AFMC/AFRL Activities in NAMs

Microphysiological Systems Laboratory
AFRL 711 HPW/RHBBB

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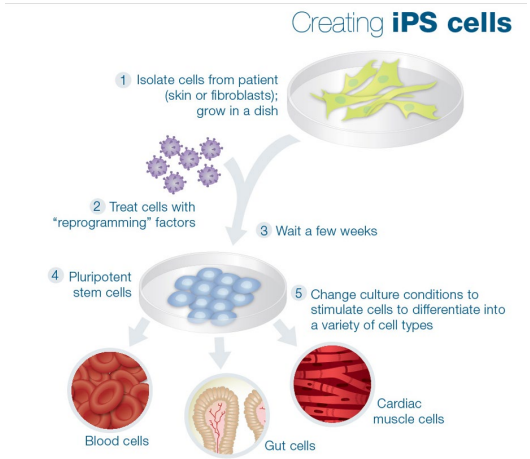
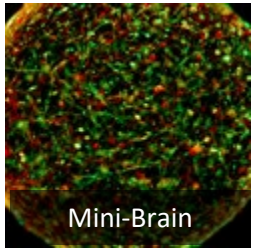
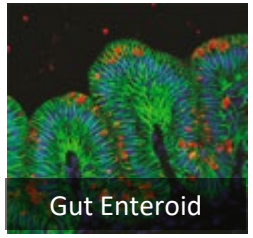
Model Development and Mechanistic Analysis Work-Flow

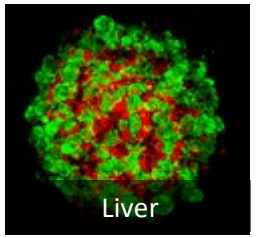
Organoid/iPSC Development



JHU (CRADA)



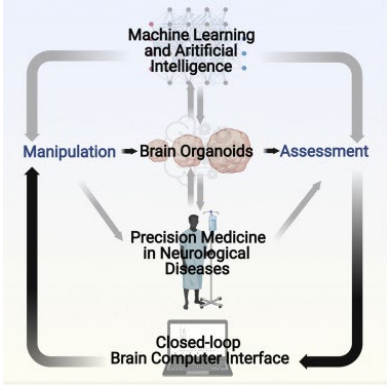


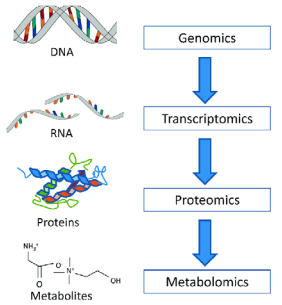


Organ-Specific Model Development

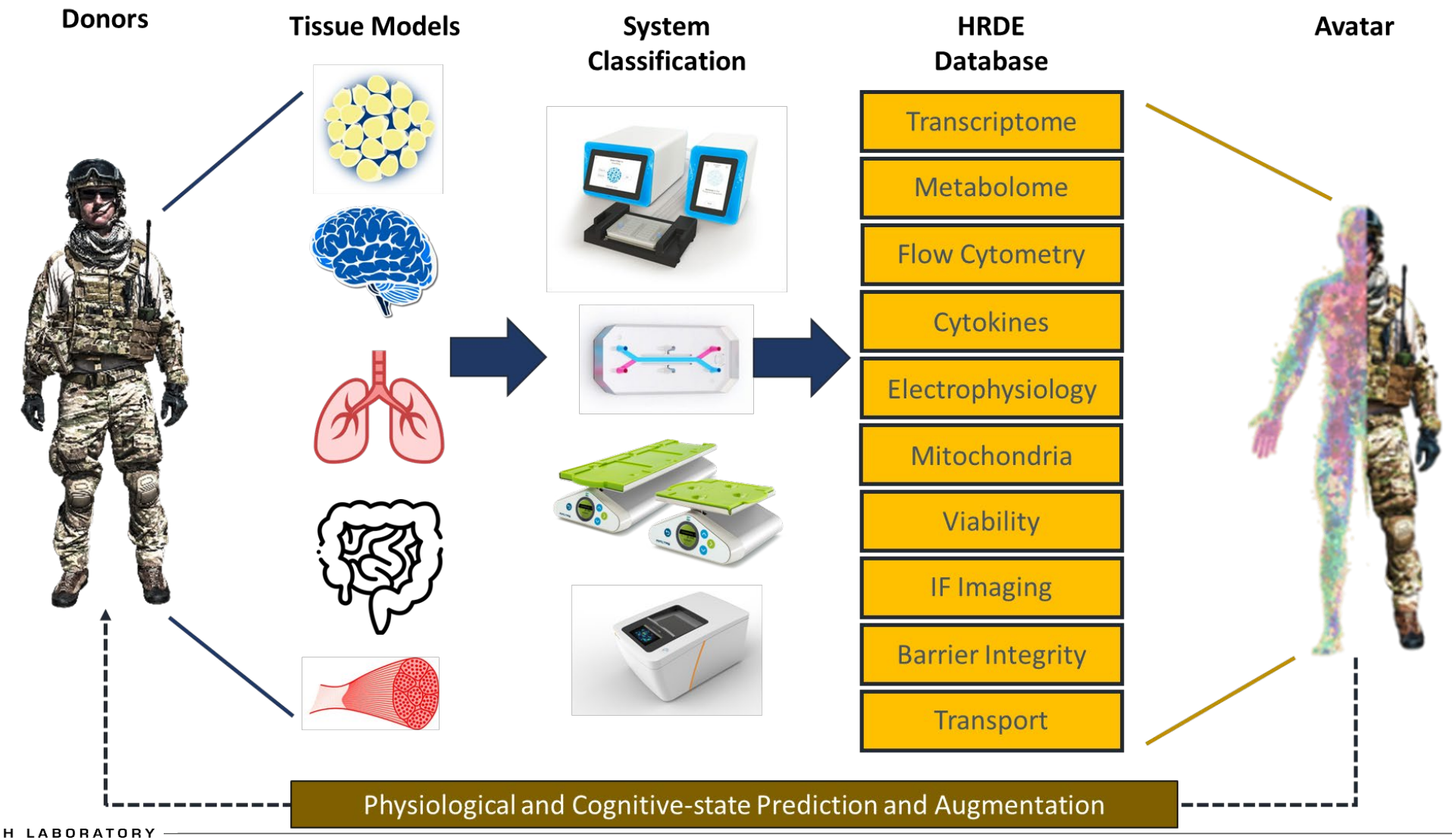
Data Acquisition

Knowledge Transition

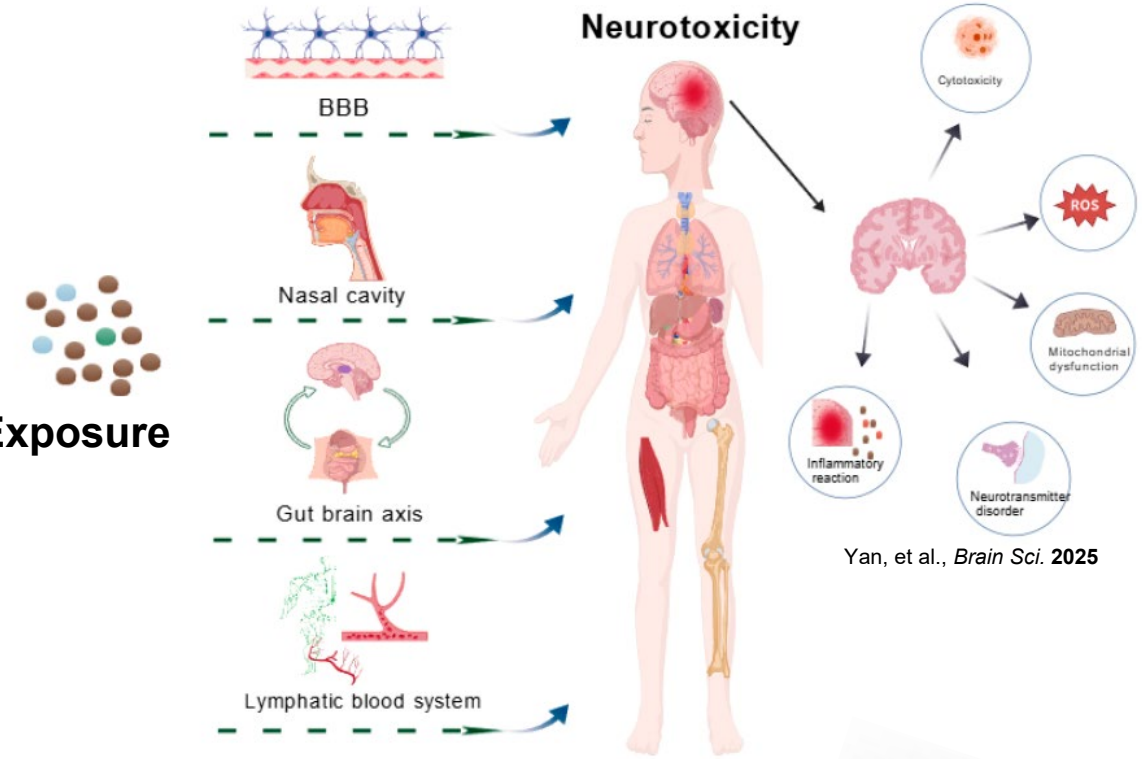




Warfighter Avatars: Leveraging MPS data to fuel predictive insights

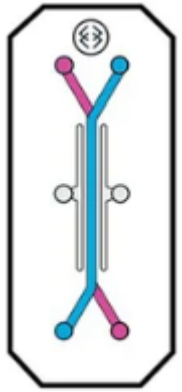


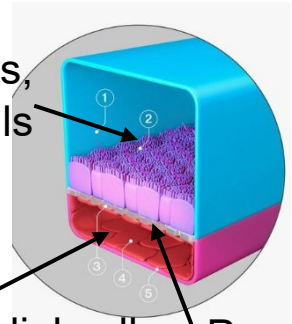
In Vitro Models for Rapid Assessment of Neurotoxicity and MCMs



Yan, et al., *Brain Sci.* **2025**

Neurovascular Unit-on-a-Chip:
3D model of brain barrier/compound delivery



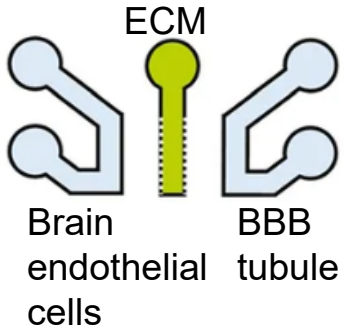


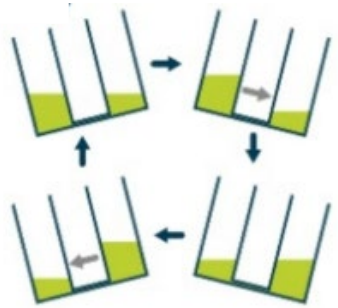
1 replicate/chip

Microelectrode Array:
Record or stimulate neuronal electrical activity

24 replicates/plate

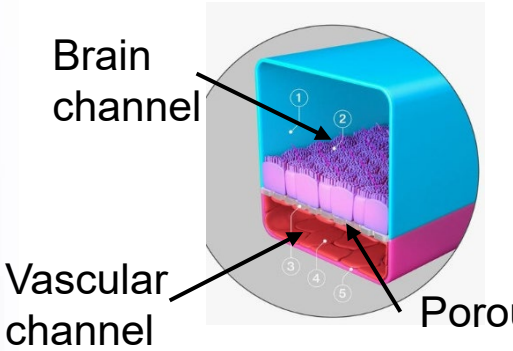
OrganoReady BBB:
3D Blood Brain Barrier Model





64 replicates/plate

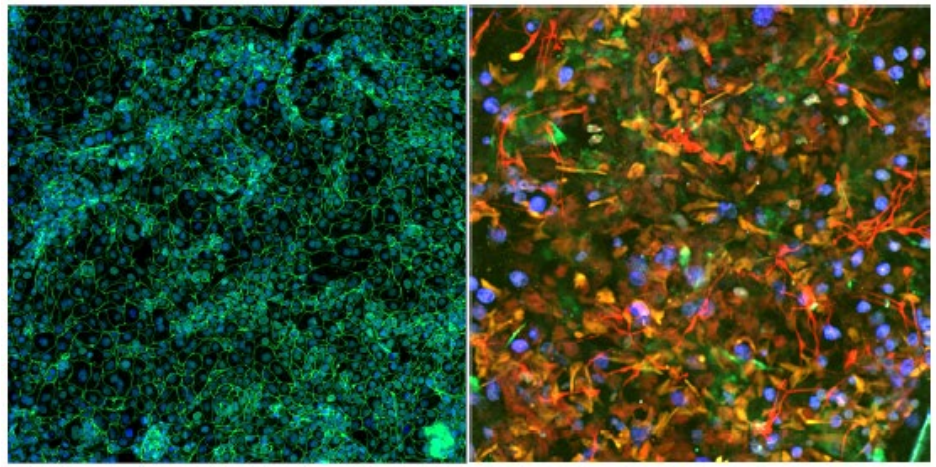
NVU-chip characterization: multicellular structure and barrier integrity

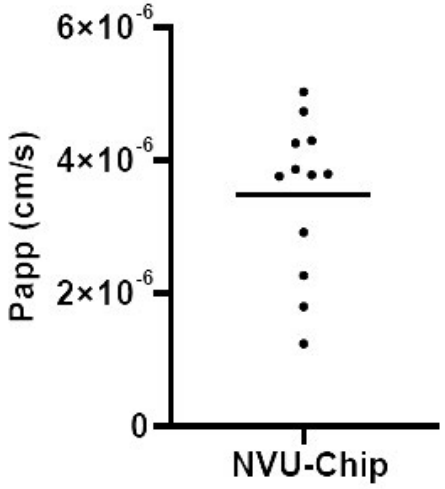


Human iPSC derived cells

- Brain channel: Neurons, Astrocytes, Microglia, Pericytes
- Vascular channel: Brain endothelial cells

- Matured for 5-6 days prior to characterization

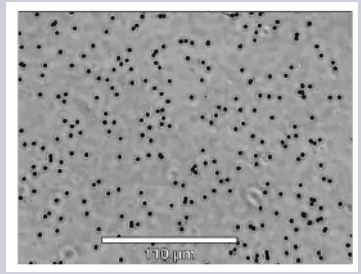
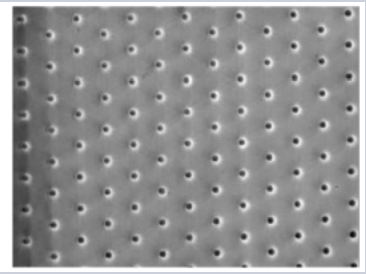


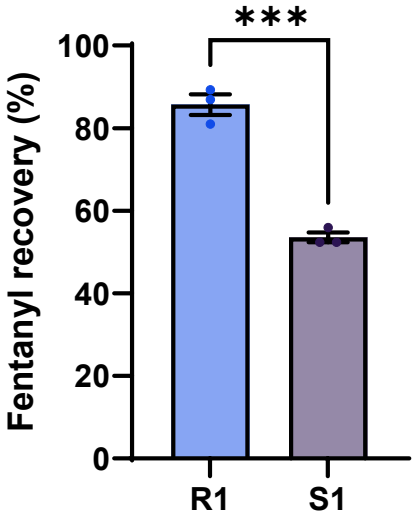


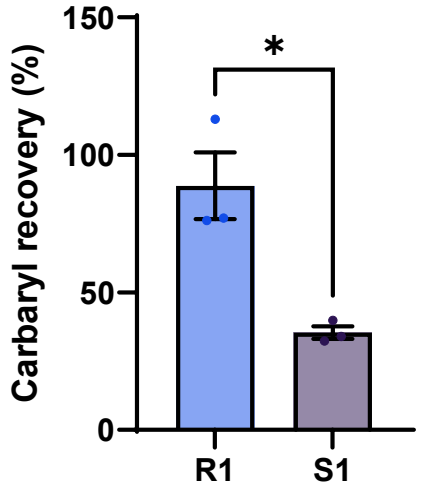
Downstream exposure analysis:

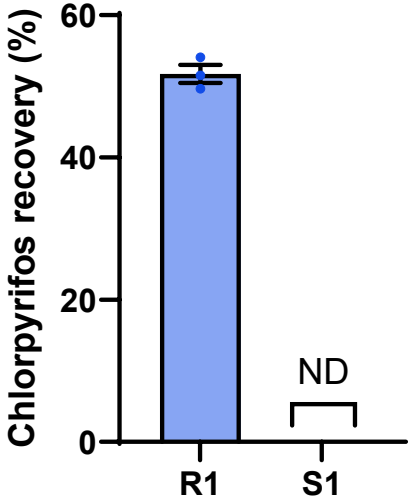
- Kinetic analysis: Barrier integrity, cytotoxicity, cytokine levels, enzymatic/metabolic activity
- Terminal analysis: Omics, microscopy

NVU-chip characterization: compound absorption studies

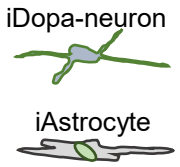
	Rigid (R1) chip	Stretchable (S1) chip
Material	Polycarbonate	PDMS
Pore size	3 µm	7 µm
Membrane	 Randomized pore distribution	 Evenly spaced pore distribution





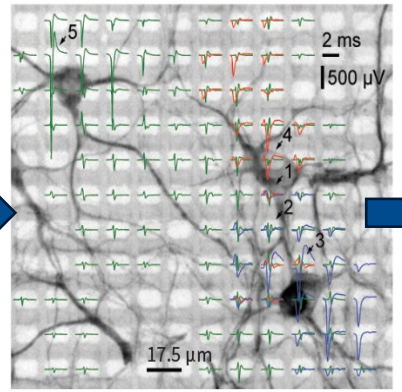


Brain-on-a-Chip – Microelectrode Array (MEA) Platform

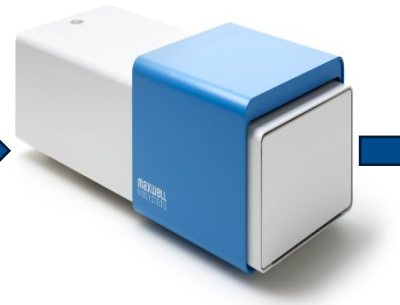


iPSC HUMAN CELLS

MAXWELL MEA PLATE

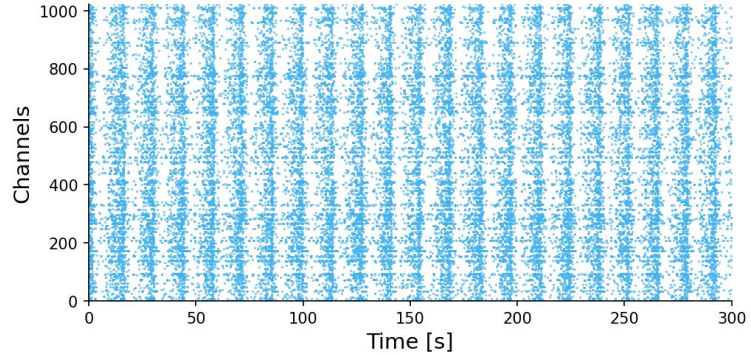


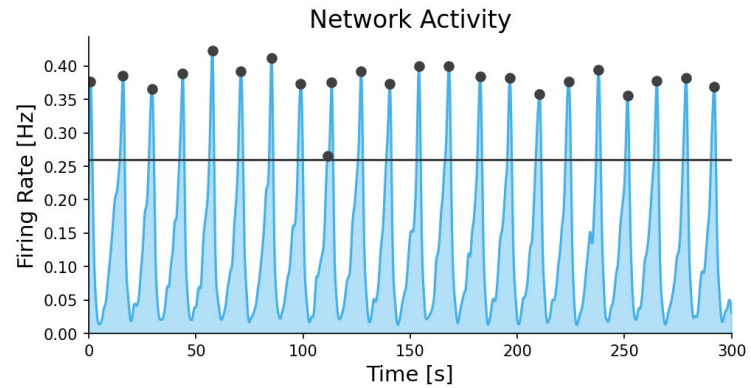
MAXWELL MEA ARRAY



MAXWELL HD-MEA

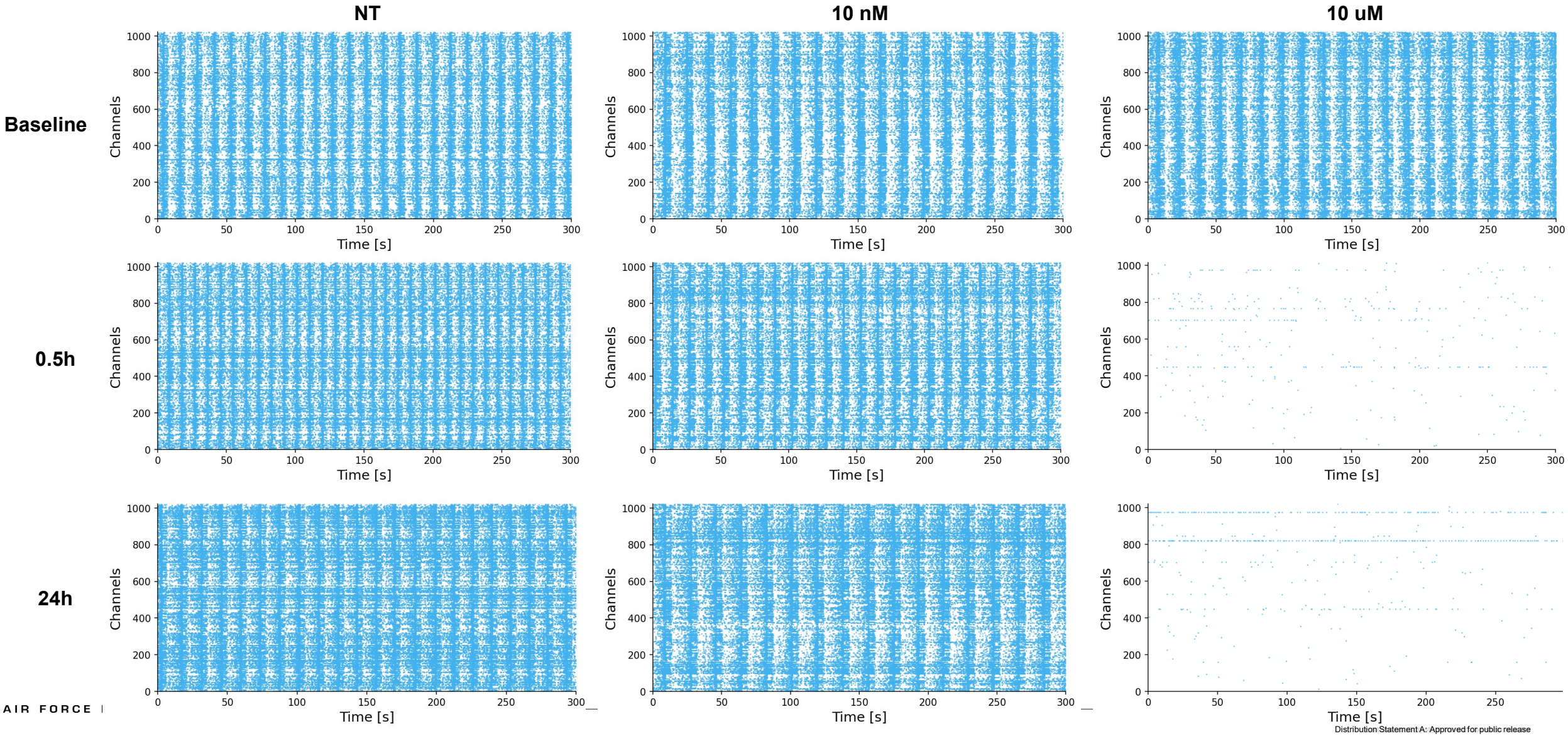
NEURONAL ACTIVITY PLOTS





- Microelectrode Array (MEA) utilizes micro-patterned electrodes to stimulate and record from neurons
- Using human induced pluripotent stem cells (iPSC) a multi-cellular culture is developed to model cortical brain tissue
- 21-28 days of maturation results in a highly mature, active, and networked cell culture
- Using semi-high-throughput approaches we are able to monitor multiple culture wells up to 26,000 electrodes at once

Brain-on-a-Chip: Fentanyl exposure by Microelectrode Array (1)



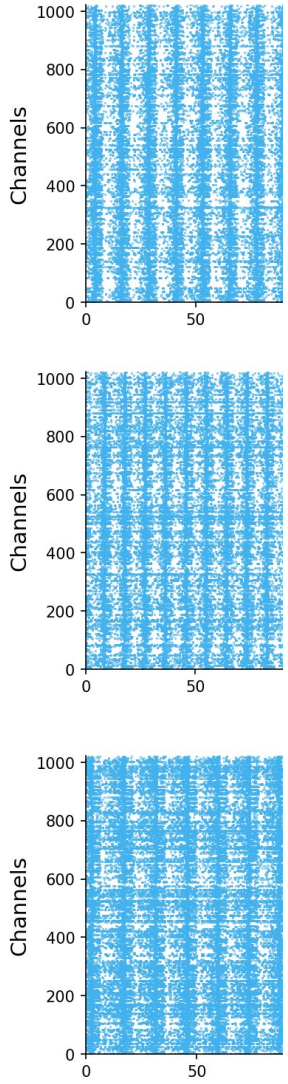
Brain-on-a-Chip: Fentanyl exposure by Microelectrode Array (2)

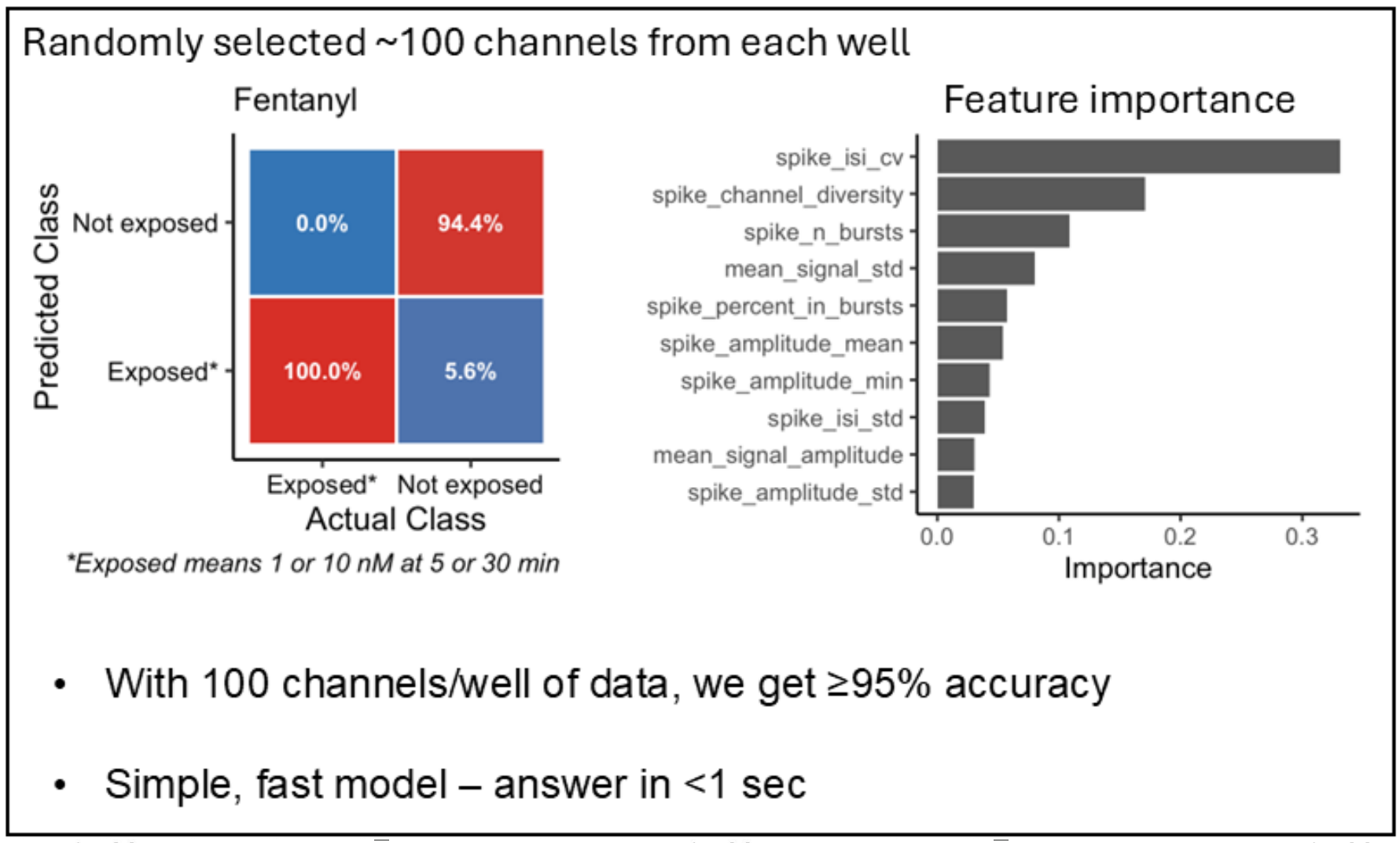
NT | 10 nM | 10 uM

Baseline

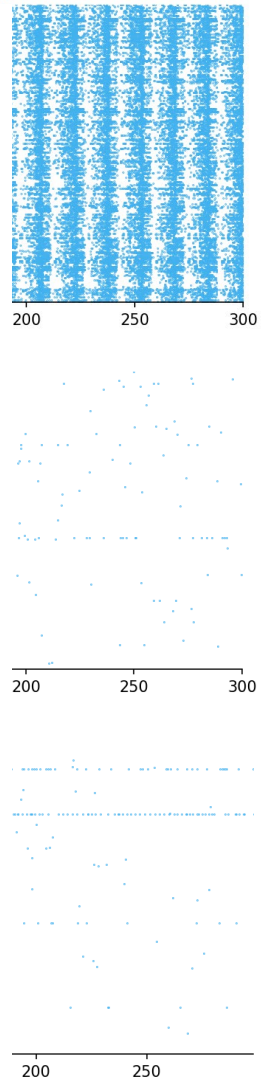
0.5h

24h



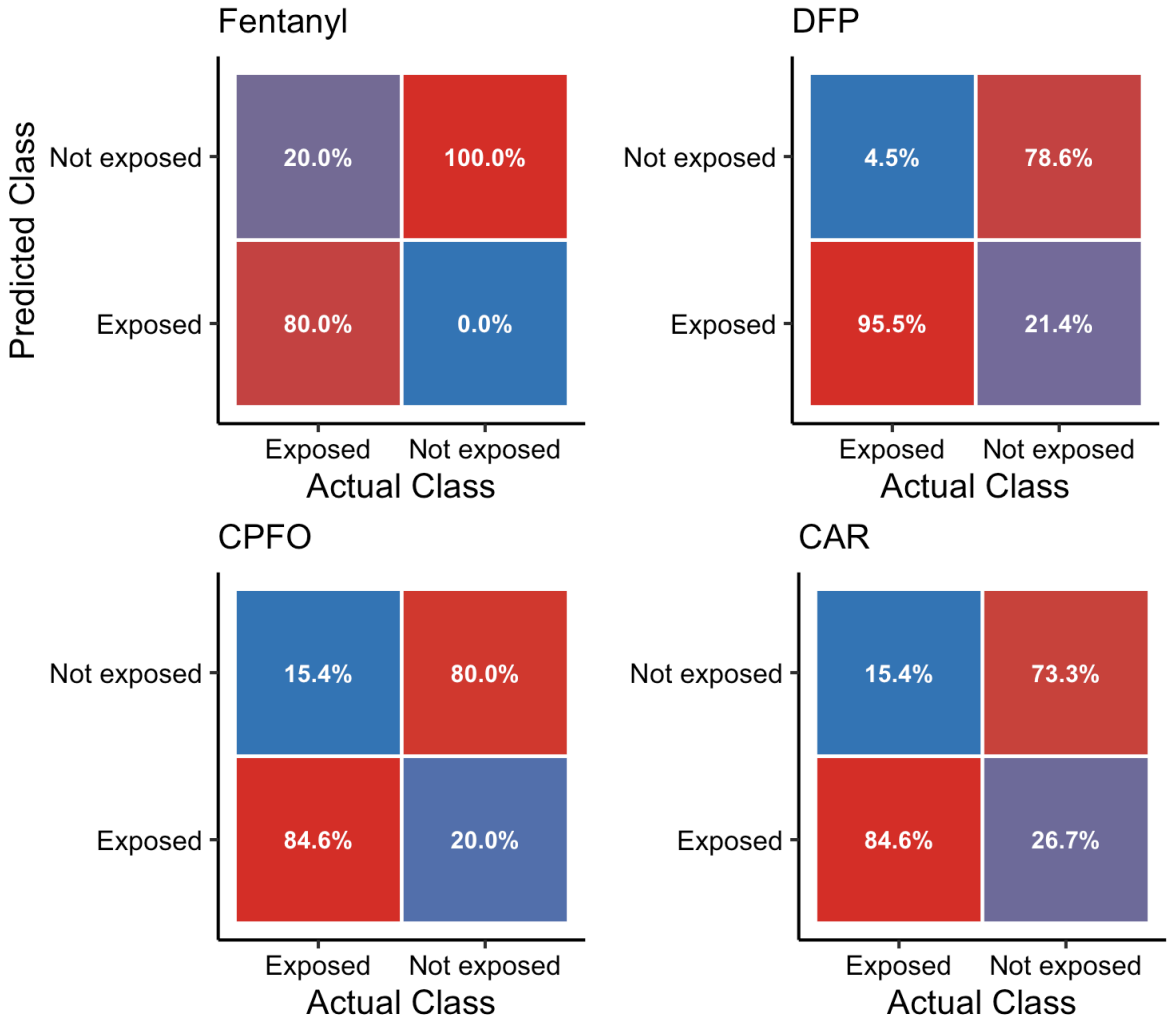


- With 100 channels/well of data, we get ≥95% accuracy
- Simple, fast model – answer in <1 sec



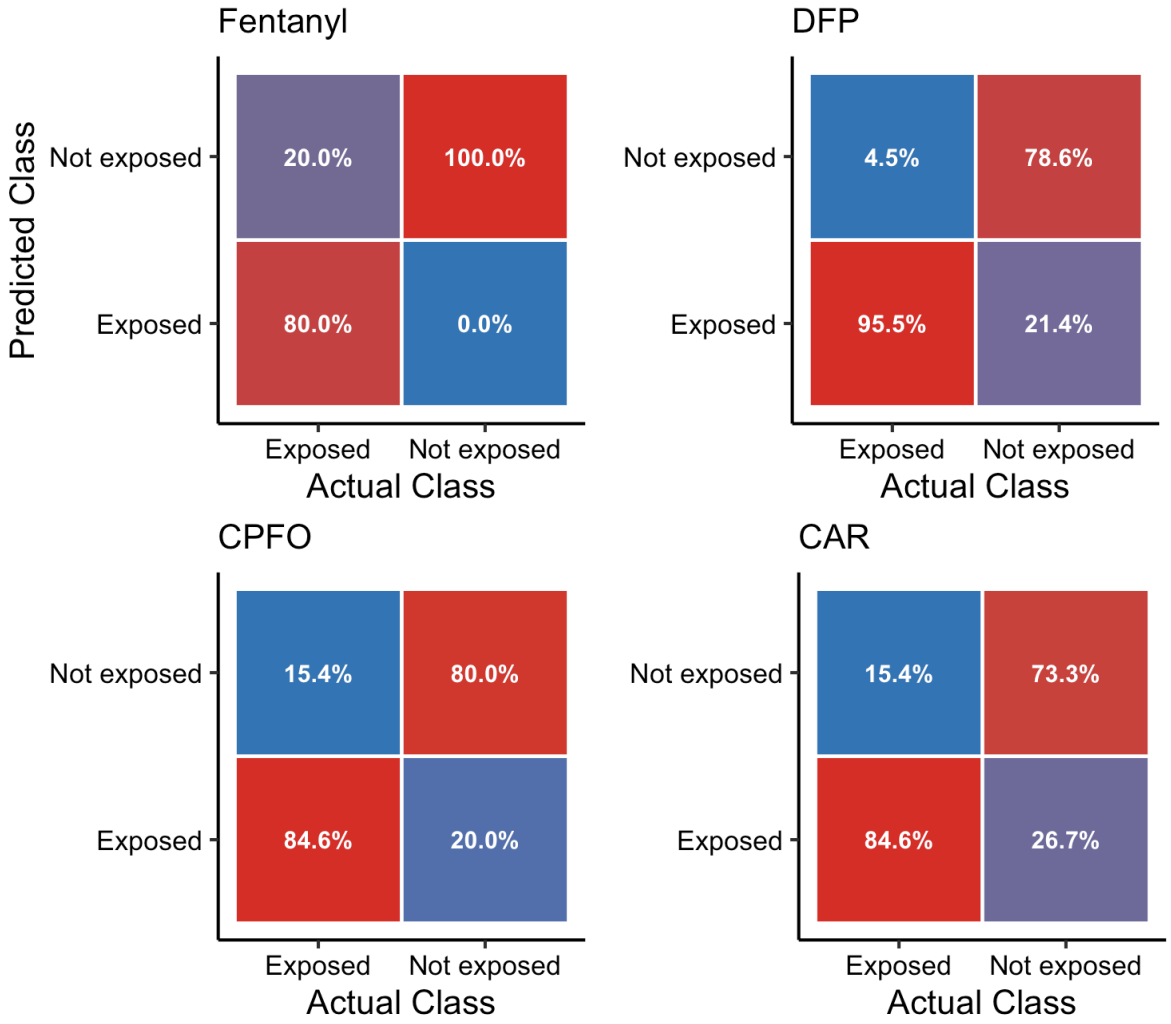
Brain-on-a-Chip: Neurotoxin exposure by Microelectrode Array (1)

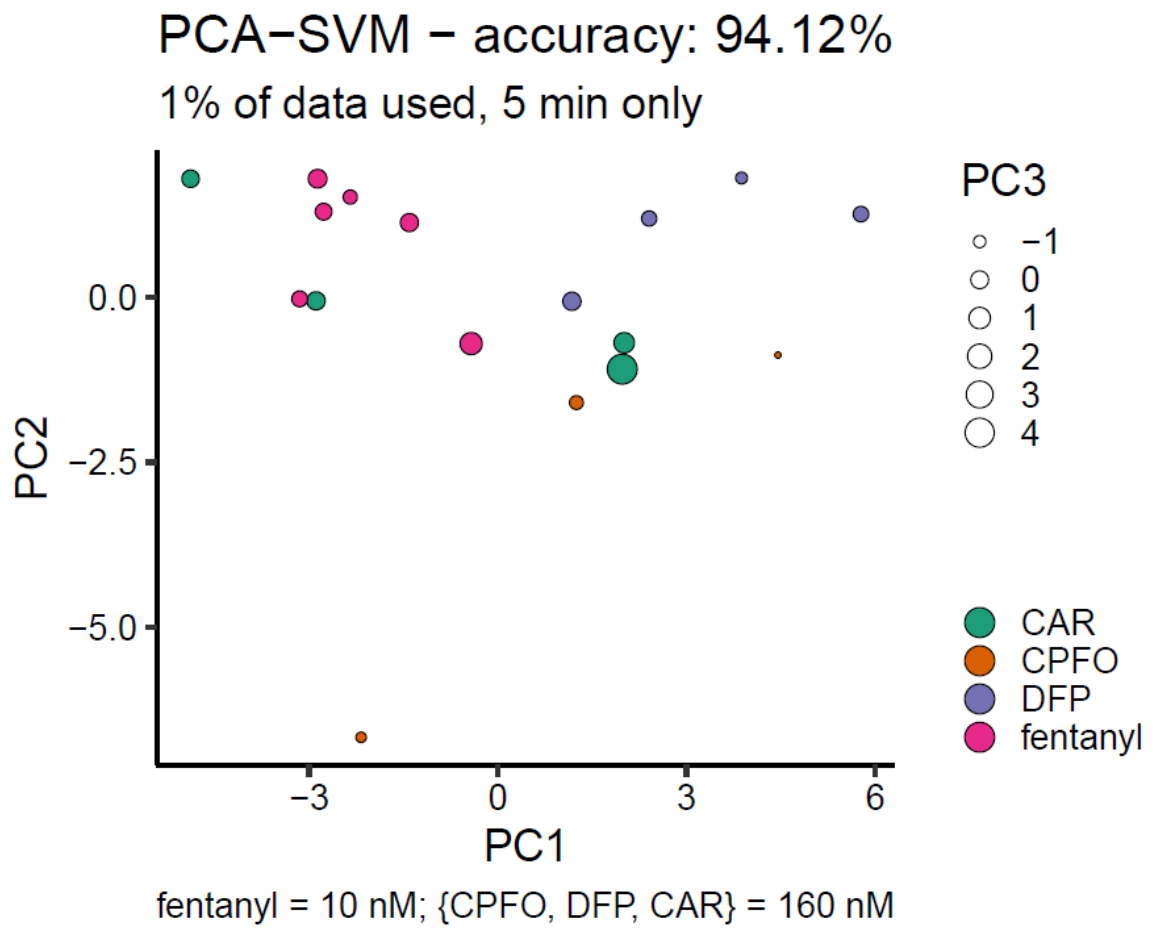
Using randomly selected single channels from each well



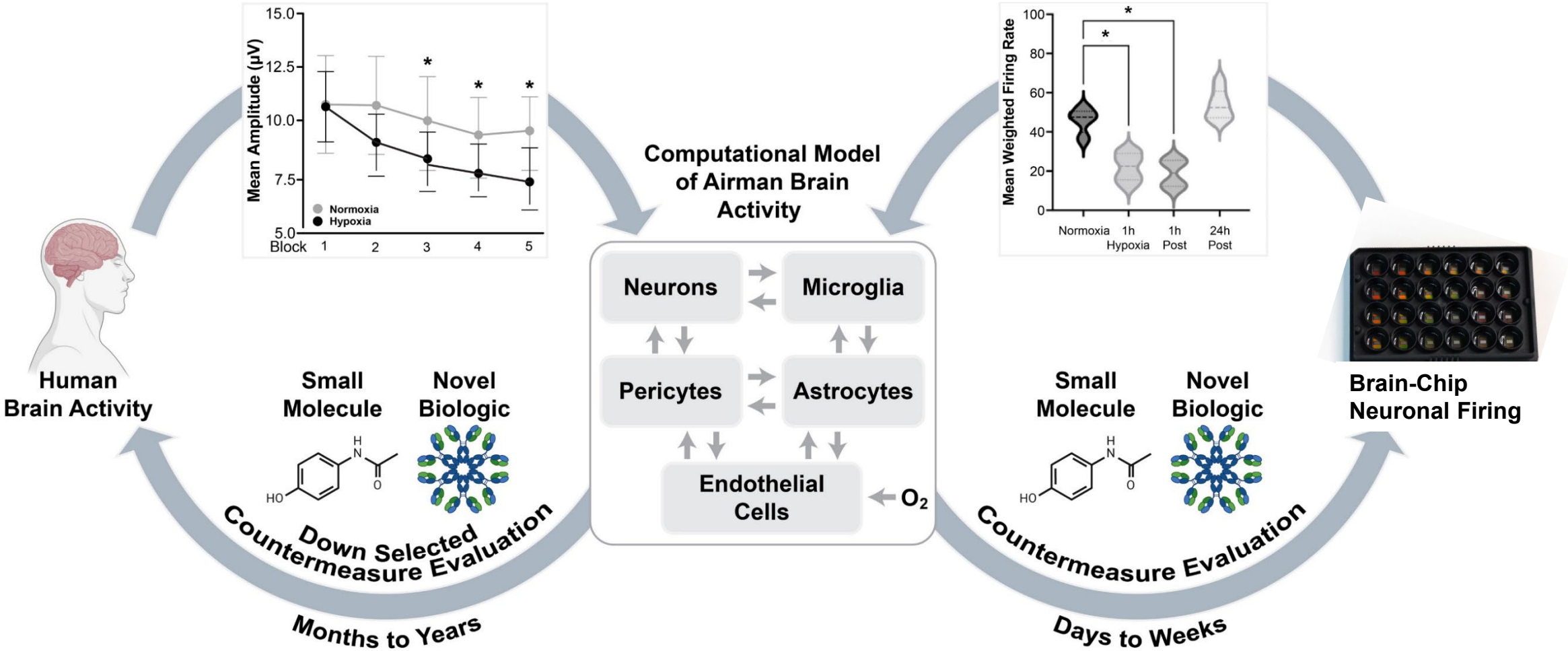
Brain-on-a-Chip: Neurotoxin exposure by Microelectrode Array (2)

Using randomly selected single channels from each well



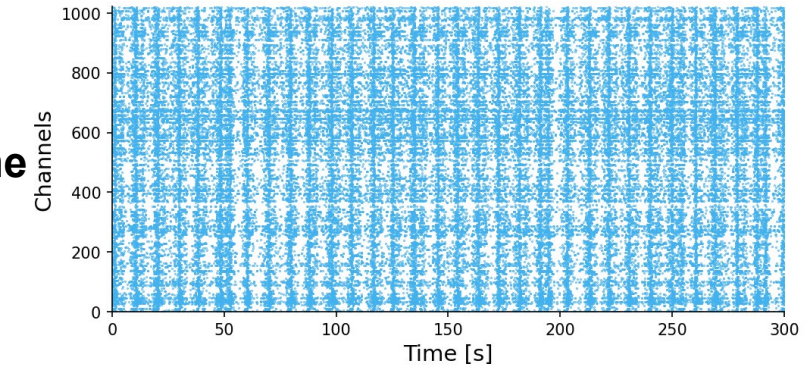


IVIVE: An Integration and Validation of In Vitro Platforms and ML-algorithms for Altered Neuronal Activity

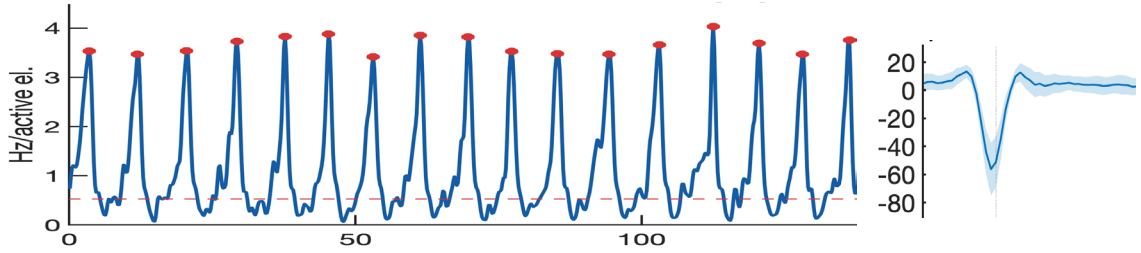


Brain-on-a-Chip: Hypoxia exposure modulates neuronal firing

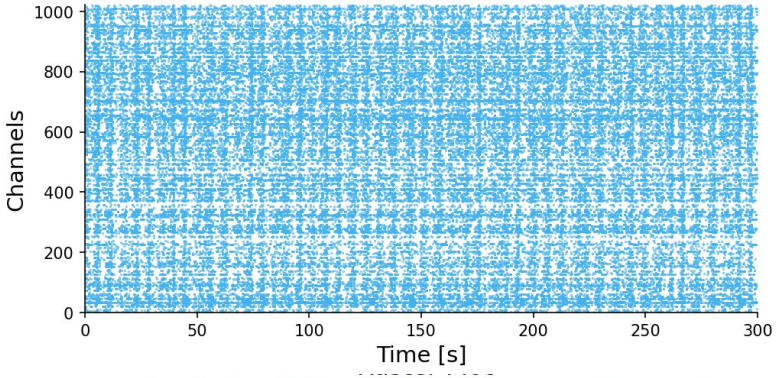
Baseline



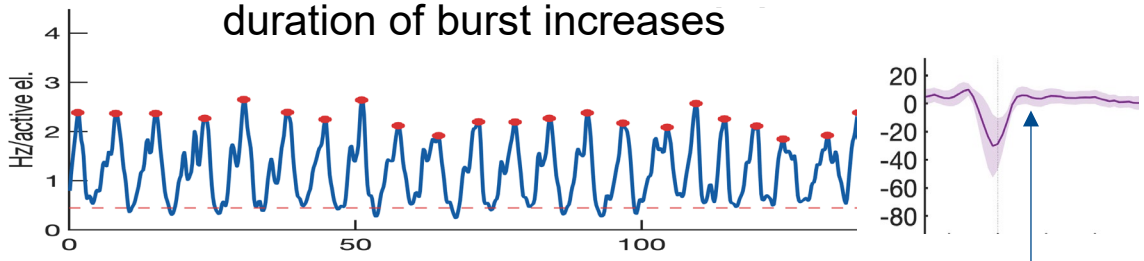
Spikes cluster together in steep peaks



2h

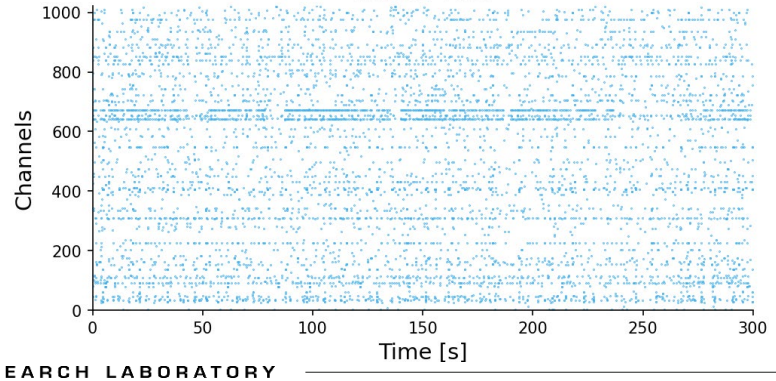


Interval between bursts decreases, duration of burst increases

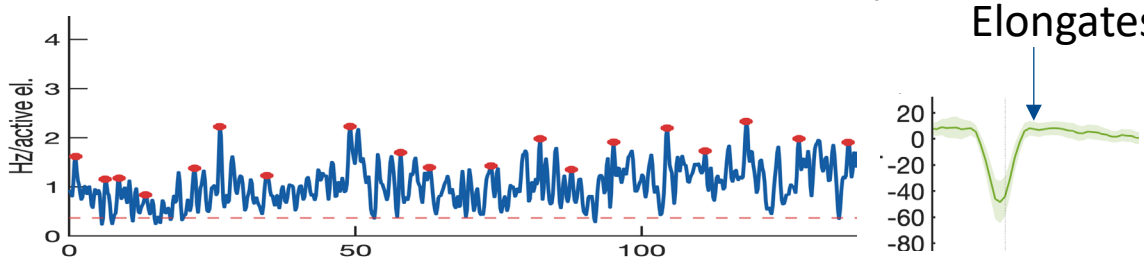


Refractory Period Elongates

4h

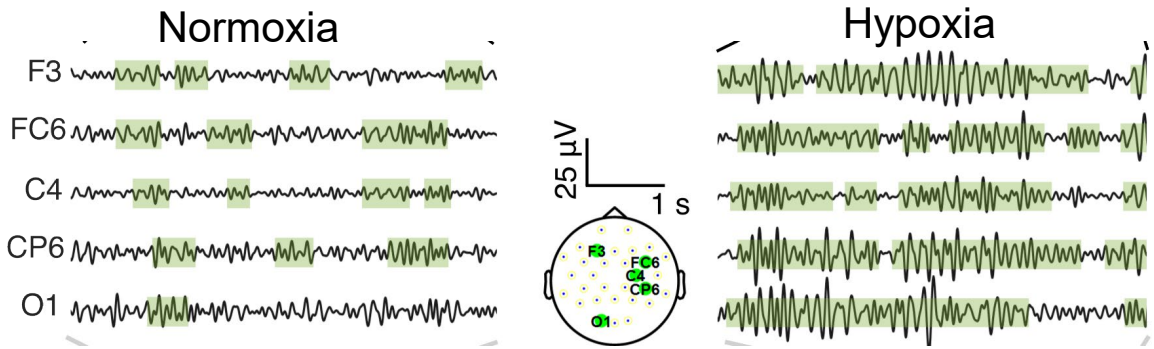


Depleted resources reduce bursts of activity

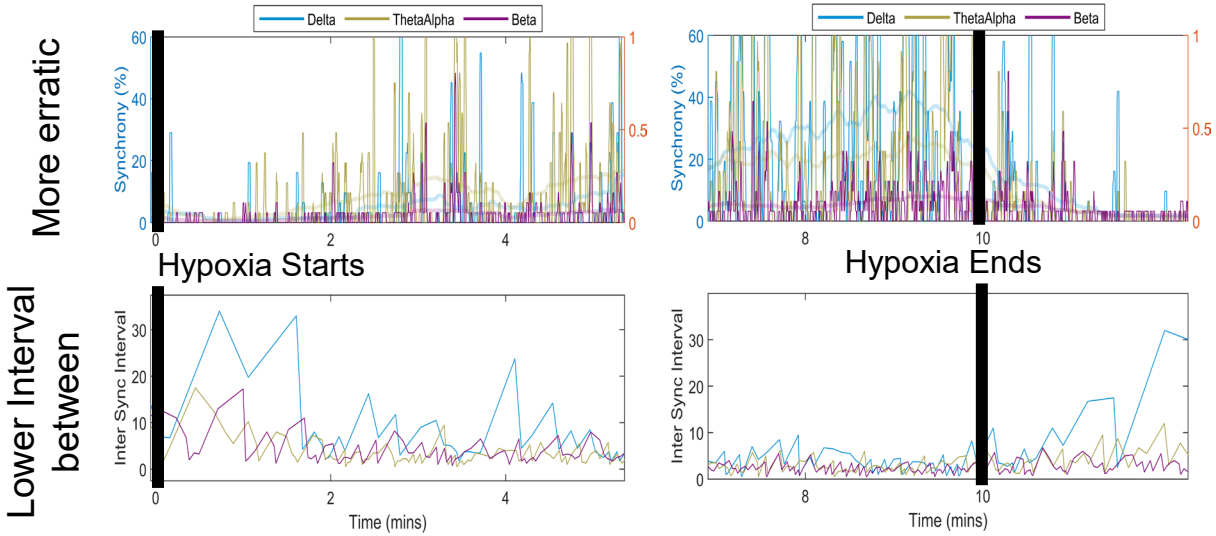


Similar neuronal activity features can be extracted from human EEG

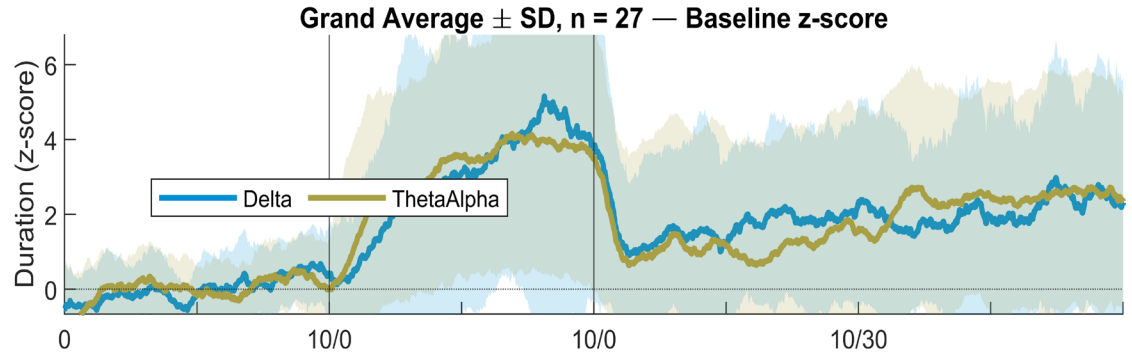
Oscillatory Bursts are detected with adaptive algorithm



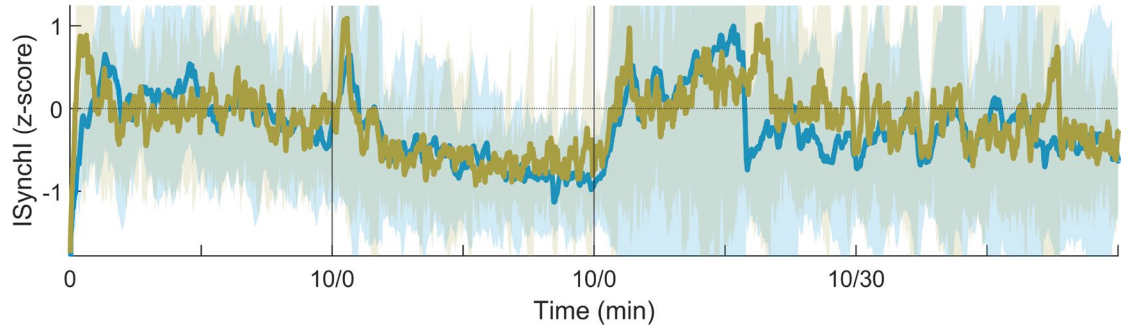
Synchronous (multi channel burst events) activity



Duration of Bursts increase



Interval between synchronous events decreases



Both MEA and EEG show increased rapid bursting and longer burst periods in hypoxia

Conclusions and Future Directions

- Brain-on-chip platforms provide physiologically relevant models for evaluating sub-lethal doses of chemical or biological exposures
- Integration with computational models enables rapid detection and prediction of future exposure scenarios
- Leveraging machine-learning approaches advances our understanding and detection of exposure-induced aberrant neuronal firing patterns
- Approach can be easily expanded to examine other organ systems and/or unknown toxicological effects of other military-relevant exposures
- Enables evaluation of exposure effects in a multi-organ-on-a-chip framework for more comprehensive toxicological evaluation
- Contributes to the development of a robust platform capable of rapid detection, analysis, and prediction of exposure scenarios to improve our ability to safeguard military personnel and assets against chemical and biological threats

Questions?

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