A grayscale microscopic image of neuronal structures, showing a complex network of fibers and cell bodies. The image is used as a background for the title text.

Network dynamics and functional connectivity in neuronal assemblies coupled to micro-electrode arrays

Pisa 27/04/2018

Daniele Poli, PhD

daniele.poli@centropiaggio.unipi.it

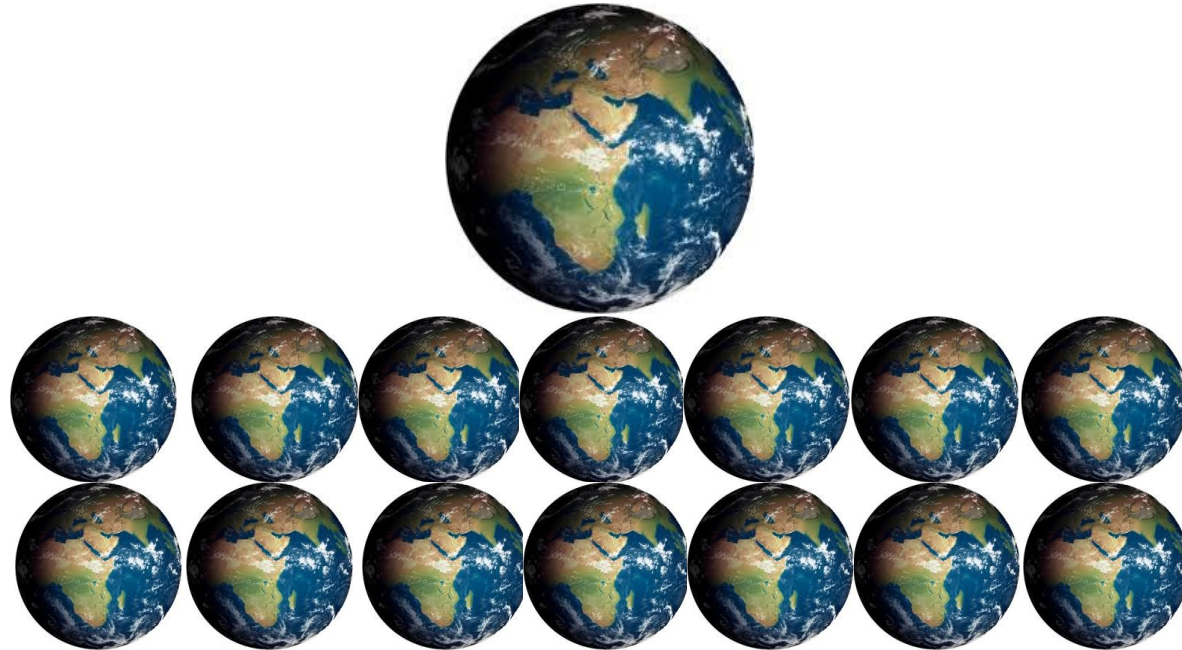
University of Pisa, Research Center 'E. Piaggio', Italy

Complexity of the brain

10^{11}

100.000.000.000

7.000.000.000



Connections

10^{14}

100.000.000.000.000

(1000:10000 connections each cell)

Information flow



Reverse engineering the brain

Why is it important to decode the neuronal information ?

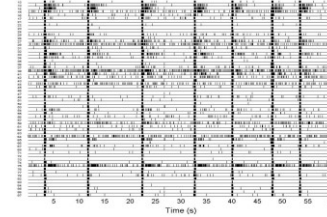
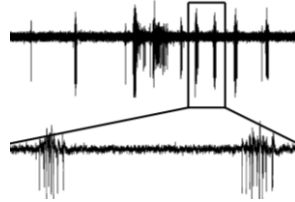
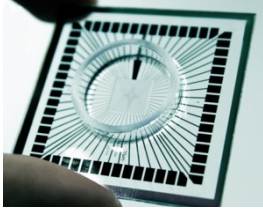
Paralysed woman moves robot with her mind

link

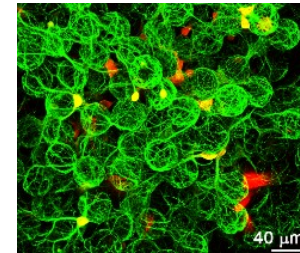
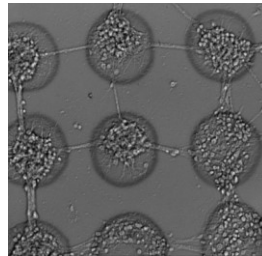
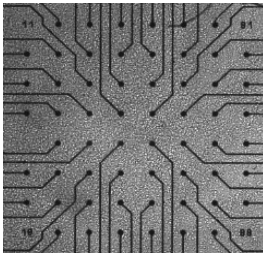
<https://www.youtube.com/watch?v=ogBX18maUiM>

Outline

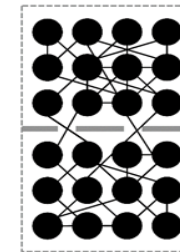
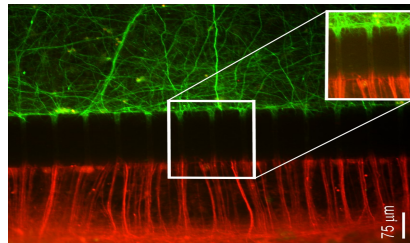
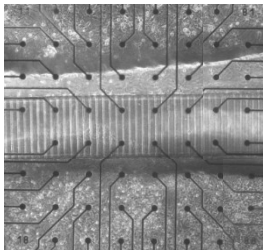
1. Neuronal networks coupled to Micro-Electrode Arrays (MEAs)



2. Engineered networks coupled to MEAs display complex dynamics



3. Interplay between connectivity and network dynamics

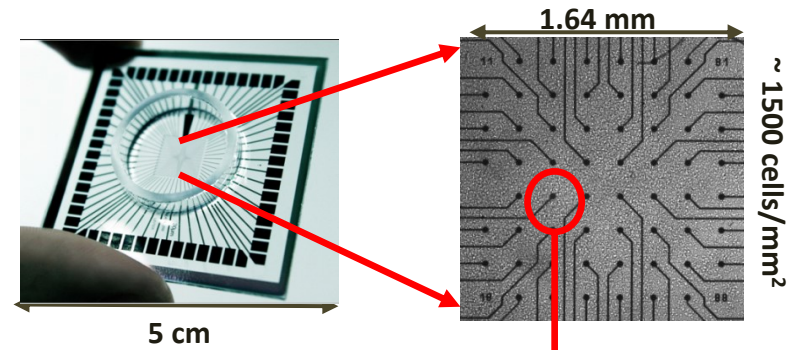


Neuronal networks coupled to MEA

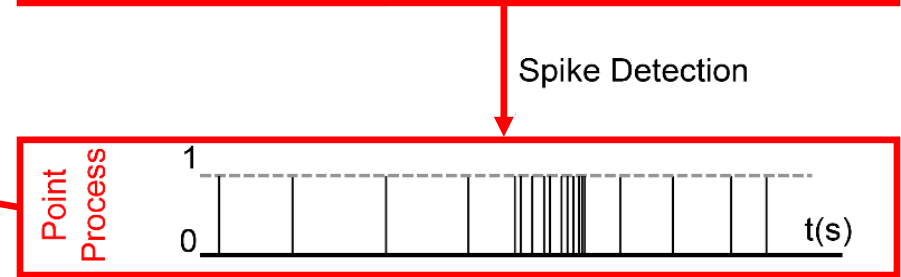
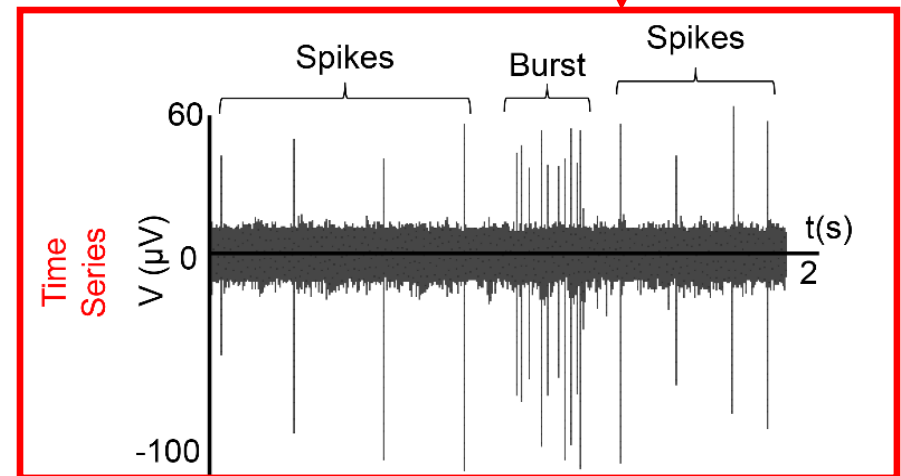
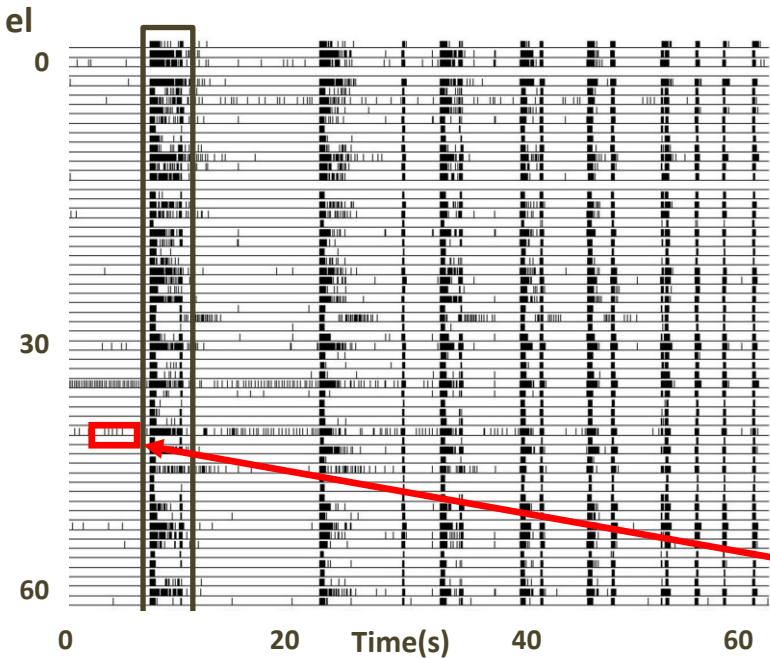
Primary cultures of rat neurons



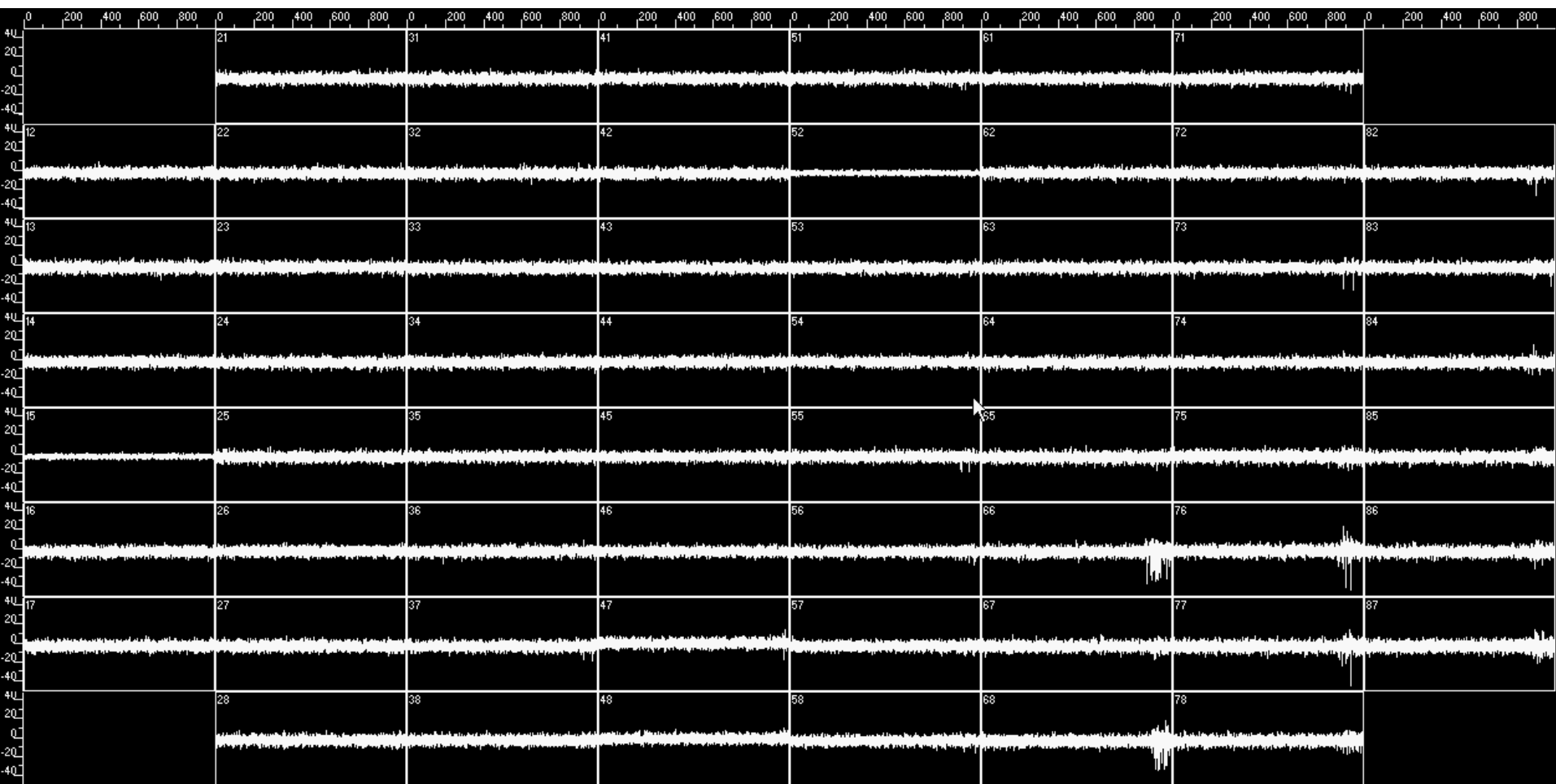
Micro-Electrode Arrays (MEAs)



Network burst / Network Spike / Up state



Electrophysiological activity of neuronal networks coupled to micro-electrode array



Robot controlled by neurons

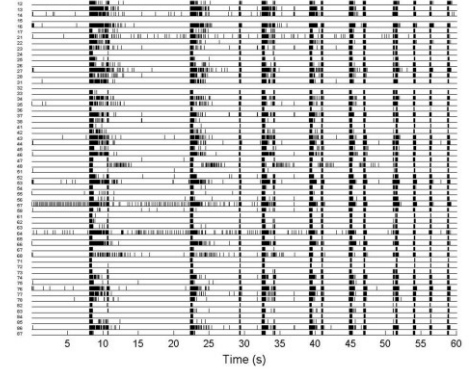
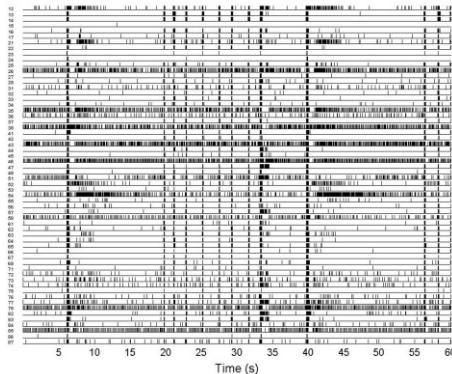
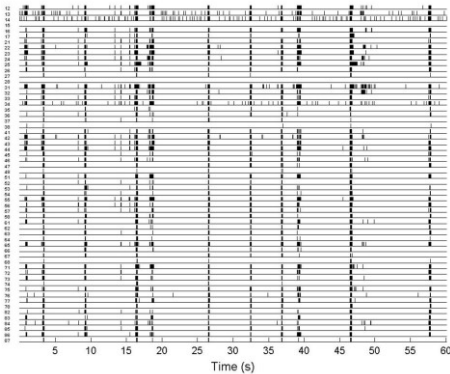
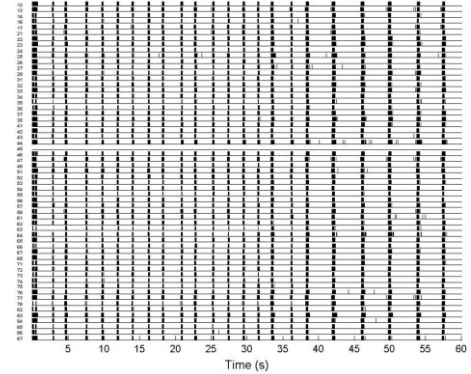
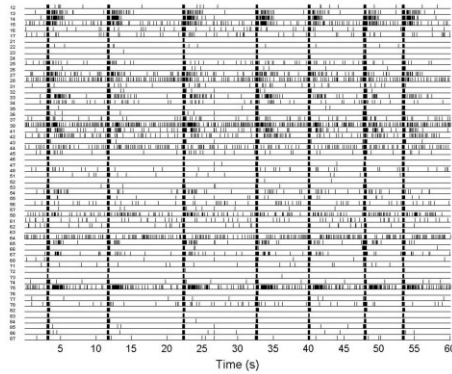
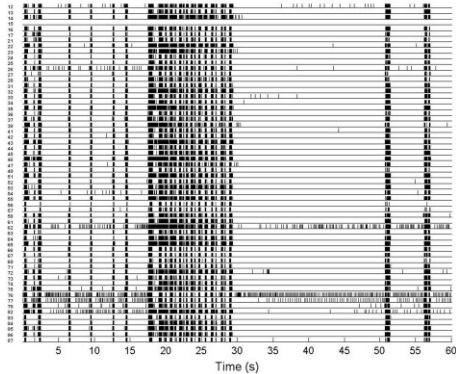
link

<https://www.youtube.com/watch?v=NZihD9QGqMs>

Great variability of activity patterns

Experimental Evidence:

Cortical networks exhibit different patterns of activity at the same degree of development

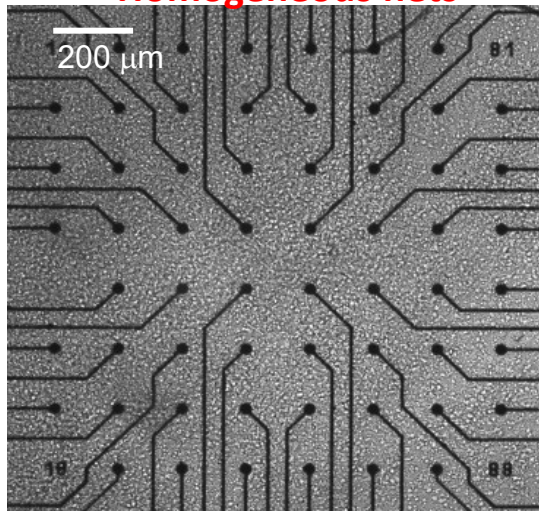


Scientific Question:

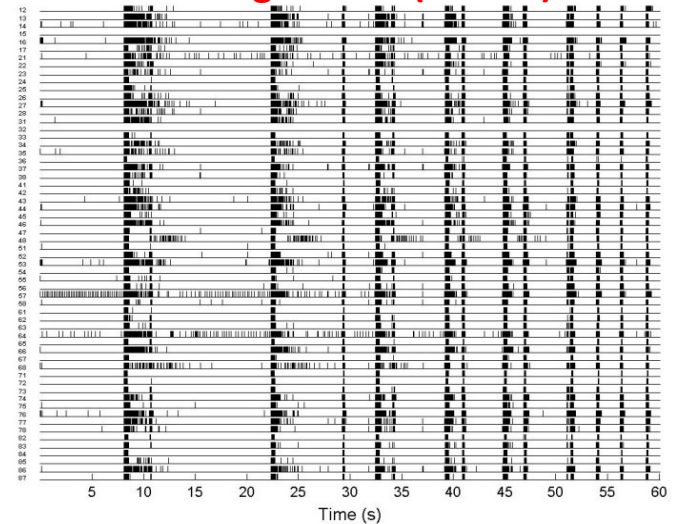
How neuronal connectivity shapes dynamics (and vice-versa) ?

Homogeneous vs. Interconnected networks

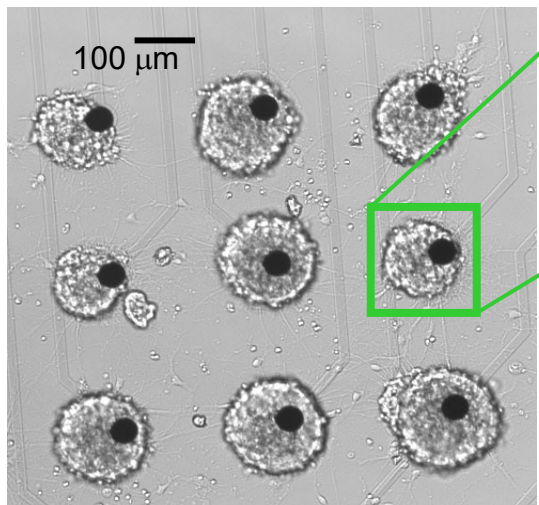
Homogeneous nets



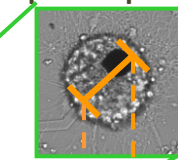
Homogeneous (DIV 21)



Interconnected nets

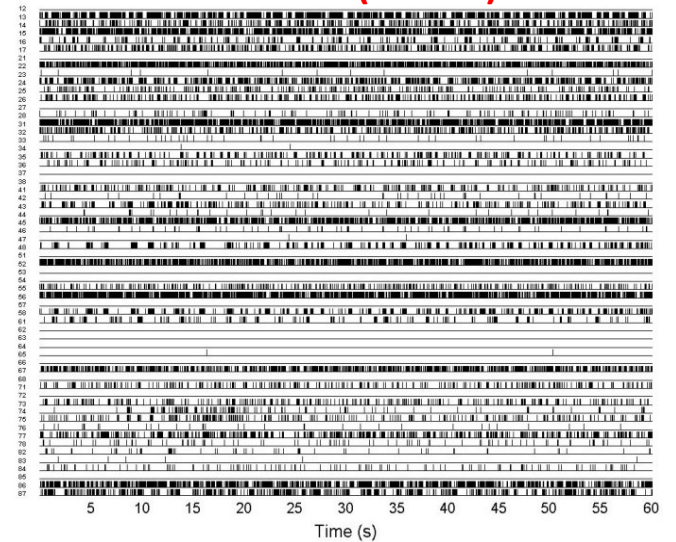


Number of neurons
per drop ~ 60

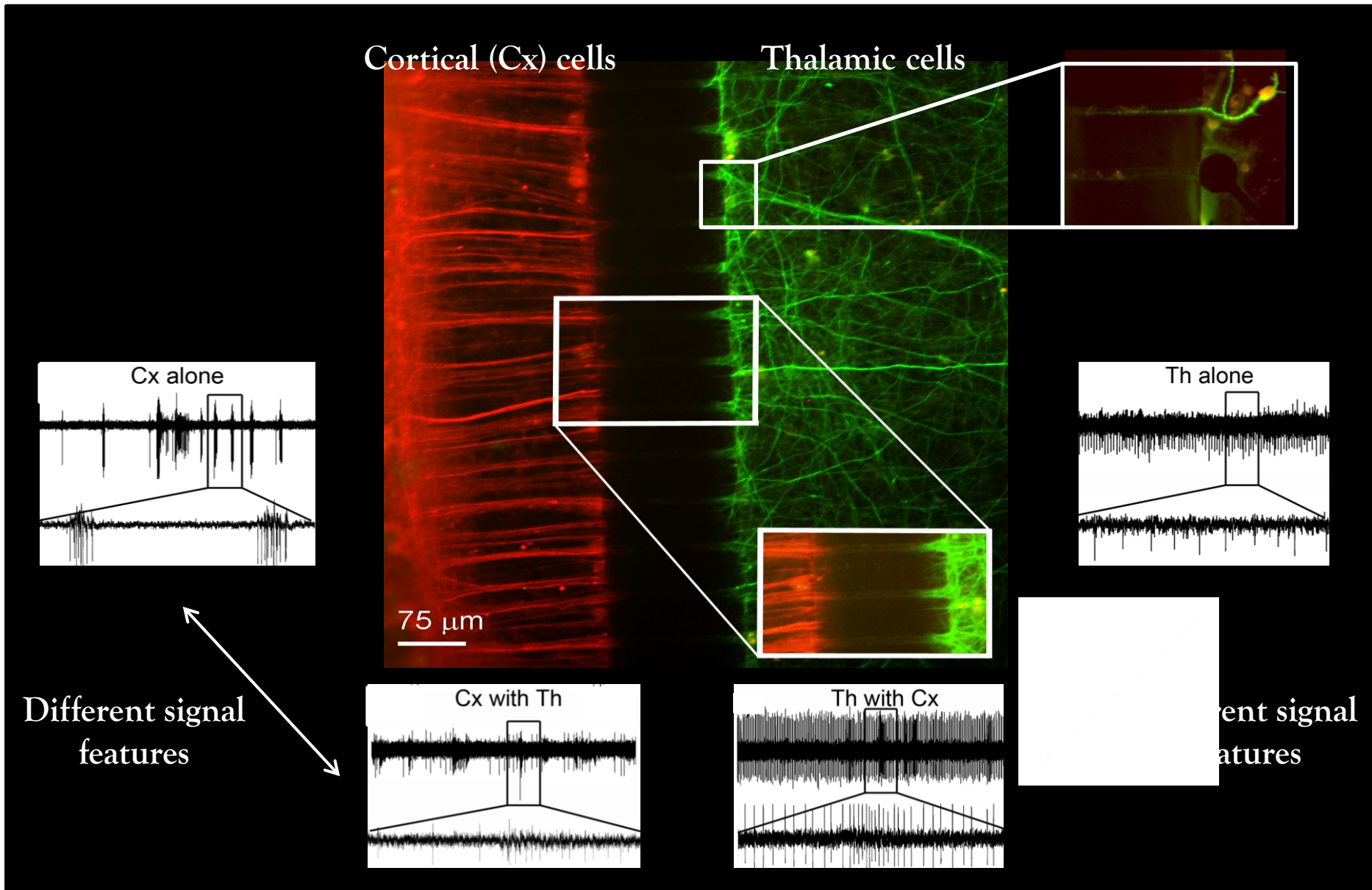


$\varnothing = 147.5 \mu\text{m} \pm 7.1 \mu\text{m}$

Patterned (DIV 21)



Homogeneous vs. Heterogeneous networks



Rat neurons grown on a computer chip fly a simulated aircraft

link

https://www.youtube.com/watch?v=1w41gH6x_30

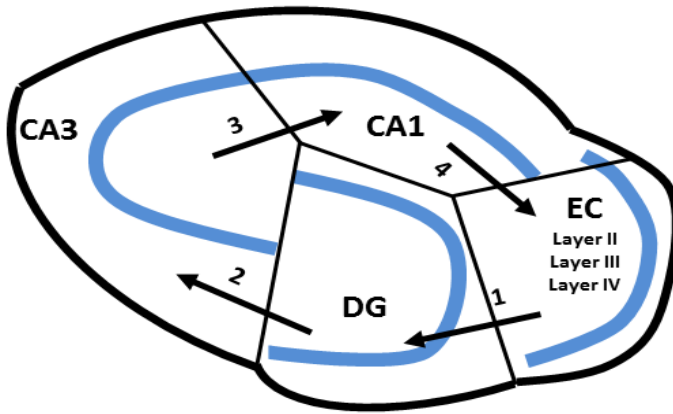
The history behind the b-27 media system

link

<https://www.youtube.com/watch?v=xQBkyo0yuzM>

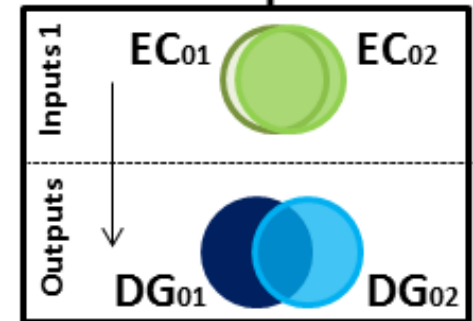
Coding of memory in engineered heterogeneous and interconnected neuronal networks reconstructed from hippocampus

Hippocampal tri-synaptic loop

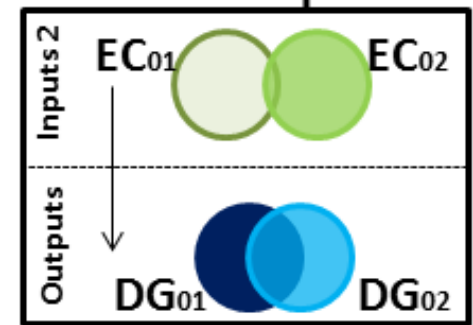


DG as a pattern separator

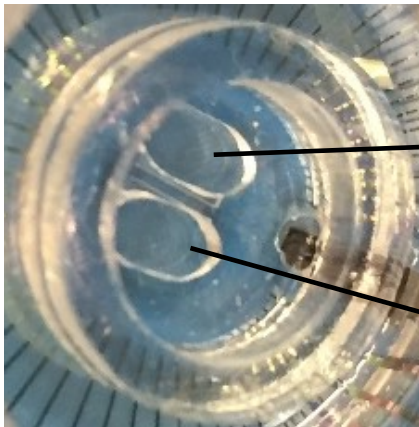
Pattern Separation



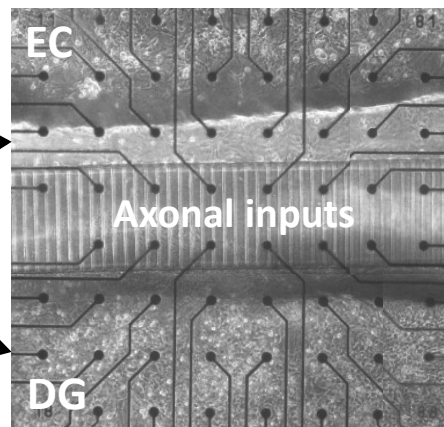
Pattern Completion



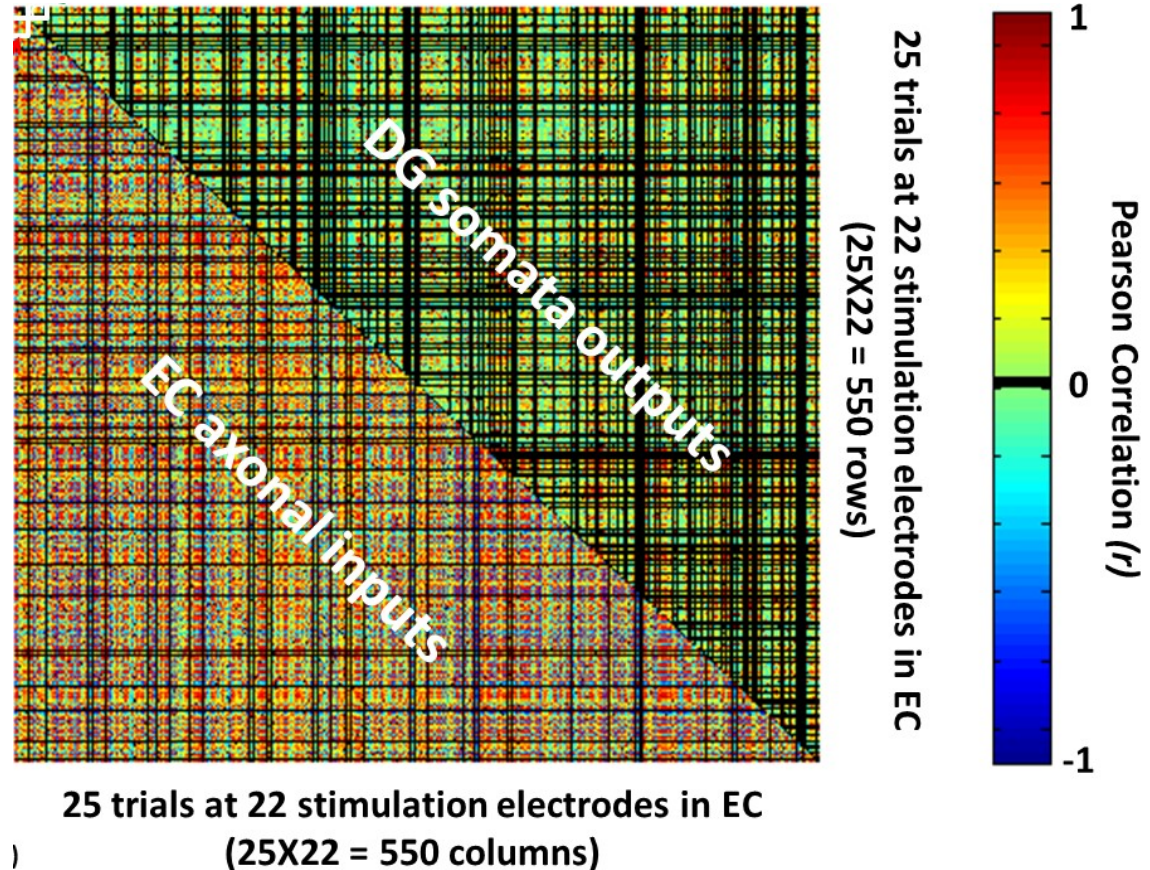
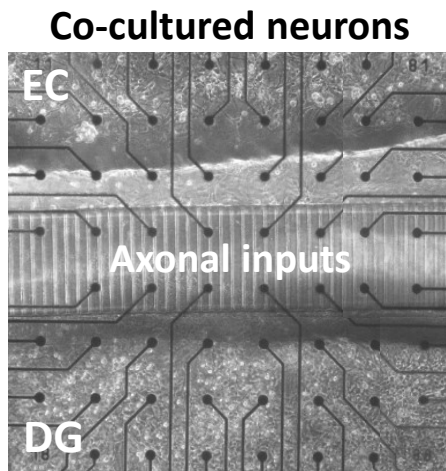
Two-chambers on MEA60



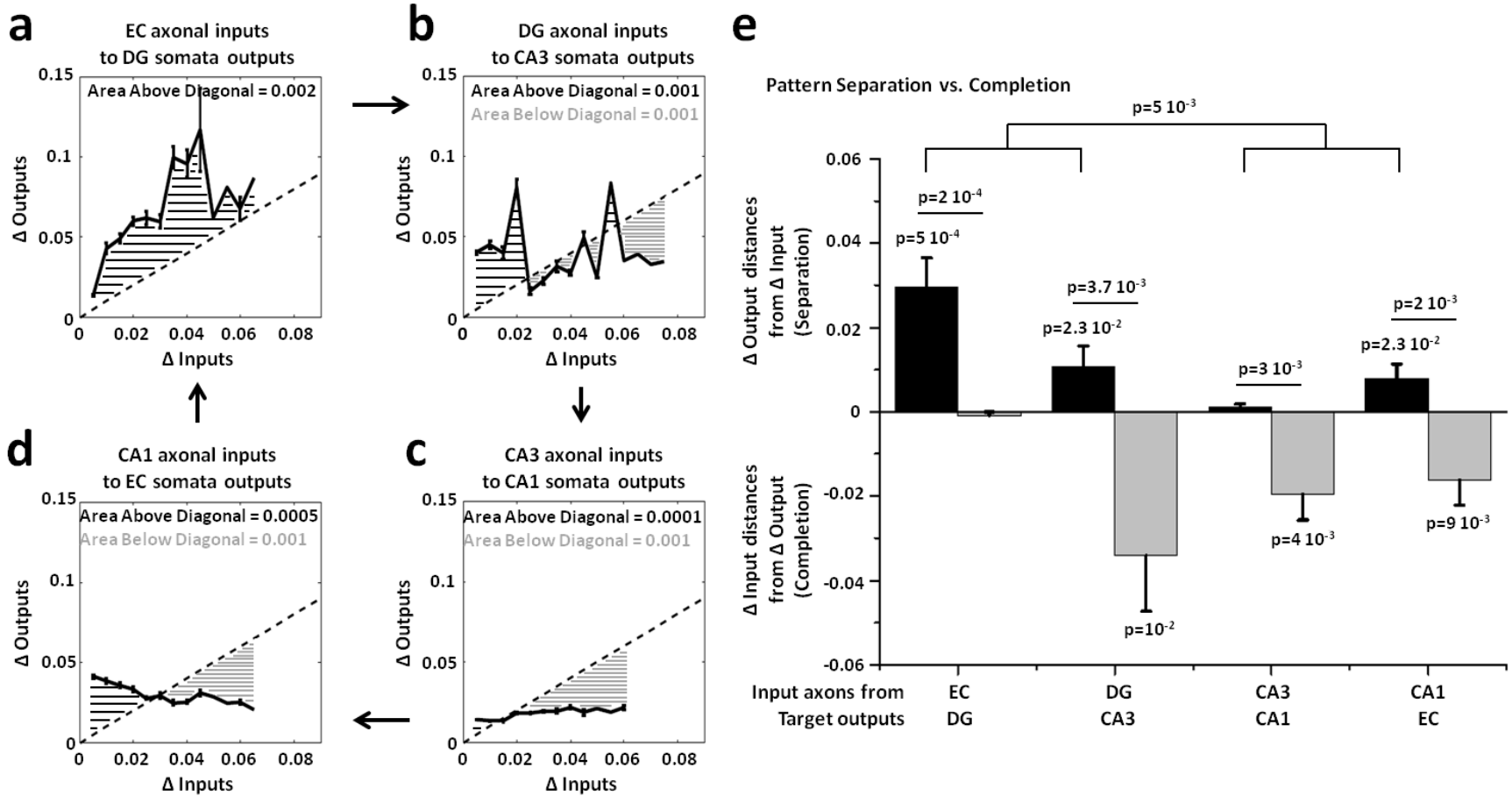
Co-cultured neurons



In vitro hippocampal networks ascribe functions for encoding episodic memories: Pattern Separation of EC axonal inputs transmitted via microtunnels into DG

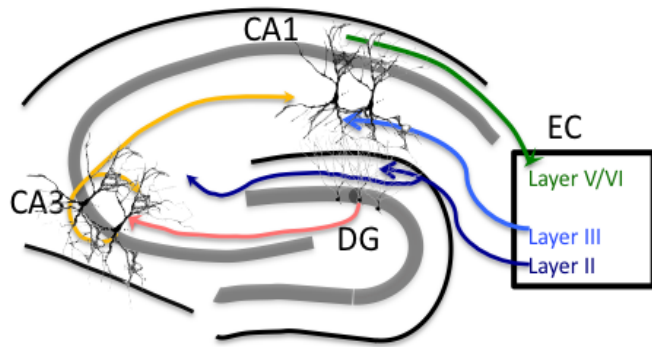


Pattern Separation of EC axonal inputs and Pattern Completion in CA3

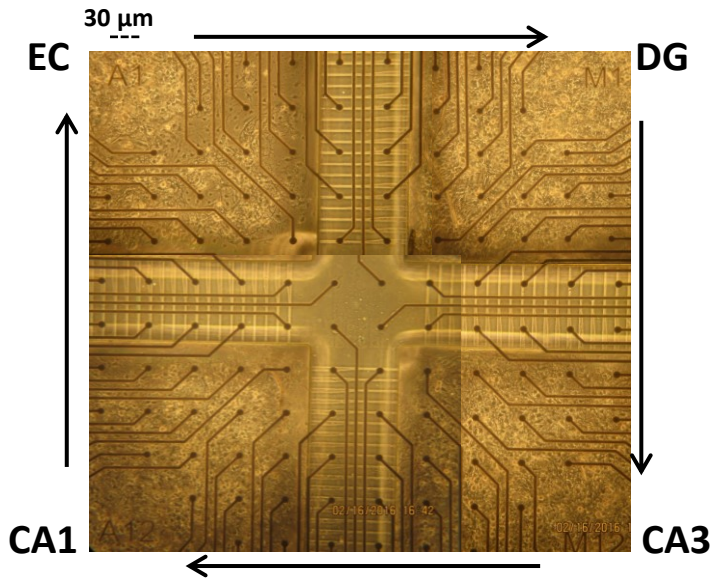


Axonal transmission between each pair of four stages of the EC-DG-CA3-CA1 circuit

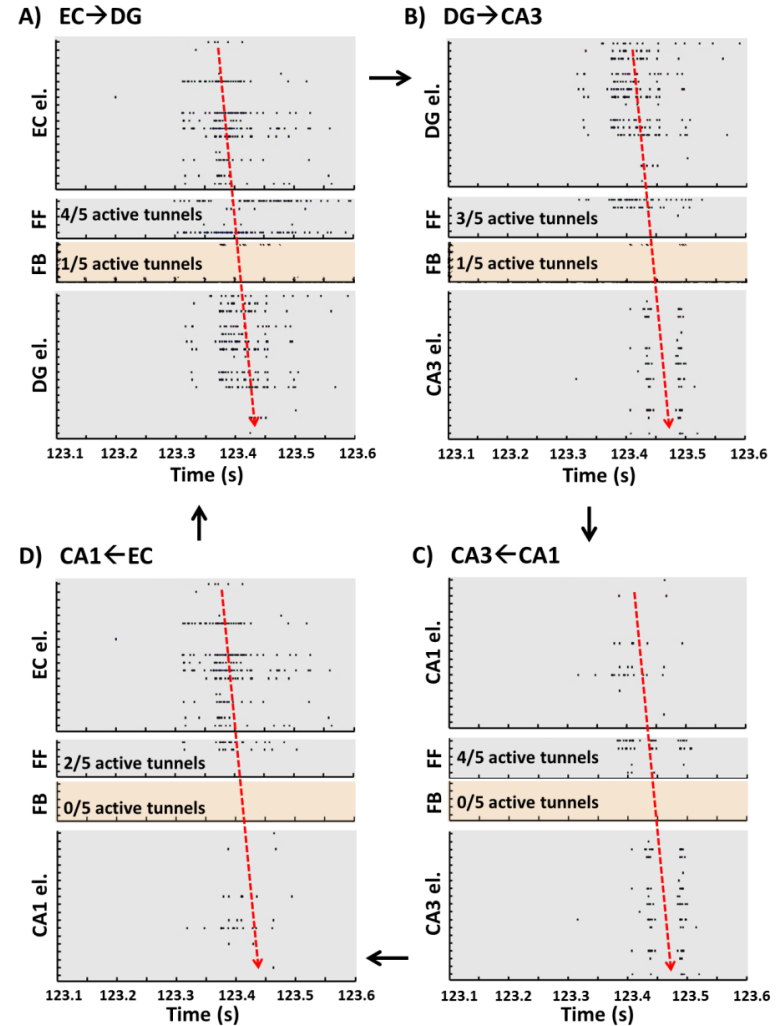
Hippocampal tri-synaptic loop



Four-chambers on MEA120

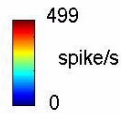
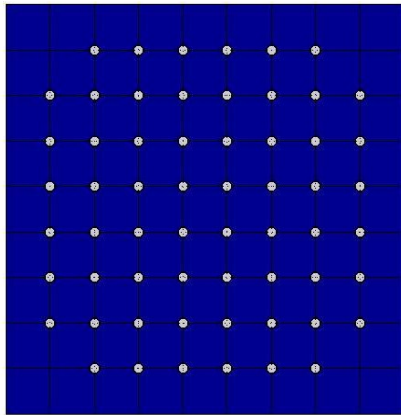
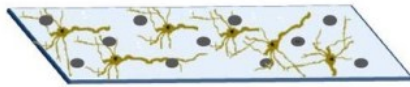


Spontaneous Activity (500 ms)

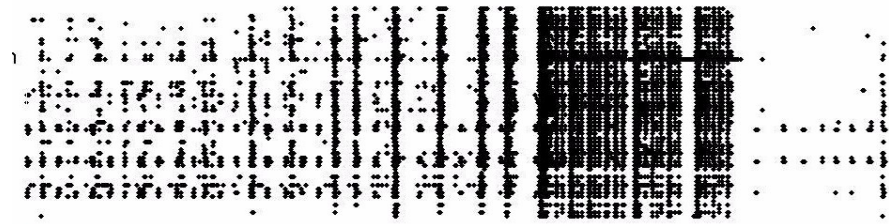
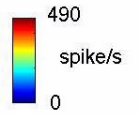
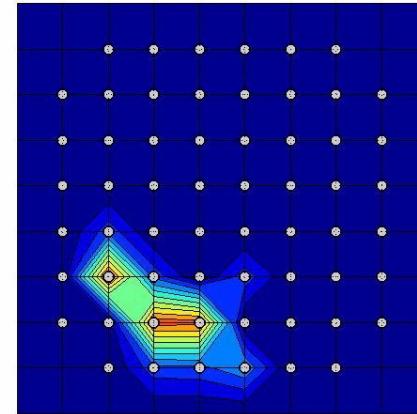
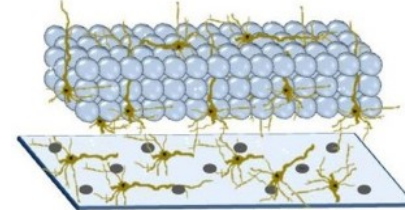


2D vs. 3D neuronal assemblies (1)

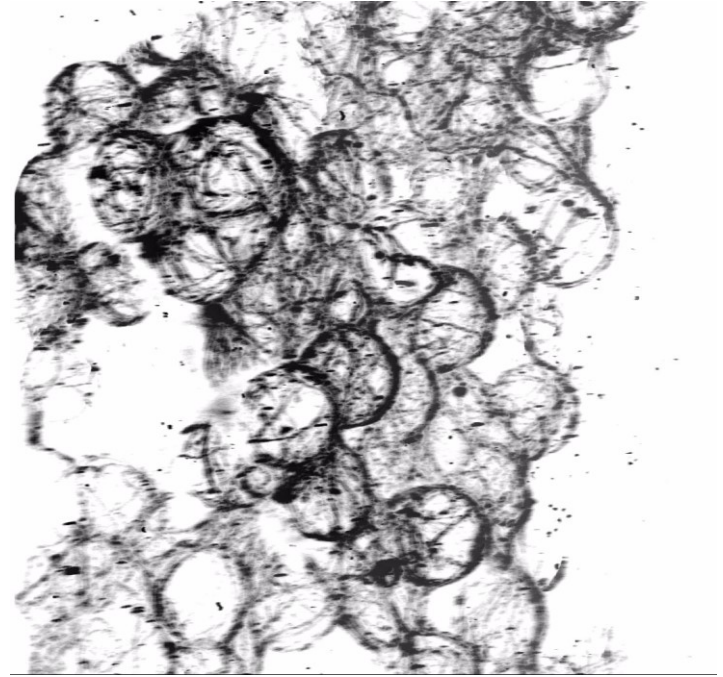
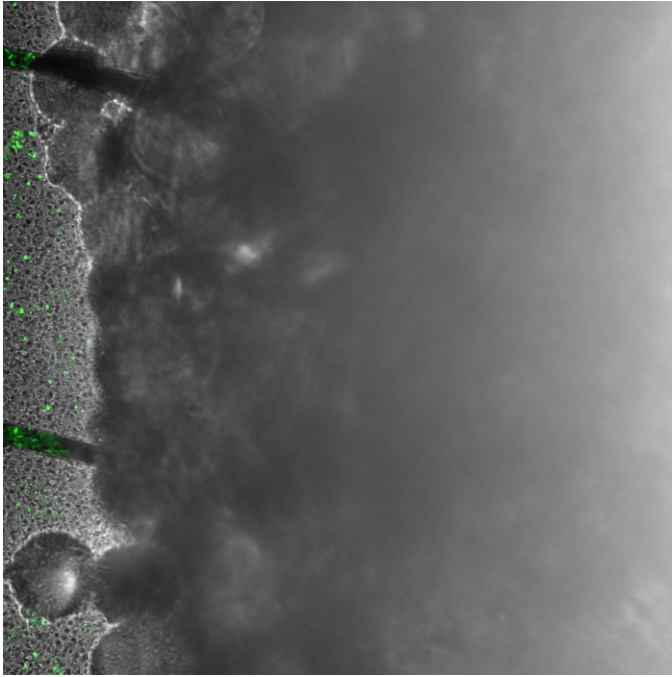
2D network on MEA



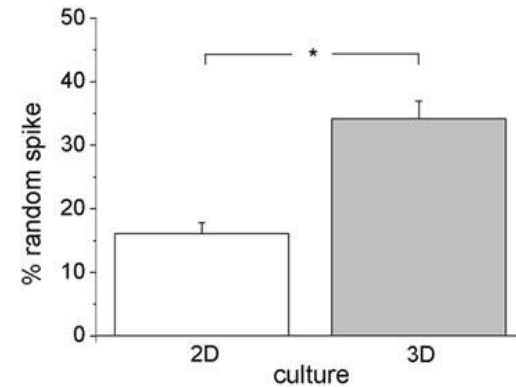
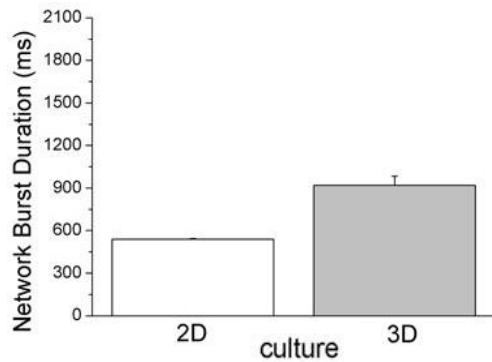
3D network on MEA



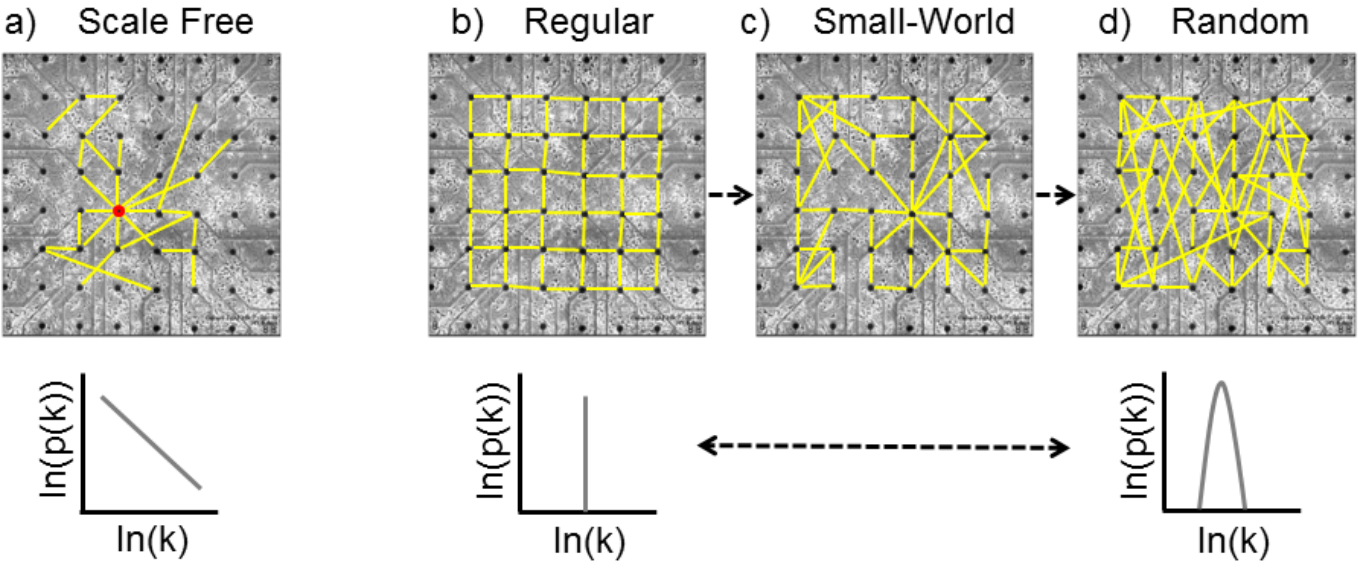
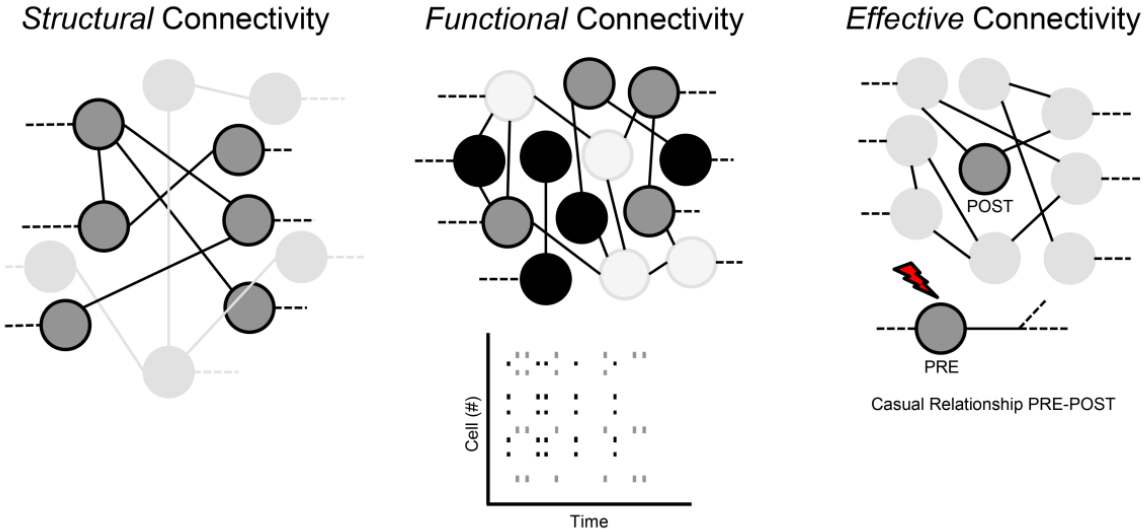
2D vs. 3D neuronal assemblies (2)



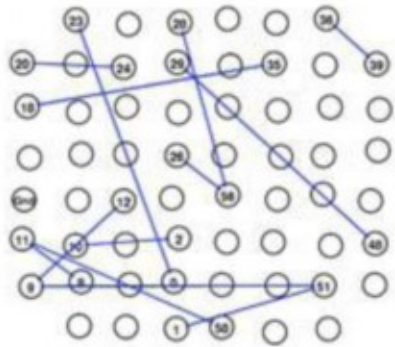
3D neuronal assemblies show network burst and random spikes (in vivo like)



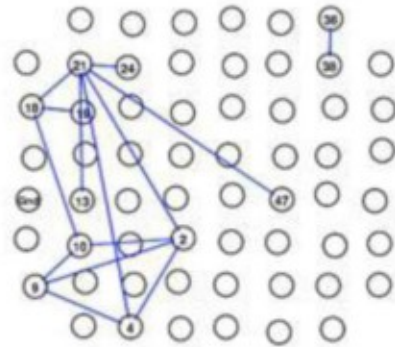
Interplay between connectivity and network dynamics



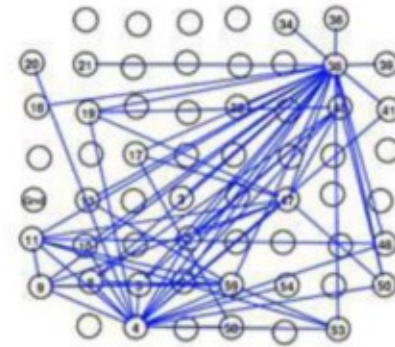
Topological network properties during development



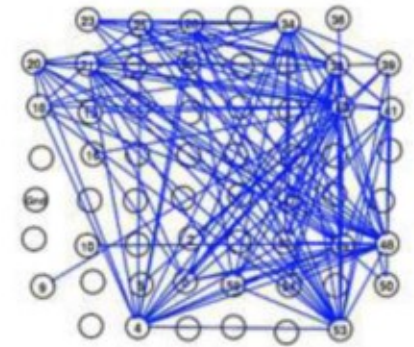
DIV 14



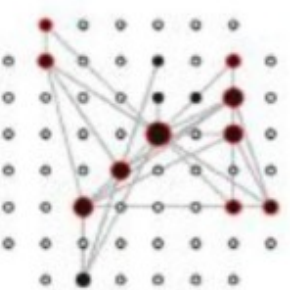
DIV 21



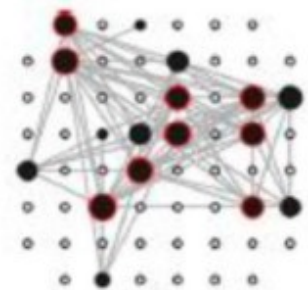
DIV 28



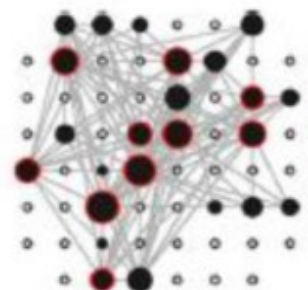
DIV 35



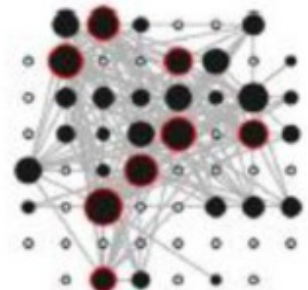
DIV 14



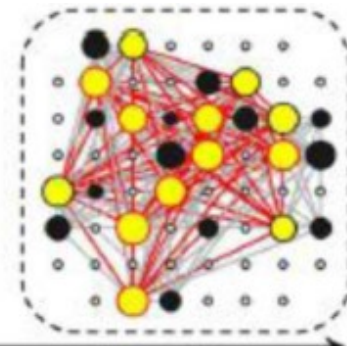
DIV 17



DIV 21



DIV 24



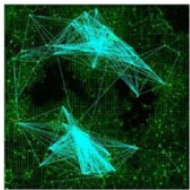
DIV 28

Interplay between functional and structural connectivity

From
Functional



To
Structural



1. interplay between functional and structural networks
2. Topology of a structural network maintained in a functional one

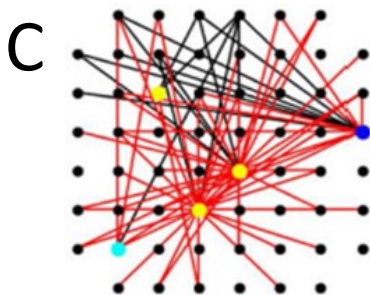
Functional connectivity may provides a useful way to infer structural connectivity (especially when structural morphological reference is not available)

Bullmore and Sporns, Nat. Rev. Neurosci. 2009

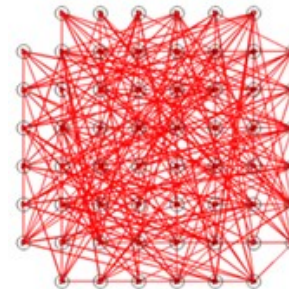
Scientific Questions:

1. Is it possible to identify functional-effective links that partly reconstruct the network architecture and therefore the topological features? YES

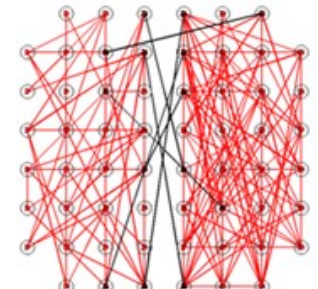
Poli D. et al., J. Neural Eng., 2016



A Homogeneous Network



B Interconnected Network



2. Does high-frequency electrical stimulation induce synaptic plasticity? YES

Chiappalone M. et al., European_Journal_of_Neuroscience , 2008

High-density MEAs with large number of electrodes would certainly provide a better picture.

Increasing of complexity

60 el.

120 el.

252 el.

4096 el.

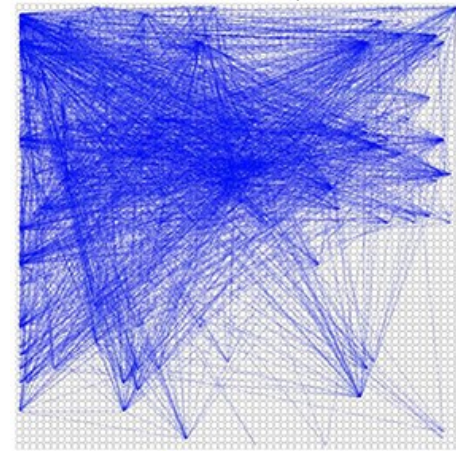
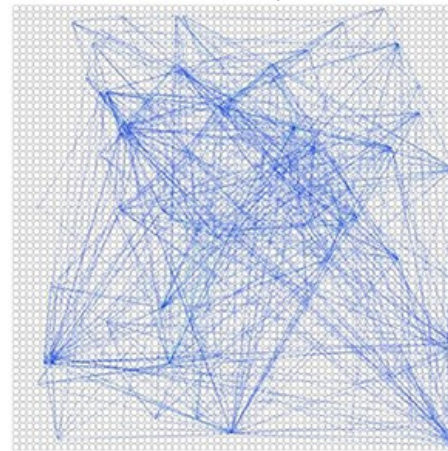
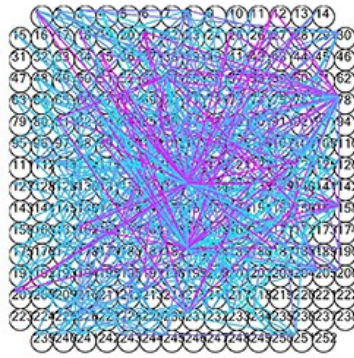
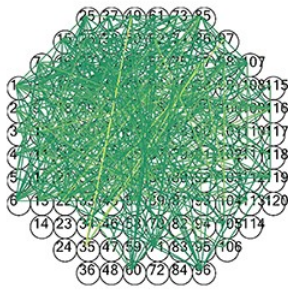
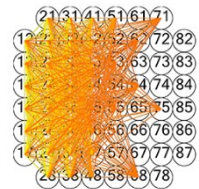
low density

80–200 cell/mm²

4096 el.

high density

350–1200 cell/mm²



1 mm

The high spatial resolution of high-density MEAs would allow a more thorough investigation of the topological architectures of neuronal assemblies

Summary

1. Reverse engineering the brain.
2. Neuronal networks coupled to MEAs show great variability of activity patterns.
3. Engineered networks show complex and specific dynamics.
4. Heterogeneous and interconnected hippocampal neurons cultured on multichamber devices over MEAs ascribe functions for encoding pattern separation and completion.
5. Strong interplay between connectivity and network dynamics.
6. Strong interplay between functional and structural connectivity