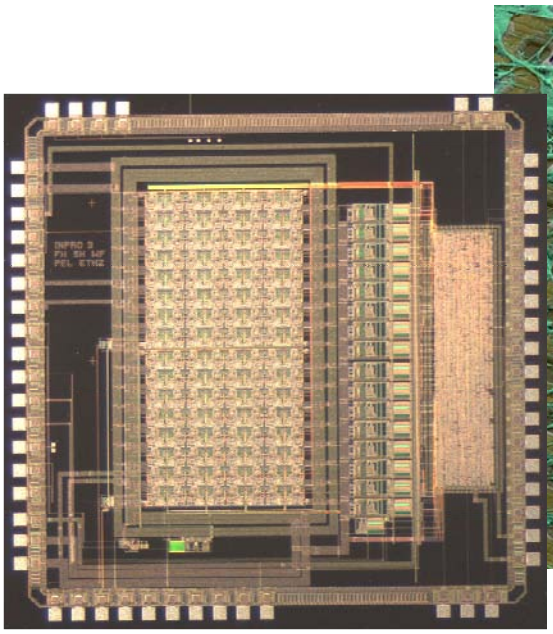
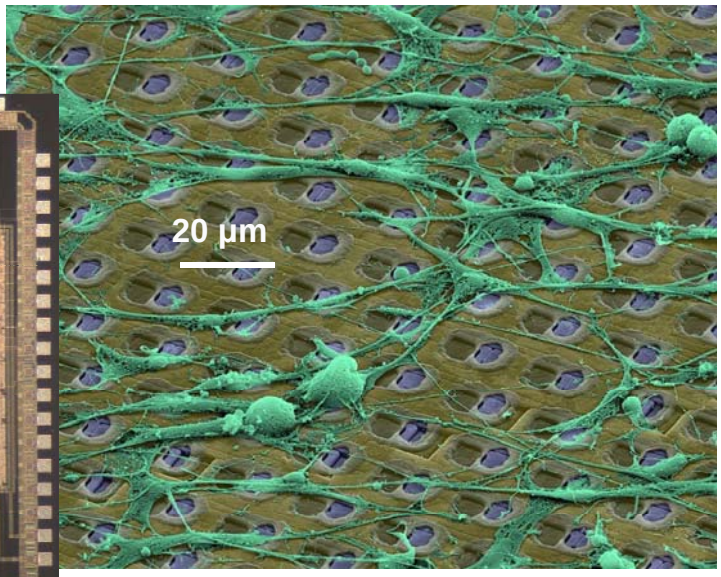
Direktes Ankoppeln von Hirnzellen an Mikroelektronik

D-BSSE





Outline

Bioelectronics Fundamentals

- electrogenic cells
- action potentials
- measurements of electric activity

CMOS Bioelectronics

- CMOS, why CMOS?
- bioelectronic chips

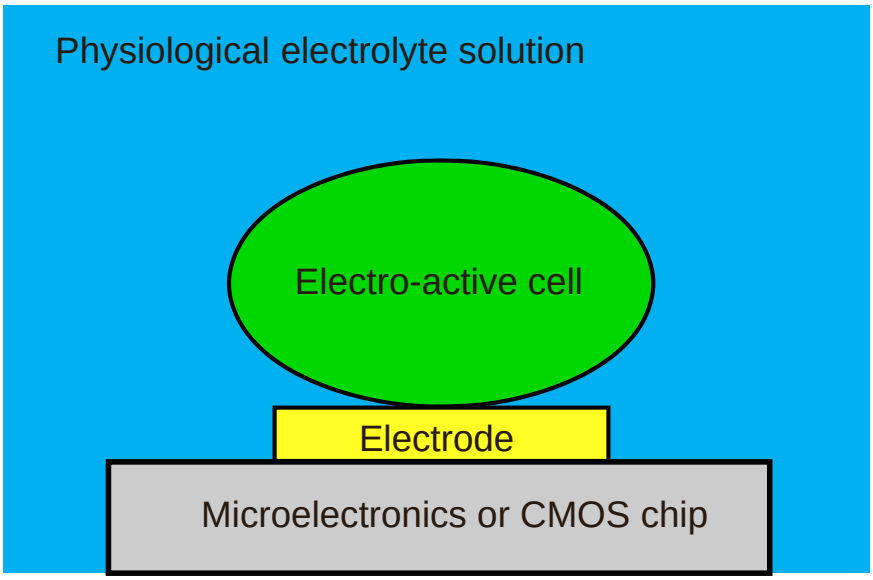
High-density CMOS Bioelectronic Chip

- high-density electrode realization
- circuitry, system and packaging

Cell Recordings

- single-cell localization in slices
- tracing of axonal signal propagation

Interfacing Cells with Microelectronics

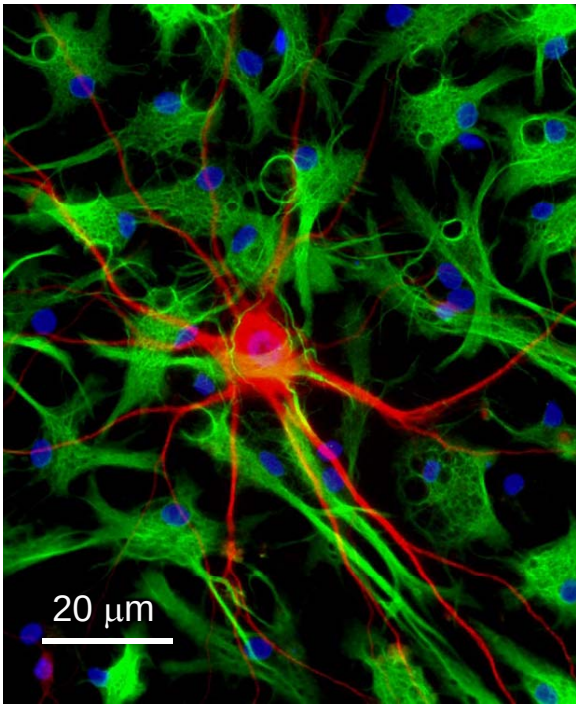


Ionic species and charge transport

Na^+, K^+ ion mobility: $5.2 – 7.6 \times 10^{-8}$ m^2/Vs

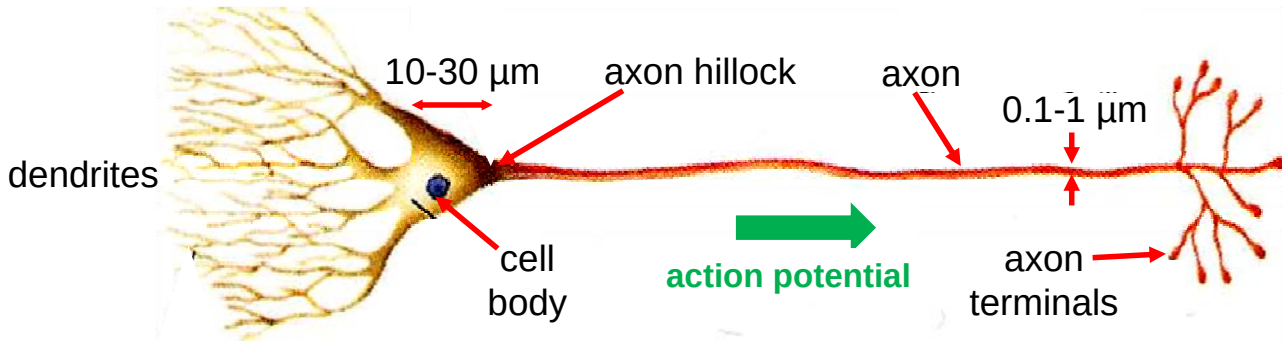
Electrons, mobility in Si: 0.15 m^2/Vs

Neurons or Brain Cells



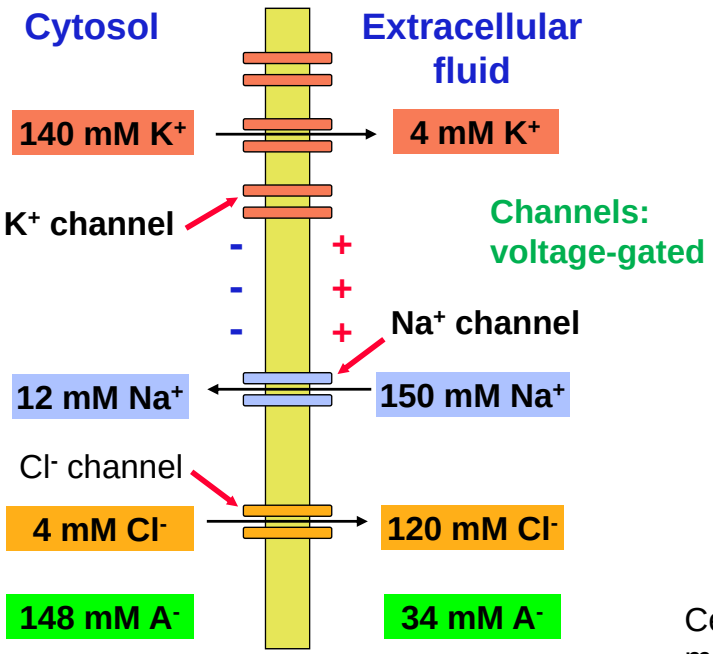
- Human brain: 10^{12} neurons
- Neuron connected to more than 1000 others
- Neurons: electro-active cells (K^+, Na^+)
- Neuronal communication:
  - electric signals, action potentials
  - chemical signals between cells (synapses)

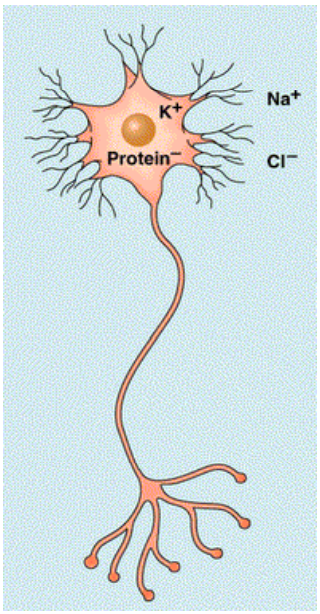
Neurons



input integration signal conduction output

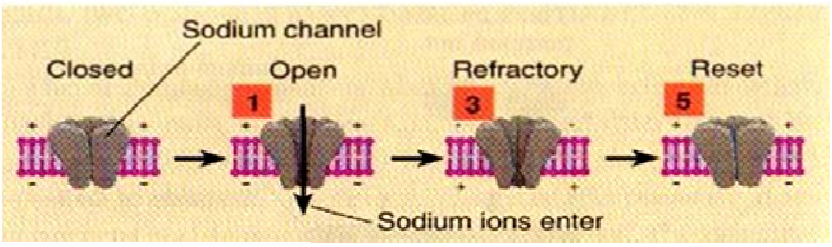
Membrane Potential

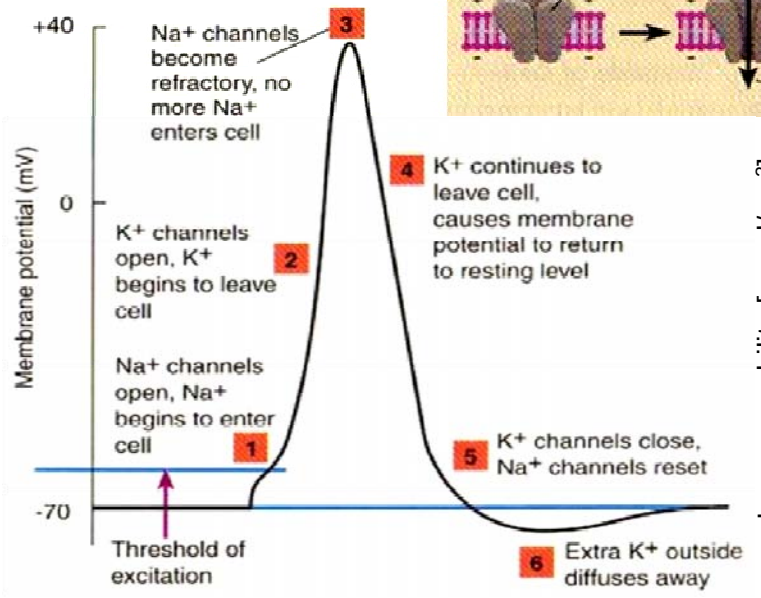


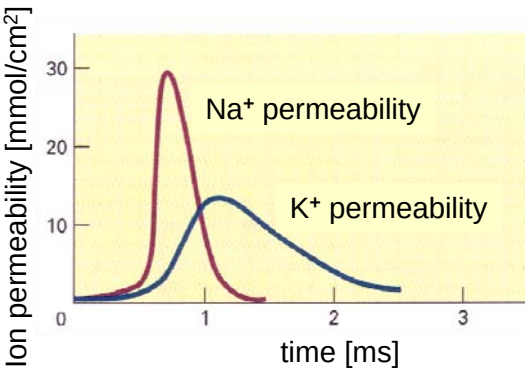


Cell resting potential about -70mV, mainly due to open K^+-channels

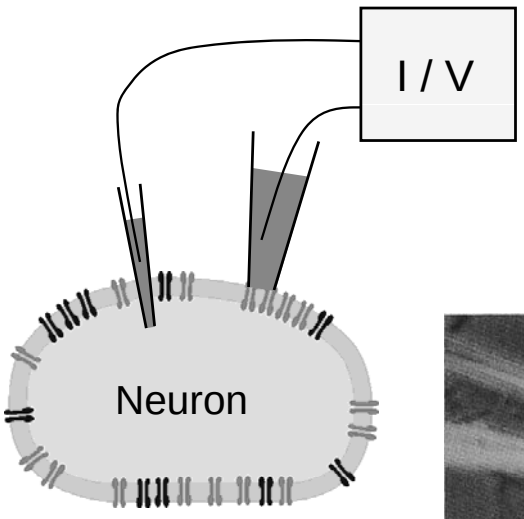
Action Potential



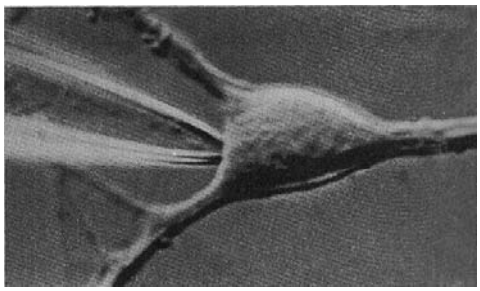




Standard Method: Patch Clamp

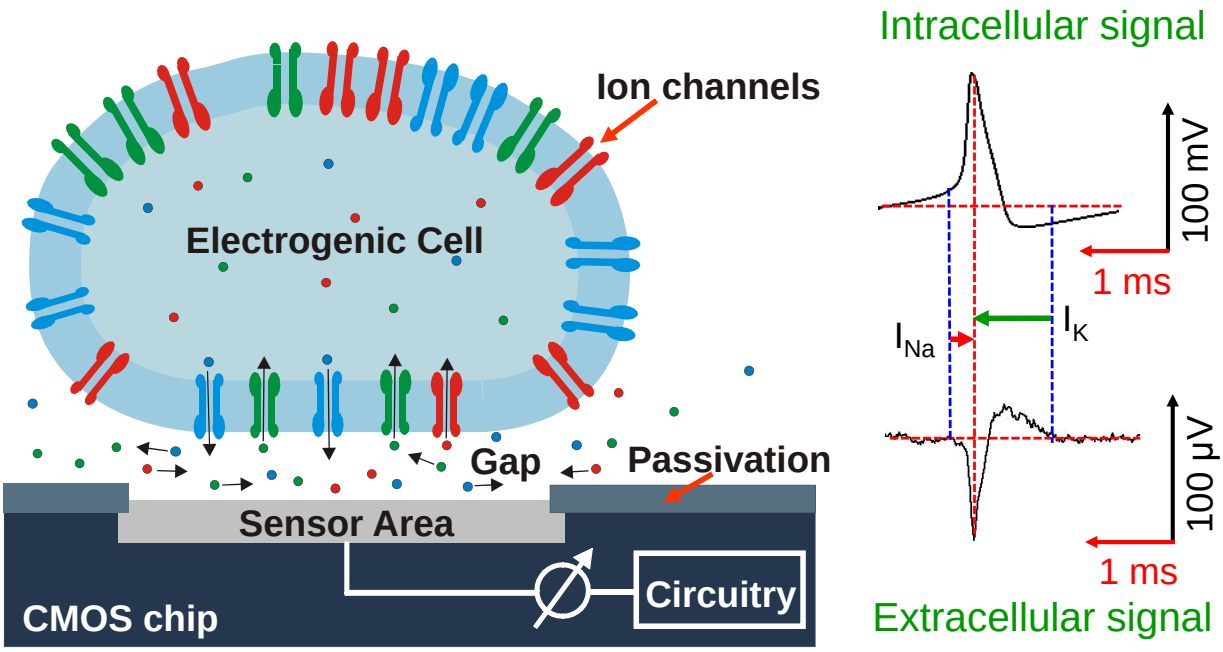


- \+ Transmembrane measurement
- \+ Action potential: 100 mV_{PP}
- \+ Single ion channels
- \- Invasive method
- \- Reduced life time
- \- Limited number of cells

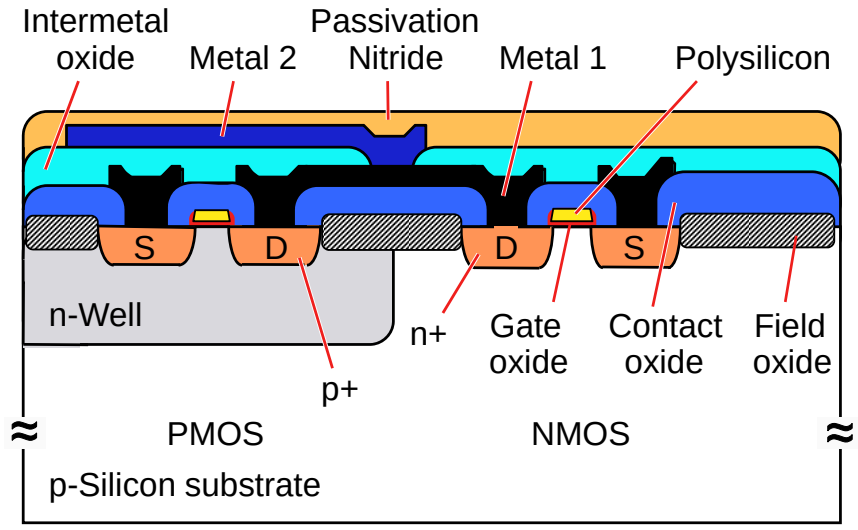


Adapted from:
Lodish et al. 1995

Extracellular Recording



Microelectronics Technology:
Complementary Metal Oxide Semiconductor (CMOS)



Materials:

- Silicon substrate
- Doped silicon
- Polysilicon
- Silicon oxide layers
- Silicon nitride layers
- Aluminum metal

Why CMOS or Microelectronics Technology ?

Signal Quality

- On-chip signal conditioning close to signal source, ***"enabling"*** function: Miniaturization without performance loss
- Capability to handle small feature size and minute signals

Connectivity

- On-chip multiplexing, signals from 10'000 transducers via few connections
- Capability of massively parallel or multi-parameter detection

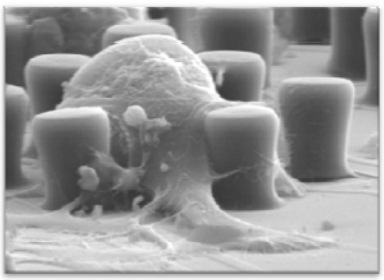
Usability

- Standard interfaces and data handling, experimental protocols
- High-performance systems (standalone) that are easy to use (nonexperts)

Standard Semiconductor Technology (CMOS)

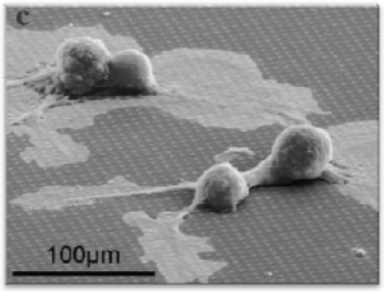
High-Density Electrode Arrays

- **Why high electrode density?**
  - Details of signal evolution
  - Subcellular resolution
  - Dynamics on network level



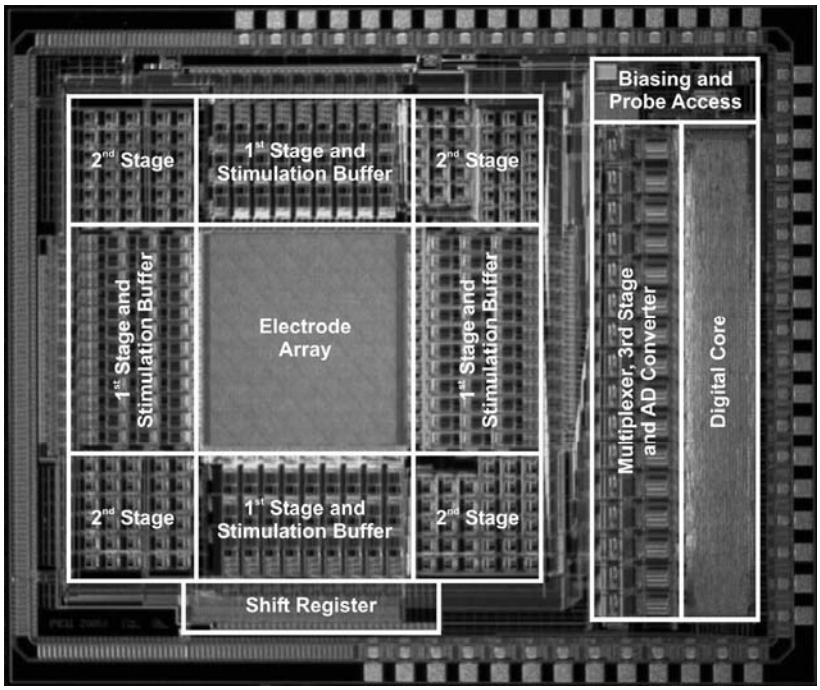
G. Zeck et al., *PNAS*, 2001

- **How to achieve (sub)-cellular resolution**
  - Constraining the cells
  - High-density electrode array



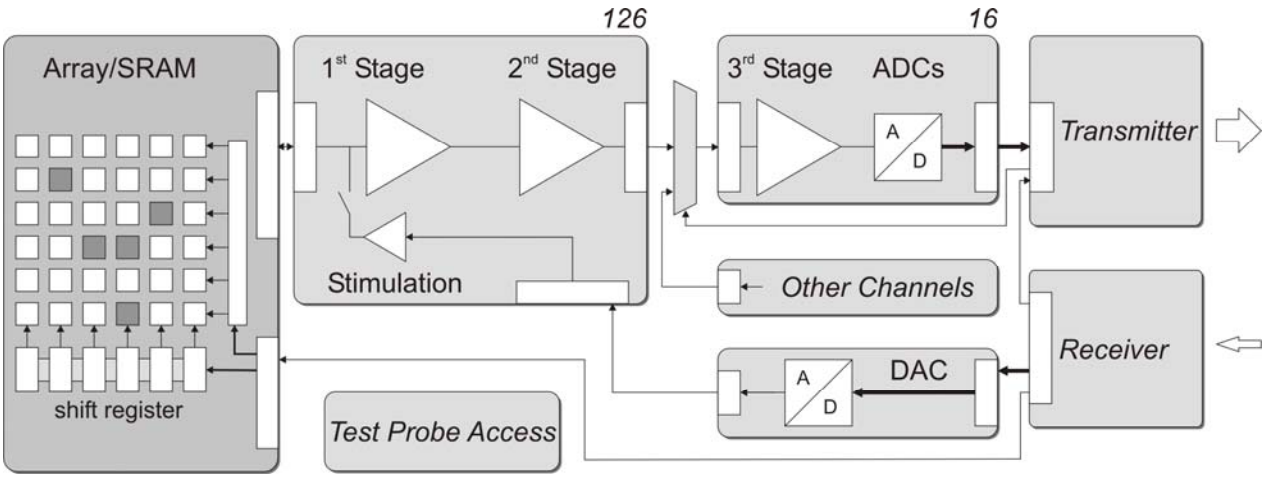
A. Lambacher et al., *Applied Phys A*, 2004

High-Density Chip Micrograph



- High-density electrodes
- High-performance electronics
- Electrode pitch: 17 µm
- Electrode diameter: 7 µm
- Sampling at 20 kHz
- 126 Electrodes simultaneously readable from 11‘016
- Chip size: 7.1 x 6.5 mm^2

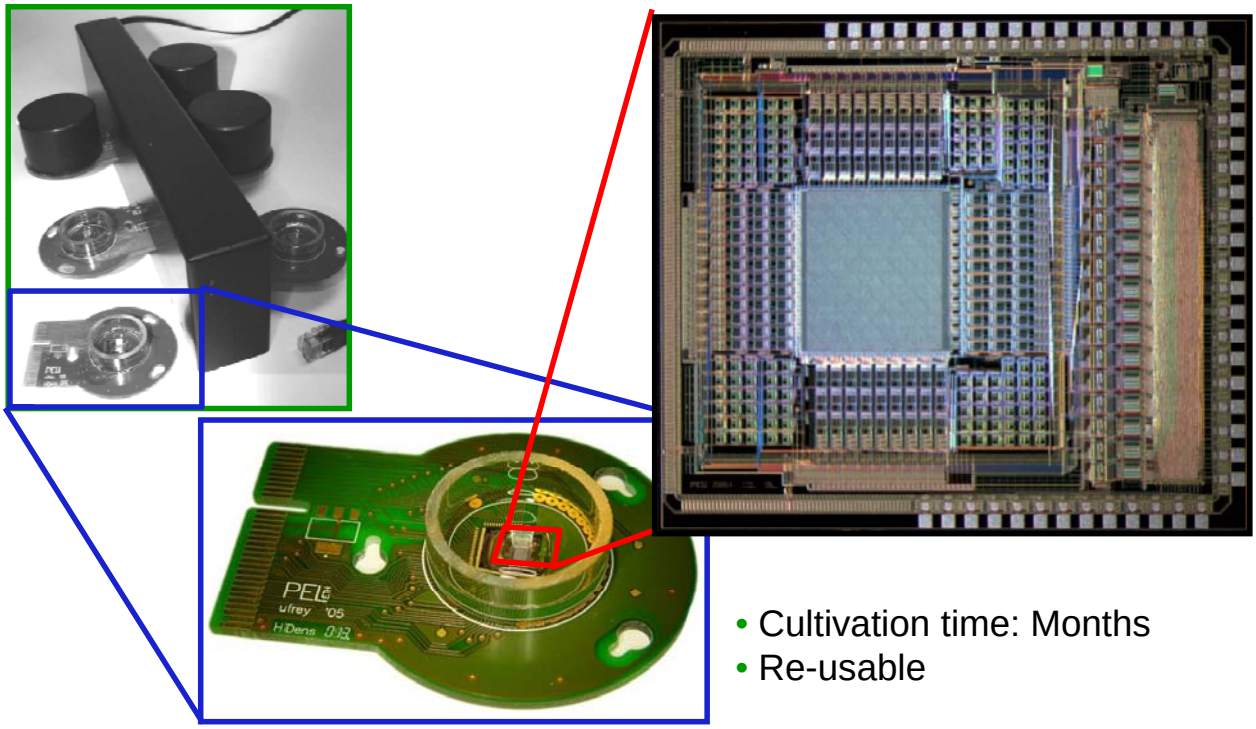
Chip Schematic



- Gain: 1 - 10’000 in 18 steps
- HP: 0.3Hz, first order
- LP: 4kHz–14kHz, second order
- ADC: 8b, SA, 20kHz/channel
- DAC: 8b (stimulation)
- Supply: 3.3V (digital), 5V (analog)
- CMOS: 0.6µm, 3M2P

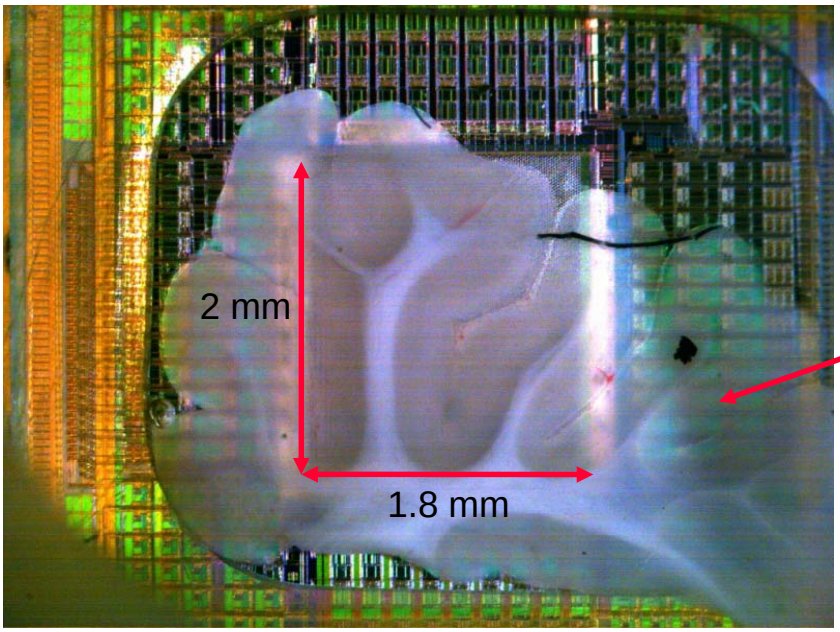
- Transmitter
  - 3.2MHz, 9b
  - MUX, ADC control
  - frame counter, CRC
- Receiver
  - serial
  - decode commands
  - configure array, settings

Fabricated & Packaged System



- Cultivation time: Months
- Re-usable

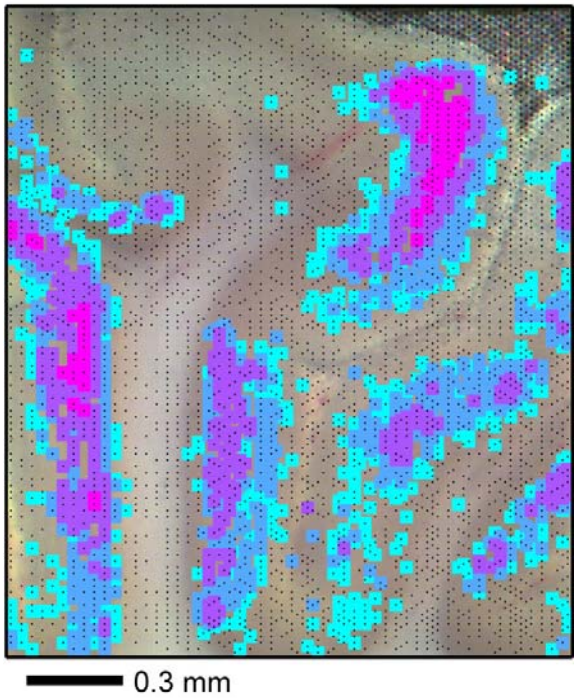
Rat Acute Parasagittal Cerebellar Slice



Long-Evans rat slice

Cooperation: Prof. U. Egert, University of Freiburg, D

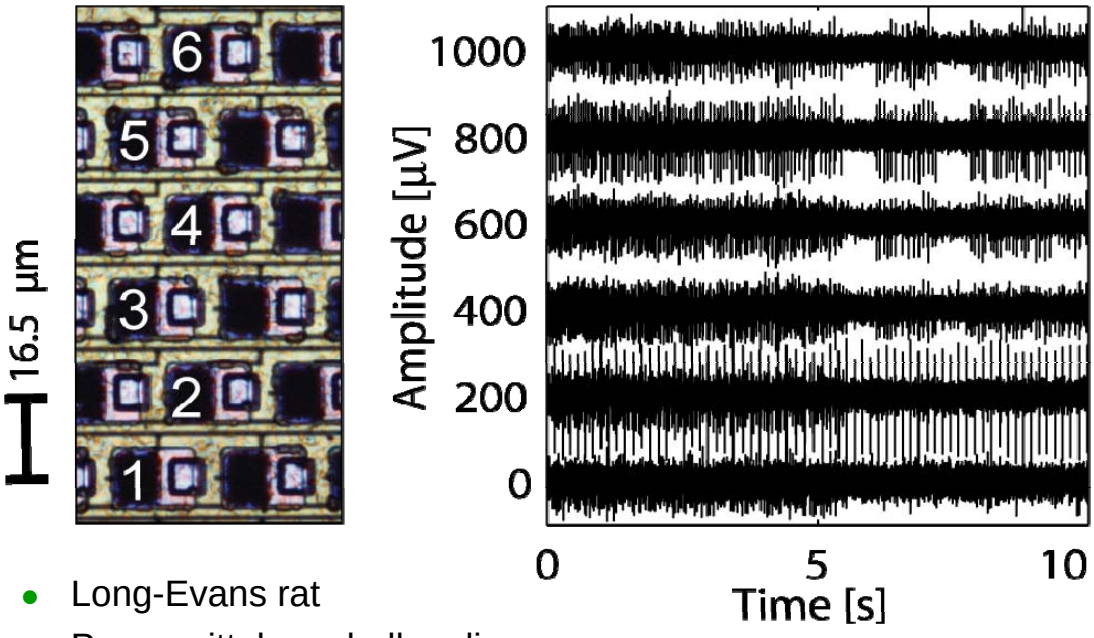
Electrical Activity Map



Spontaneous activity

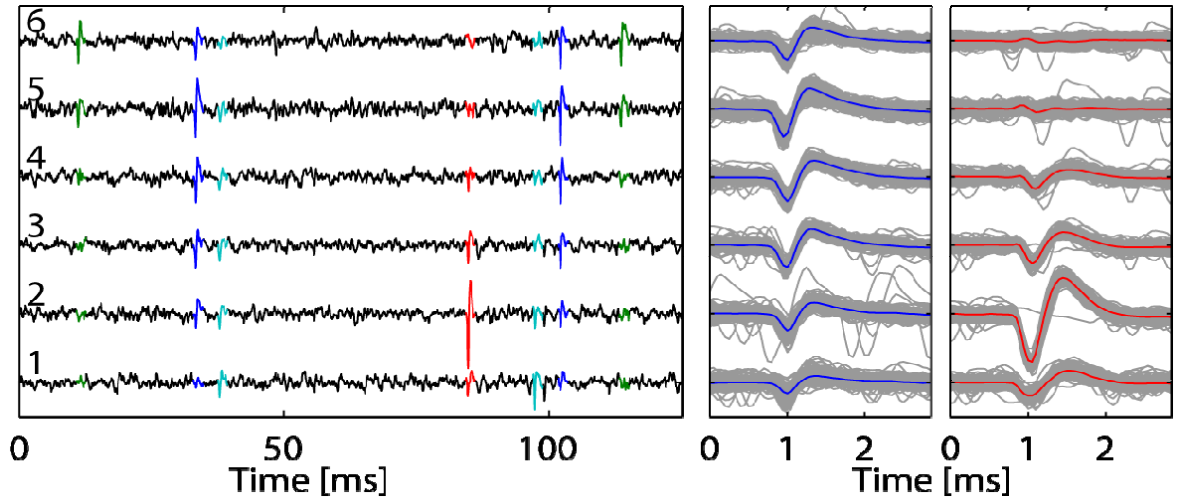
- Probed electrodes
- Events detected with a threshold of ±36 µV and an event rate of:
  - 0.2 Hz – 1 Hz
  - 1 Hz – 10 Hz
  - 10 Hz – 100 Hz
  - > 100 Hz

Acute Brain Slices: Spike Traces



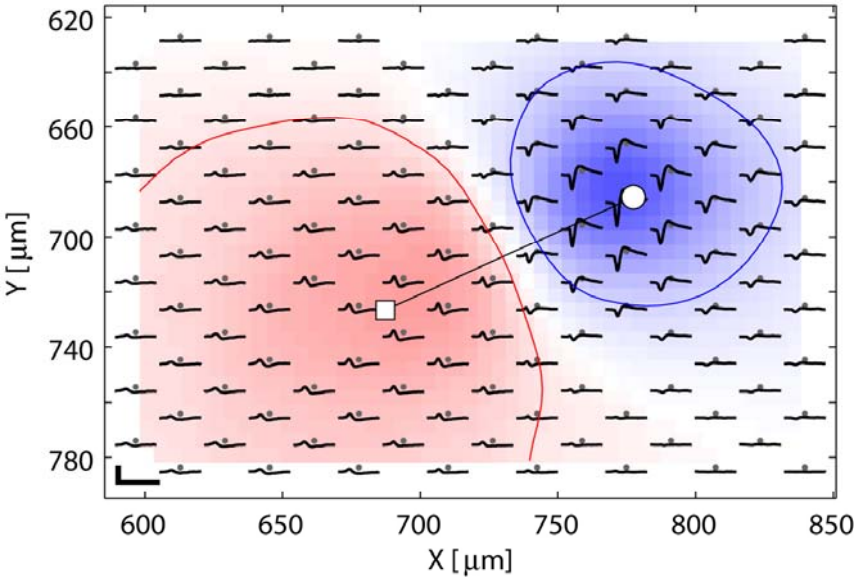
- Long-Evans rat
- Parasagittal cerebellar slice
- Spontaneous activity

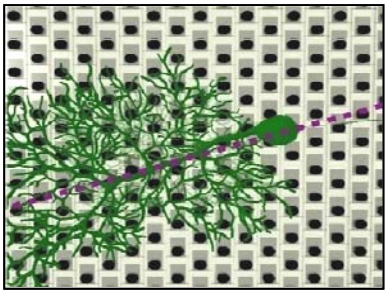
Spike Sorting



- Assign ‘events’ according to signal shape to different neurons
- High electrode density allows to apply *Independent Component Analysis* (ICA)
- Output: - time stamps
  - spike-triggered averages, footprints

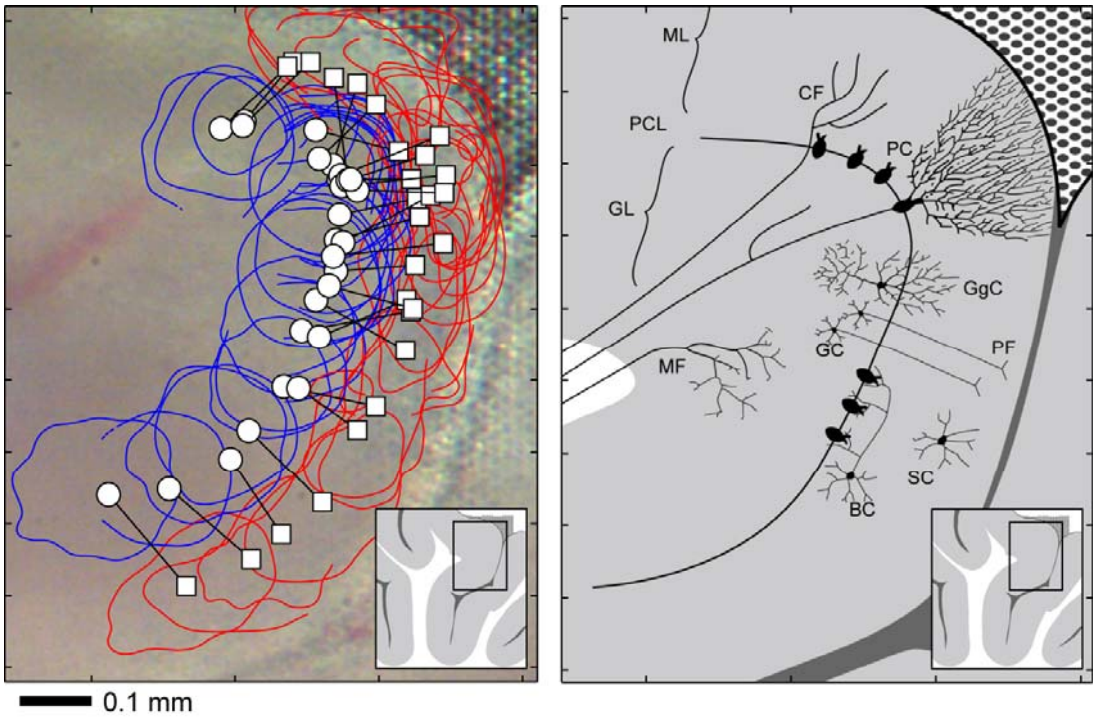
Purkinje Cell: Extracellularly Measured Action Potential



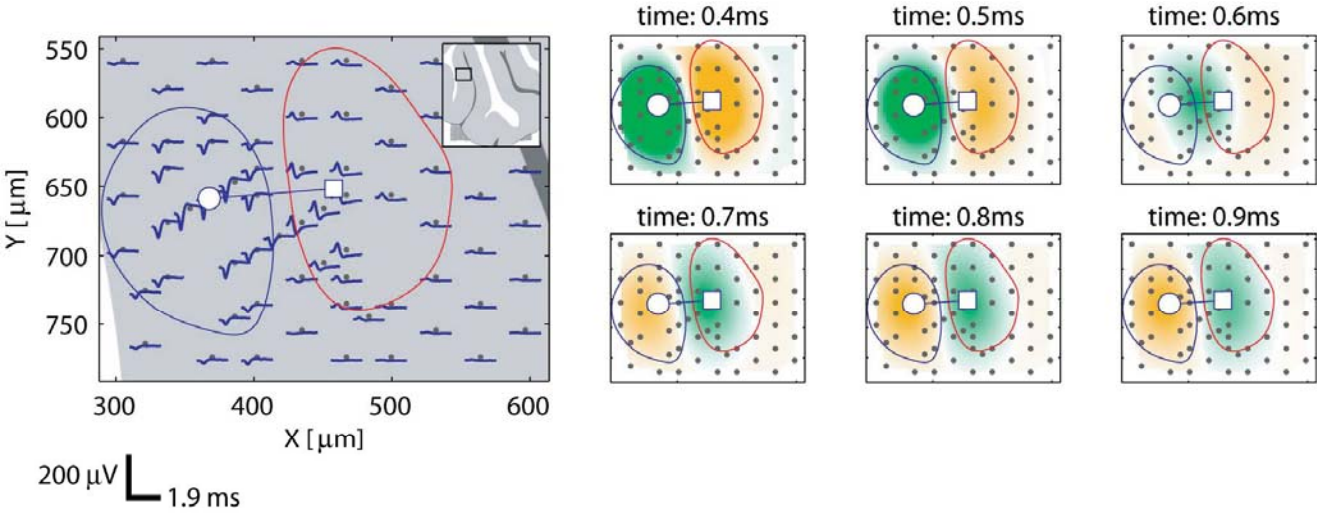


- ○ Center of negative peaks
- – Equipotential at half min. peak (-63 µV)
- □ Center of positive peaks
- – Equipotential at half max. peak (18 µV)

Localization of Identified Cells

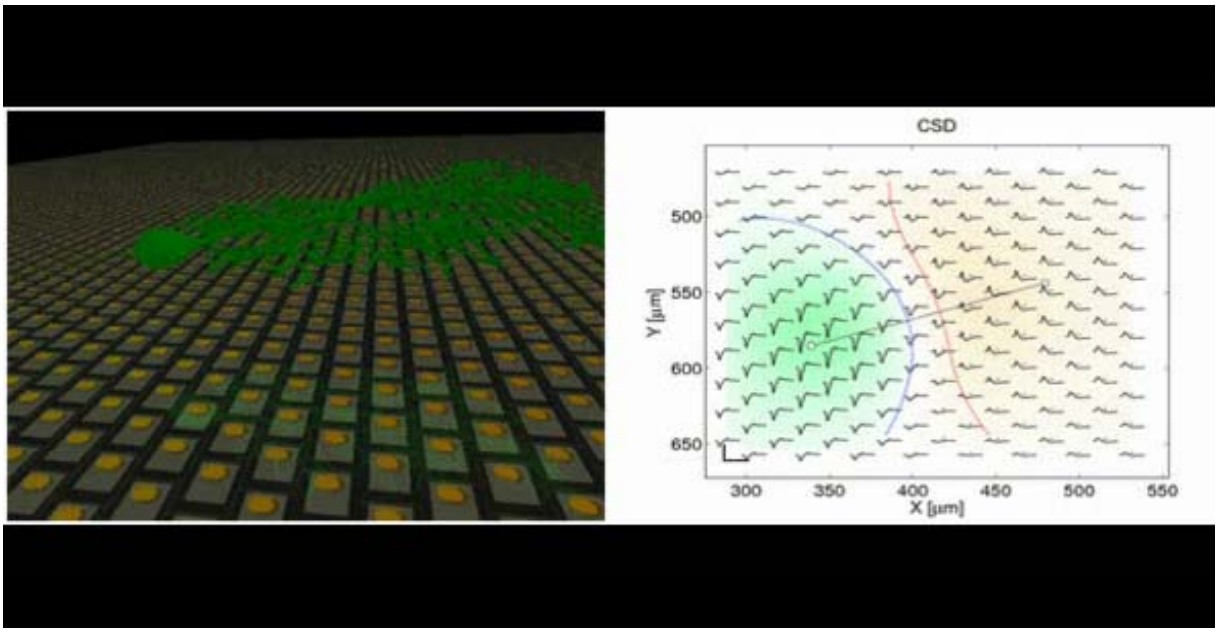


Temporal Evolution of Action Potential



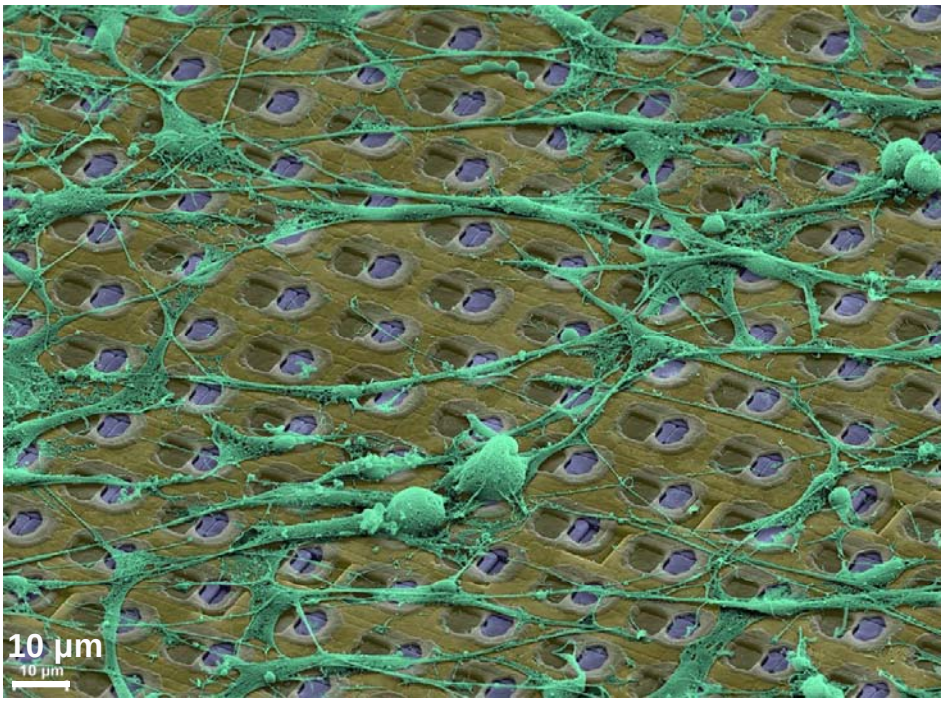
- Dynamic evolution of measured action potential
- Current sources / sinks

Temporal Evolution of Action Potential



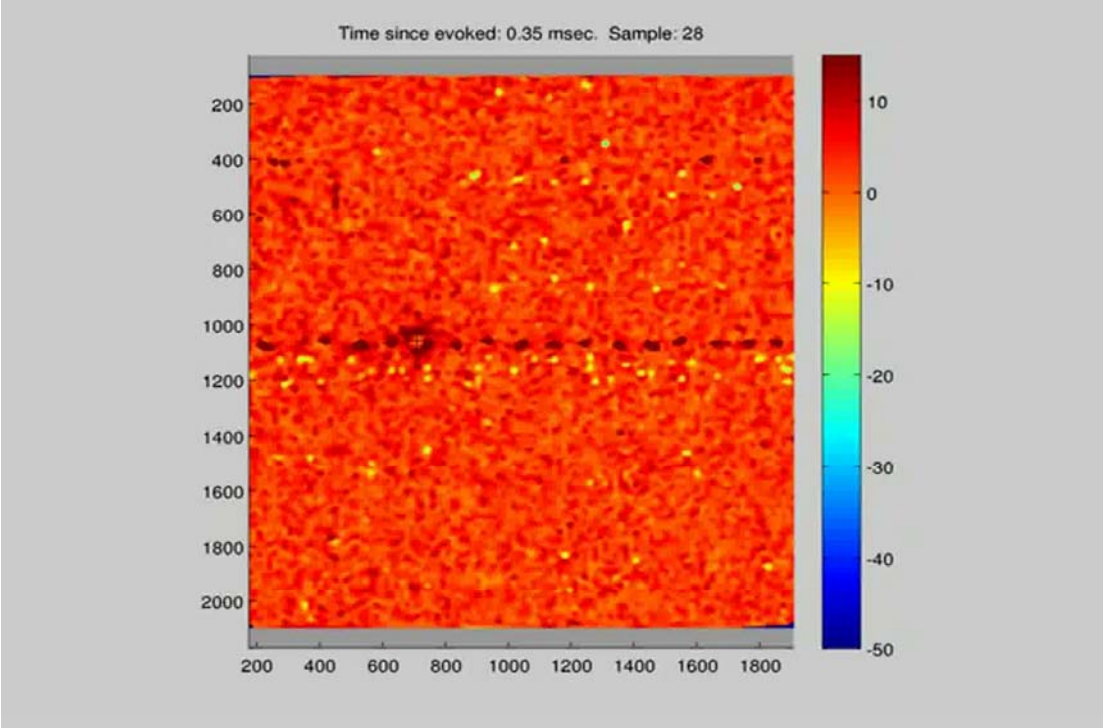
- Current sources / sinks
- Action potential: ~ 0.6 ms

High-Density Chip: Dissociated Neurons



- 3200 Electrodes per mm^2
- Pitch: 17 µm
- Electrode Ø: 7 µm
- DRG neurons (DIV 2)

Elicited Activity upon Stimulation



Summary

- CMOS suitable technology platform to interface with living cells
  - Chips function in biological environment and vice versa
  - Important features:
    (1) Signal quality: Signal conditioning, A/D conversion on chip
    (2) Connectivity: Multiplexing to overcome interconnection limitation
    (3) Ease of use due to integrated functionality
- Bioelectronic systems
  - High temporal and spatial resolution recording capabilities
  - Recording of physiological details at sub-cellular resolution and, at the same time, at network level (dynamic configuration in 1 ms)
  - Use: Fundamentals of information processing or pharmacological testing