Forebrain Organoids: Biosynthetic Neural Networks

Matthew Lyn – 2024-10-30

About Matt

[Mostly] Educated:

New York U. (Business)

Georgetown (Industrial Sciences)

Jobs:

Disaster Risk Analyst (World Bank)

Healthcare Data Analyst (NeueHealth)

Fun Fact:

Has the same birthday as Bob Marley and Ronald Reagan.

Okay, nice, cool, get back to the brains in jars

Some Context:

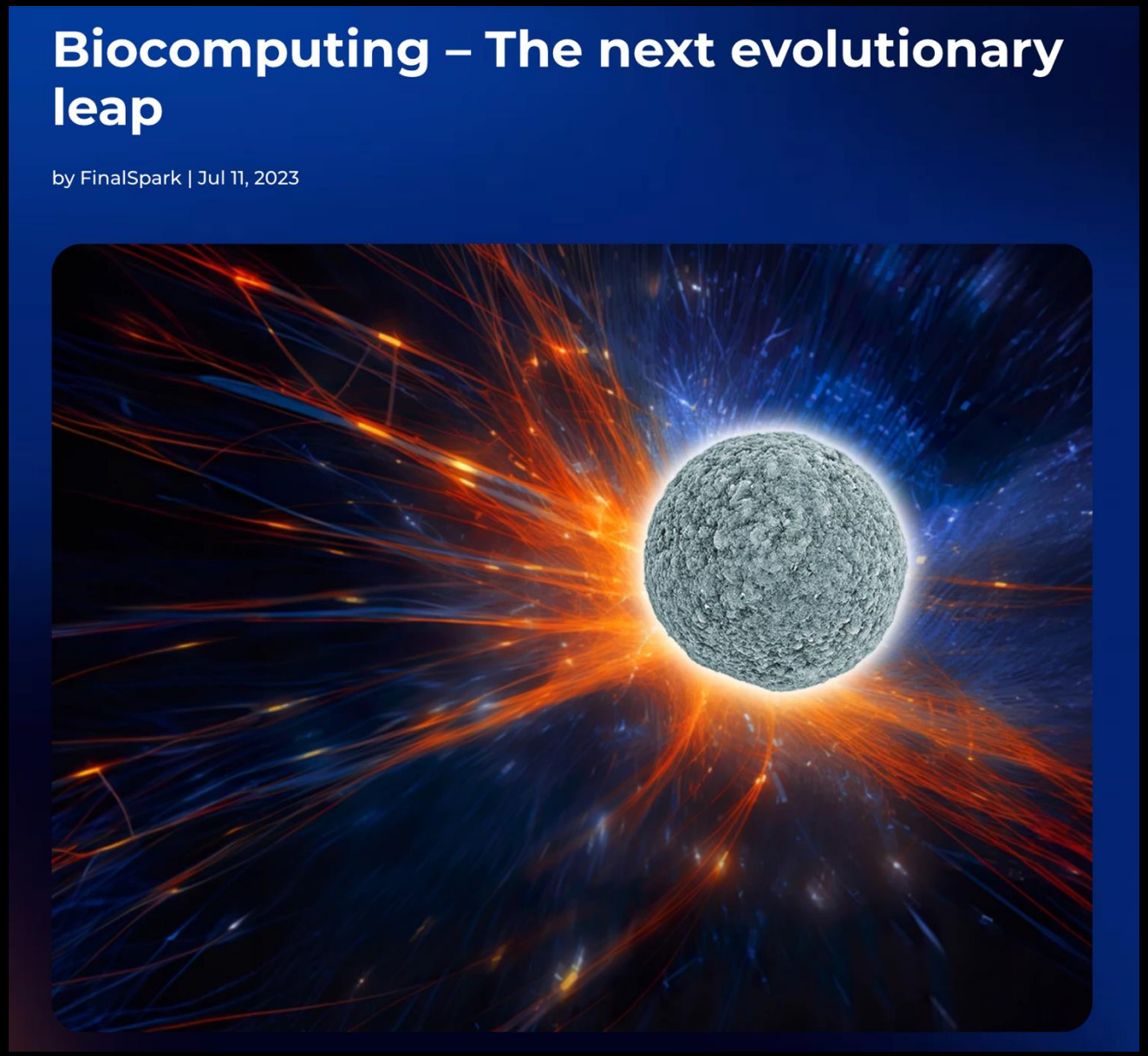
1. (2024-03) AWS buys a $650M Nuclear Plant (960 MegaWatts).
2. (2024-FQ4) NVIDIA made $60B Rev. this year from its data-center services, 78% was AI-related.
3. (2023-10) Researchers (UT-Riverside, Arlington) predict “*water withdrawal of global AI may reach 4.2 – 6.6 billion cubic meters in 2027*”

So… Brains?

“We’re creating the solution with biological neural networks.

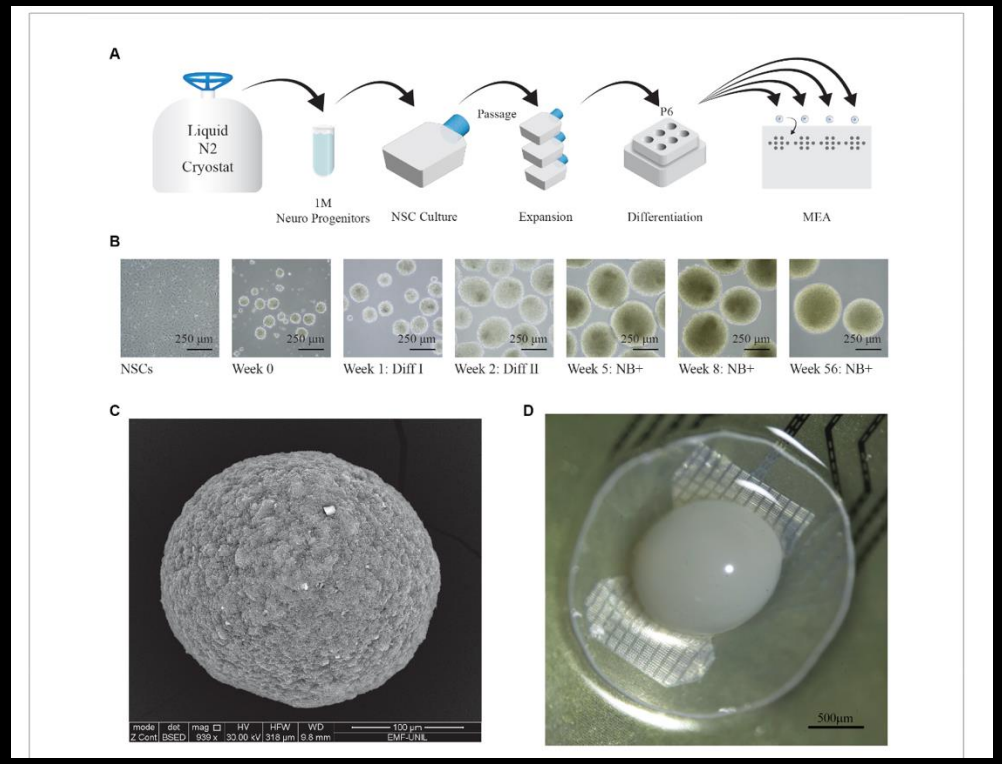
We’re growing neurons in cell cultures and making great progress in their use as computing power.

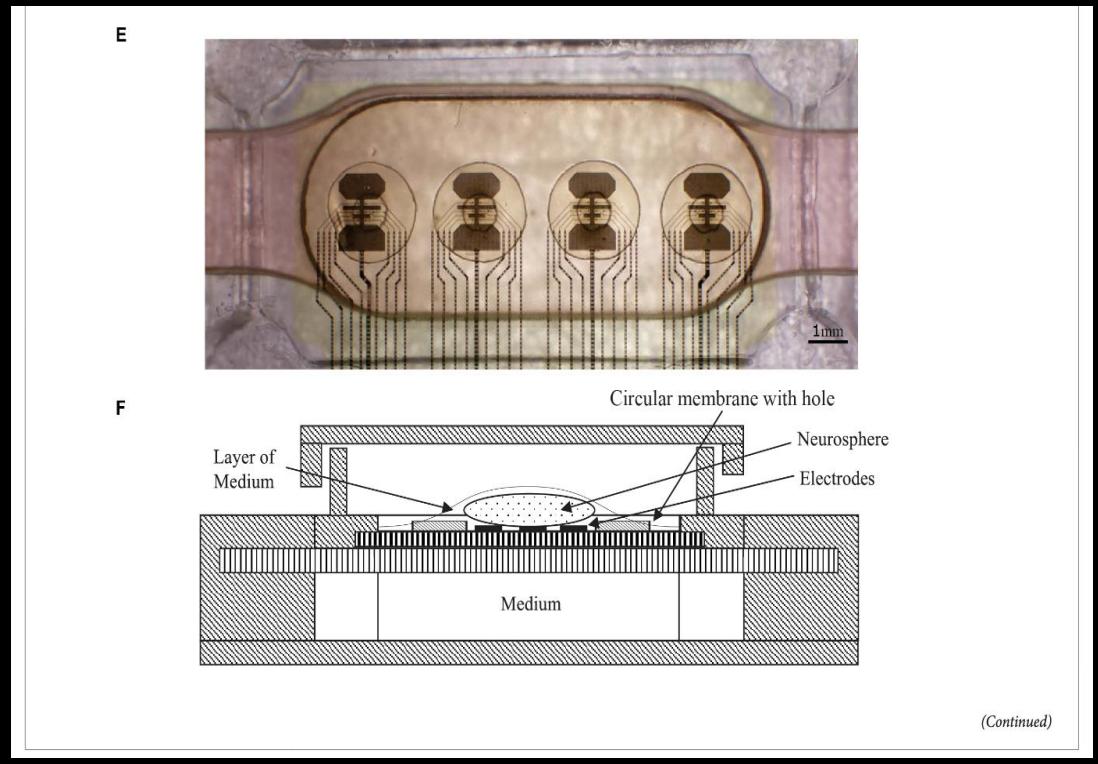
…[S]urpassing nature's success with limitless potential for enhancing life on earth.”



FinalSpark. 2023. “Biocomputing - The next Evolutionary Leap.” July 11, 2023. https://finalspark.com/biocomputing-the-next-evolutionary-leap/.

...What?





Jordan, Fred D., Martin Kutter, Jean-Marc Comby, Flora Brozzi, and Ewelina Kurtys. 2024. “Open and Remotely Accessible Neuroplatform for Research in Wetware Computing.” *Frontiers in Artificial Intelligence* 7 (May). https://doi.org/10.3389/frai.2024.1376042.

How's the process different?

SILICO-AI

1. **DATA** fed into computer.
2. **COMPUTER** fires electricity into silicone wafer.
3. **MACHINE LEARNING MODEL** computes the "best" response.
4. **TRAINING** occurs by selection of model which made the "optimal" answer.

BRAIN ORGANOID-AI

1. **DATA** fed into computer.
2. **COMPUTER** fires lasers, or electricity into organoid.
3. **MACHINE LEARNING MODEL** measures neuron activation.
4. **TRAINING** occurs by iterative release of dopamine into organoid housing after organoid signals the "optimal" answer.

Neuronal Attachment to Micro Electrodes

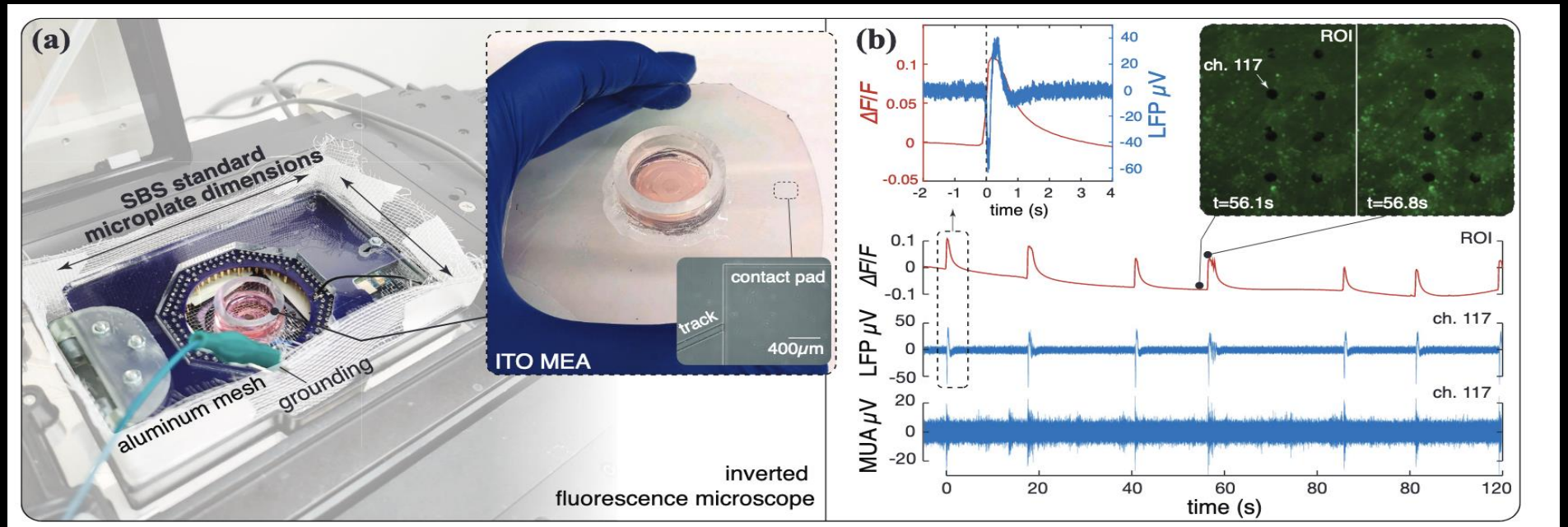
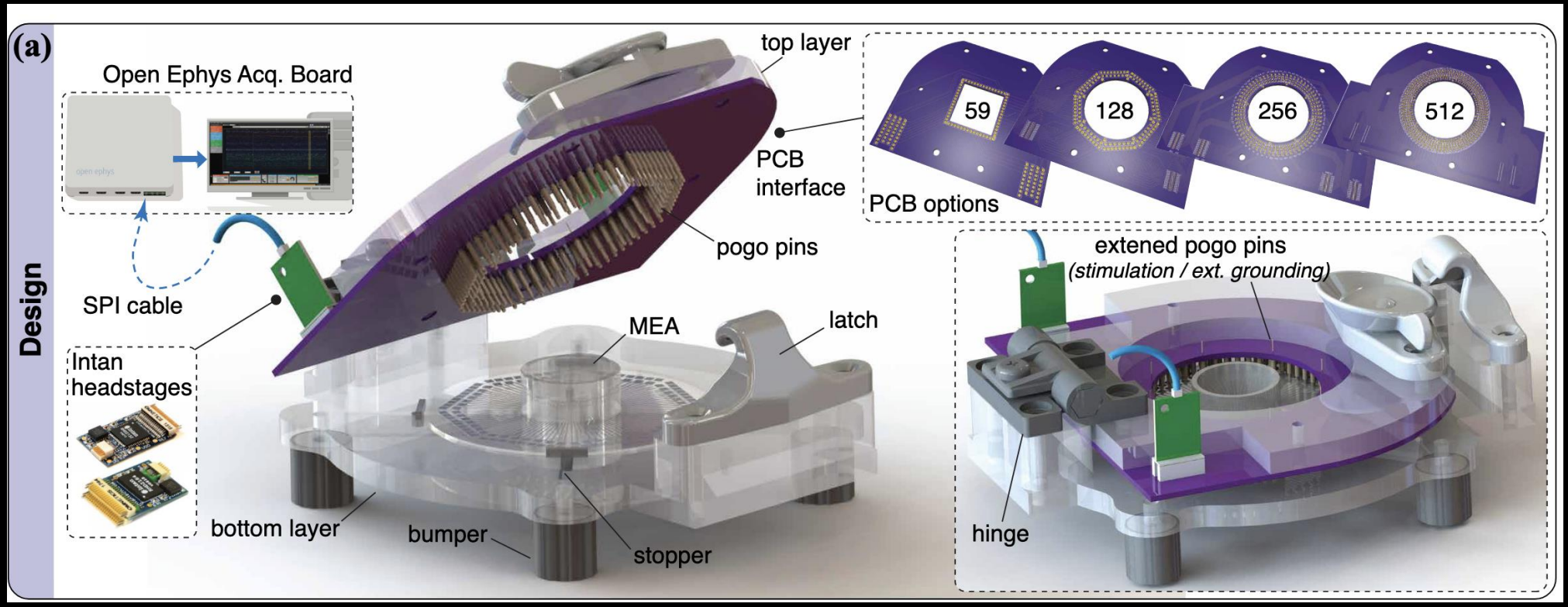


Figure 6: Alteration of the recording platform to facilitate concurrent electrophysiology and microscopic imaging. **(a)** Placing of the recording device inside an inverted microscopic chamber. A thin layer of aluminum mesh is fabricated to wrap around the device and serve as Faraday cage. ITO MEAs and PNs are utilized in this experiment. **(b)** Examples of simultaneously acquired fluorescence signal and electrophysiology data. Video analysis is performed within a ROI of 0.57×0.82mm, while electrical data are recorded from a channel located near the center of the ROI. Left inset: A peak in the $\Delta F/F_0$ signal and a LFP event share similar temporal characteristics, where a rapid initiation period (<150ms) is followed by a gradual restoring phase (1s for LFP and 3s for $\Delta F/F_0$). We align the two signals according to their first edge. Right inset: snapshots of the fluorescence signal before and during a burst event.

Zhang, Xiaotian, Zhi Dou, Seung Hyun Kim, Gaurav Upadhyay, Daniel Havert, Sehong Kang, Kimia Kazemi, et al. 2024. "Mind In Vitro Platforms: Versatile, Scalable, Robust, and Open Solutions to Interfacing with Living Neurons." *Advanced Science* 11 (11): 2306826. https://doi.org/10.1002/advs.202306826.

What was the purple bit in the machine?



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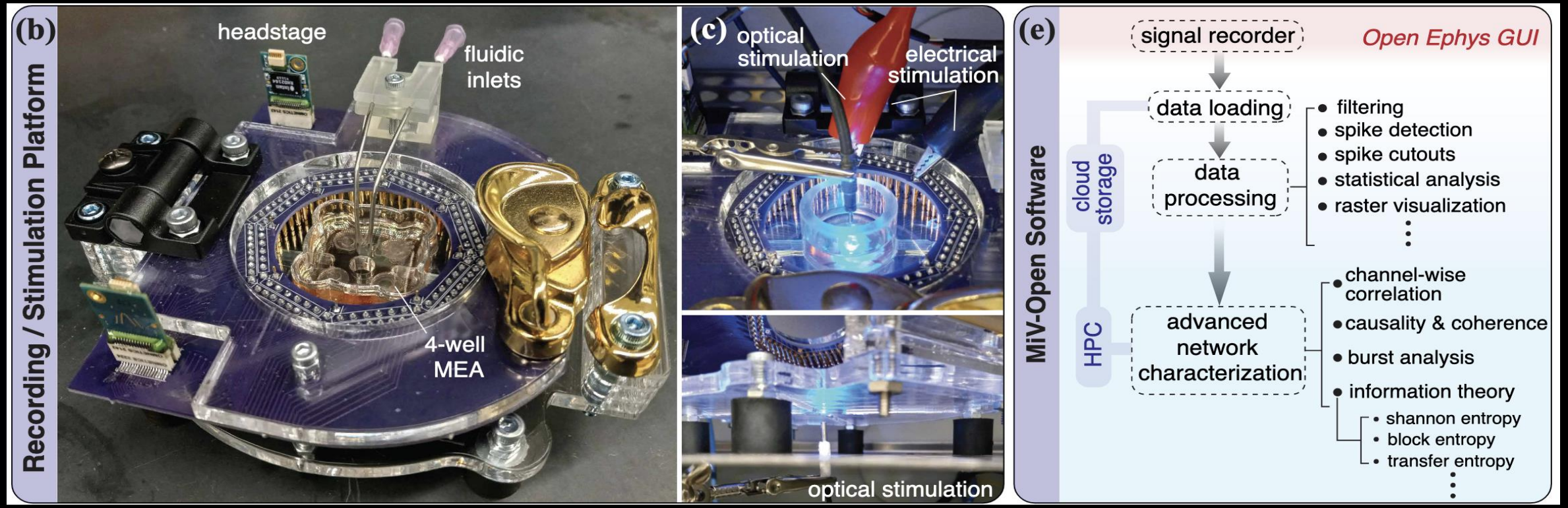
Microfluidics = Vasculature



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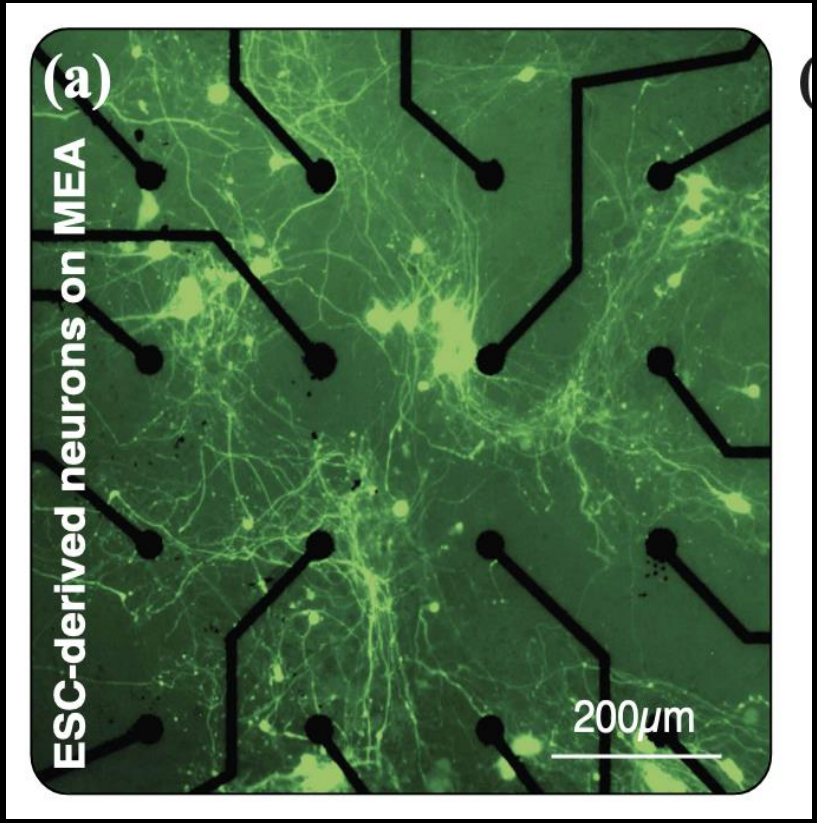

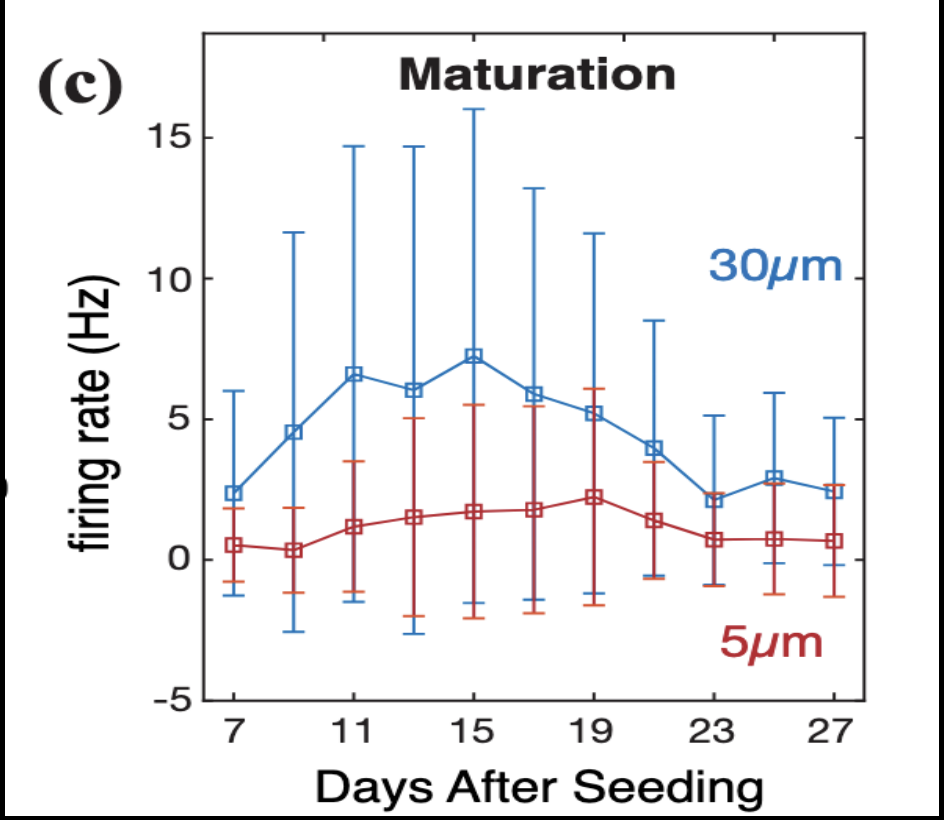

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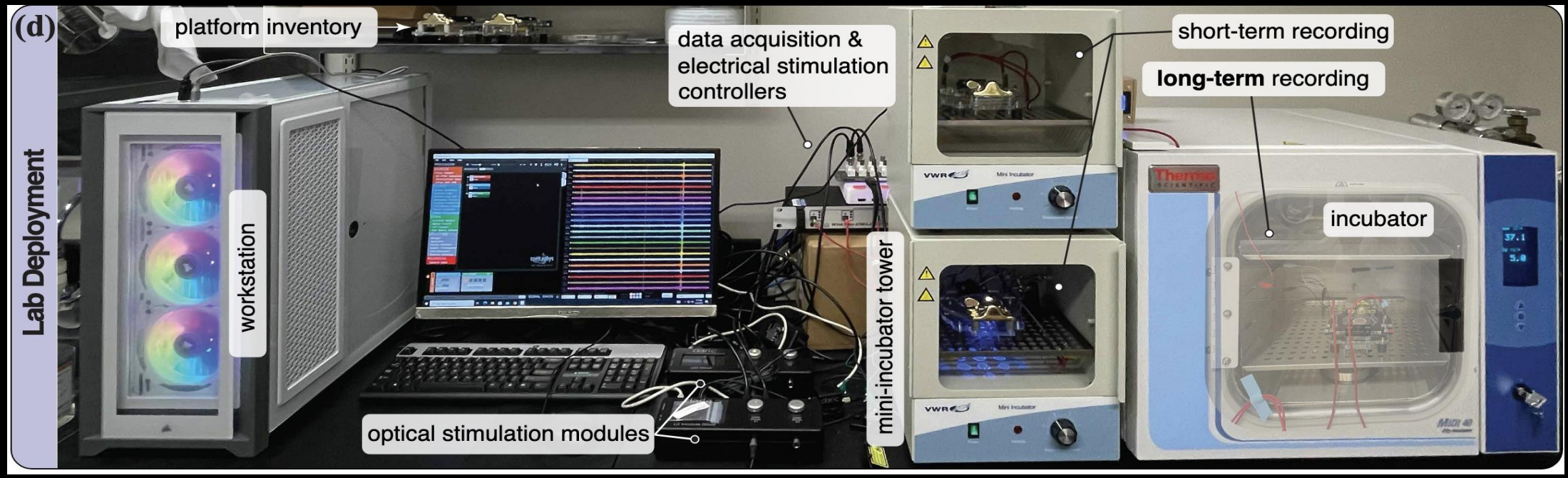
Incubator Unit



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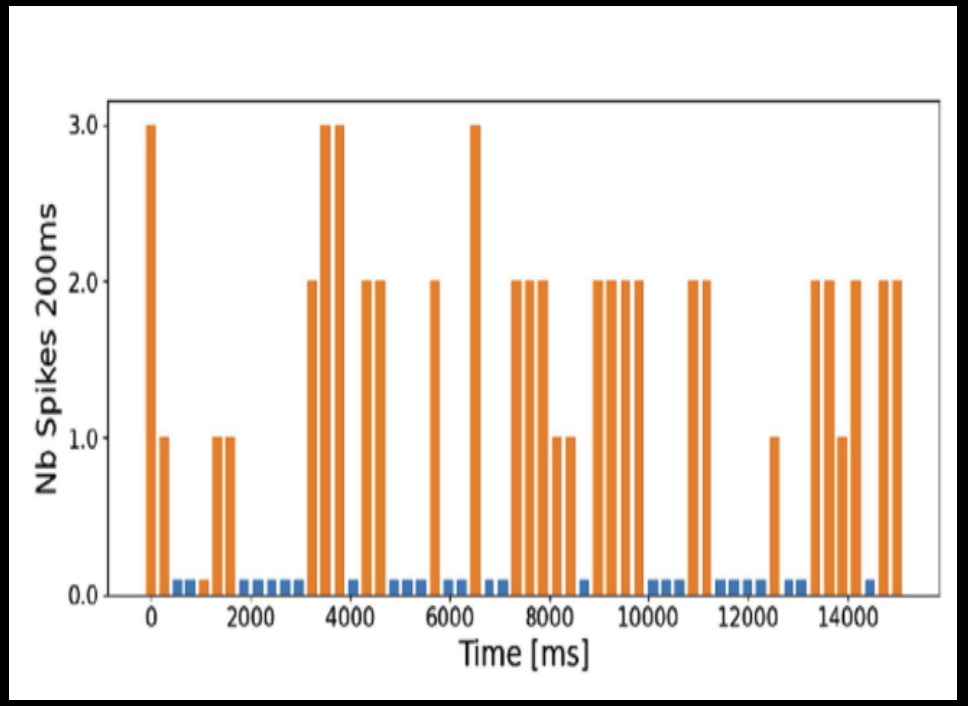
Code Execution

“The bar chart in Figure 7A displays a segment of the experimental results. It shows a 15-s recording from a single electrode, corresponding to one execution of step 4 in the pseudo code above… **The orange bars in this plot are the result of the parameters selected in step 1 of the pseudo code.**”

```
for _ in range(4*60):
    for i in range(8):
        trigger.send(recordingTriggers[i])
        time.sleep(0.01) # 10 ms

        # Read number of spikes
        nb_spikes = read(trigger, intan, listeningTrigger)
        nb_spikes_ns = np.sum(nb_spikes[all_electrodes])

        diff_spikes = nb_spikes_ns-nb_spikes_ns_history[-1]
        nb_spikes_ns_history.append(nb_spikes_ns)

        if diff_spikes > 0: # Increase of spike activity
            triggerUV.send(800) # trigger UV for 100 ms
            time.sleep(30) # Wait 30s before removing dopa

            # Increase speed of the pump to 5 rpm (to remove dopa)
            peristaltic.rpm(5, PeristalticDirection.CounterClockWise)

        time.sleep(60) # wait 1 min
```



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Conclusion(s)?

Questions to answer before markets get serious:

1. **What's the return on investment?**
   - Current Unknowns: Cost per Organoid, Lifetime

2. **What's political/regulatory risk?**
   - Current Unknowns: lmao

3. **Is it 10x better than standard alternatives?**
   - Current Unknowns:
     - How fast to retrain an organoid model?
     - How many models can one organoid learn?
     - What kind of mistakes/risk do organoid-intelligences entail?

Appendix: Lifetime of Organoids

“Initially, their lifetime was only a few hours, but various improvements, especially related to the microfluidics setup, have extended this to up to 100 days in best cases.” (Jordan et al., 2024, p. 14).

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Appendix: Dopamine

“Carboxynitroveratryl (CNV)-caged dopamine (Tocris Bioscience) was dissolved in Neurobasal Plus at the concentration of 1 mM, and injected in the fluidic system.

After 3 h from the injection, the uncaging experiment started as described in paragraph 5.3. UV Silver-LED fiber-coupled LED (Prizmatix) was used to uncage the dopamine at the wavelength of 365 nm for 800 ms each time.”

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Appendix: Facts on Efficiency

“Since June 2022, the USA’s Frontier has been the world’s most powerful supercomputer, reaching 1102 petaFlops (1.102 exaFlops) on the LINPACK benchmarks. **The power consumption of the new supercomputer is 21 megawatts, while the human brain operates at the estimated same 1 exaFlop and consumes only 20 watts** (Table 1) (8–11).

Thus, humans operate at a ***10^-6 fold better*** power efficiency relative to modern machines albeit while performing quite different tasks.” (Smirnova et al., 2023, p. 3)

Smirnova, Lena, Brian S. Caffo, David H. Gracias, Qi Huang, Itzy E. Morales Pantoja, Bohao Tang, Donald J. Zack, et al. 2023. “Organoid Intelligence (OI): The New Frontier in Biocomputing and Intelligence-in-a-Dish.” *Frontiers in Science* 1 (February). https://doi.org/10.3389/fsci.2023.1017235.

Appendix: Organoid-on-Organoid Action

“A sensory organ, such as a retinal organoid, could then be connected with a brain organoid. **Eventually, networks of organoids will be interconnected to implement more complex [Organoid Intelligence] (OI).**

The organoid will be interfaced with electrical and fluidic-sensing and simple outputs controlling machines through biofeedback on the cellular level; i.e. giving the brain organoid control by feeding back the results of its induced actions.” (Smirnova et al., 2023, p. 13)

Smirnova, Lena, Brian S. Caffo, David H. Gracias, Qi Huang, Itzy E. Morales Pantoja, Bohao Tang, Donald J. Zack, et al. 2023. “Organoid Intelligence (OI): The New Frontier in Biocomputing and Intelligence-in-a-Dish.” *Frontiers in Science* 1 (February). https://doi.org/10.3389/fsci.2023.1017235.

Appendix: Ethical Dilemmas

"**Could organoids experience pain and, if so, would they suffer – even in rudimentary ways?** These concerns will mount during the development of OI, as the organoids become structurally more complex, receive inputs, generate outputs, and – at least theoretically – process information about their environment and build a primitive memory." (Smirnova et al., 2023, p. 15)

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Appendix: Biomarkers

FINALSPARK

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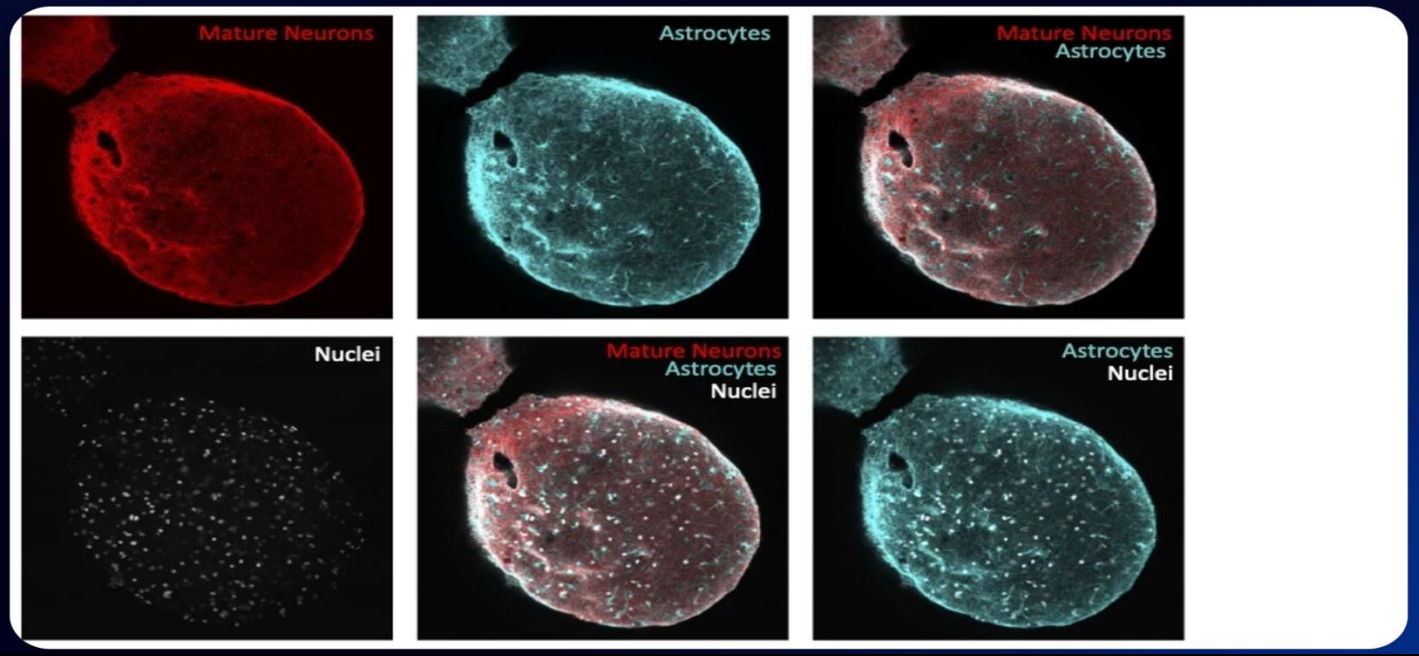
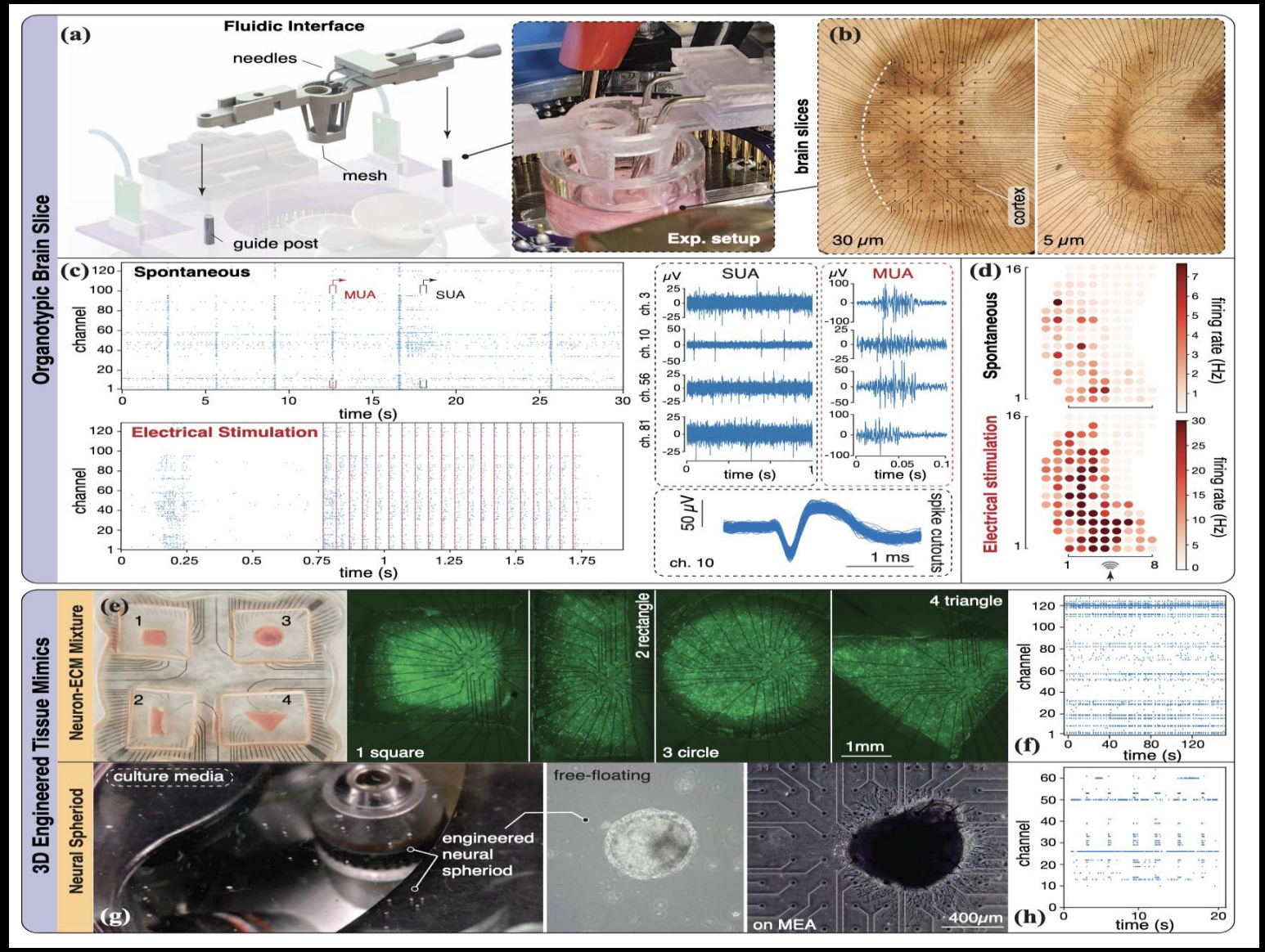
MAP2 is a marker of neural growth, axonal regeneration, and synaptic plasticity. The MAP2 neuronal marker plays a pivotal role in neuroscientific research by aiding in the identification and analysis of neurons in laboratory settings. As a microtubule-associated protein, MAP2 is primarily expressed in the dendrites of neurons, making it an invaluable tool for distinguishing neuronal structures from other cell types. Its importance lies in its specificity to neurons, allowing us to visualize and characterize neuronal morphology, dendritic branching patterns, and synaptic connections. Here are the FinalSpark results on the immunofluorescent staining for MAP2 in our neural cells. We combined our staining with DAPI, which is a standard marker of cellular nuclei. It helps us to localise all living cells in the sample and estimate their density (as each cells, regardless of its type, contain a nucleus).



Kurtys, Ewelina. 2024. “How Do We Know We Have Real Neurons in Our Lab?” June 18, 2024. https://finalspark.com/how-do-we-know-we-have-real-neurons-in-our-lab/.

Appendix: Micro-Fluidics



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Appendix: Research

	Specifications	Kim et al. 2020	Middya et al. 2021	Weaver et al. 2022	O'Leary et al. 2022	This Work
Recording Platform	Amplification/acquisition electronics	Open Ephys+Intan	Multi-Channel Systems	Open Ephys+Intan	Self-assembled FPGA+Intan	Open Ephys+Intan
	Open source electronics	Yes	No	Yes	Yes	Yes
	Open source CADs	No	No	Yes	Yes	Yes
	Multiple rec. capacities	No (256)	No (59)	No (61)	No (59)	Yes (**59/128/256/512**)
	Media circulation	No	No	No	Yes	Yes
MEA	Tested topologies / open-source	1 / No	1 / No	1 / No	1 / No	**7 designs** / Yes
	Photolithography	masked	masked	masked	masked	**maskless**
	Electrode diameters	10, 30, 50μm	30μm	20μm	50, 500μm	**5, 10, 20, 30μm**
	Material/transparency	metal / No	PEDOT:PSS / Yes	ITO / Yes	metal / No	**metal & ITO** / Yes
Experimental Demonstrations	Neural culture type	primary	primary	primary	brain tissue	**primary, ESC-derived brain tissue 3D eng. tissue mimic**
	Short term recording	Yes	Yes	Yes	Yes	Yes
	Electrical stim.	No	No	No	Yes	Yes
	Optical stim.	No	No	No	No	Yes
	Long-term recording	No	No	No	No	Yes (**24hrs**)
	Concurrent imaging &recording	No	No	No	No	Yes
	Demonstrated portability	No	No	No	No	Yes
	Demonstrated reproducibility	No	No	No	No	Yes
Software	Open source software	No	No	No	Yes	Yes
	HPC / Cloud support	No	No	No	No	Yes

Figure 2: Comparison among recent custom electrophysiology approaches [27, 28, 29, 26]

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