An innovative approach for conducting 3D electrophysiological recordings within intact brain organoids

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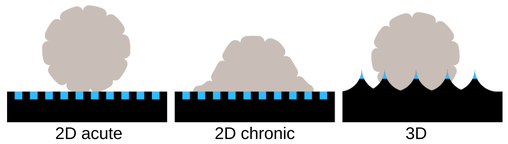
Introduction and summary

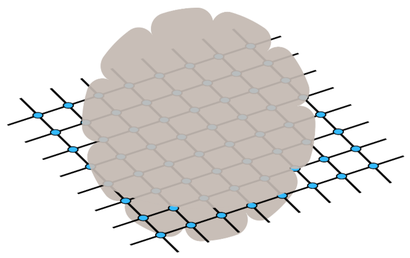
- Neurological disorders often lack translatability in animal models.[1]
- iPSC-derived brain organoids offer a human-relevant model system.[1]
- Electrophysiology is crucial for assessing neural circuit activity and drug effects.

- We present a mesh microelectrode array (MEA) device for 3D neural tissue *in vitro*.[2,3]
- Compared to classical planar MEAs, the mesh MEA should allow chronic recordings and minimal disruption to the 3D tissue.
- Neural tissue envelops the mesh filaments, enabling recordings from within the tissue.
- The mesh enables medium flow from all sides and keeps the tissue suspended away from all surfaces.

Spheroids are constrained by the solid surfaces of planar or 3D MEAs, which may diminish physiological relevance.

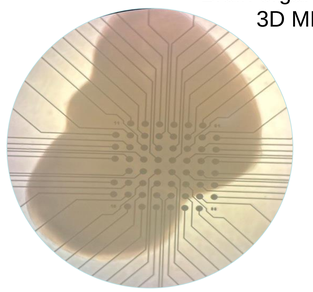


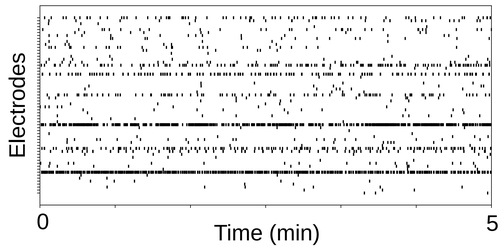
Mesh MEAs do not constrain spheroids, and microelectrodes are internalized to record from within 3D structures.



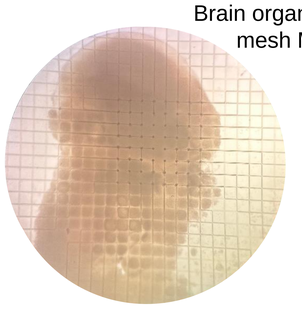
Recording of human brain organoids

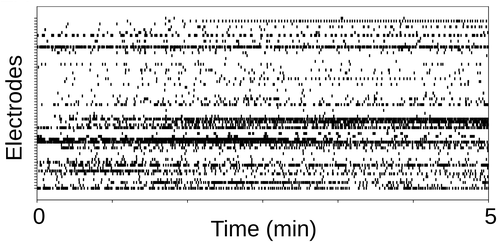
Brain organoid on a 3D MEA





Brain organoid on a mesh MEA

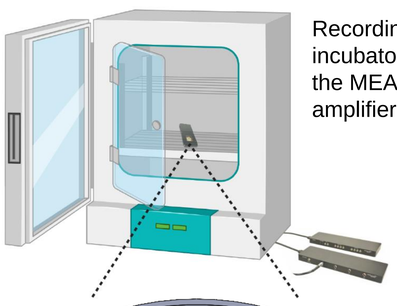




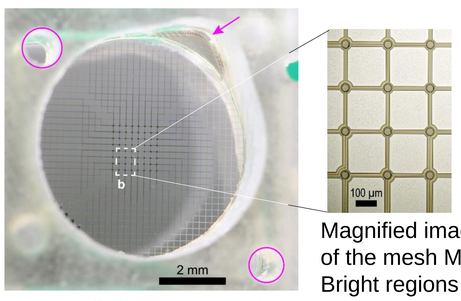
Outlook

- Mesh MEAs allow repeated long-term measurements within neural spheroids, organoids, and other 3D tissue models.
- The well design allows simple medium exchange, culture at an air-liquid interface, and perfusion.
- This new tool should contribute to a better understanding of electrophysiological activity in 3D *in vitro* models.
- Functional electrical readout will help to develop advanced 3D models of human neurodevelopment and disease.

Mesh MEA design

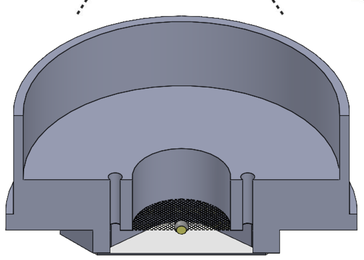


Recordings in an incubator using the MEA Mini amplifier (MCS).

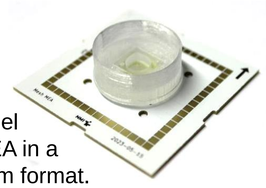


Inner well with two in-/outlets and a pipetting ledge

Magnified image of the mesh MEA. Bright regions are open space.

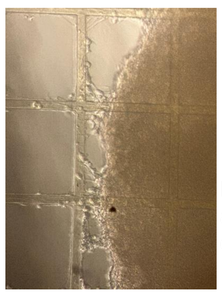


Cross section of the mesh MEA. The mesh suspends spheroids 2 mm above the bottom window.



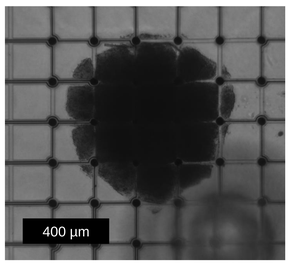
60-channel mesh MEA in a 49×49 mm format.

Neuron growth on the mesh

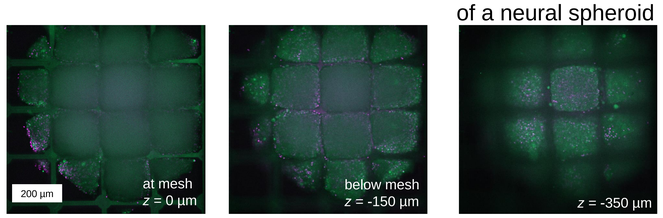


Neuronal migration after seeding shows cell viability

Neural spheroid placed on the mesh



Live and dead staining of a neural spheroid



Propidium iodide (dead)
Cal-520AM (alive)

Contributions & acknowledgements

TS, HC, MM, DP, AS, HC & UK & PDJ: development and fabrication of mesh MEAs and evaluation using neural spheroids.
SM, JH: evaluation of MEAs using brain organoids
AH, MG: analysis of recordings
SS, JA: amplifier hardware and software

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To learn more about using mesh MEAs in your lab, visit the Harvard Bioscience booth.

References

[1] Engle, S.J., Blaha, L., Kleiman, R.J., (2018) **Best Practices for Translational Disease Modeling Using Human iPSC-Derived Neurons.** Neuron, 100, 783–797.

[2] Stumpp, T.; Mierzejewski, M.; Pascual, D.; Stumpf, A.; Jones, P. D. (2023) **Scalable Mesh Microelectrode Arrays for Neural Spheroids and Organoids.** Current Directions in Biomedical Engineering, 9 (1), 575–578.

[3] McDonald, M. *et al.* (2023) **A Mesh Microelectrode Array for Non-Invasive Electrophysiology within Neural Organoids**. Biosensors and Bioelectronics, 228,