DIGITAL SIGNATURE LIBRARY USING NEURONS AS UNIVERSAL BIO-DIGITAL SENSORS

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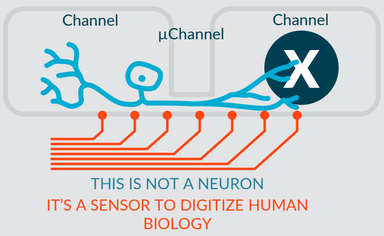
BACKGROUND

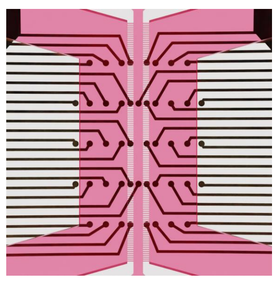


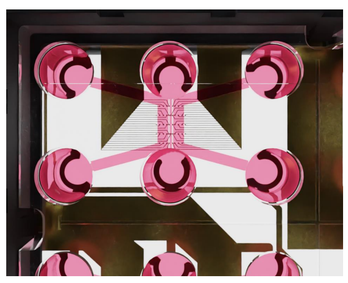
Neurons are processing their inputs through firing or not firing, which can be equated to producing zeros and ones. Since every single organ in the body is innervated, the nervous system can essentially by seen as distributed network of bio-digital sensors. By connecting (and fluidically isolating) neurons to a target organ, be it other neurons in CNS applications or any organs in PNS applications, we aim to encode organ states (healthy, diseased, altered…) into digital signatures that in turn populate a Digital Library, creating a framework for fingerprinting and ranking effects of screened drug compounds based on the desired functional outcome.

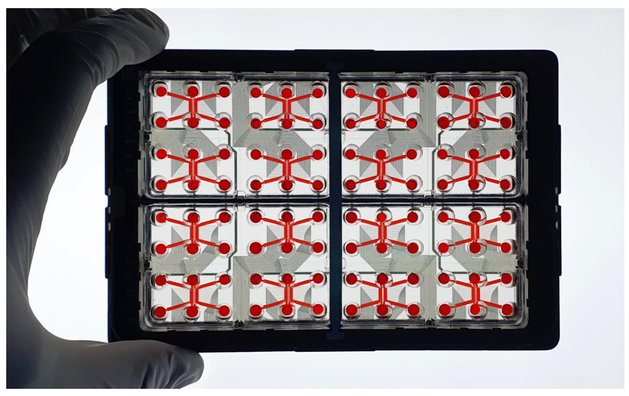
RESULTS

HARDWARE (HW) AND SOFTWARE (SW) PLATFORMS

We use the NeoBento™ standard SBS format outfitted with DuaLink MEA chips, that combine NETRI's microfluidic architectures with a bespoke multi-electrode array (MEA) surface from Axion Biosystems.
Metrics are extracted using NETRI's UpLink software piloting Axion Biosystem's Axis Navigator. Data processed in NETRI's database DataLink.







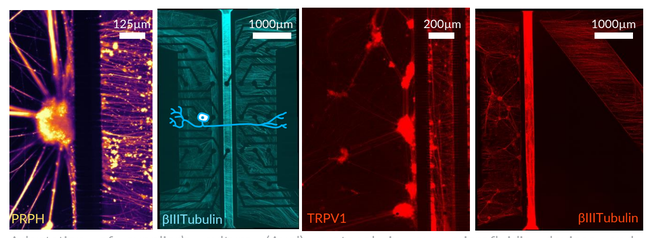
This HW/SW platform allows to :

- Fluidically isolate somas from endings (and target organs) through microchannels
- Perform compartmentalized functional activity recording, specifically in the µchannels that hosts axons ferrying data from the sensed compartment to the sensing compartment.

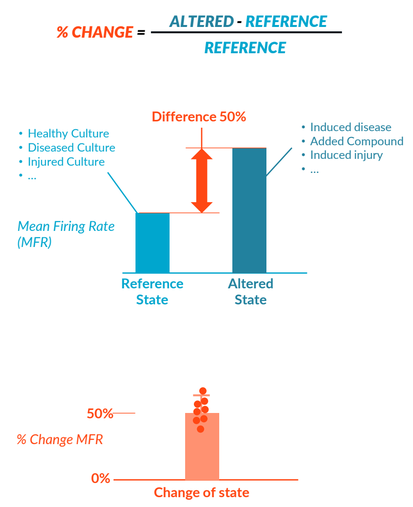
SENSOR REPEATABILITY

Repeatability is achieved through

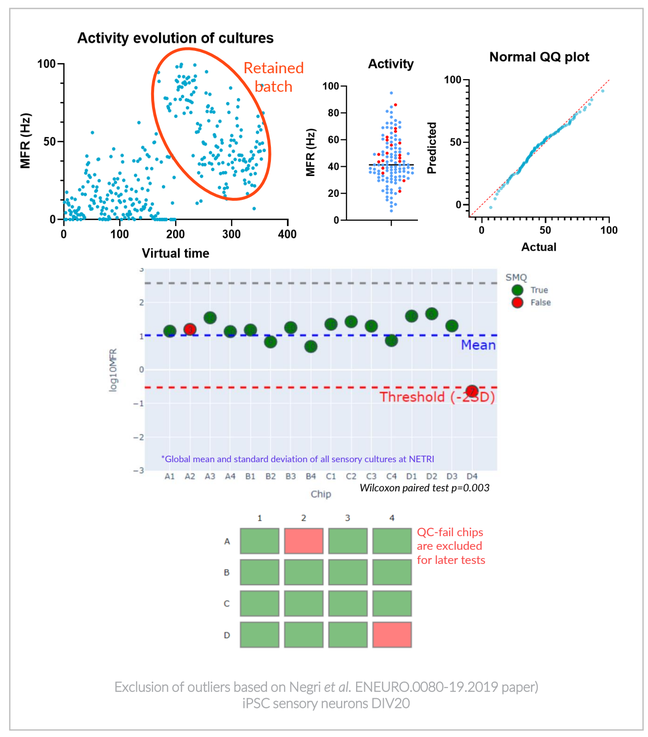
- Vendor, batch selection, and characterization
- Standardized Quality Control (QC) method for each culture
- Focusing on the % change within a single culture thanks to MEA non-destructiveness.



Adaptation of supplier's culture (Axol) protocol in our microfluidic devices and confirmation of marker expression.



MEA recording is non-destructive. We look at relative change within a single chip, between a Reference State and an Altered State. This self-referencing approach mitigates (inevitable) culture variability remaining after QC and allows statistical analysis



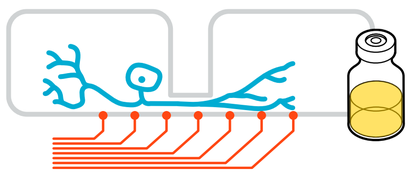
Exclusion of outliers based on Negri *et al.* ENEURO.0080-19.2019 paper)
iPSC sensory neurons DIV20

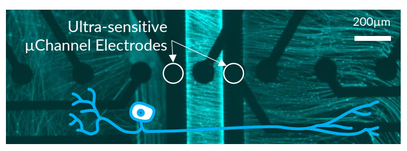
SENSOR SENSITIVITY

We have assessed the sensitivity of our neuron sensors through a variety of reference compounds, using :

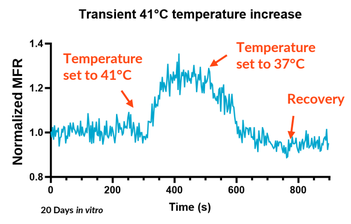
- A Fast Acting method, that records momentaneous activity for an Altered State of a Reference State baseline.
- A Slow Acting method, that records activity over 2 consecutive periods: Reference State period and a subsequent Altered State period.

Sensor sensitivity can already serve multiple applications using application-specific altered state references.
This is especially enabled for sensory neurons by recording activity in the microchannel that connect compartments.

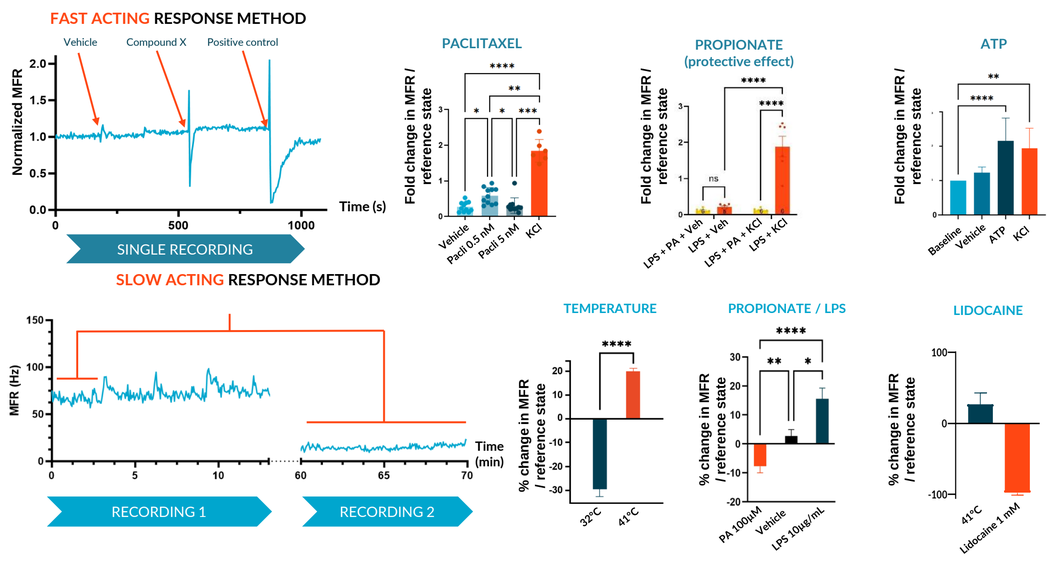




NETRI DuaLink MEA Chip with hiPSC Sensory Neurons

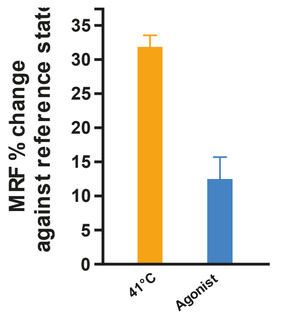


Recording of sensor activity over a transient temperature profile illustrates the sensitivity of the sensory neurons.

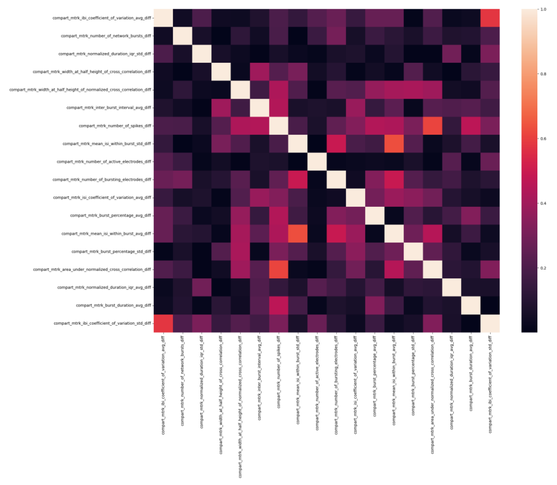


SENSOR SPECIFICITY (ONGOING)

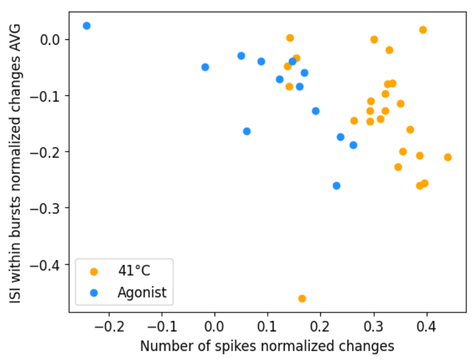
Sensitivity is limited in its ability to discriminate between altered states. We can therefore leverage the full gamut of metrics that MEA offers to attempt and tell seemingly alike signals apart and confer specificity to our sensors.

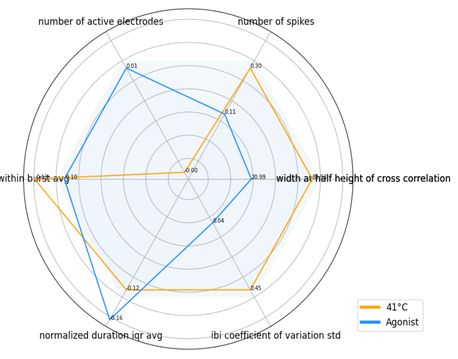


% Change in MFR for 2 Altered States (Temperature 41°C and an Agonist) Early tests, small dataset.



Out of 42 MEA metrics, we isolated the ones that have a Pearson correlation score less than 0.7, among which we select the ones that have the highest Information gain.
Based on the selected metrics we managed to discern meaningful difference between the 2 altered states.





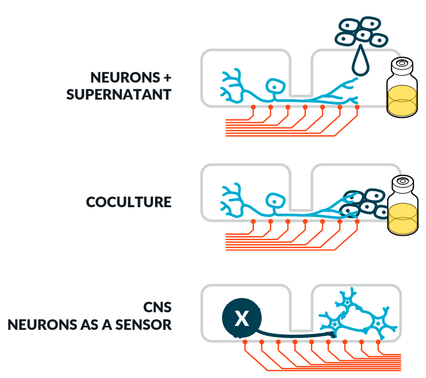
Discrimination Method : Information Gain

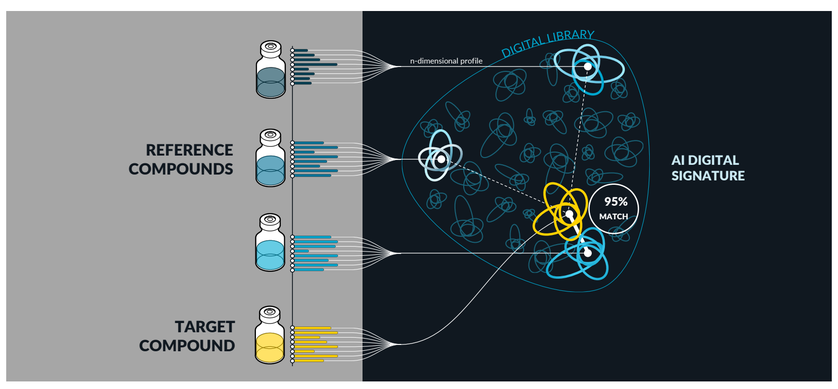
The early findings above suggest the ability to plot meaningful metrics that show a discriminating pattern when standard Mean Firing Rate readouts did not. This suggest that we can achieve sensor specificity and pave the way for digital signatures of Altered States.

CONCLUSION & PERSPECTIVES

TOWARDS A DIGITAL LIBRARY

The central notion emerging from this effort is the standardized digitization power that well calibrated fluidically-isolated neuronal cultures bring to organ functional analysis. From assessing the effects of compounds on a disease, a cream on a skin, a nutrient in the gut, or orienting the repositioning of a drug, using neurons-as-biodigital-sensors offer an impactful and agnostic platform solution in a wide variety of applications that extend far beyond neuroscience.





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