ETH zürich | LBB

A physicist's approach to neuroscience

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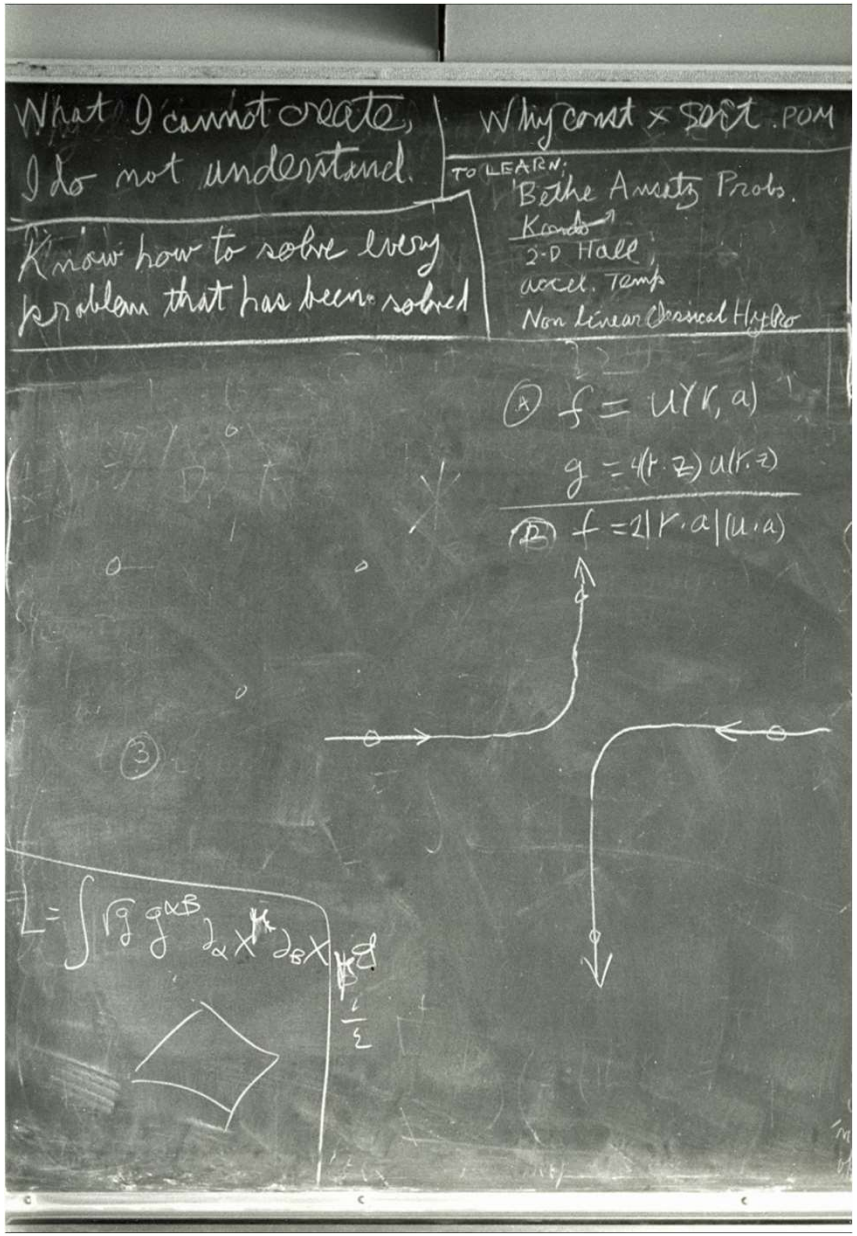


Richard Feynman
May 11, 1918 – February 15, 1988

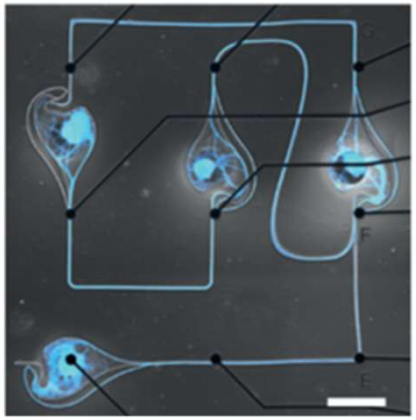
How do we study the brain?

Top-down approach

Whole brain
1-100 billion neurons

+ Studying the “real thing”
- Low resolution on humans (MRI)
- Limited intervention
- Only a fraction of the neurons are measured
- Too complex to model

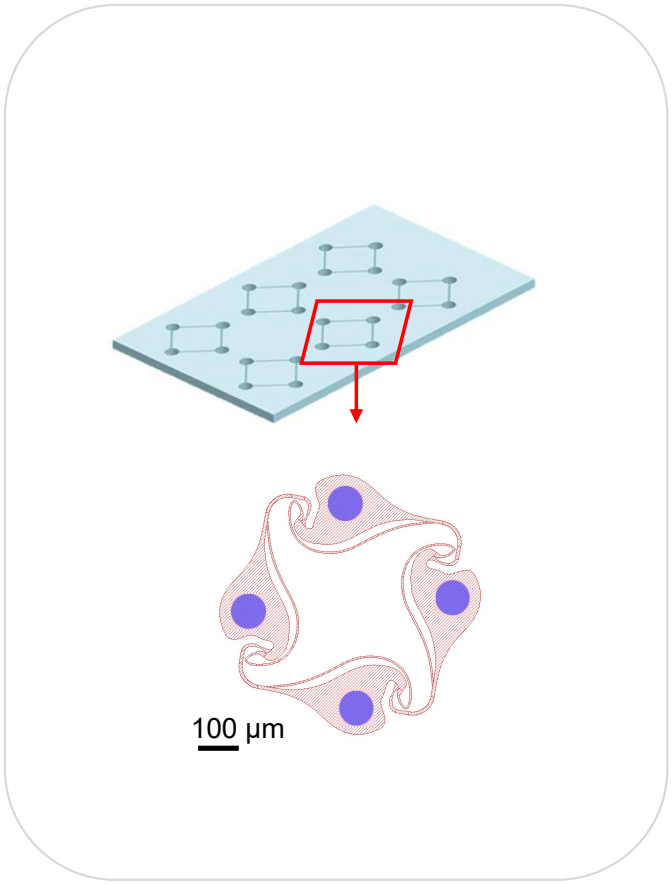
Bottom-up approach

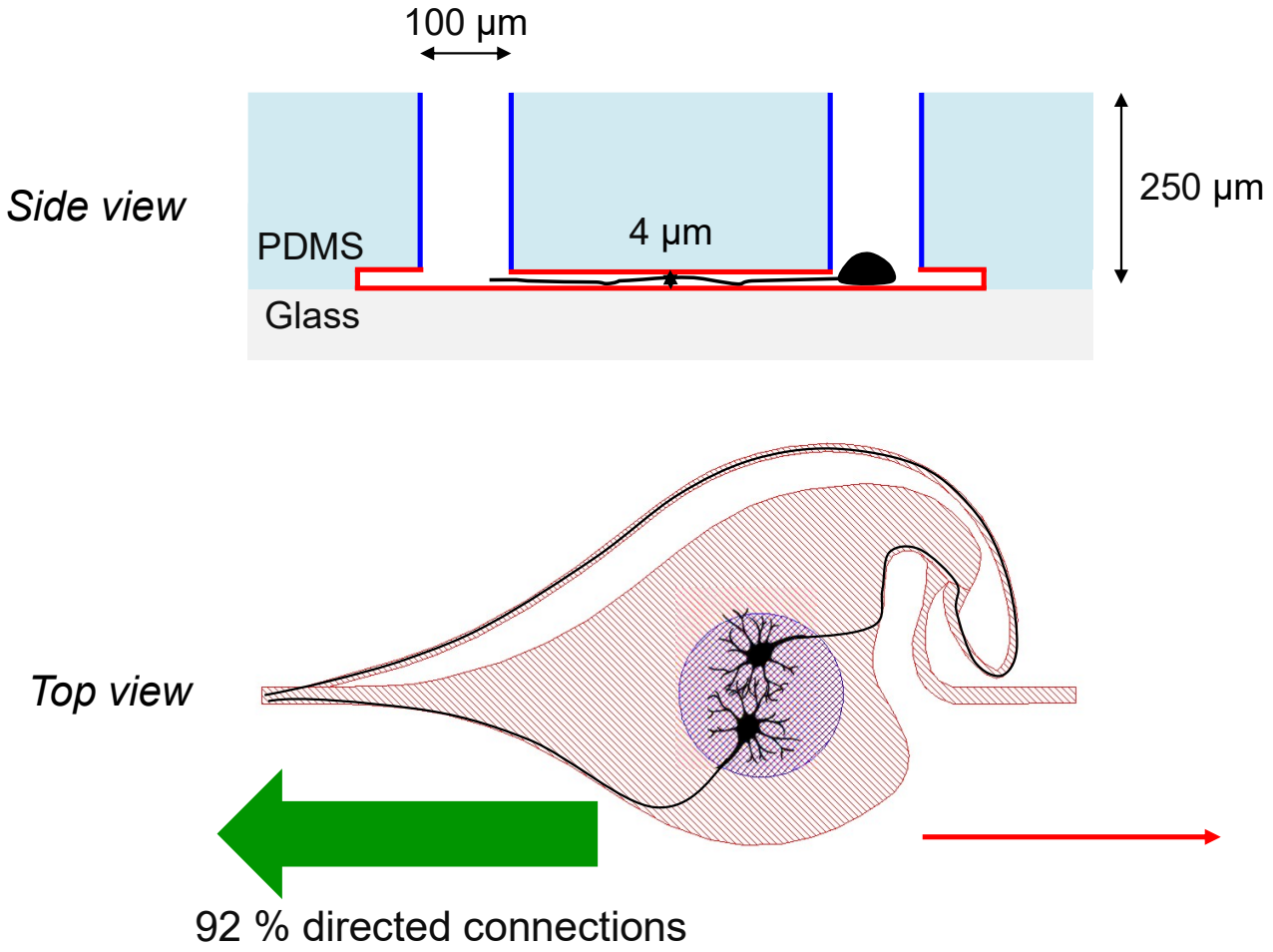


Patient iPSC-derived
1-10’000 cells

- Artificial neural network
+ Well-defined = more reproducible
+ Many interventions (adding, removing cells, drugs)
+ Each neuron can be measured
+ Directly comparable to computational models

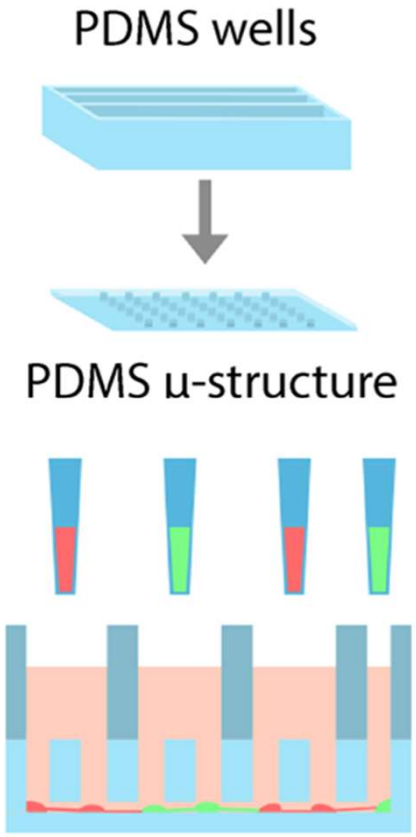
Axon-guiding microstructures enable oriented connections

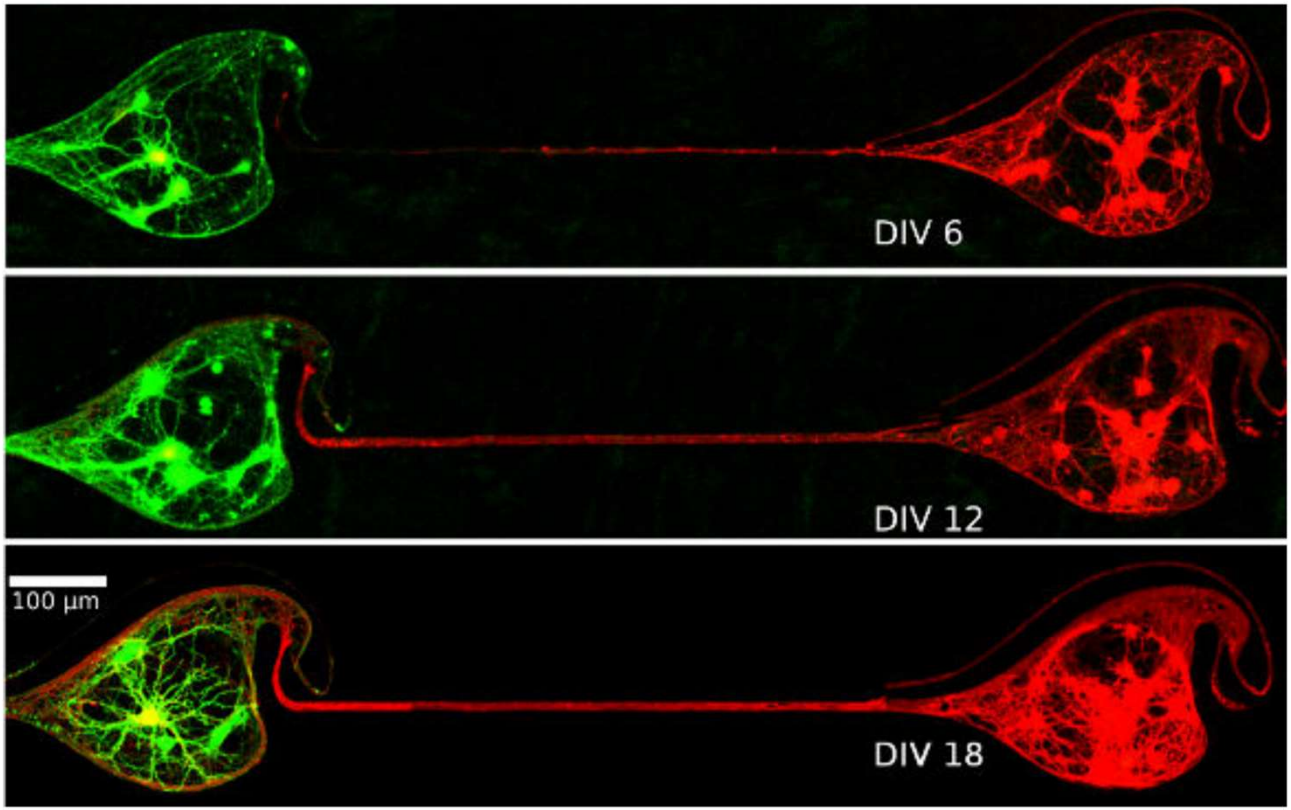




Forró C. *et al.*, *Biosens Bioelectron;* 2018

Microstructure-based oriented connectivity

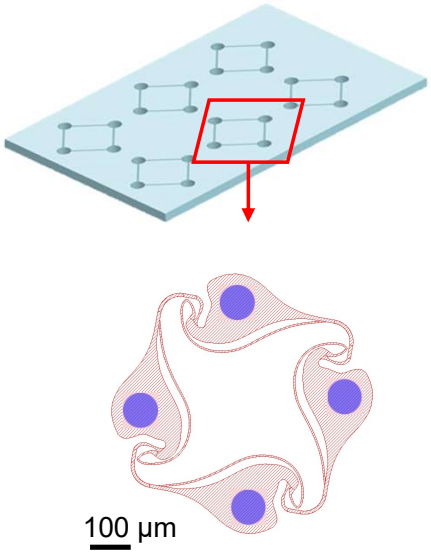




Forro C. et al., Biosensors and Bioelectronics, 2018.

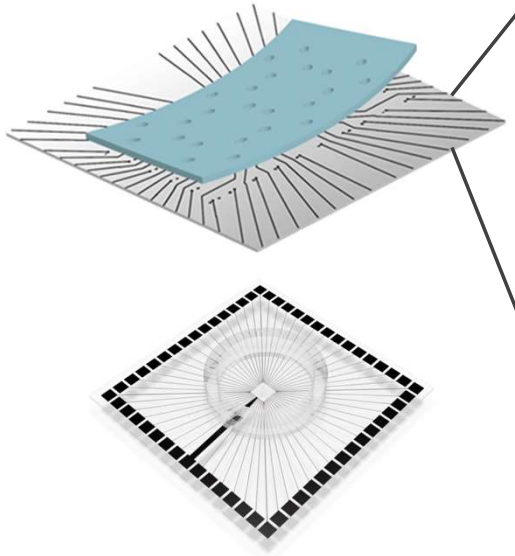
It is a scalable technology – we have hundreds of networks

Well-defined PDMS micro-structures to guide neurons

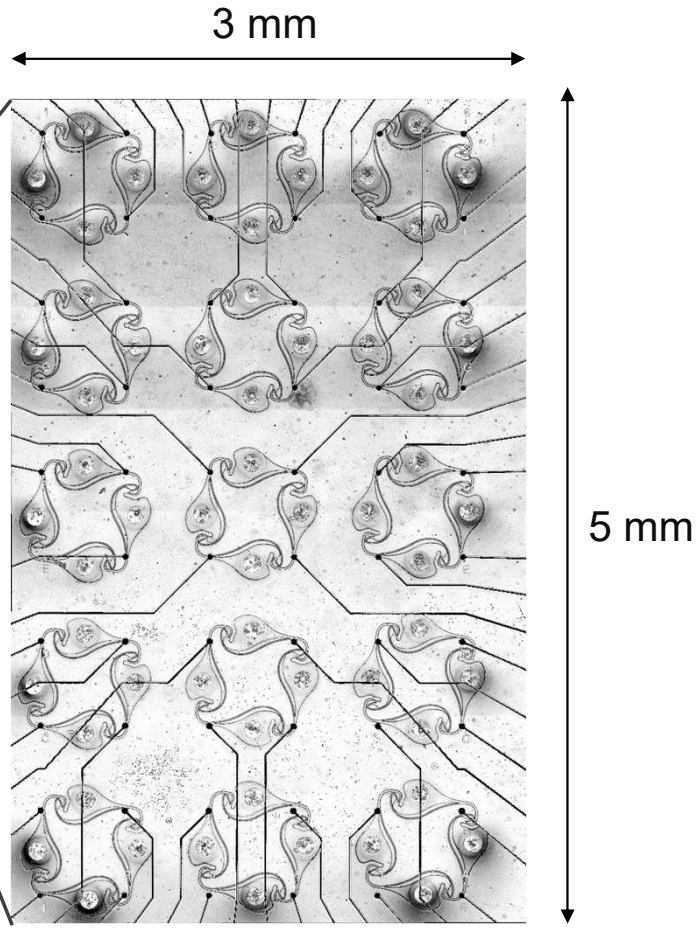


92 % directed connections

PDMS circuits placed on microelectrode array (MEA)

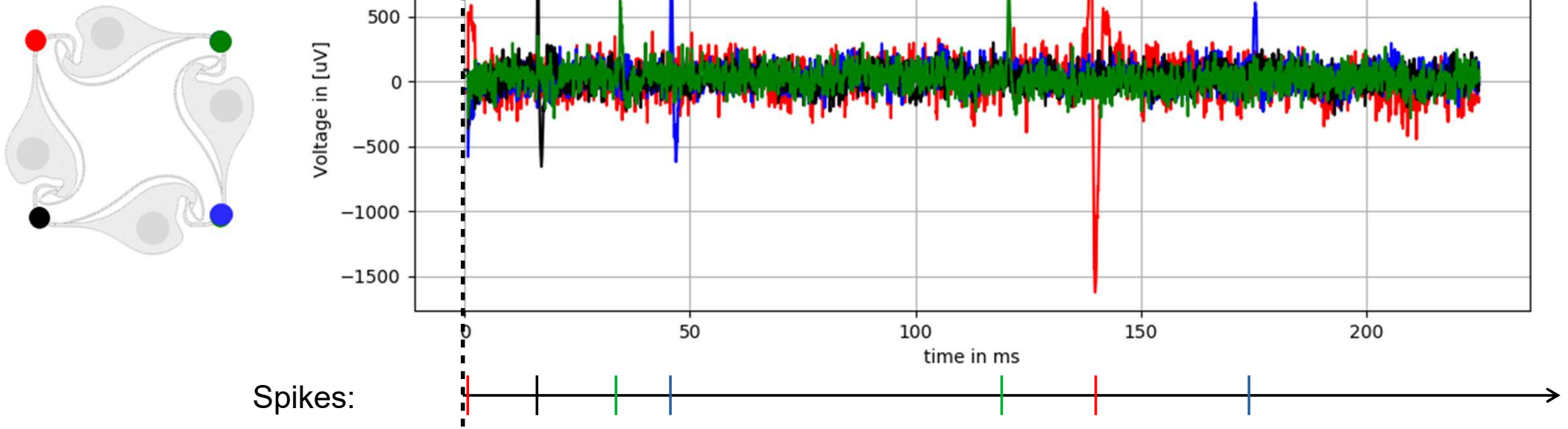


60 electrode MEA



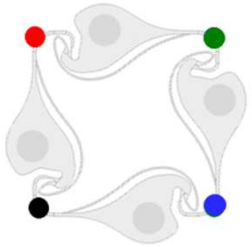
Forró C. *et al.*, *Biosens Bioelectron;* 2018

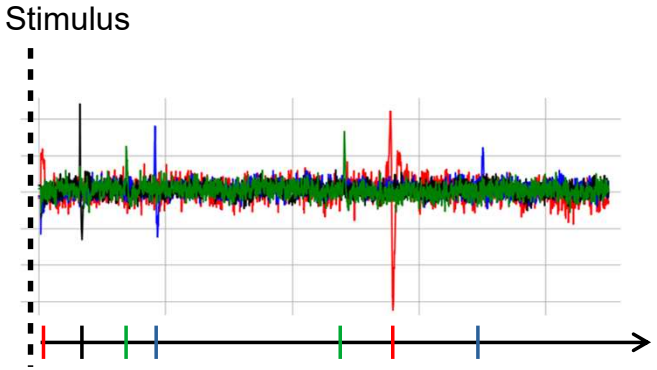
We stimulate one or more electrodes and record the response with all four electrodes

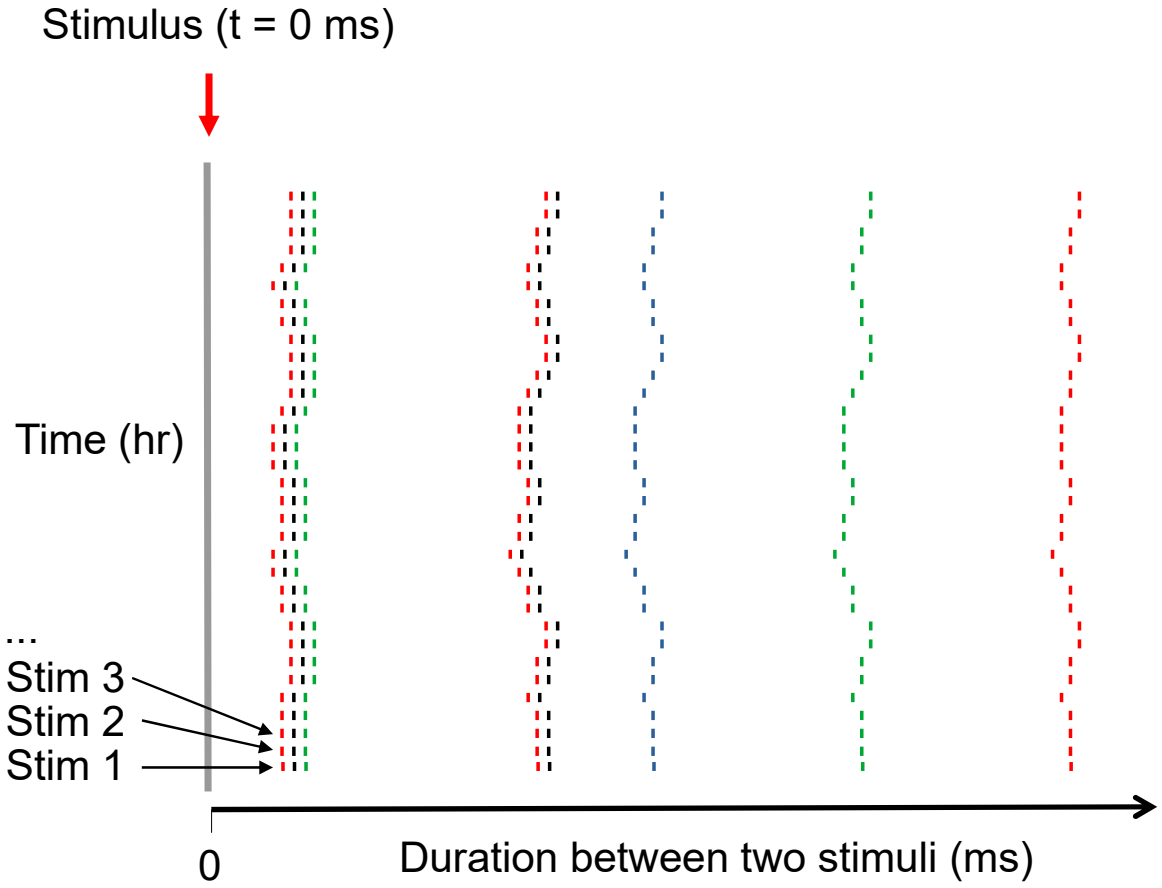


Ihle S. *et al.*, Biosensors and Bioelectronics, *2021.*

Plotting the response this way helps visualizing network behavior (Note the hours time scale on the y-axis!)



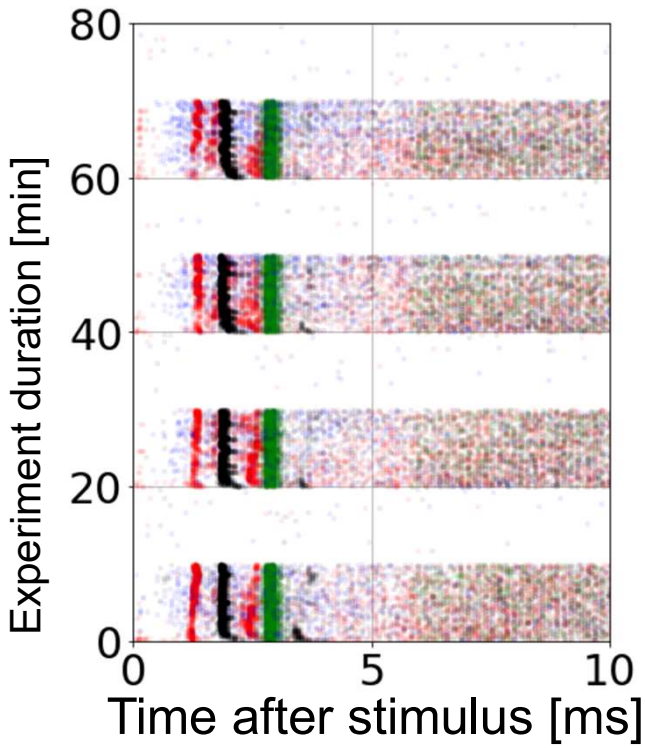


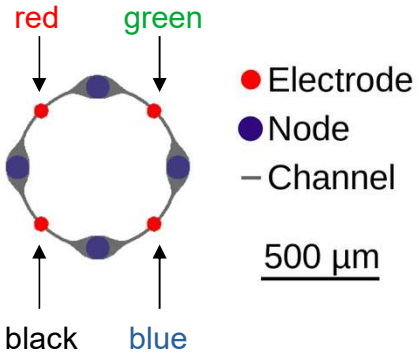


Reproducible and stable network responses are obtained

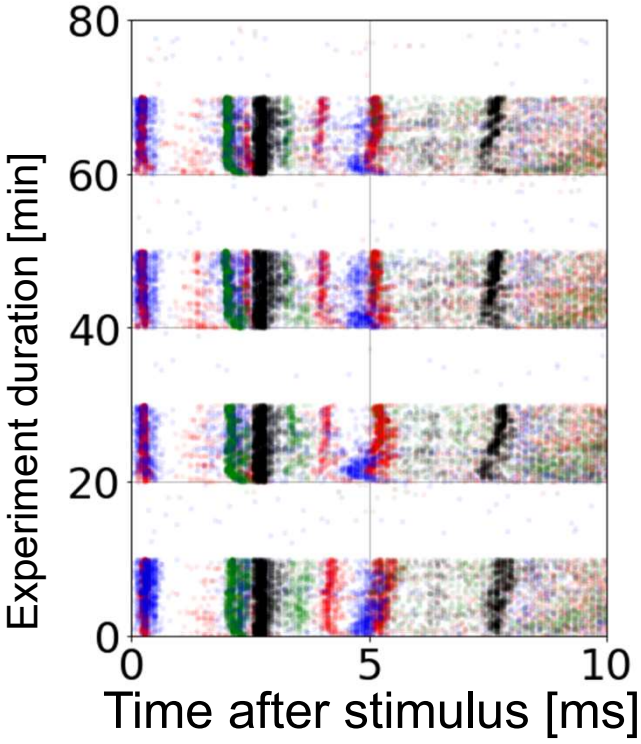
Stimulate every 250ms with two different patterns.

Clock-wise stimulation

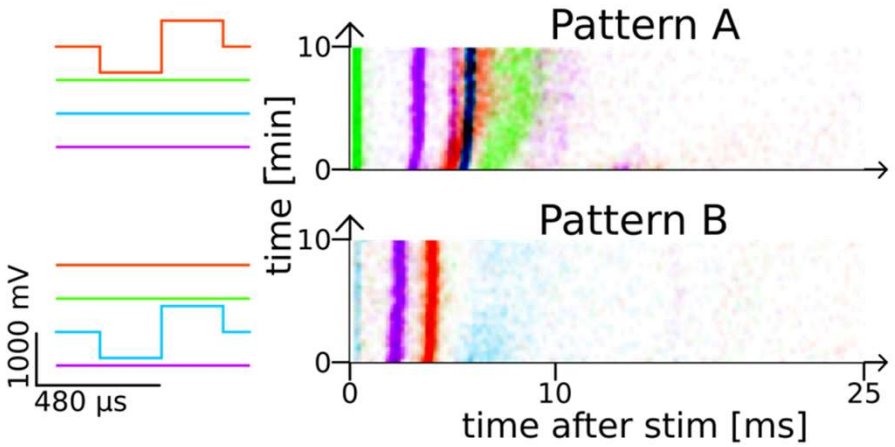


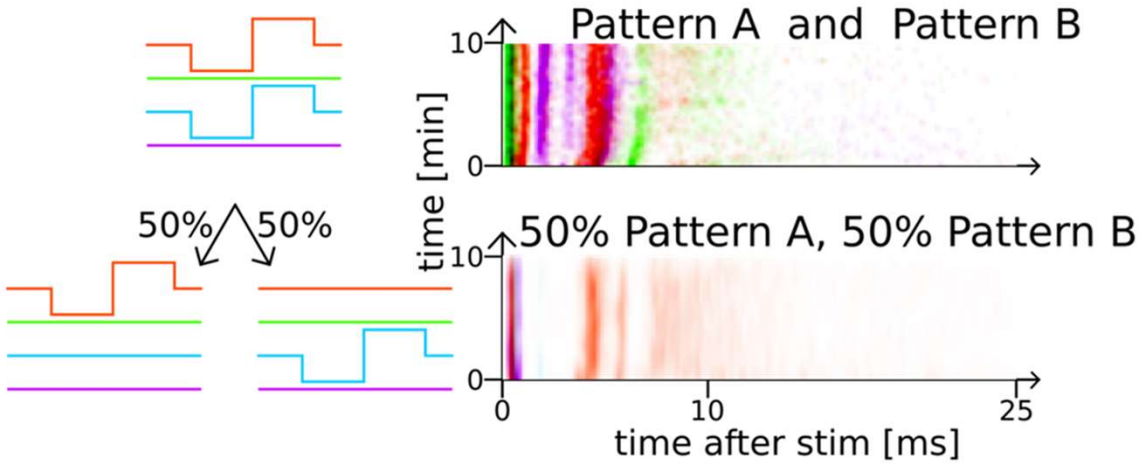


Counter-clock-wise stimulation



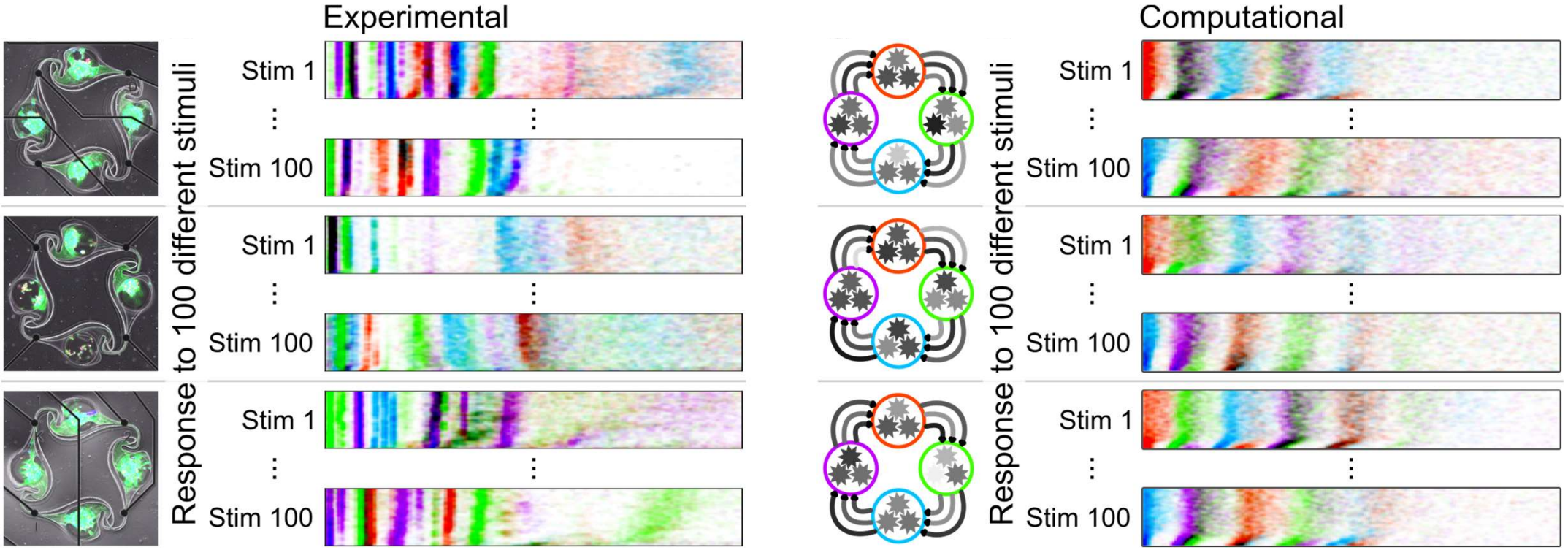
Neural network input “math”



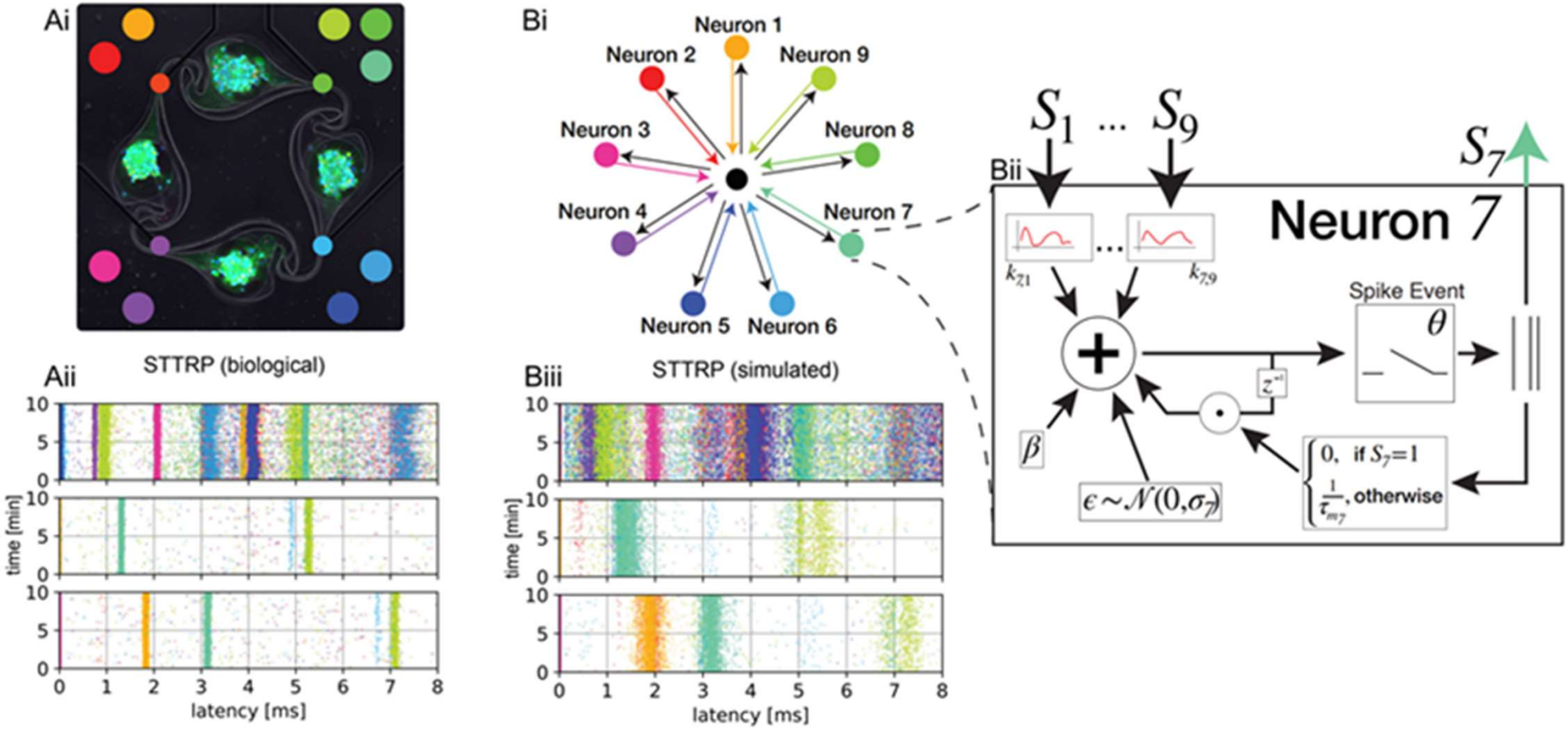


Ihle S. *et al.*, Biosensors and Bioelectronics, *2021.*

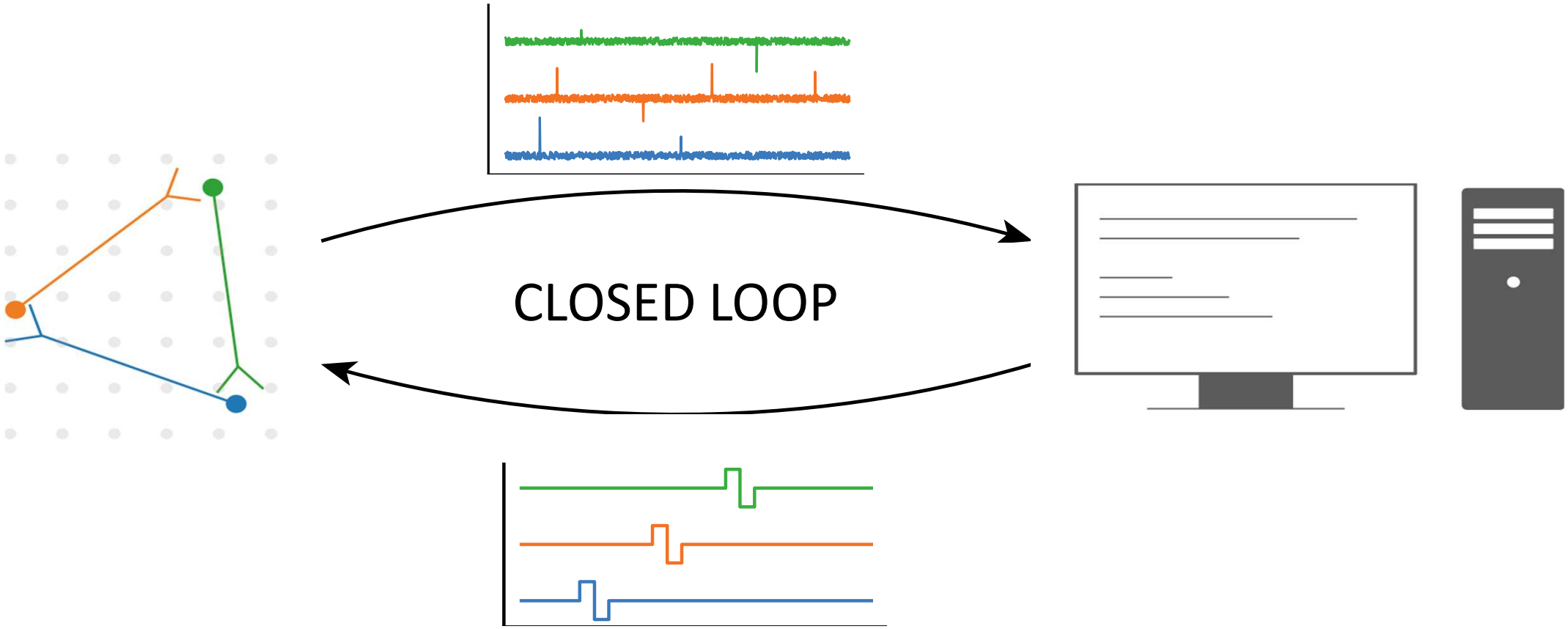
Comparing experiments with simulations



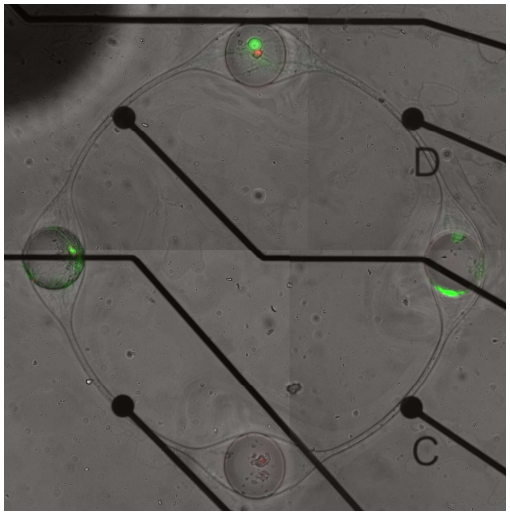
Selected example of successfully simulating network behavior

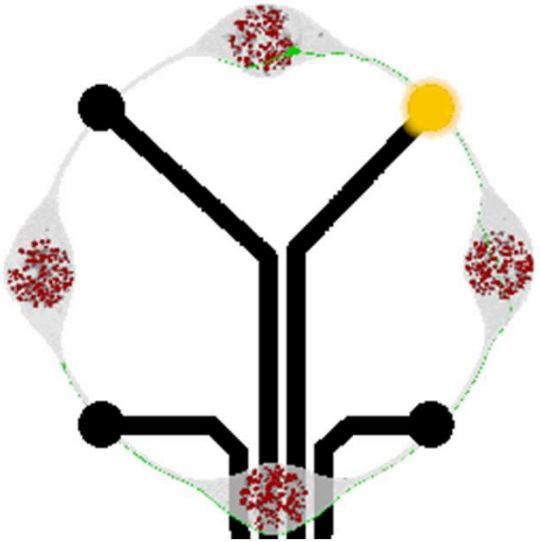


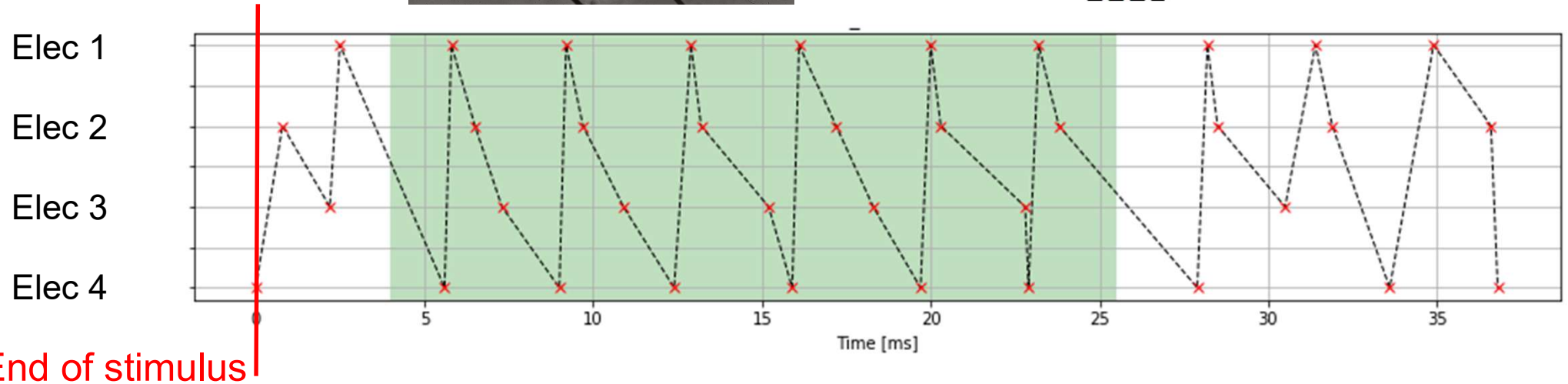
Closed-loop stimulation



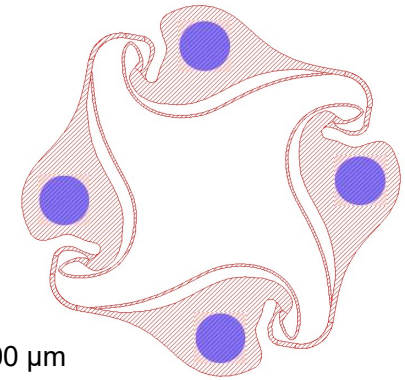
Network spiking in a circle







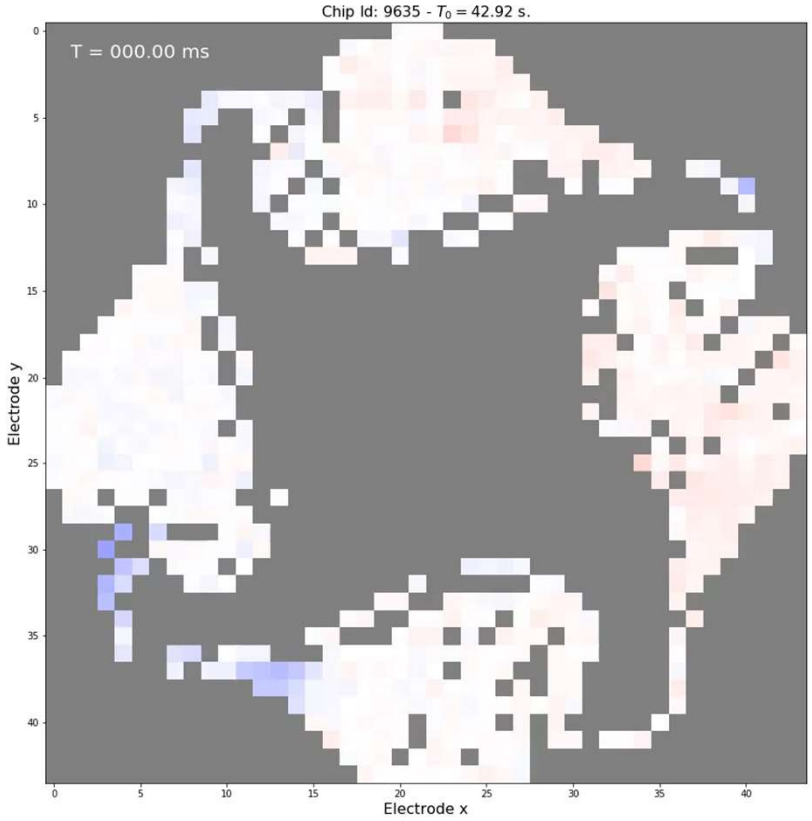
A well-defined neuron network on a CMOS MEA



100 µm

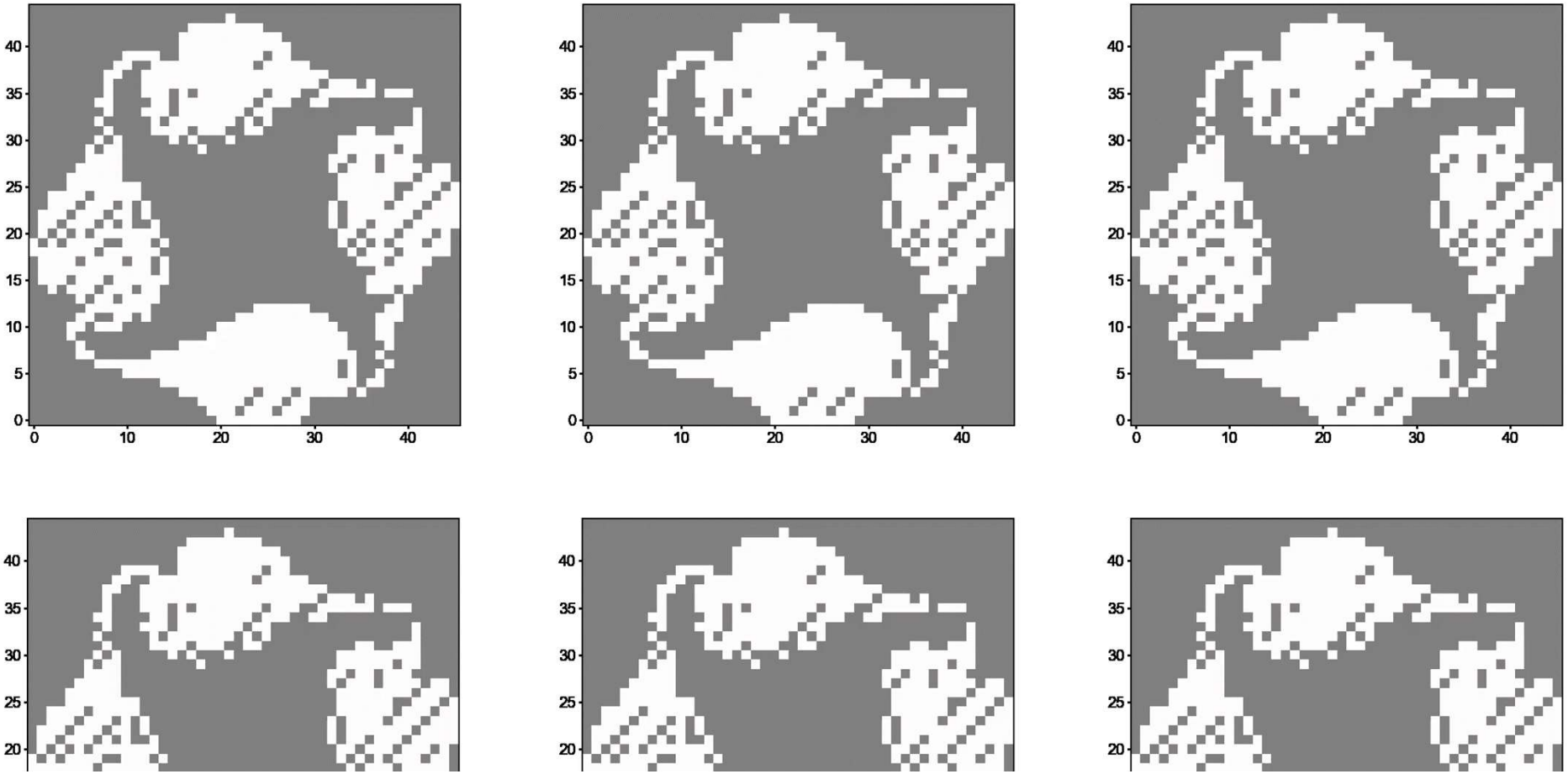
MaxWell Biosystems

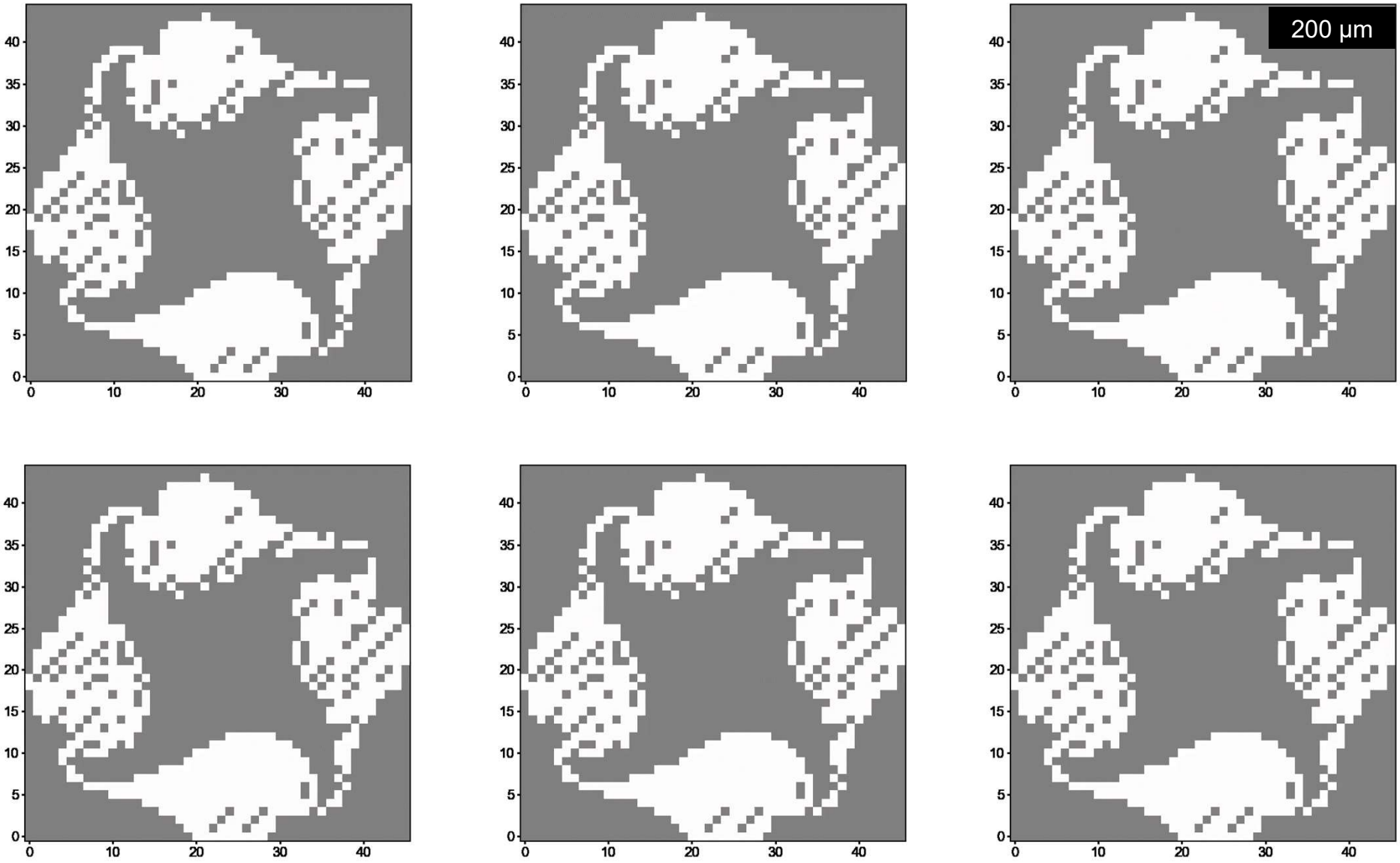
Rat cortical primary neurons, DIV21, filtered raw data without averaging



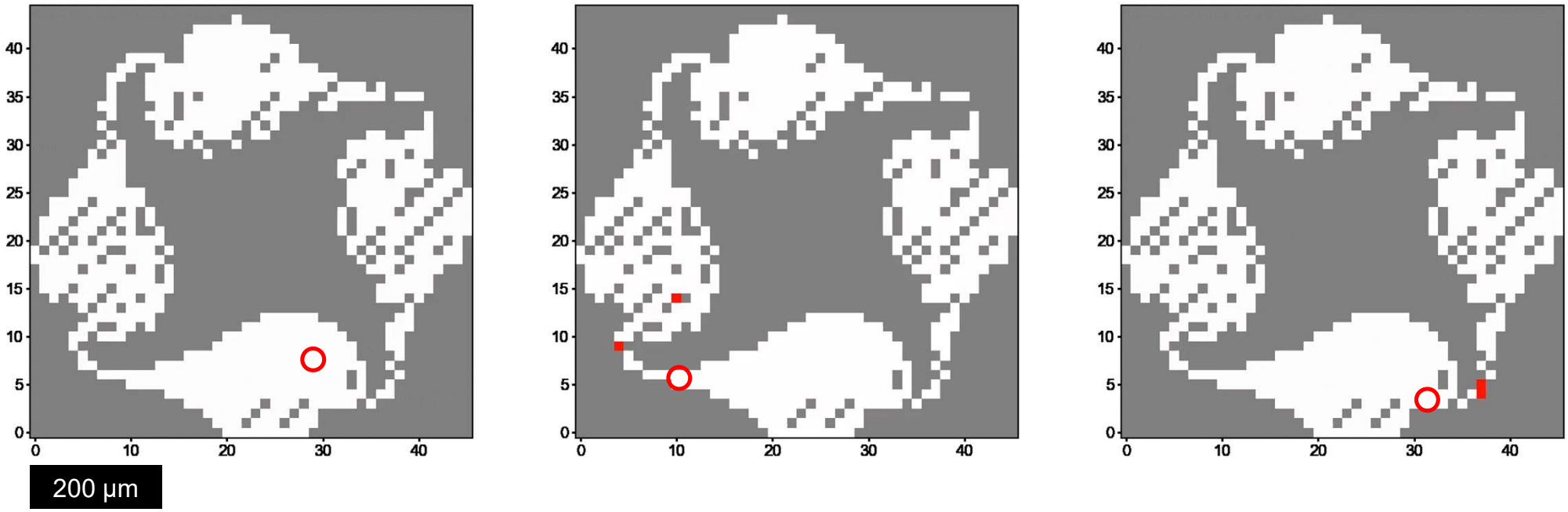
Duru J. *et al.*, *Frontiers in Neuroscience, 2023.*

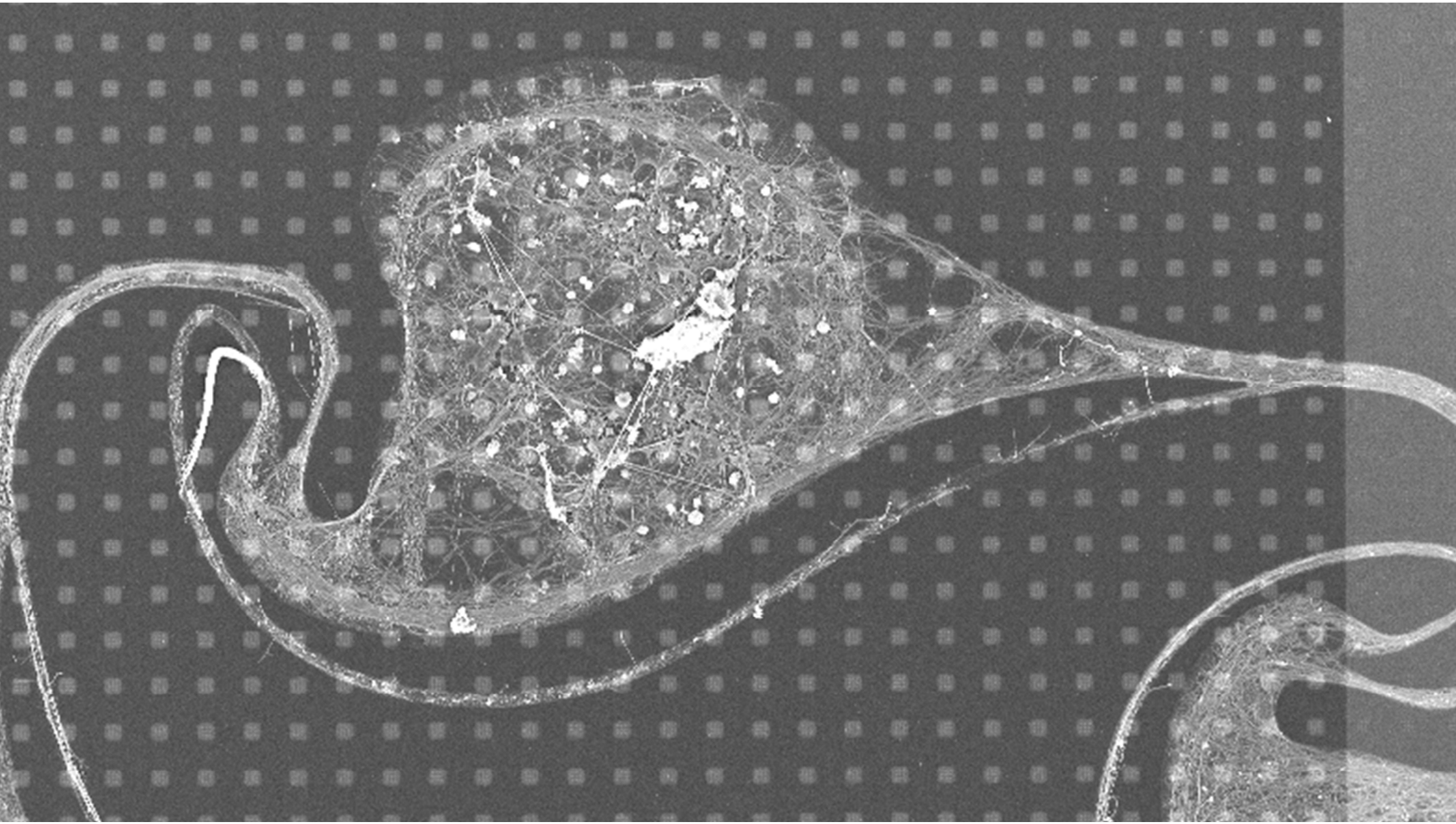
The post-stimulus answer is always the same (if you stimulate at the same location)

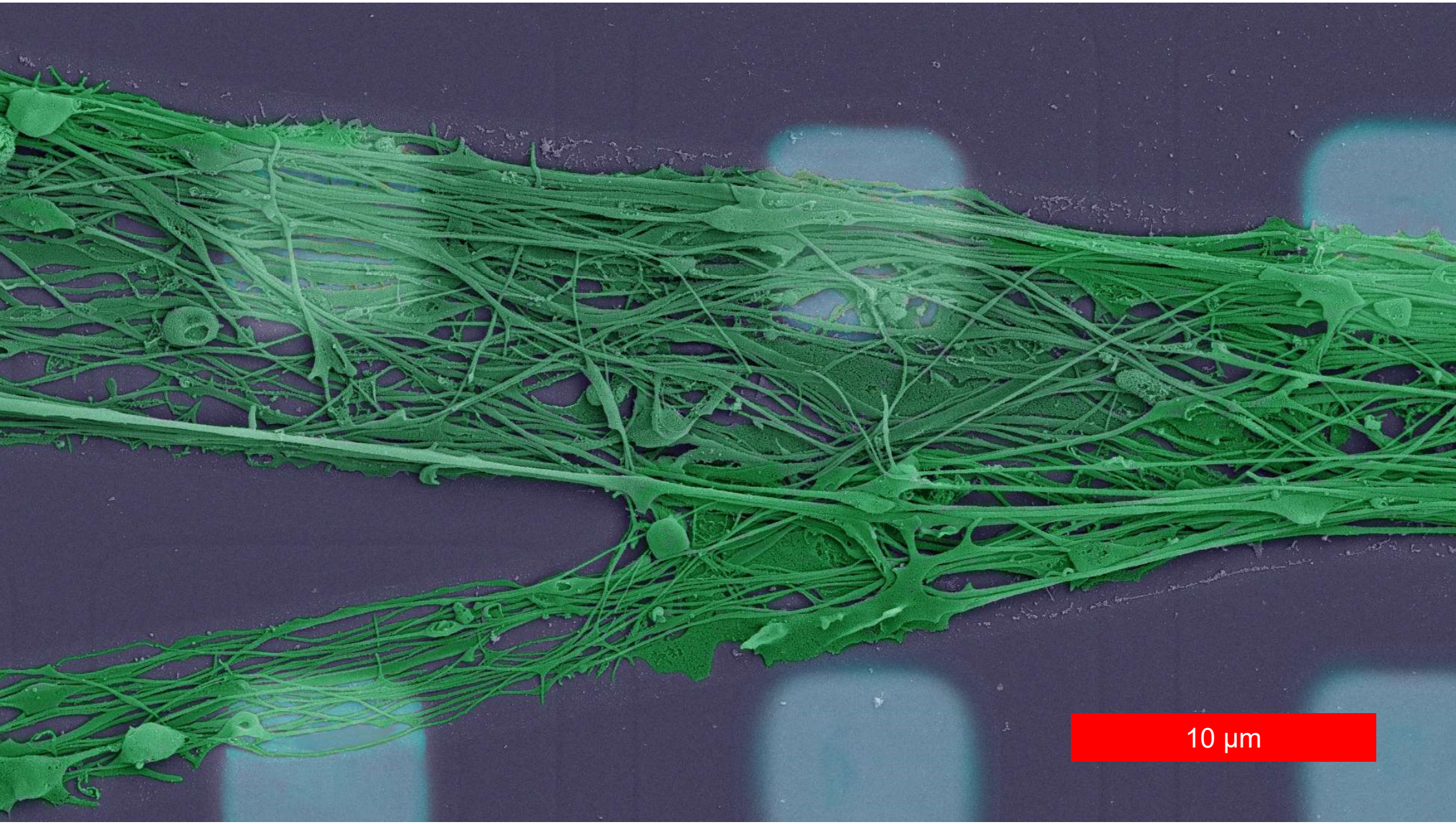



200 µm

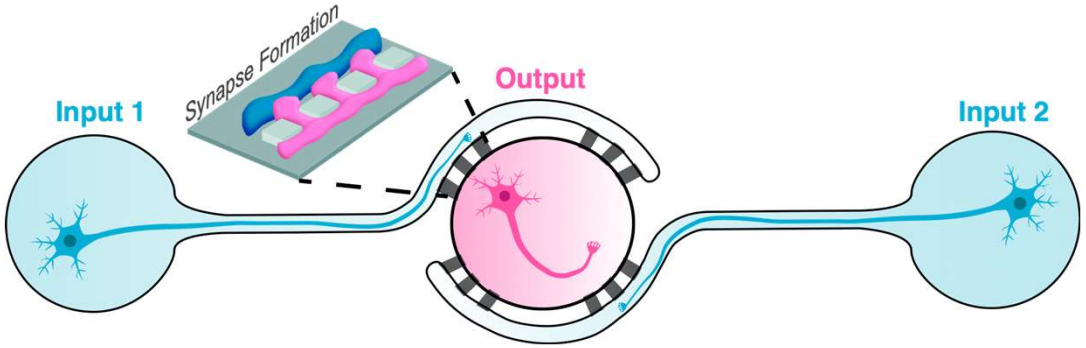
The post-stimulus information flow depends on the stimulation site

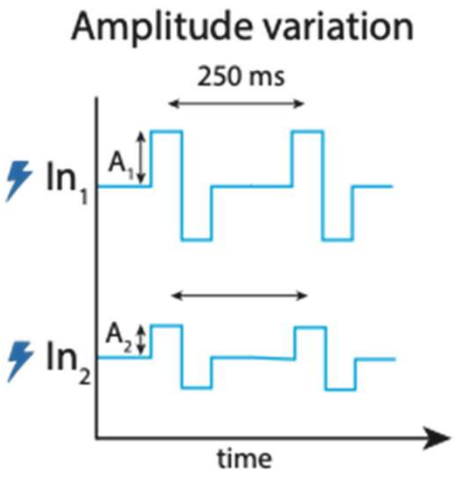


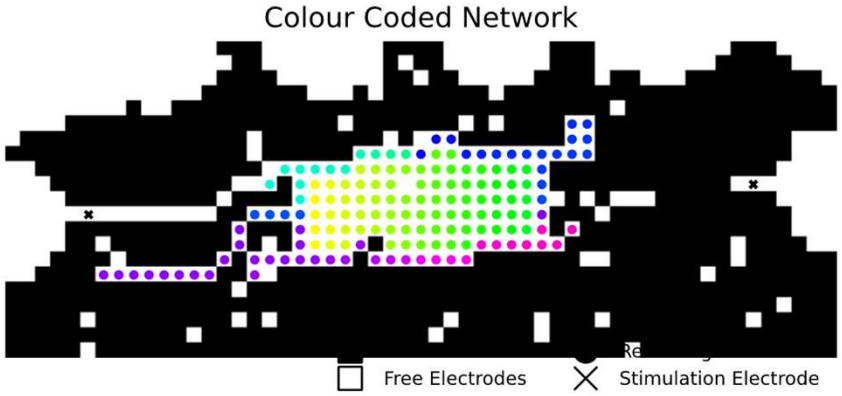


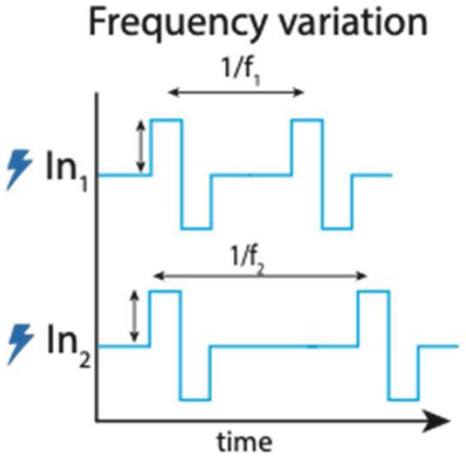

10 µm

A neural network with two inputs and one output



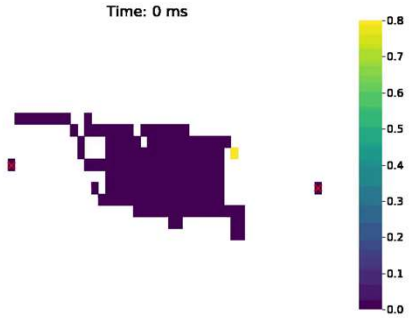


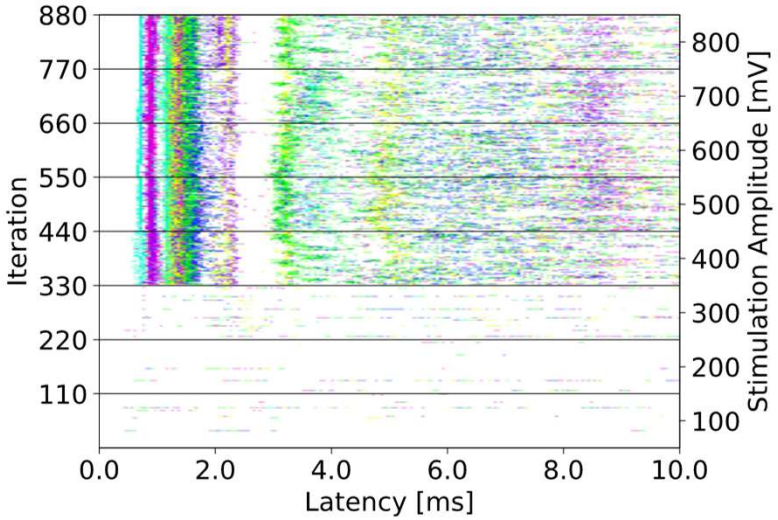


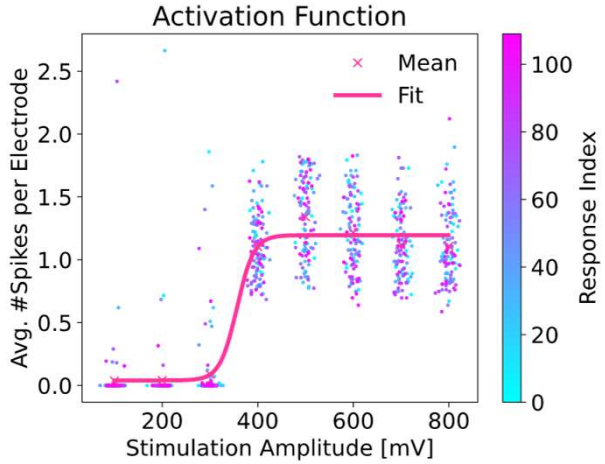


Same input on both stimulation electrodes

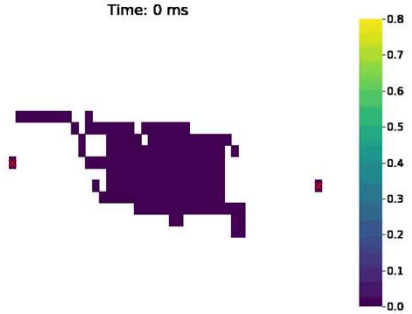
100 mV

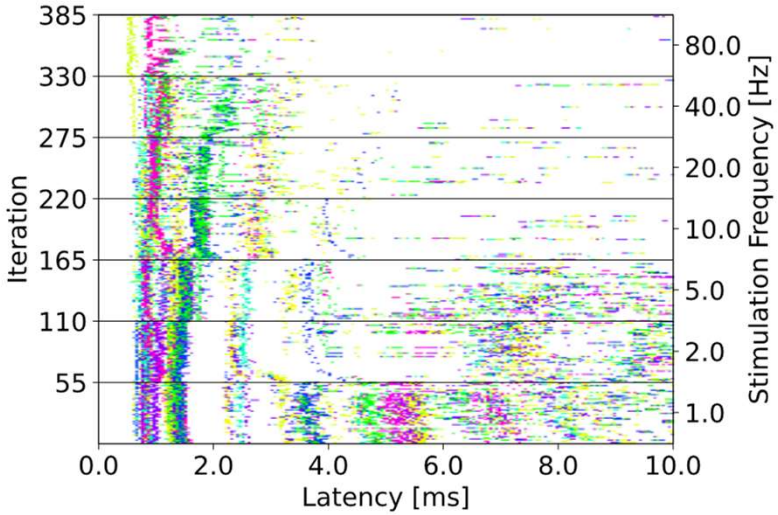


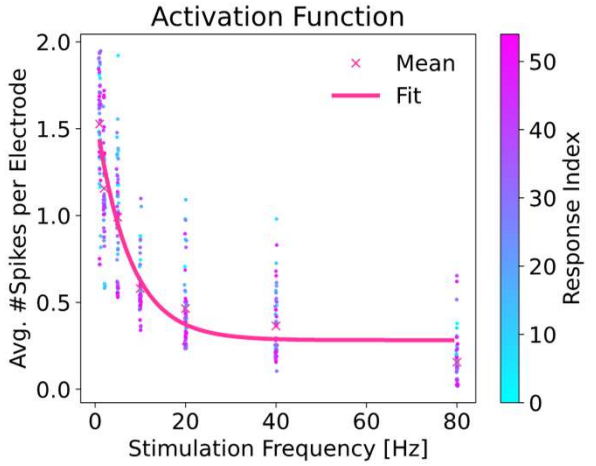




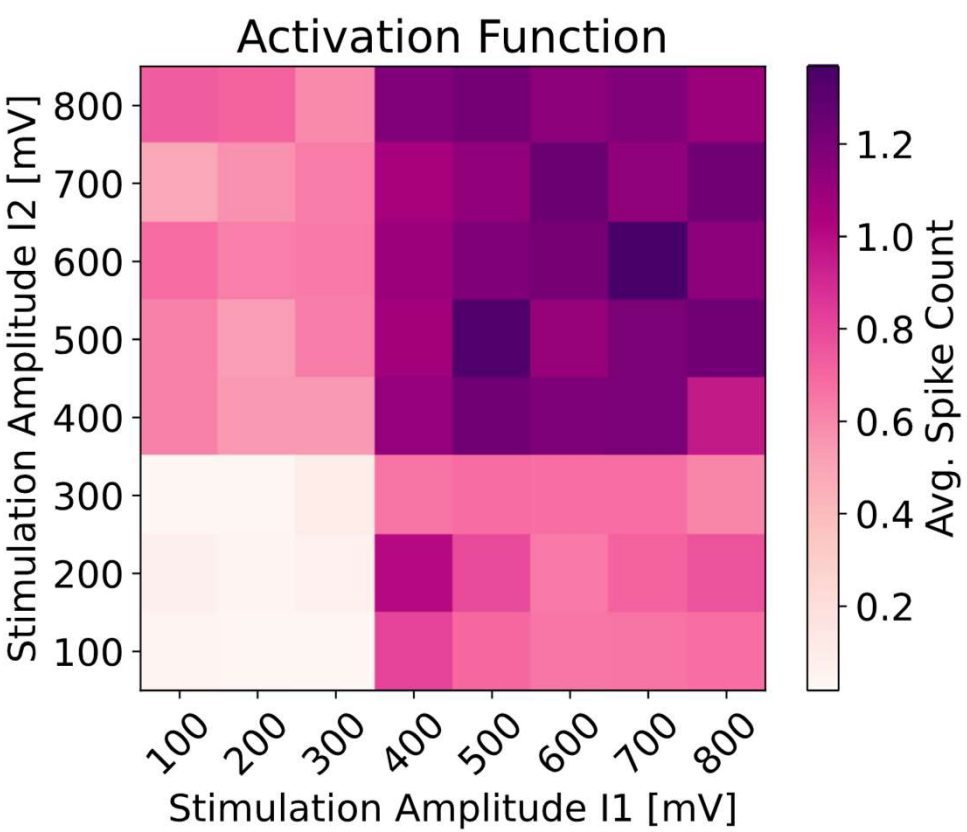
800 mV

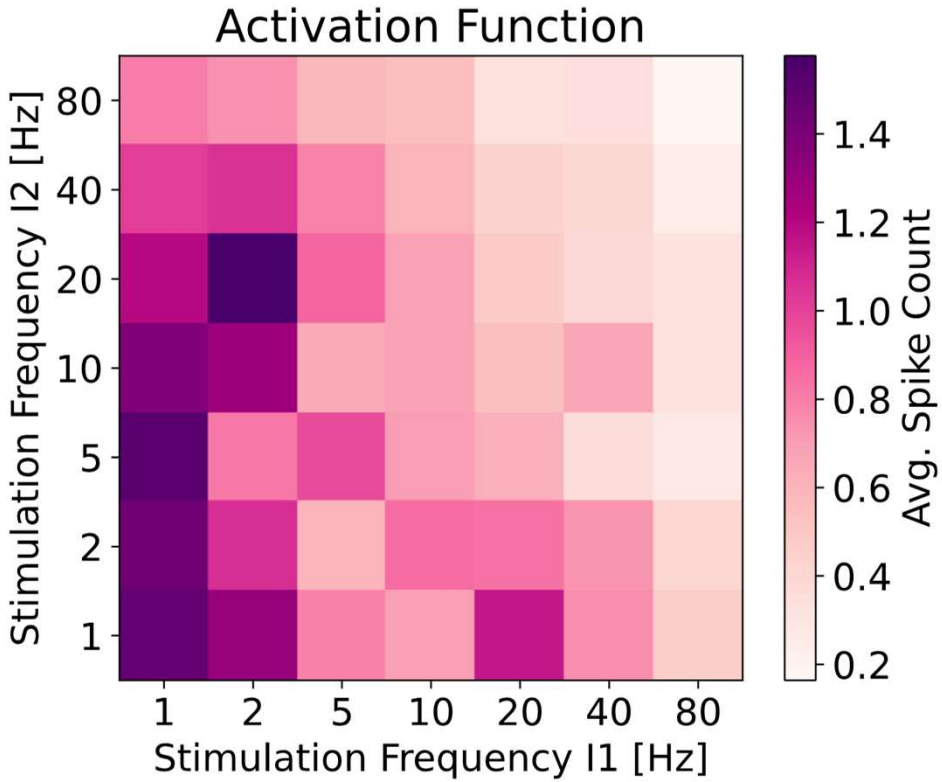






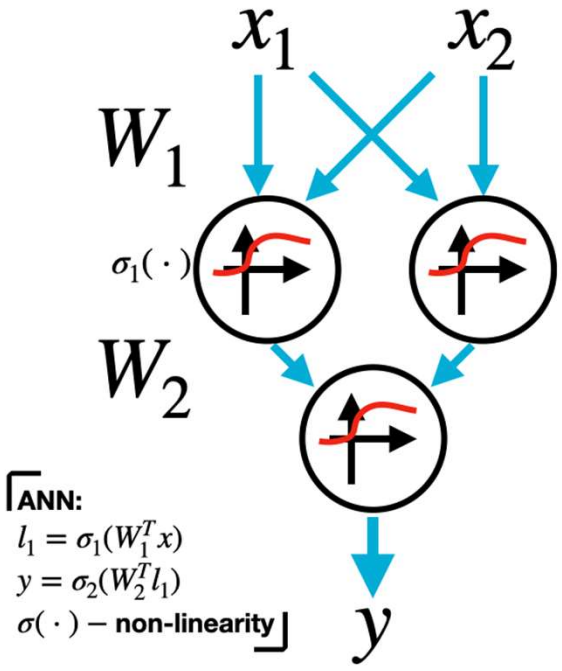
Response to different inputs



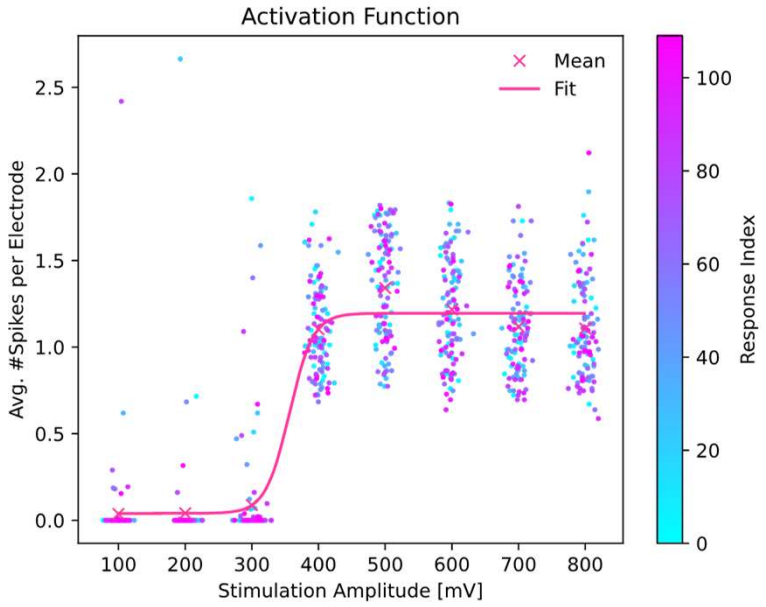


Nonlinear behavior can be used as activation functions of existing ANNs

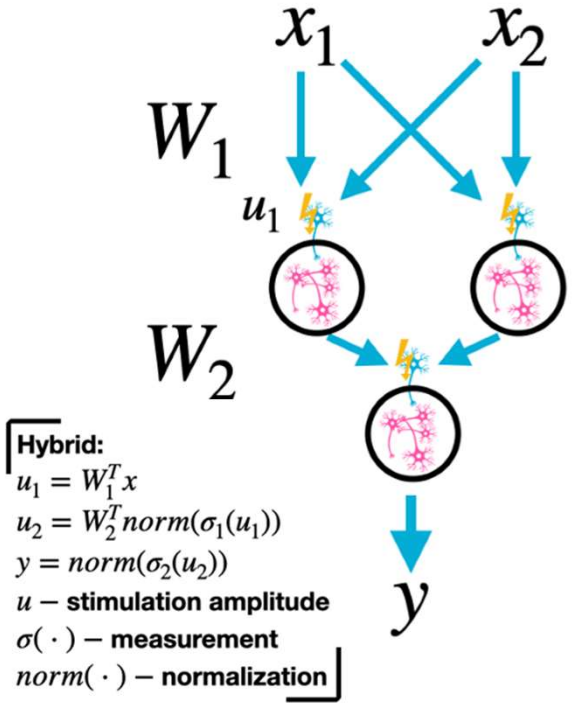
ANN



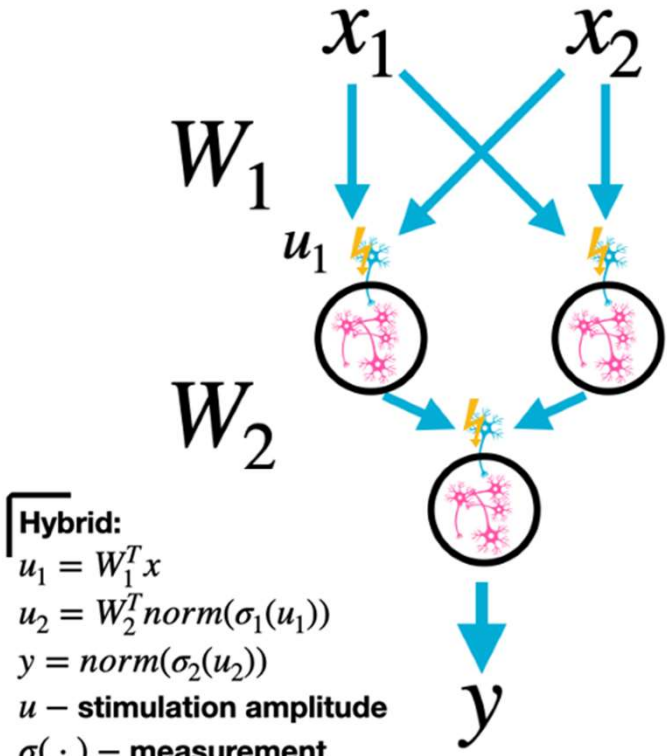
Fitted differentiable function



Hybrid neural network



Performance of a simple “hybrid” neural network as XOR



Hybrid:

$u_1 = W_1^T x$

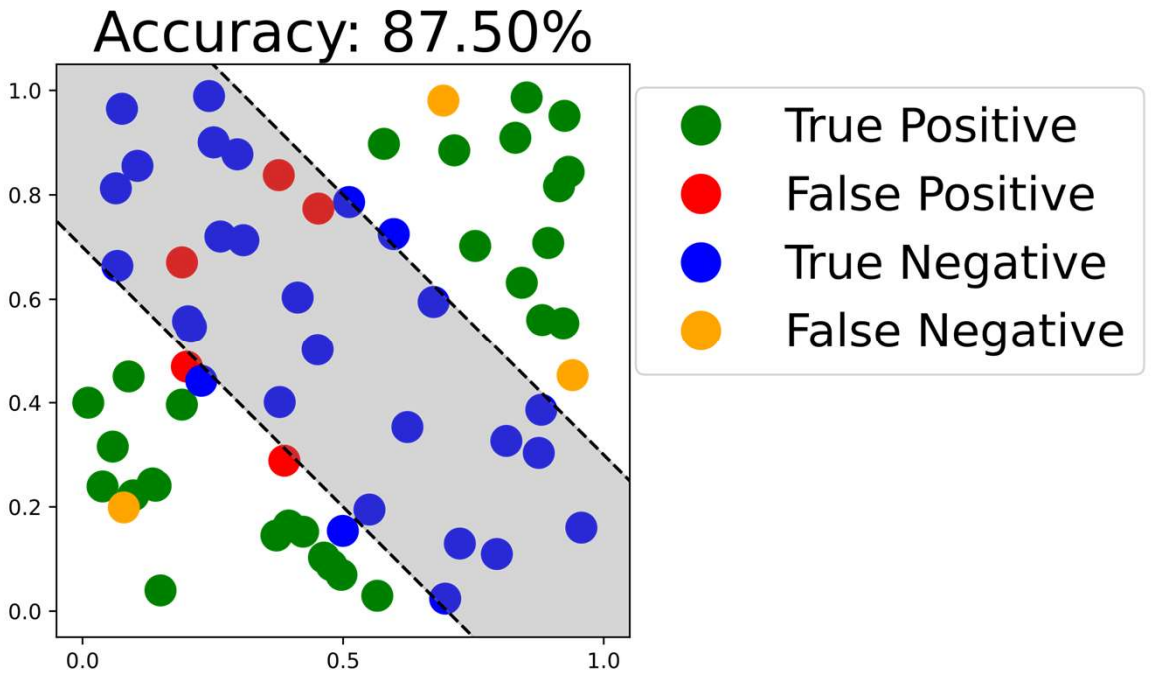
$u_2 = W_2^T norm(\sigma_1(u_1))$

$y = norm(\sigma_2(u_2))$

u – **stimulation amplitude**

$\sigma(\cdot)$ – **measurement**

$norm(\cdot)$ – **normalization**



Future potential of bottom-up neuroscience technology

Fundamental neuroscience

- Highly reproducible “big” data
- Stimulate and record protocols
- Extreme control over the local environment (including drugs)
- Can be combined with (opto)genetics

Personalized medicine and drug discovery

- Compatible with human iPSC-derived neurons – 3R
- Patient derived cells in combination with drugs

Hybrid intelligence

- Highly modular system without size constrains
- Can be interfaced with computational (spiking) neural networks

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ETHZ

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Innosuisse

Team: Laboratory of Biosensors and Bioelectronics 2023

Thank You !

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