

A perfused Biochip for continuous electrophysiological monitoring of 3-D neural tissues derived from Human pluripotent stem cells

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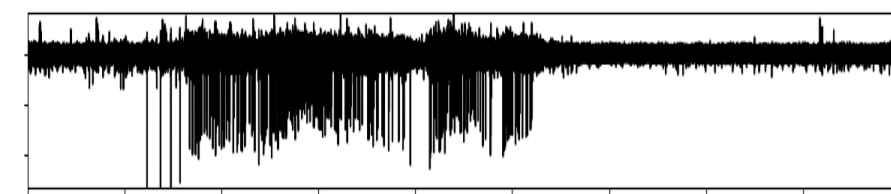


Introduction

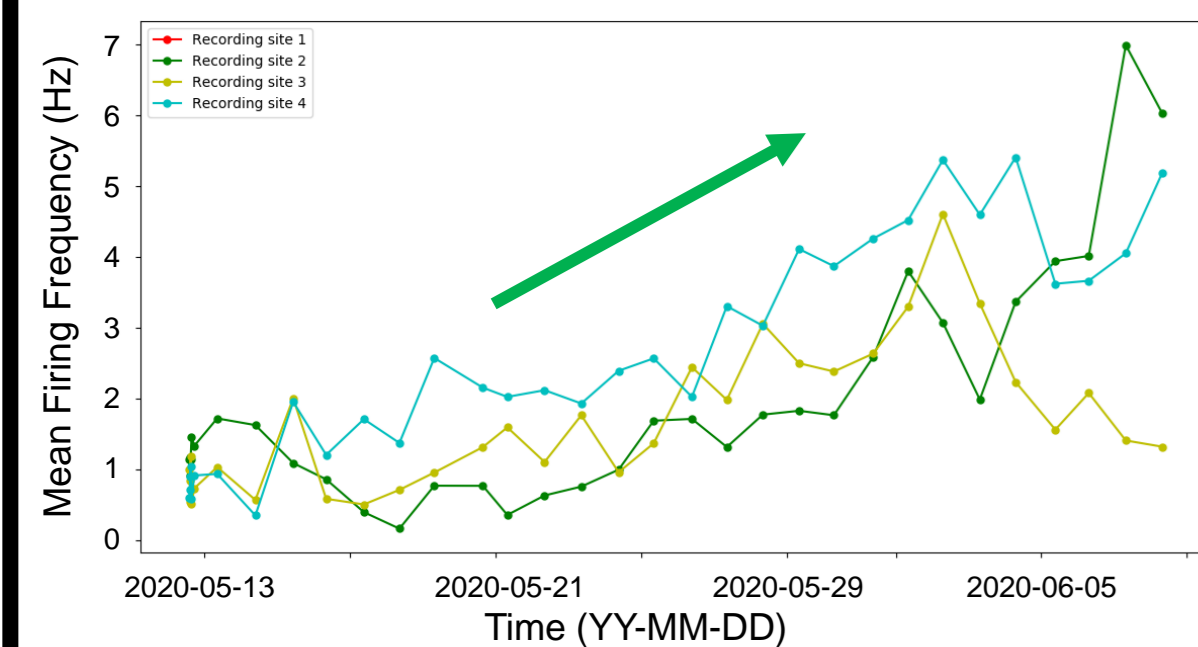
Testing of 3-D engineered neural tissue made of glial cells and neurons derived from human induced pluripotent stem cells (hiPSC) are among the most promising tools for the next decade in drug discovery and neurotoxicology. Micro-Electrode Arrays (MEA) recordings of spontaneous activity in 3-D neural tissue offer a non-invasive, rapid as well as possibly real-time and long-term assessment of compounds' effects. 3-D neural tissues are extremely sensitive to experimental conditions in particular to traditional methods using immersion of the tissues in a culture medium that does not provide sufficient short-term stability nor allow long-term survival of 3-D neural tissues.

Results

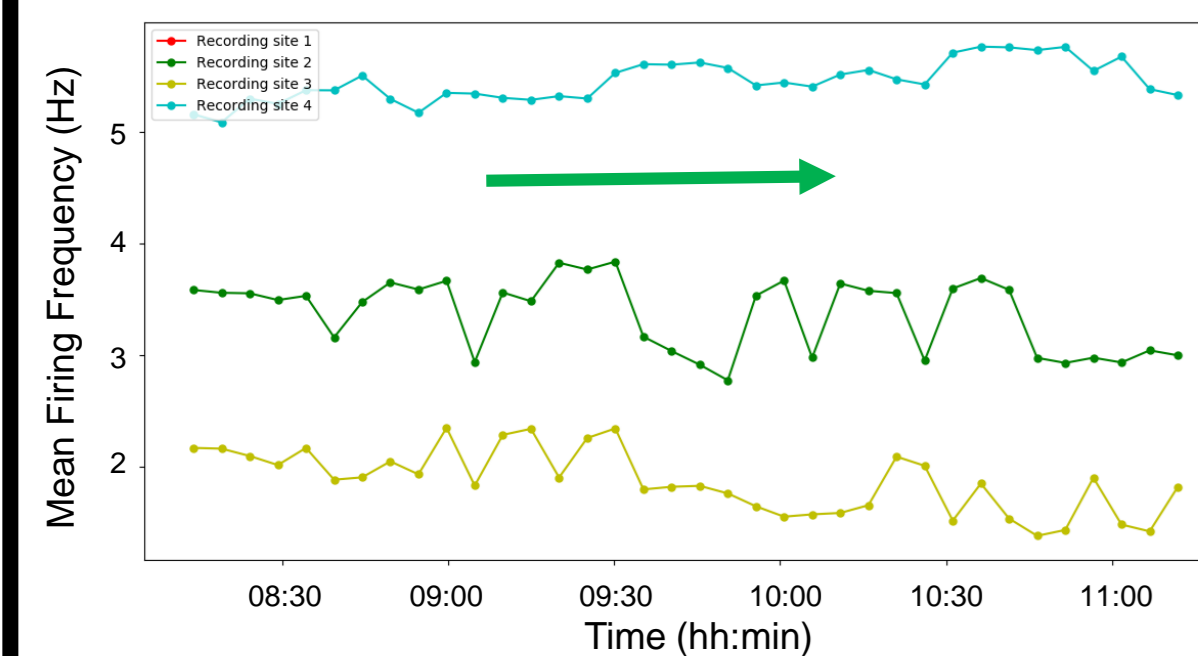
Baseline



Maturation over 4 weeks

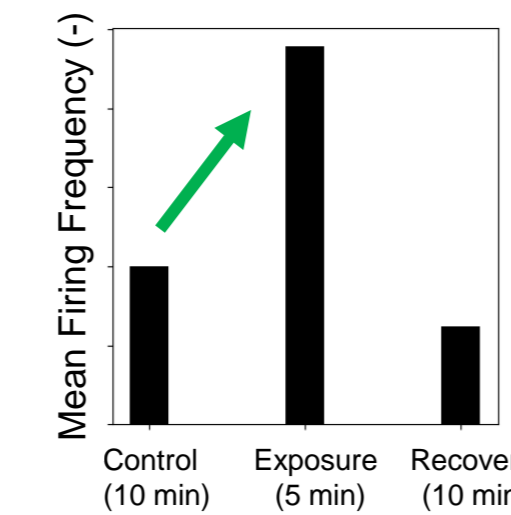
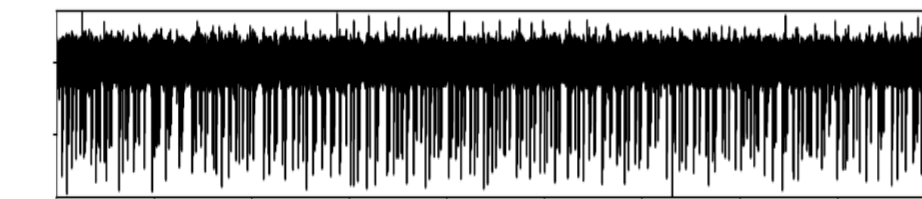


Stability over 3 hours



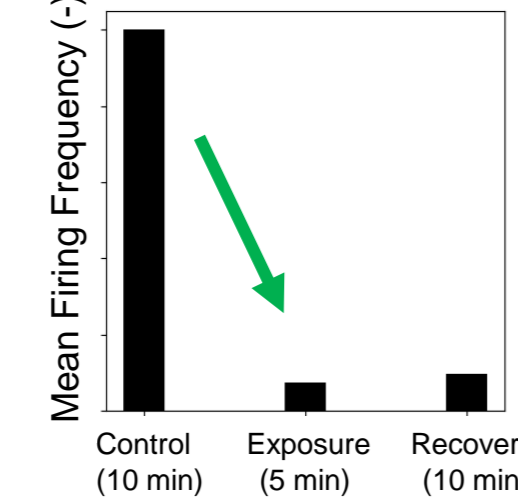
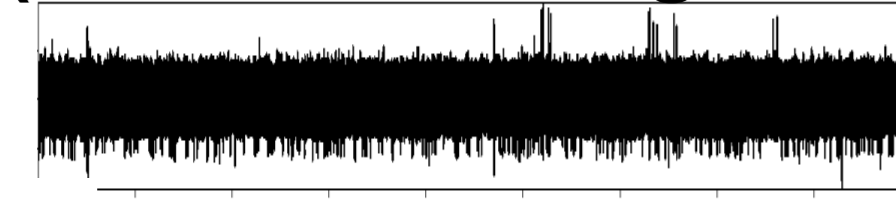
3-hour stability allows pharmacological experiments

Effect of 20- μ M NMDA (Glutamate agonist)



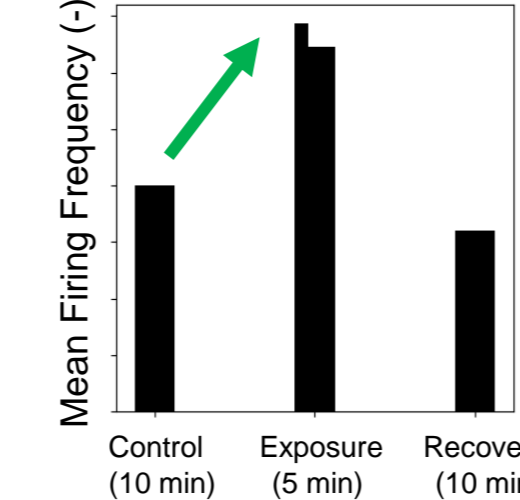
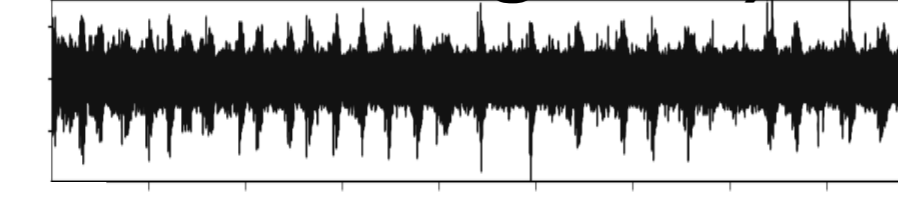
~140% increase

Effect of 50- μ M D-AP5 (Glutamate antagonist)



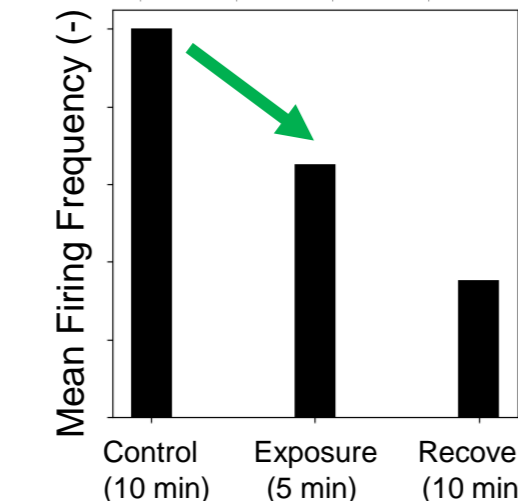
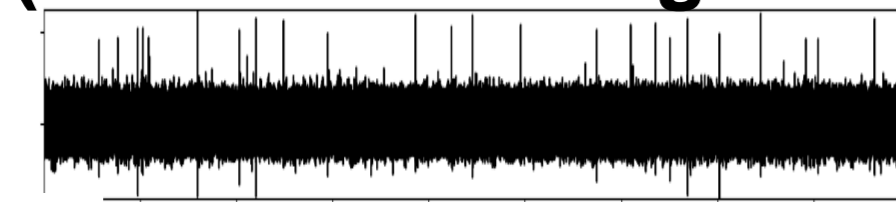
~93% decrease

Effect of 2- μ M kainic acid (Glutamate agonist)



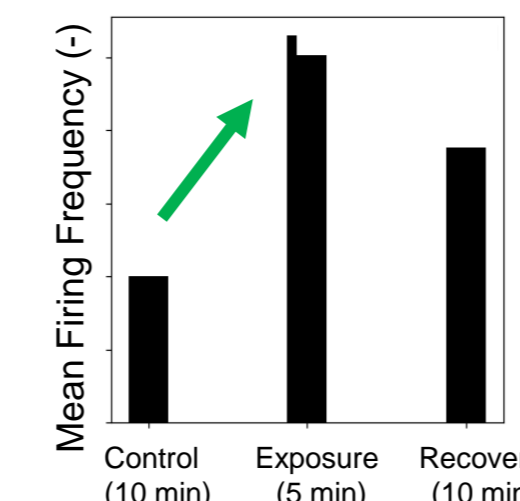
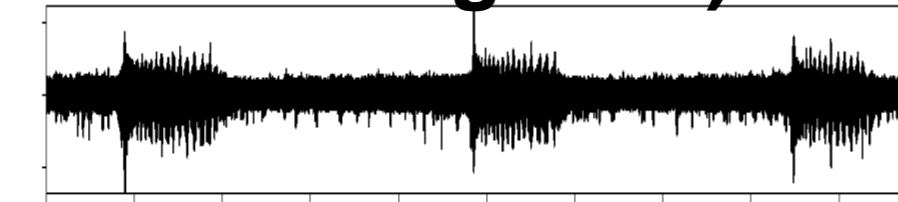
~70% increase

Effect of 100- μ M CNQX (Glutamate antagonist)



~40% decrease

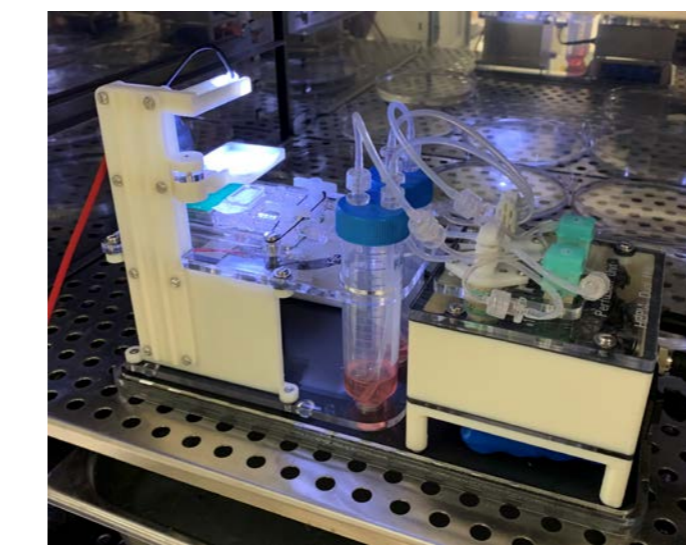
Effect of 10- μ M Bicuculline (GABAs antagonist)



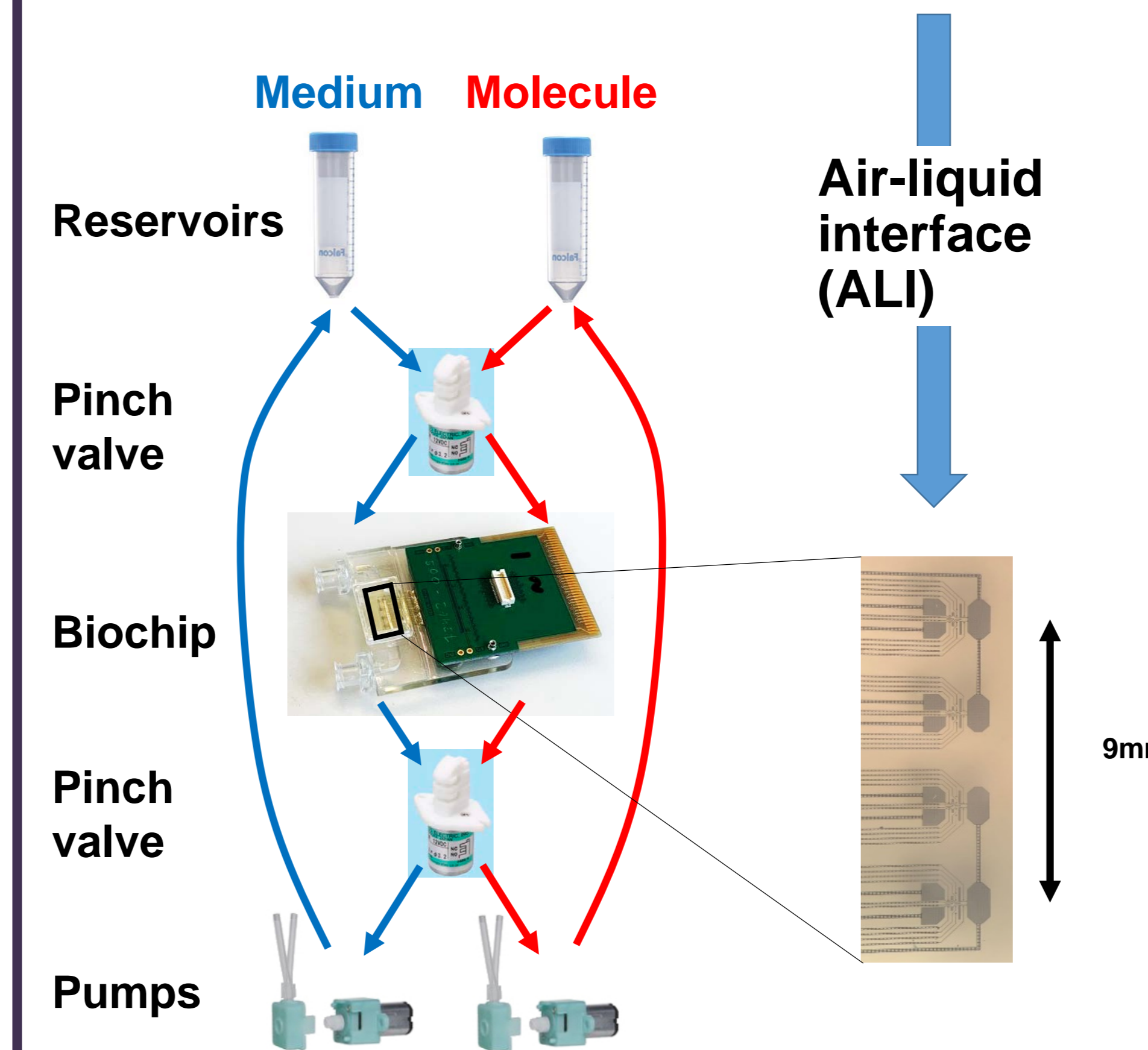
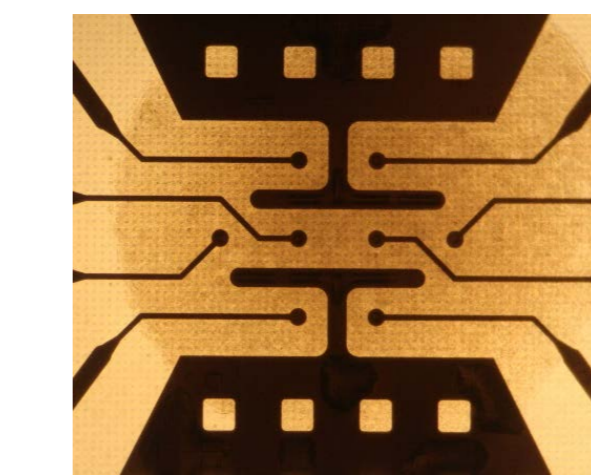
~160% increase

Material & Methods

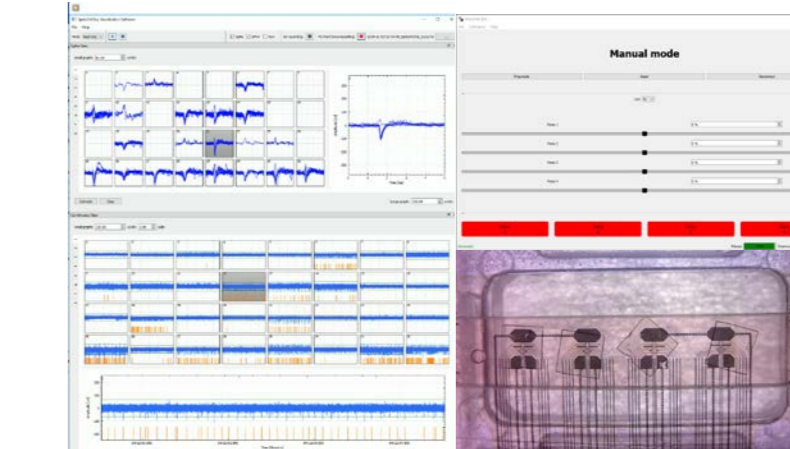
Setup



3-D Human neural tissue on MEA

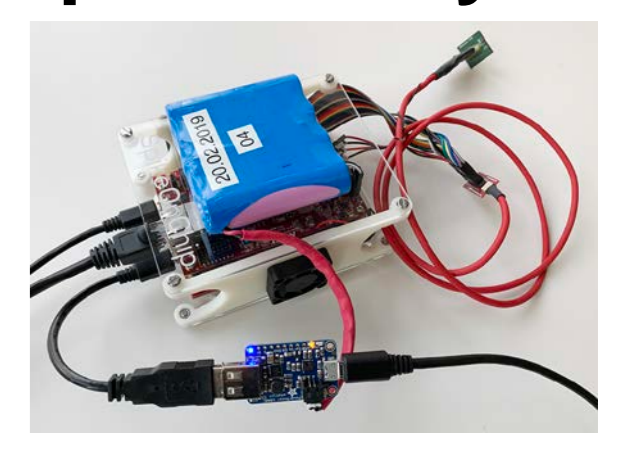


PC + software



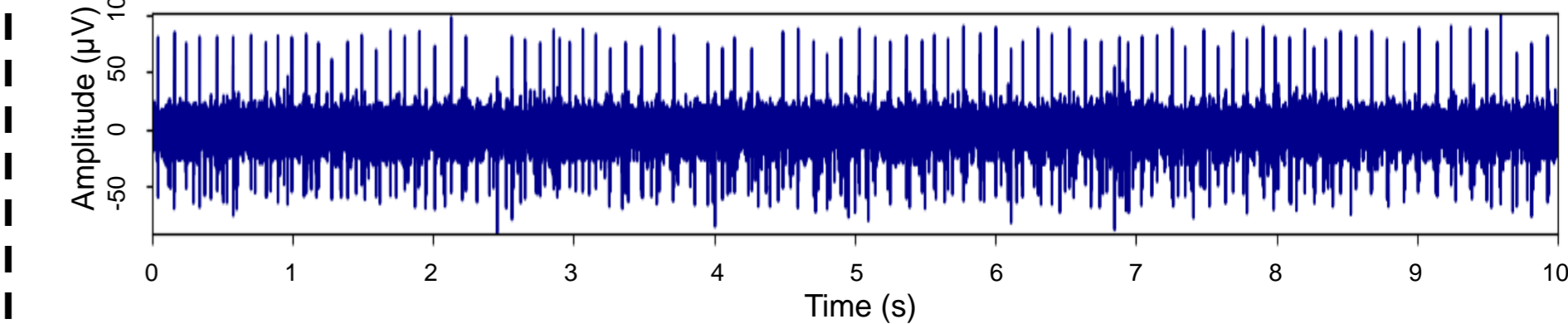
- Electrophysiology
- Pumps/valves control
- Vision

Acquisition system

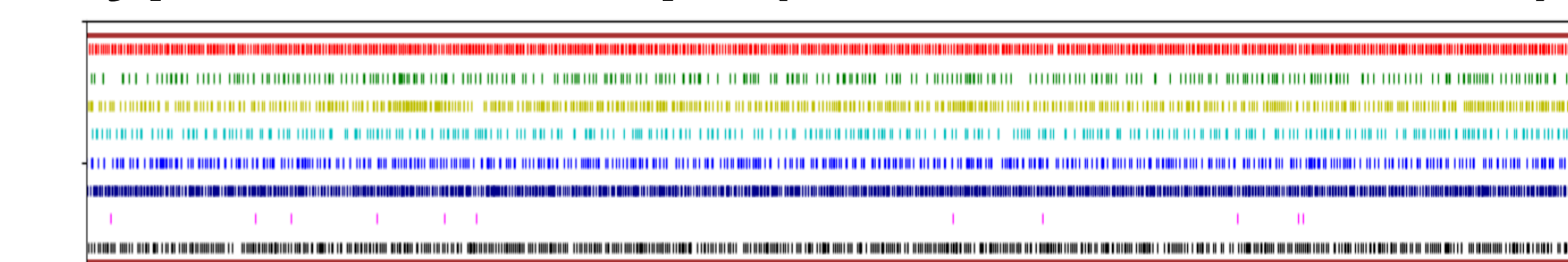


- Intan chip
- FPGA for pre-analysis
- Data recording

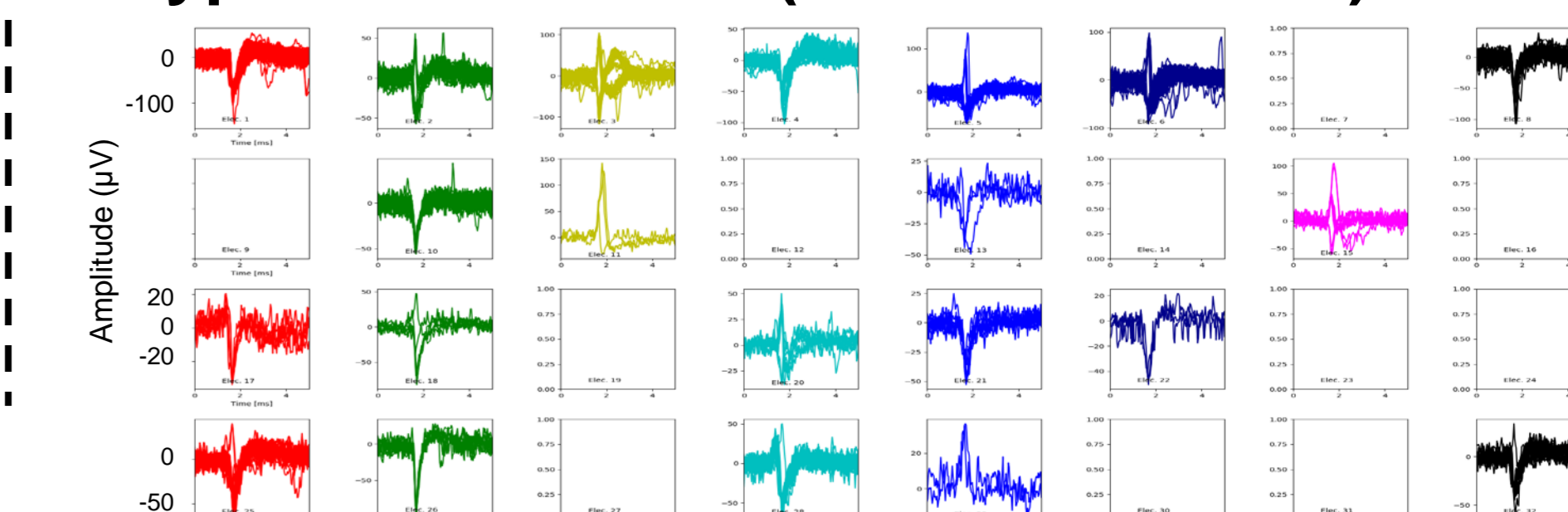
Typical raw data (1/32 electrode, 10s)



Typical timestamps (8/32 electrodes, 1min)



Typical waveforms (21/32 electrodes)



Conclusion

We have developed a small-volume Biochip perfusion *in vitro* system in which 3-D human neural tissues were transferred and maintained for several weeks up to few months onto porous membrane MEAs at ALI. Neural networks electrophysiological activities were continuously recorded and characterized using pharmacological reference compounds.

These human "brain" surrogate integrated Biochips will be a useful tool to enable the determination of toxicological profiles over a long timescales of new drug candidates or chemicals present in our environment.