



Office of Research and Development
Center for Computational Toxicology and Exposure

A New Approach Methodology (NAM) using Human iPSC-derived BrainSpheres for Developmental Neurotoxicity Screening

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ORISE Research Participant

Disclaimer

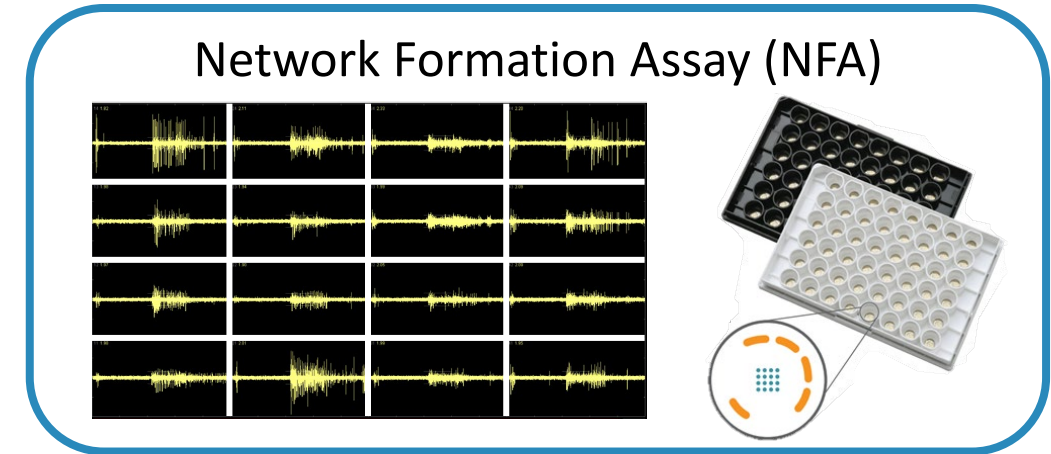
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Developmental Neurotoxicity (DNT) *in vitro* Battery

The Organization for Economic Co-operation and Development (OECD) recognized an *in vitro* battery (IVB) of assays for screening developmental neurotoxicity:

- Apoptosis
- Proliferation
- Migration
- Neurite outgrowth
- Synaptogenesis
- Network Formation



Current
Assay

Primary Rat
Cortical
Cells

2D Culture

Lower
Electrode
Density

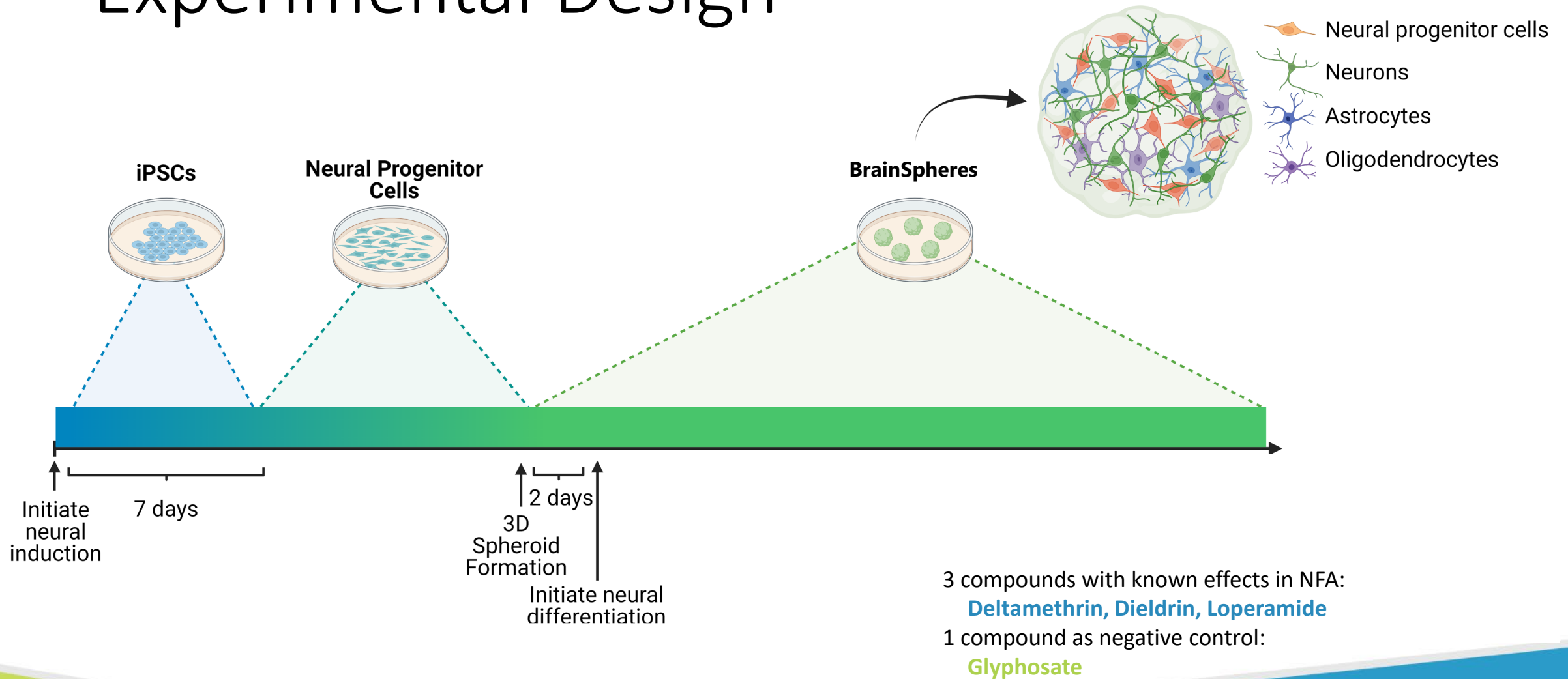
Assay in
Development

Human
iPSC-derived
Cells

3D Culture

Higher
Electrode
Density

Experimental Design

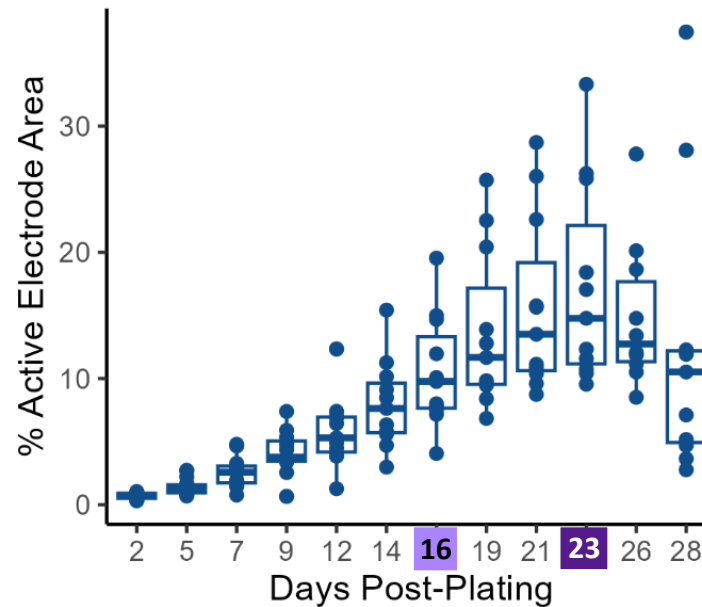


Activity Analysis

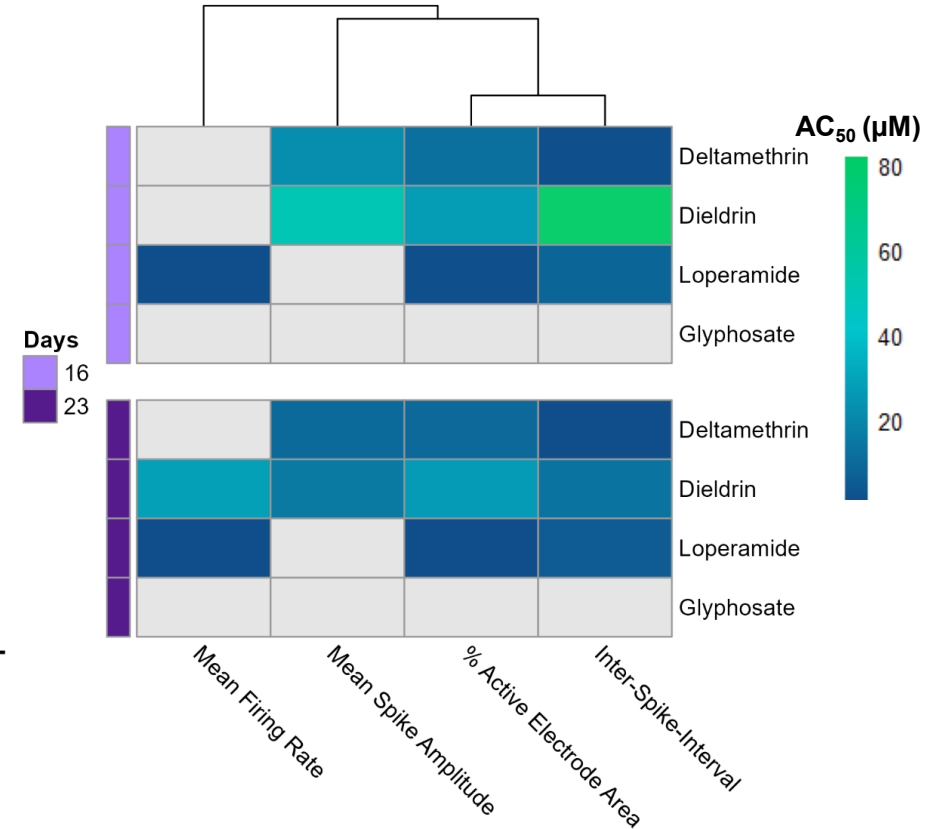
Day 28

Firing Rate (Hz)

Activity Ontogeny of Controls



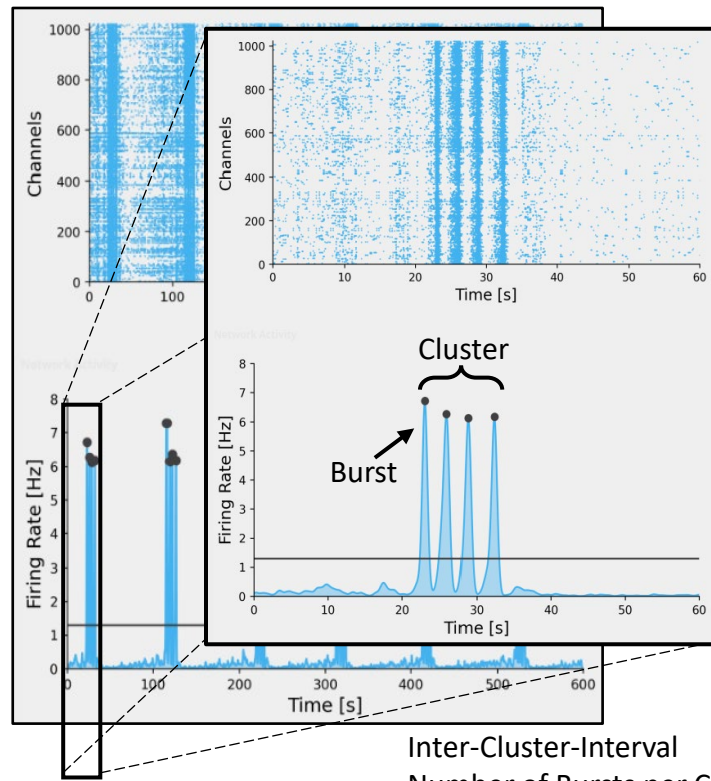
AC₅₀ Values for Activity Analysis



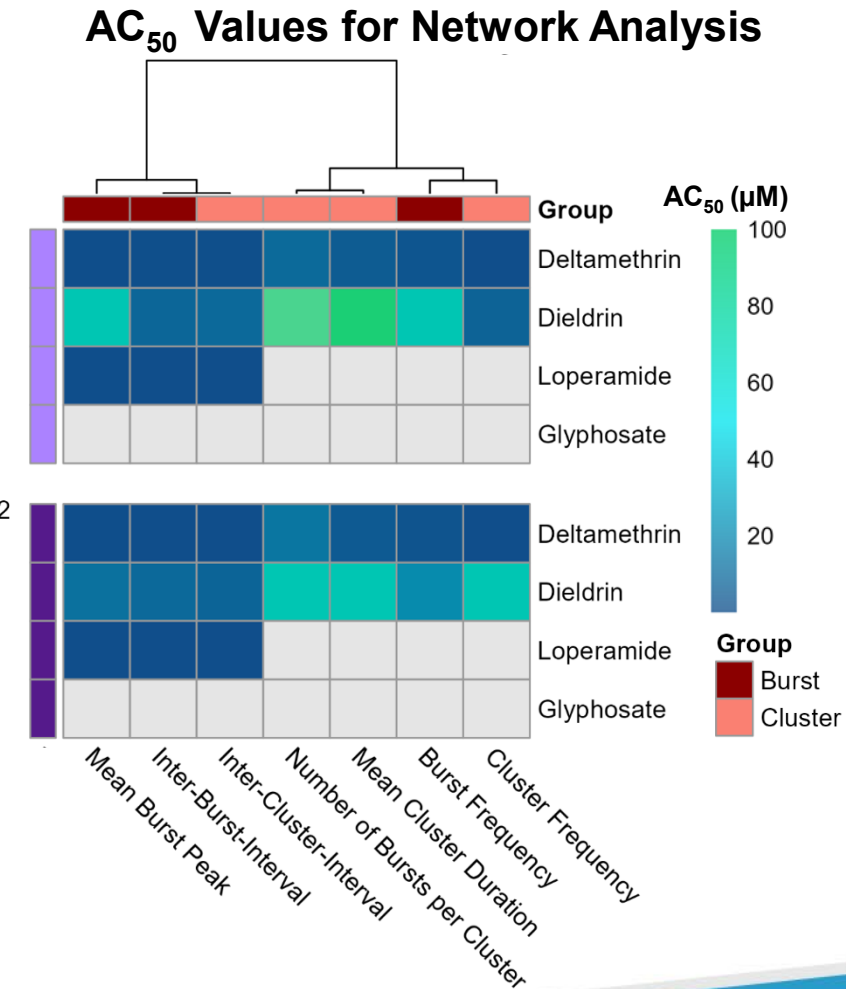
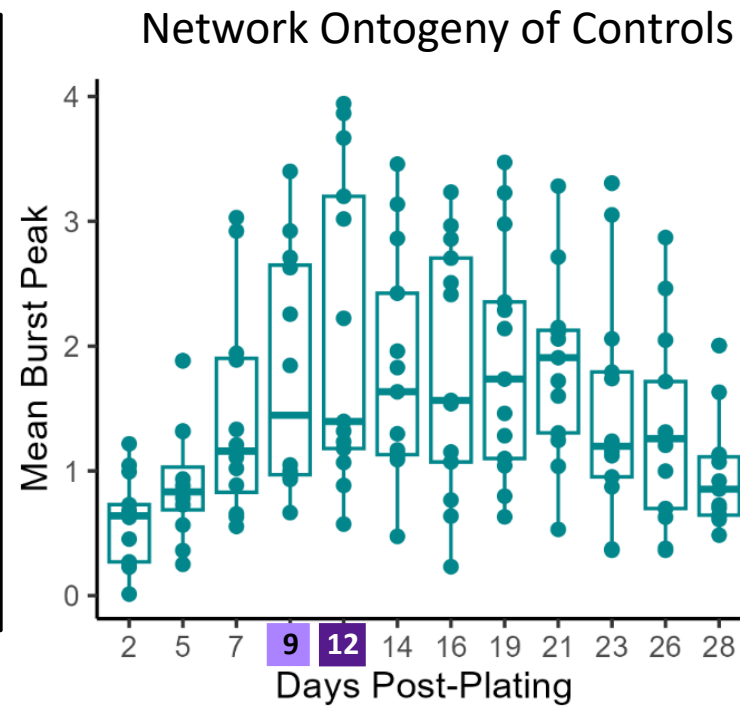
AC₅₀: Concentration that elicits half maximal response

BrainSpheres show developmental disruption for all tested chemicals except glyphosate, with greater effects from Deltamethrin and Dieldrin at Day 23 compared to Day 16.

Network Analysis

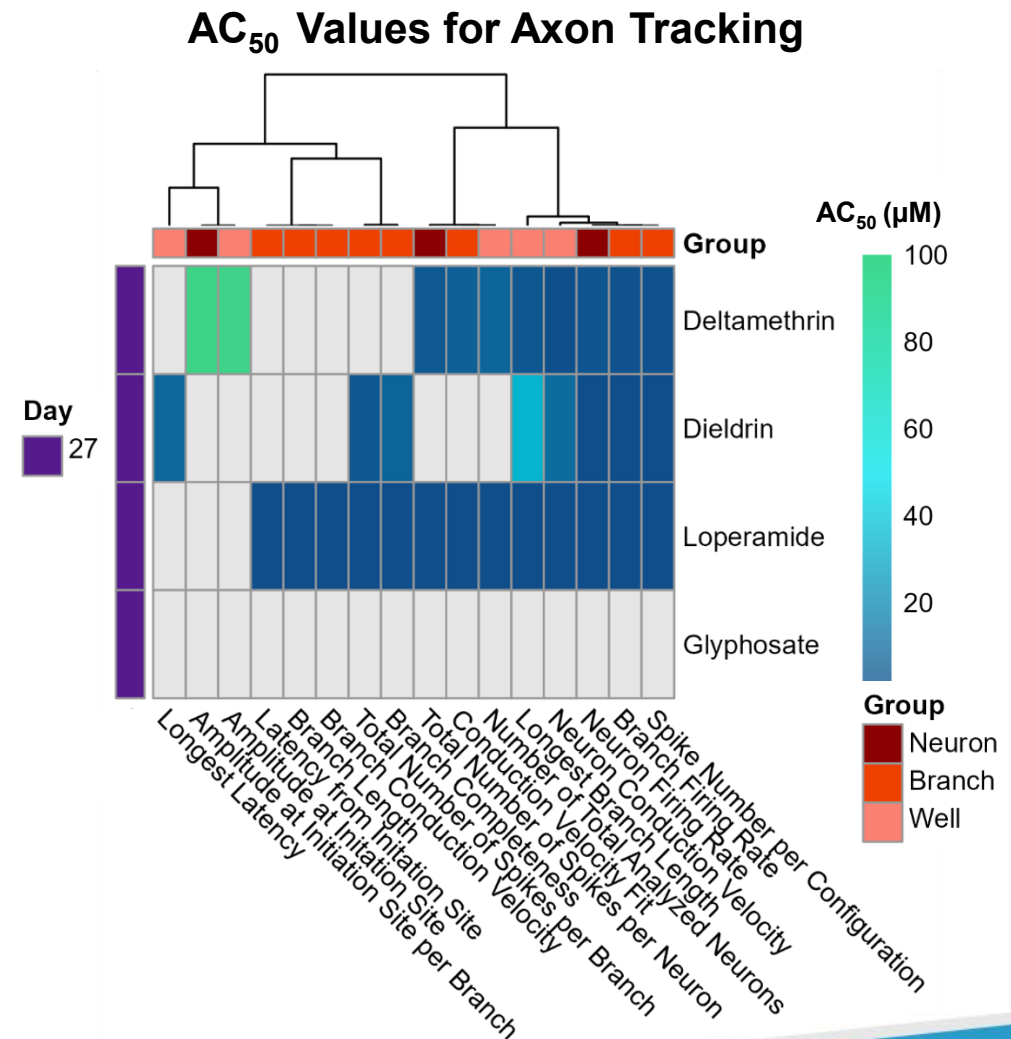
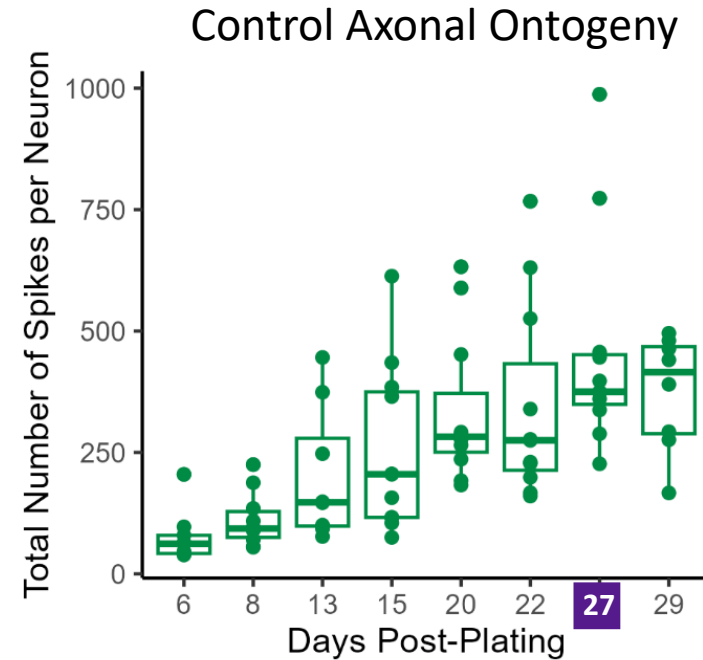
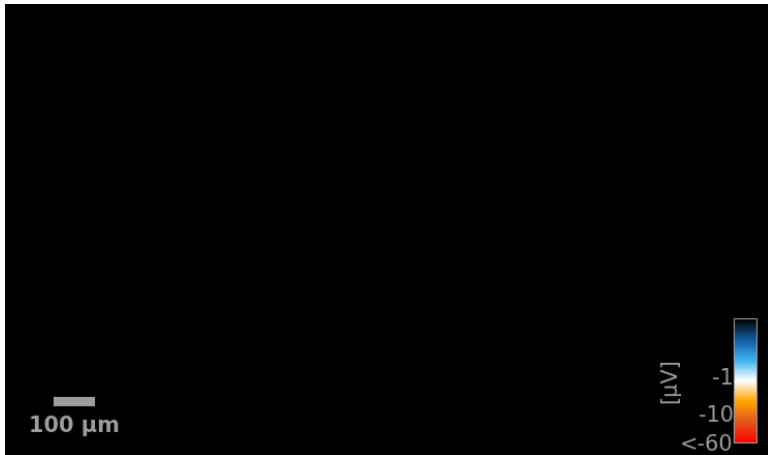
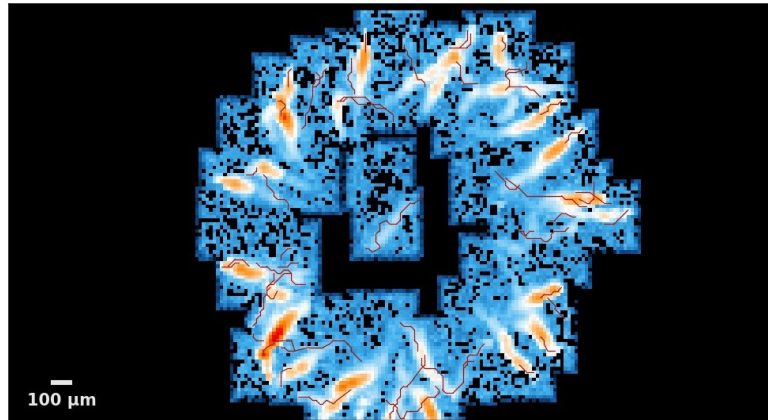


Inter-Cluster-Interval
Number of Bursts per Cluster
Cluster Duration
Cluster Frequency



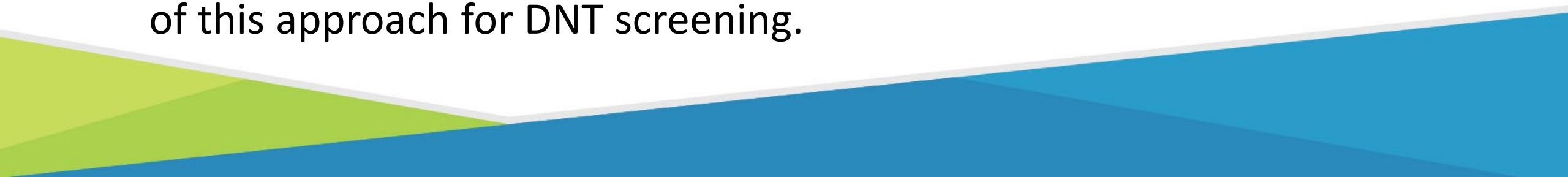
Deltamethrin, Dieldrin,
and Loperamide disrupted network formation,
with greater effects from Dieldrin seen at Day 12 compared to Day 9.

Axon Tracking Analysis



Several action potential propagation endpoints at the well, branch, and neuron levels are disrupted by exposure to dieldrin, deltamethrin, and loperamide.

Conclusion & Future Directions

- The neurospheres show clear ontogeny of neural activity on hdMEAs.
 - Dieldrin, deltamethrin and loperamide disrupt network formation in human neurospheres without cytotoxicity similar to the rat NFA.
 - BrainSphere functional assay could be a valuable addition the DNT-IVB.
 - Future studies will expand testing of environmentally relevant compounds, including neonicotinoid insecticides and per- and polyfluoroalkyl substances (PFAS), to further demonstrate the capability of this approach for DNT screening.
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Please stop by my
poster for more details

Questions?

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