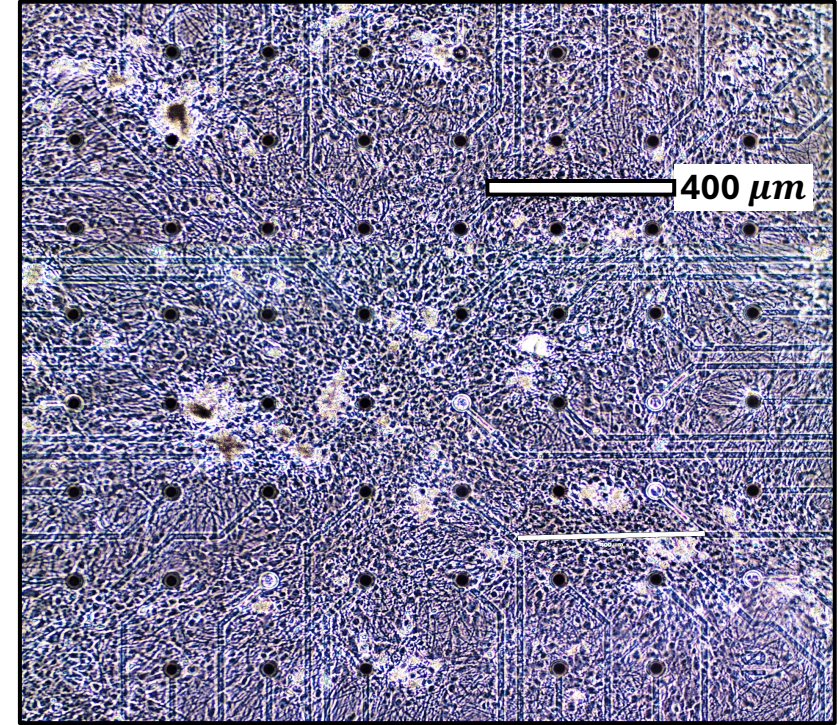


Bursting *in-vitro* vs *in-vivo*...



***Delta* waves first to appear in the brain
~24 weeks (168 days):**

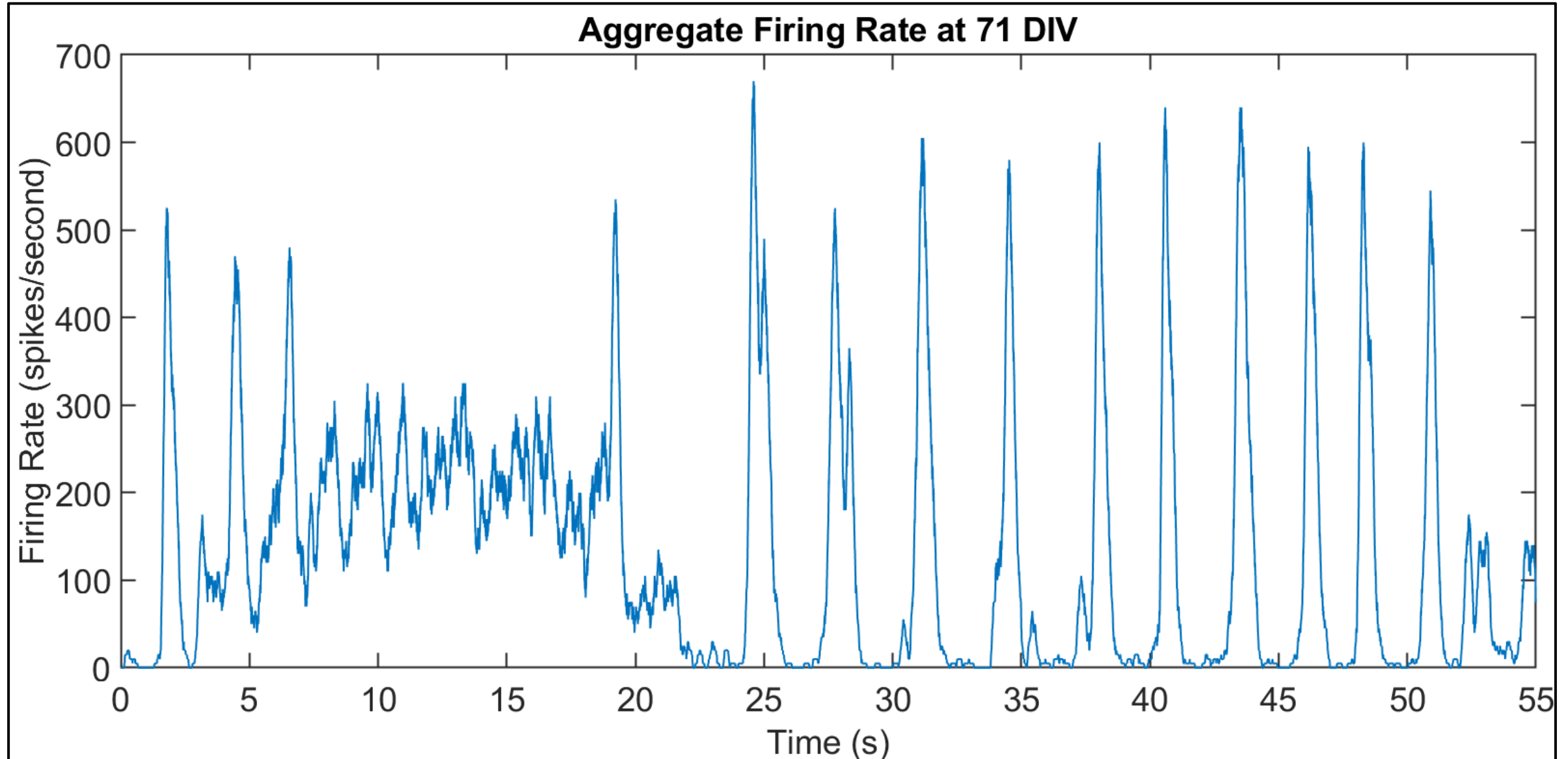
Low frequency (0.3–1 Hz)



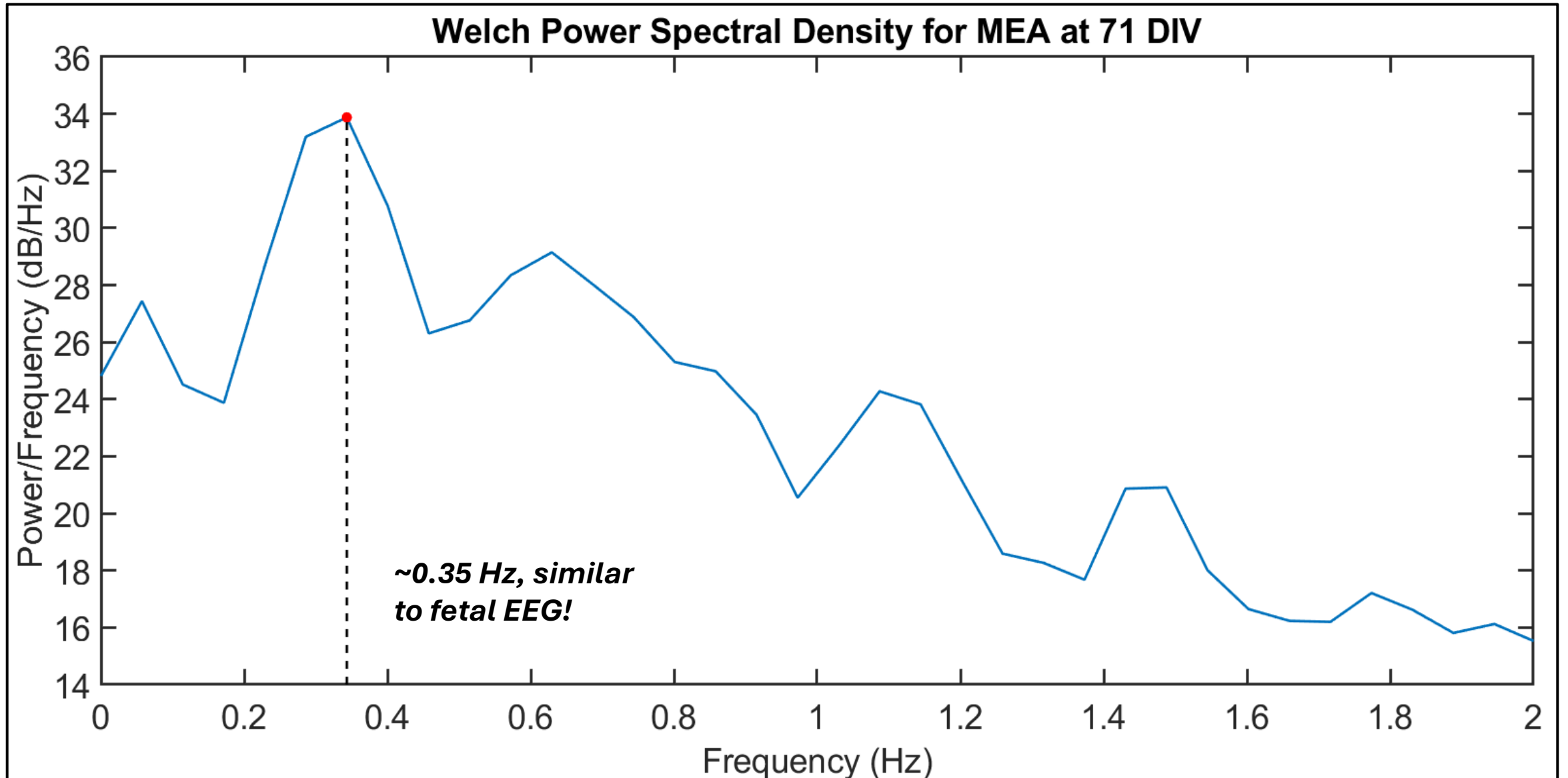
Recordings performed at ~70 DIV:

Let's investigate frequency of bursting...

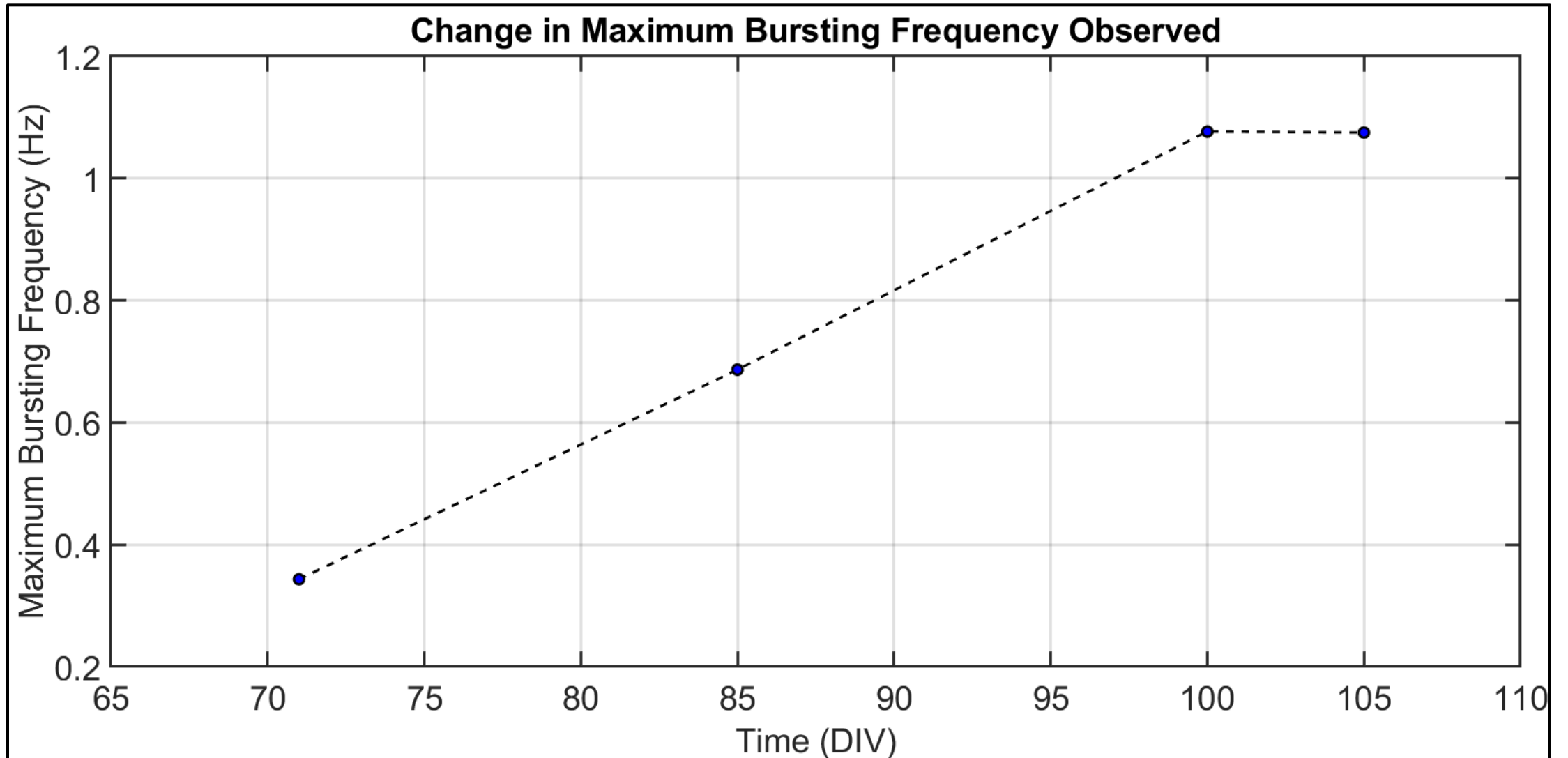
Calculate bursting...



Calculate bursting...

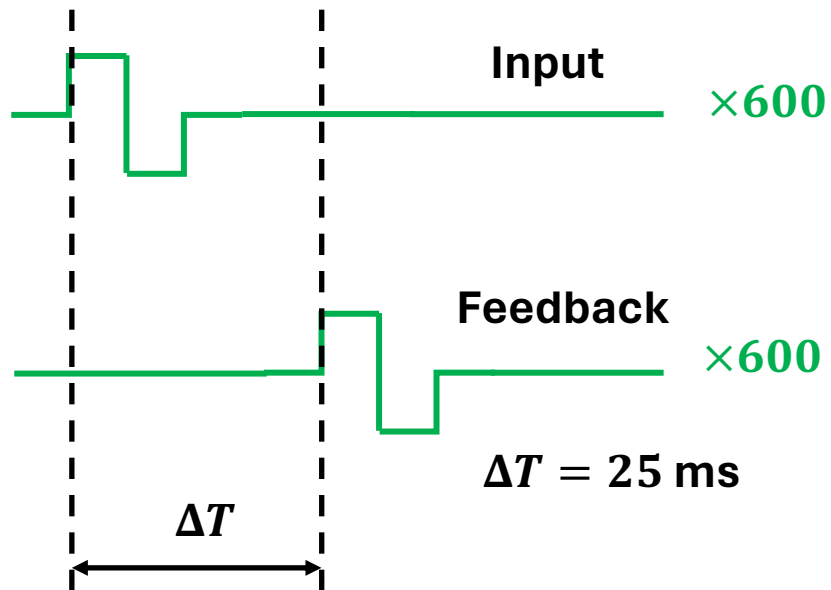


Does our culture mature over time?



Stimulation Experiments

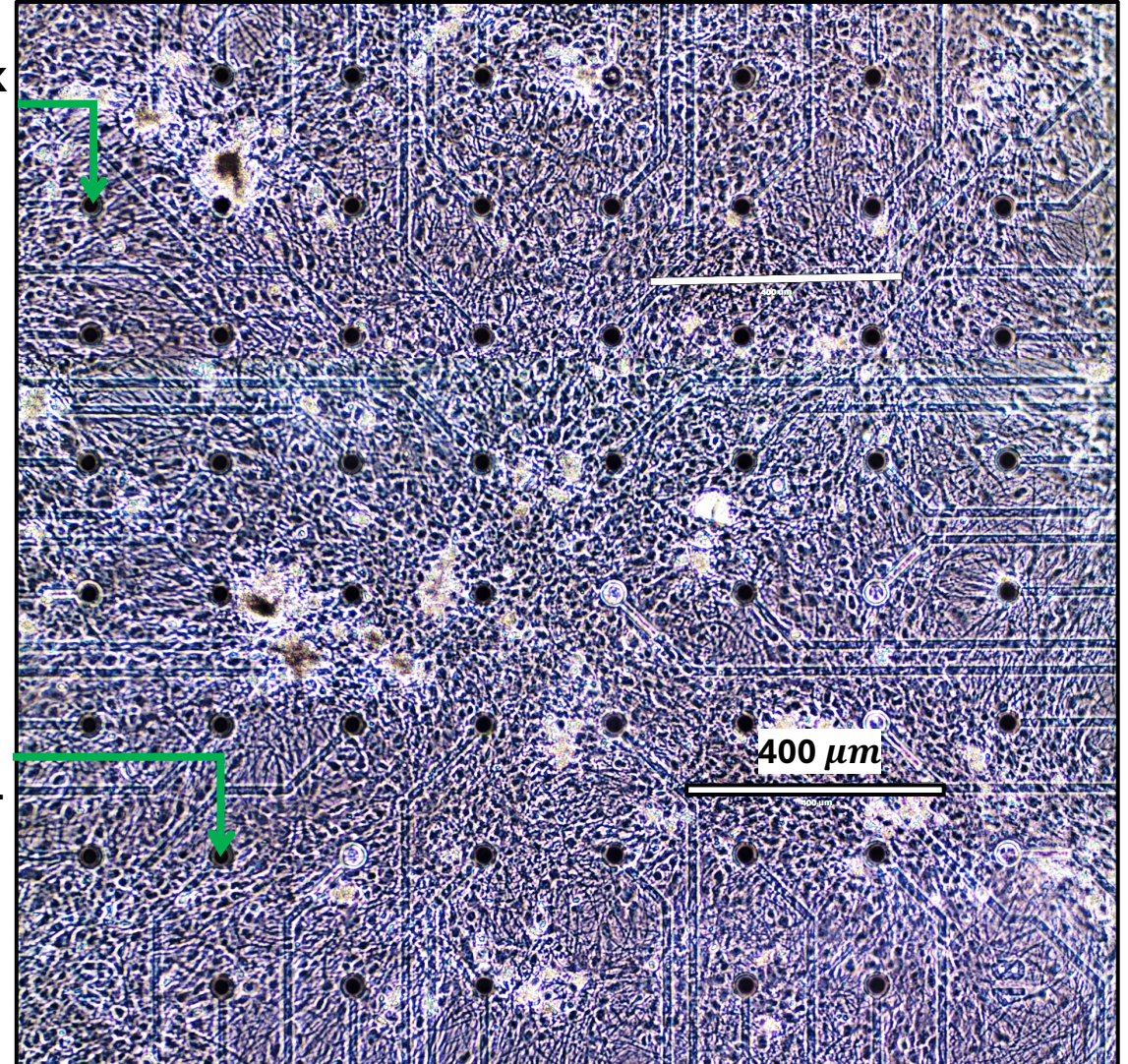
*Neurons that fire together,
wire together...*



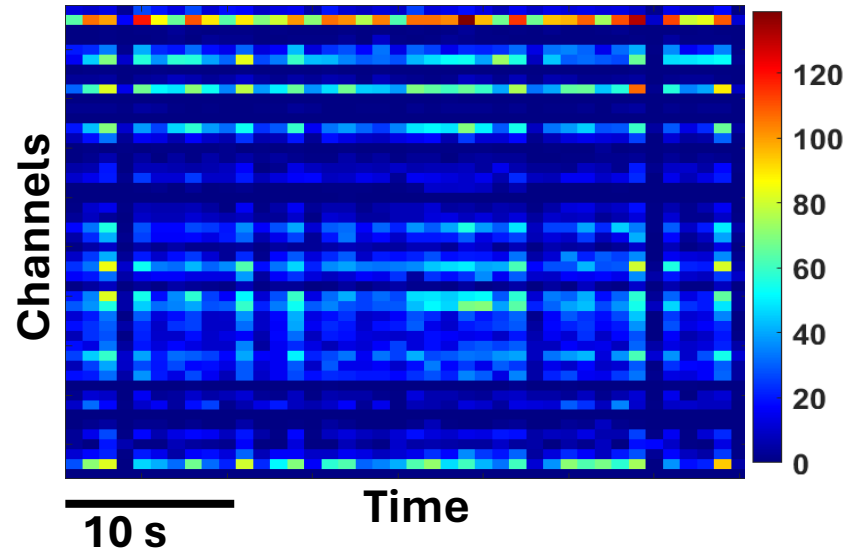
2 weeks and 2 sessions later...

Feedback
Channel

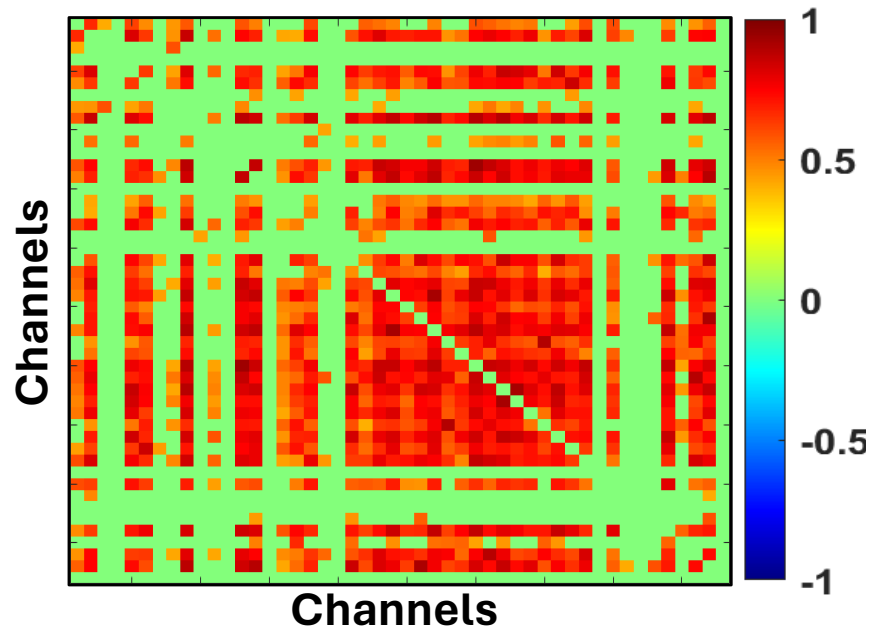
Input
Channel



Firing Rate (APs/s)

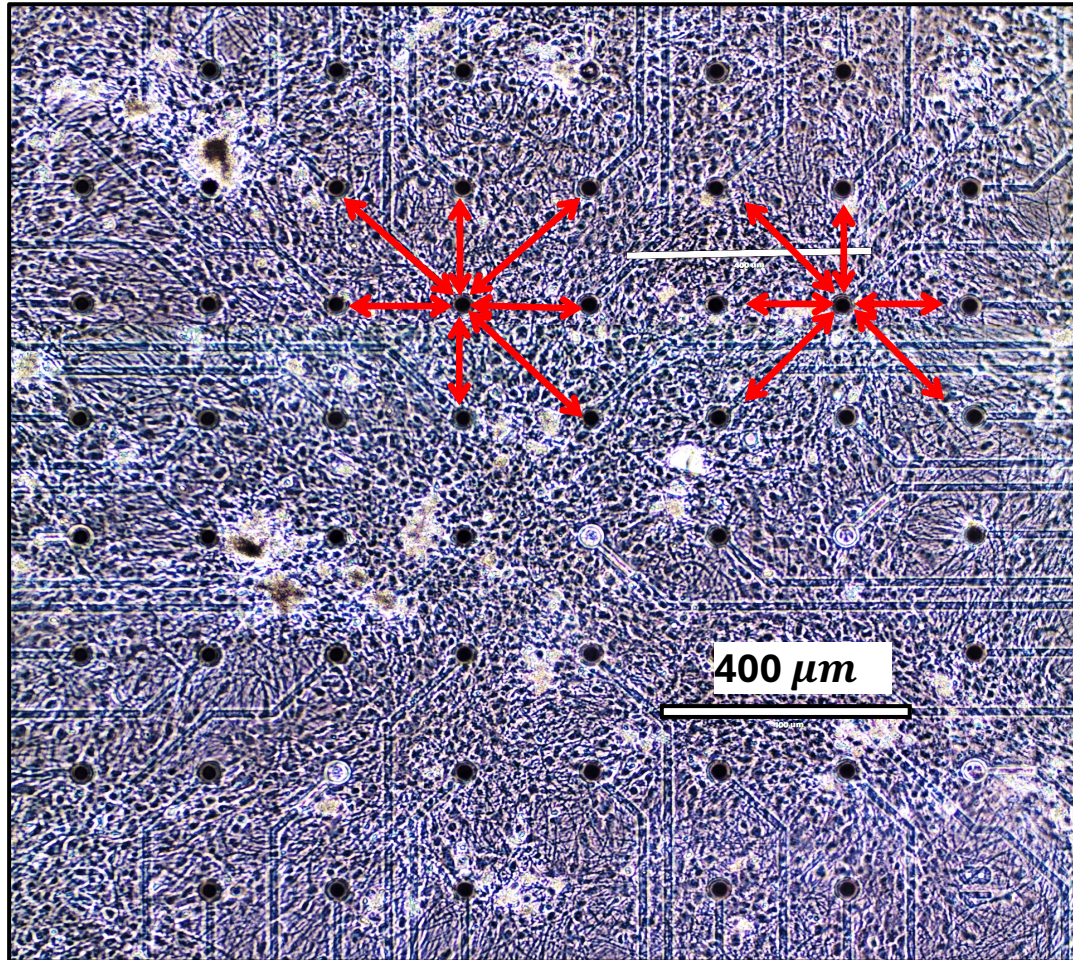


Correlation Coefficient



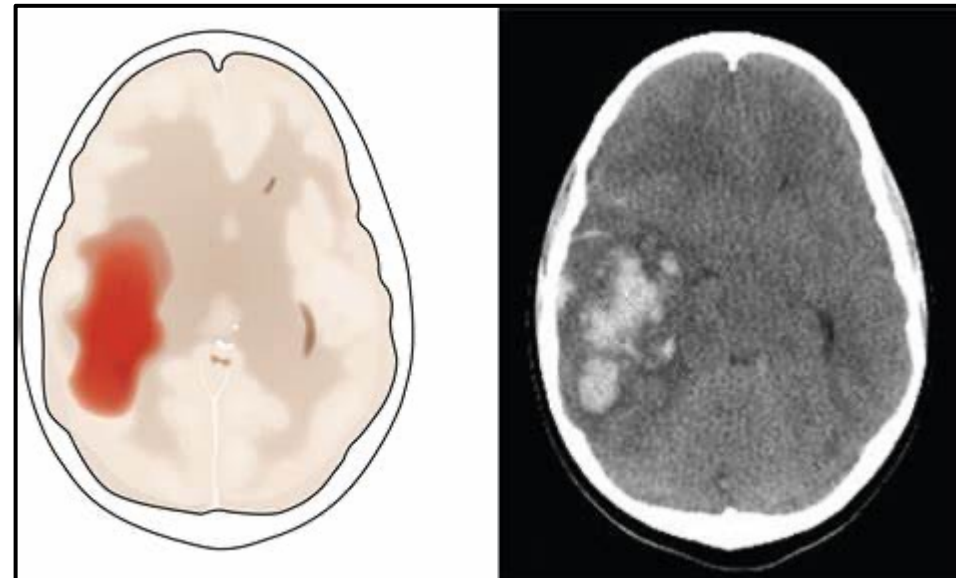
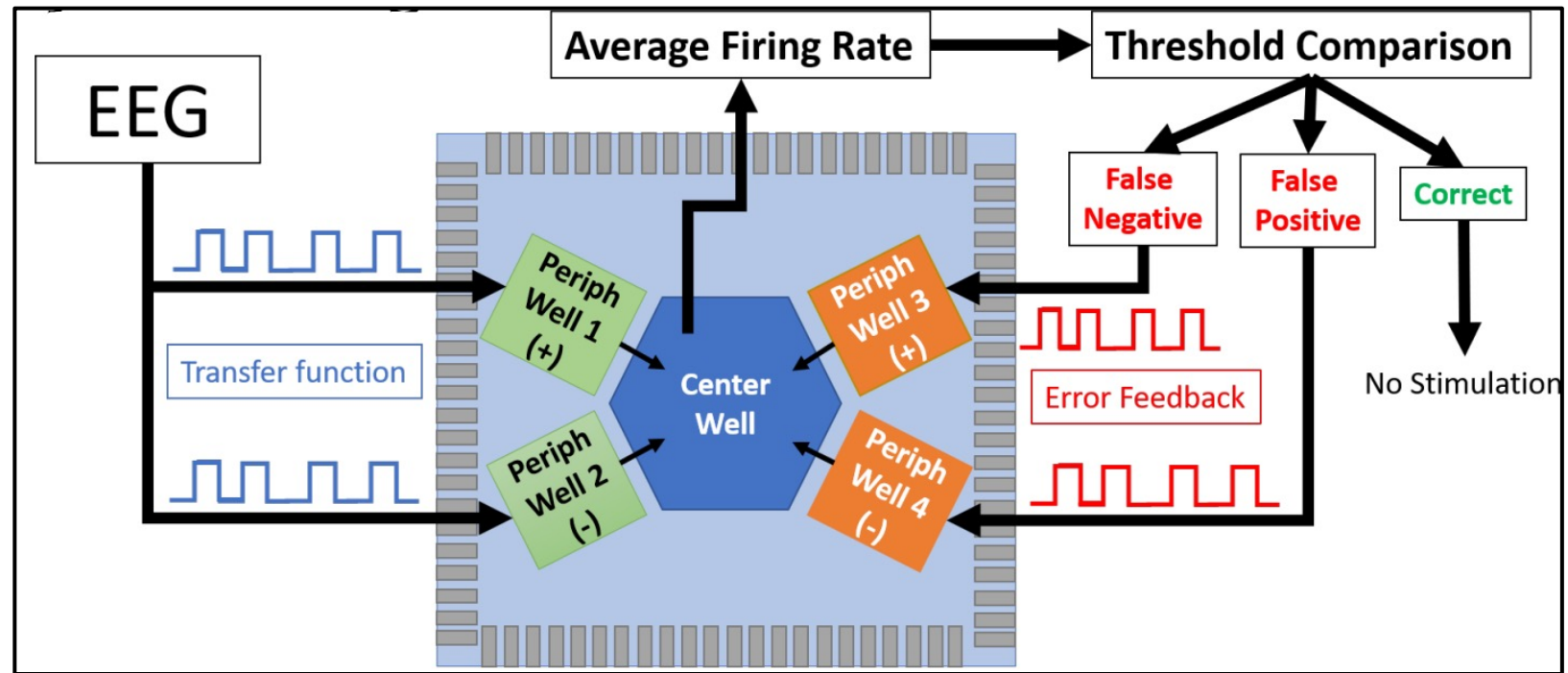
Before “Training”

Before “Training”



Moving Forward...

- Challenges maintaining human cultures long-term (>100DIV)
- Repeat experiments (currently $n = 1$)
- Explore different stimulation paradigms



Thank You!

Christina Tu

Shravan Thaploo

Lab Undergrads:

- Chengyan Zhao
- Anessa Mikenas
- Ahmed Baig

Funding Sources:

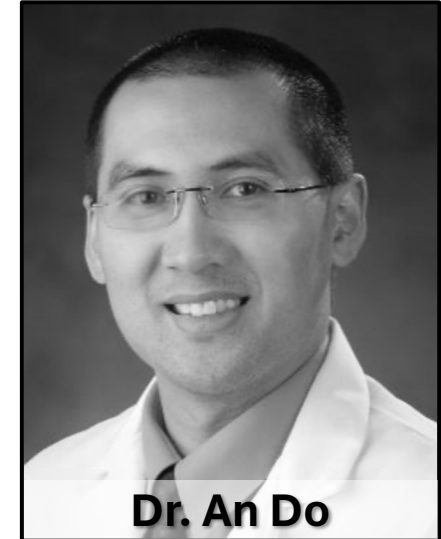
- NSF
- CALIT2
- UCI (School of Medicine, UROP)



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Dr. Zoran Nenadic



Dr. An Do



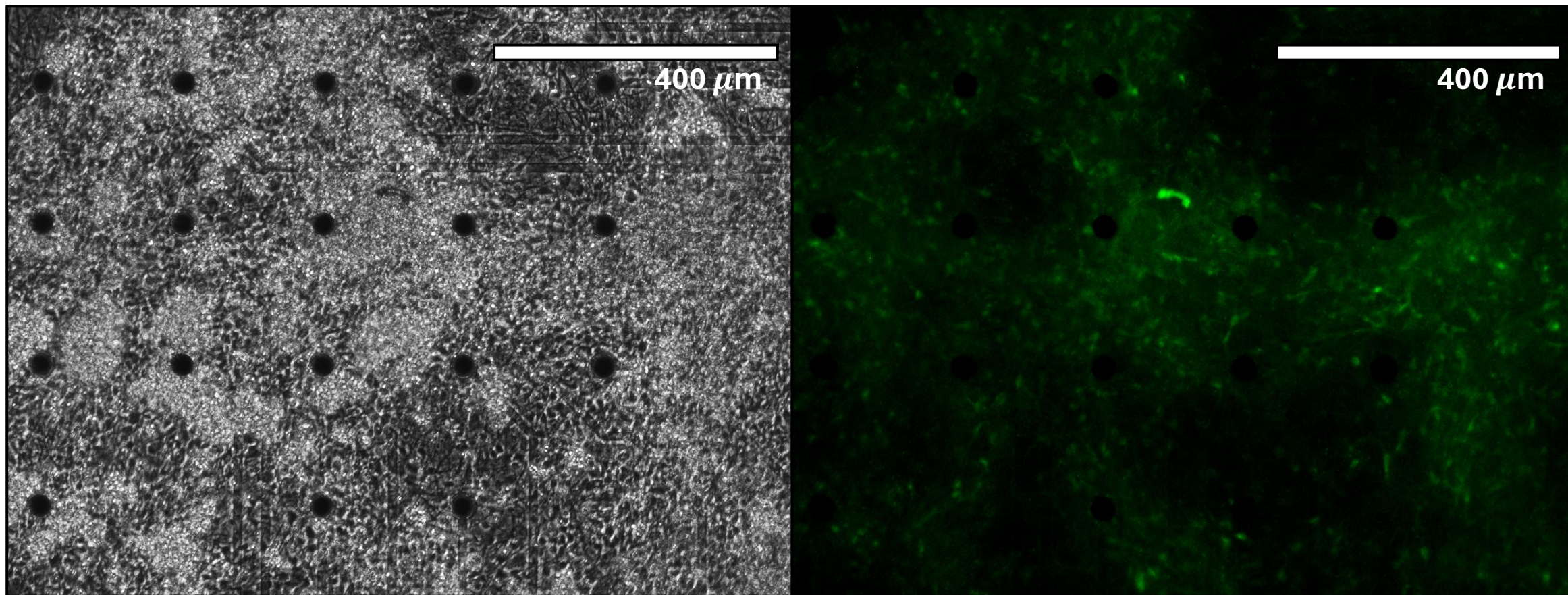
Dr. Gregory Brewer



Dr. Po T. Wang

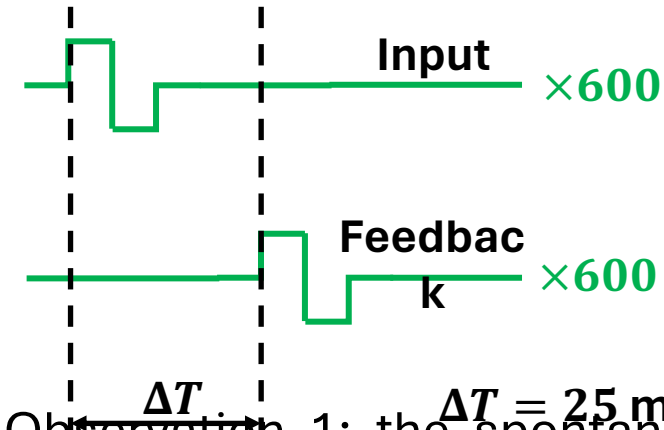
References

- [Electroencephalography in premature and full-term infants. Developmental features and glossary – ScienceDirect](#)
- [Bellemare - What is a Megawatt. \(nrc.gov\)](#)
- [UsingRenewablesToOperateLow-CarbonGrid.pdf \(caiso.com\)](#)



MEA imaging performed after NeuO fluorescence live stain
showing presence of mature neurons at 80 DIV.

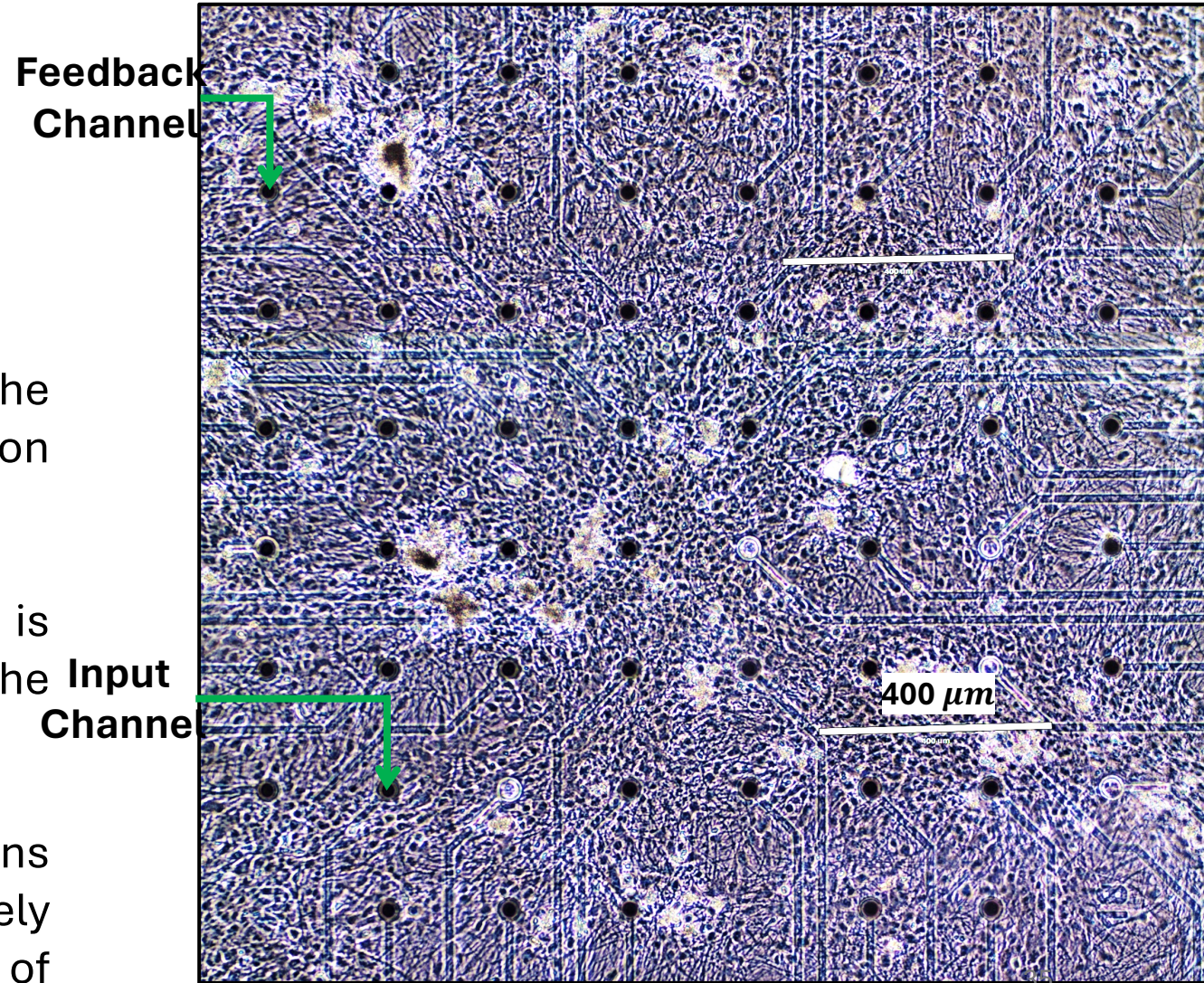
Hypothesis: repeated paired stimulation at two distinct network locations will change the functional connectivity of the network. This scenario mimics the network training process where one stimulation sequence serves as an input and the other as feedback.

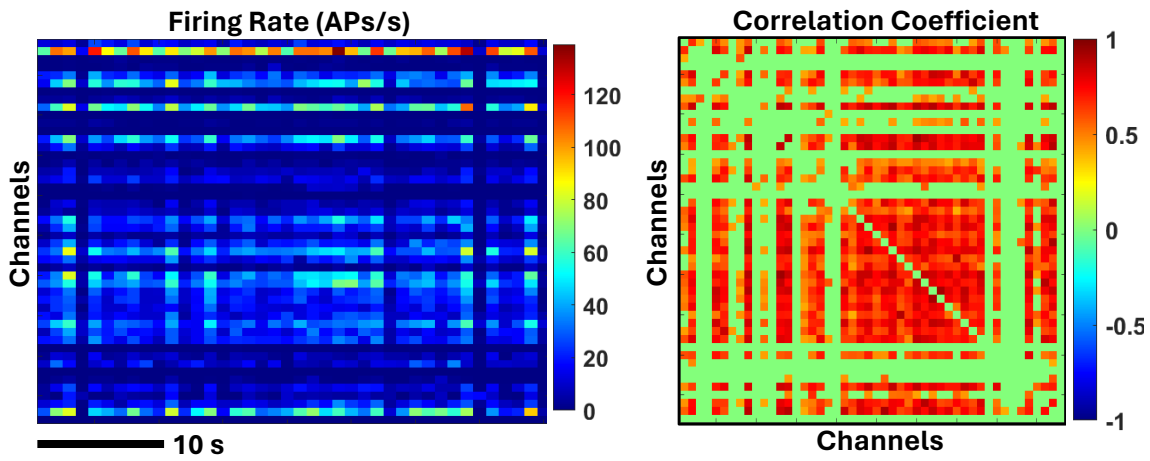


Observation 1: the spontaneous firing rate of the network did not substantially change upon “training.”

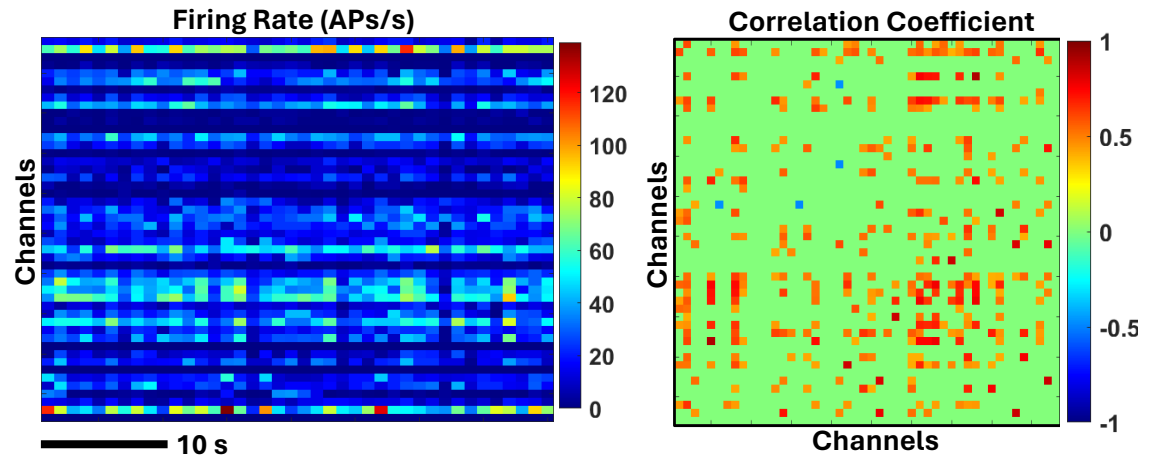
Observation 2: the spontaneous activity is significantly less correlated after “training,” i.e., the functional network is significantly pruned.

Observation 3: emergence of network regions whose spontaneous activities are negatively correlated after “training,” i.e., the emergence of inhibition.

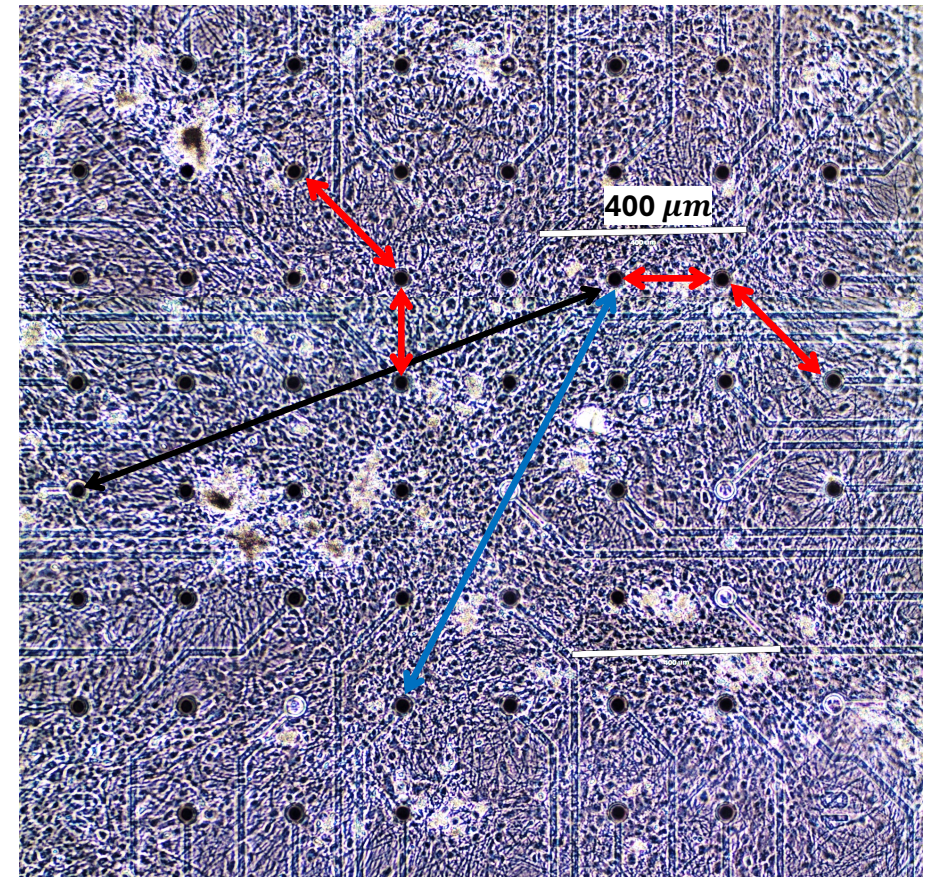
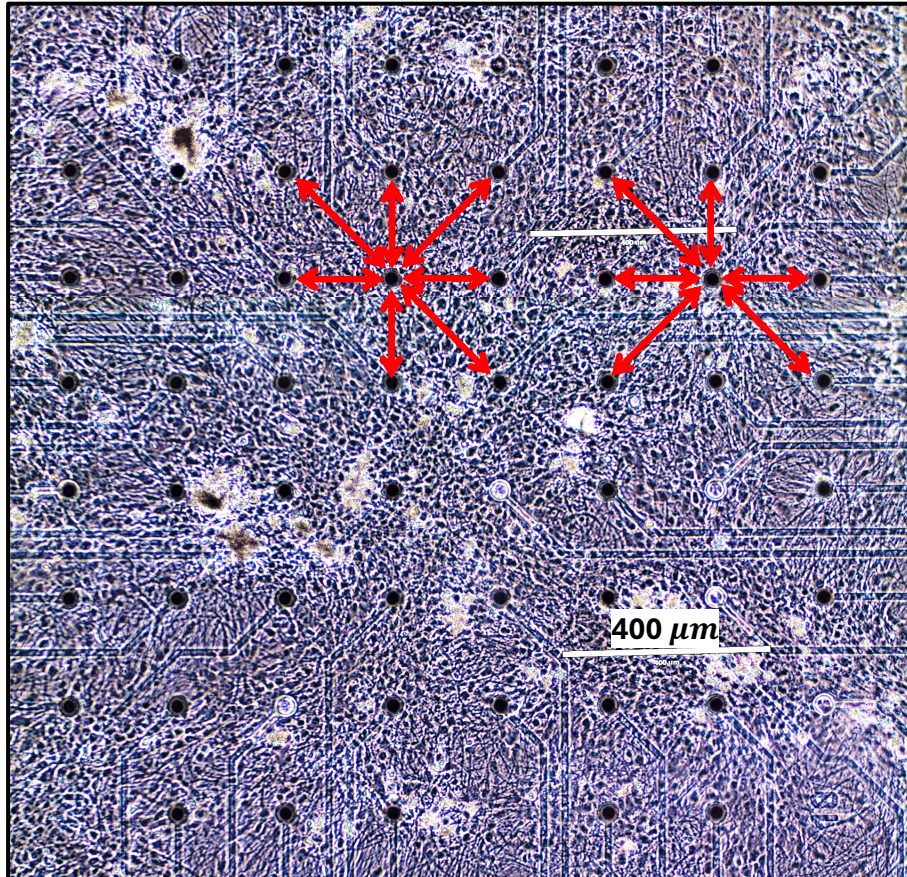




Before “Training”



After “Training”



“+” Functional Connections
↔

“—” Functional Connections
↔