

- Dominic Giannangeli designs a custom MEMS device which allows to investigate neuroplasticity, the spatial and network reorganization of neurons in response of other neurons feedback. The device has three compartments, cells in one chamber is connected to the two others, the two other chambers are only connected to the central one.
- Primary rat cortical neurons are grown in each microfluidic chamber, each side extending their axons through micro-channels with the other side.
- Electrical stimuli are applied to the neurons of one of the extreme chambers and not to neurons in the other one, thus creating neural feedback in only one direction: from one of the peripheral chambers to the central chamber. Neuronal activity and physiological changes in the connections between each well are then studied and compared.
- Organotypic cells compared to cell cultures maintain cytoskeleton and are less limited in term of axon growth or synapse formation. We keep the interconnection of the three chambers used in the initial model, but instead of cortical neurons, rat cortical slices of about 350  $\mu\text{m}$  will be cut using a tissue chopper and placed onto petri dishes with three polydimethylsiloxane (PDMS) wells separated by microchannels. Cultures will be covered with a medium and placed into a tissue incubator. Each slice will be perfused with artificial cerebro-spinal fluid (aCSF) and drugs. Electrical activity will be stimulated by electrodes in the peripheral dish with carefully calibrated pulses to generate an action potential, the neuronal response will be recorded with microelectrodes placed on the slice of the central well. An electrode will also be attached to the neurons of the dish with no explicit stimuli, to record if neural activation is sent from the central well to this compartment, which will allow us to have an understanding of the full pathway from the feedback slice to the other terminal slice.
- The previous model is simple but may not fully represent the complexity of interactions between neurons. 2-D cultures may affect the spatial growth of the neural network. In addition, a 3-D cultures like organoids have better cell-cell interactions and simulate cellular functions and neural signaling which resemble better in-vivo tissues. However, brain organoids derived from human PSCs begin to apoptosis due to lack of vascularization and exogenous factors, and cannot be used to study the development of human fetal brain after the first trimester. If the aim of the study is to study neuroplasticity in presence of neurological diseases which can appear in adult or in advanced ages, organoids cannot be used.
- However, the various models previously discussed will show significant limitations to understand the neural network reconstruction which happens like in stroke or brain injury where some components of the microenvironment are beneficial like blood capillaries, oxygen and neurotrophic factor or damaging like neuroinflammatory. In order to mimic closer, the in-vivo environment in which these cells evolve, the design of a more complex model like organ-on-a-chip may ultimately be required.

- 1) Yevgeny Berdichevsky et al., Lab on Chip, Issue 8, 2010 - Building and manipulating neural pathways with microfluidics
- 2) Michael P. Schwartz et al., 2015-10-06, Human pluripotent stem cell-derived neural constructs for predicting neural toxicity, <https://doi.org/10.1073/pnas.1516645112>
- 3) Kimura, H., Sakai, Y. (2018). Organ/body-on-a-chip based on microfluidic technology for drug discovery. Drug Metabolism and Pharmacokinetics. Vol. 33, Issue 1. pp. 43-48.
- 4) Wang, Z., Wang, S., Xu, T., et. al. (2017). Organoid technology for brain and therapeutics research. CNS Neuroscience and Therapeutics. Vol. 23, Issue 10.