Probing the Retina

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UC Santa Cruz
28 July 2004

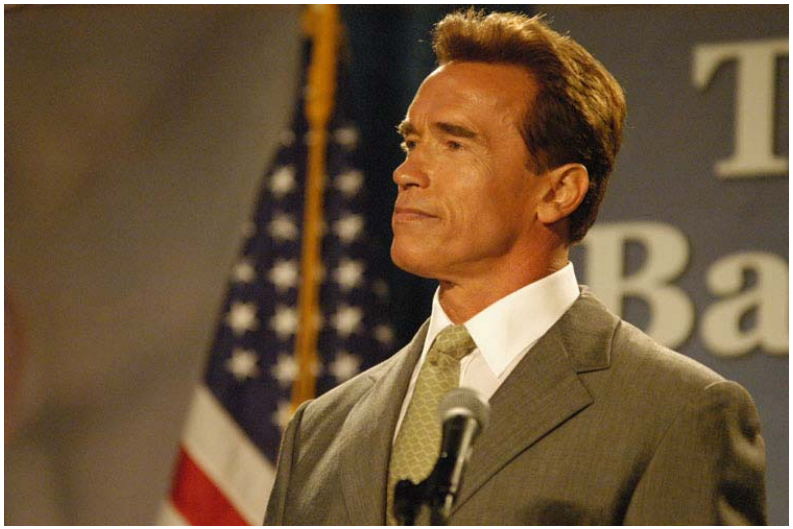
1. The Retina Project
   - understand the language used by the eye to send information about the visual world to the brain
2. First Results
3. Future Activities and Directions
4. Summary

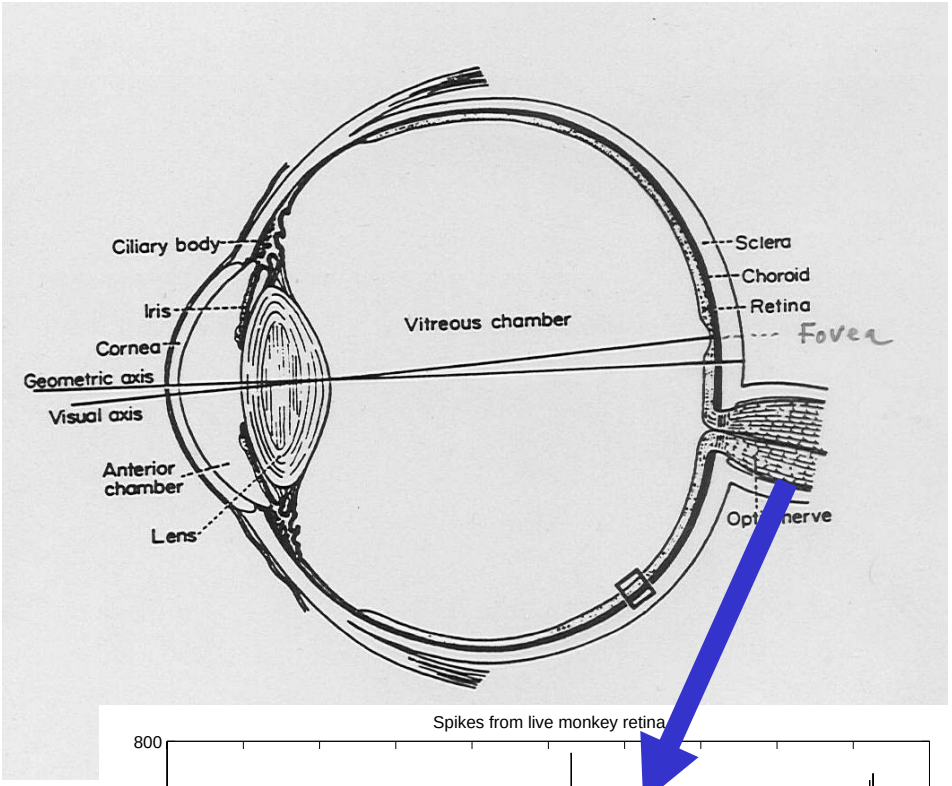
Collaborators

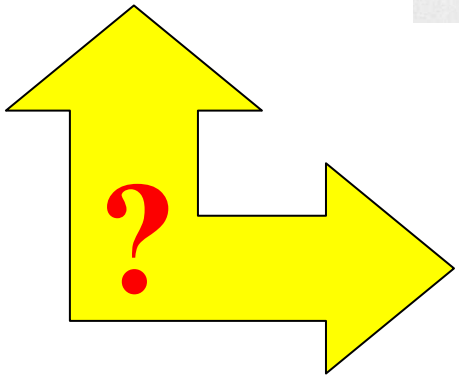
- UC Santa Cruz:
  A. Grillo, M. Grivich, S. Kachiguine, D. Petrusca, A. Sher
- AGH U. of Science and Technology, Krakow (I C design):
  W. Dabrowski, P. Grybos, P. Hottowy
- U. Glasgow (high density electrode array fabrication):

W. Cunningham, D. Gunning, K. Mathieson, M. Rahman

- The Salk Institute (neurobiology):
  E. J. Chichilnisky, R. Kalmar




Ciliary body
Iris
Cornea
Geometric axis
Visual axis
Anterior chamber
Lens
Vitreous chamber
Sclera
Choroid
Retina
Fovea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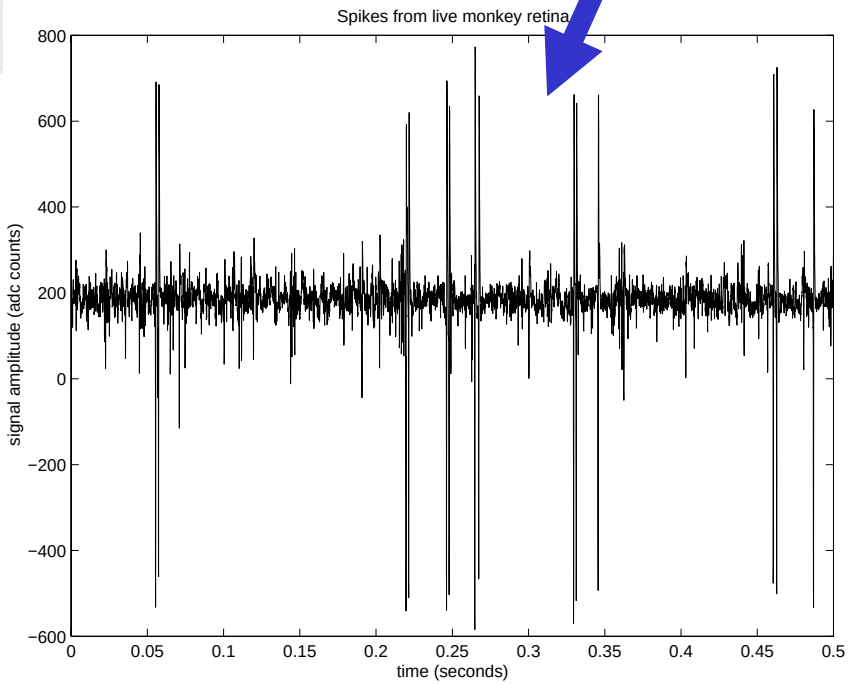
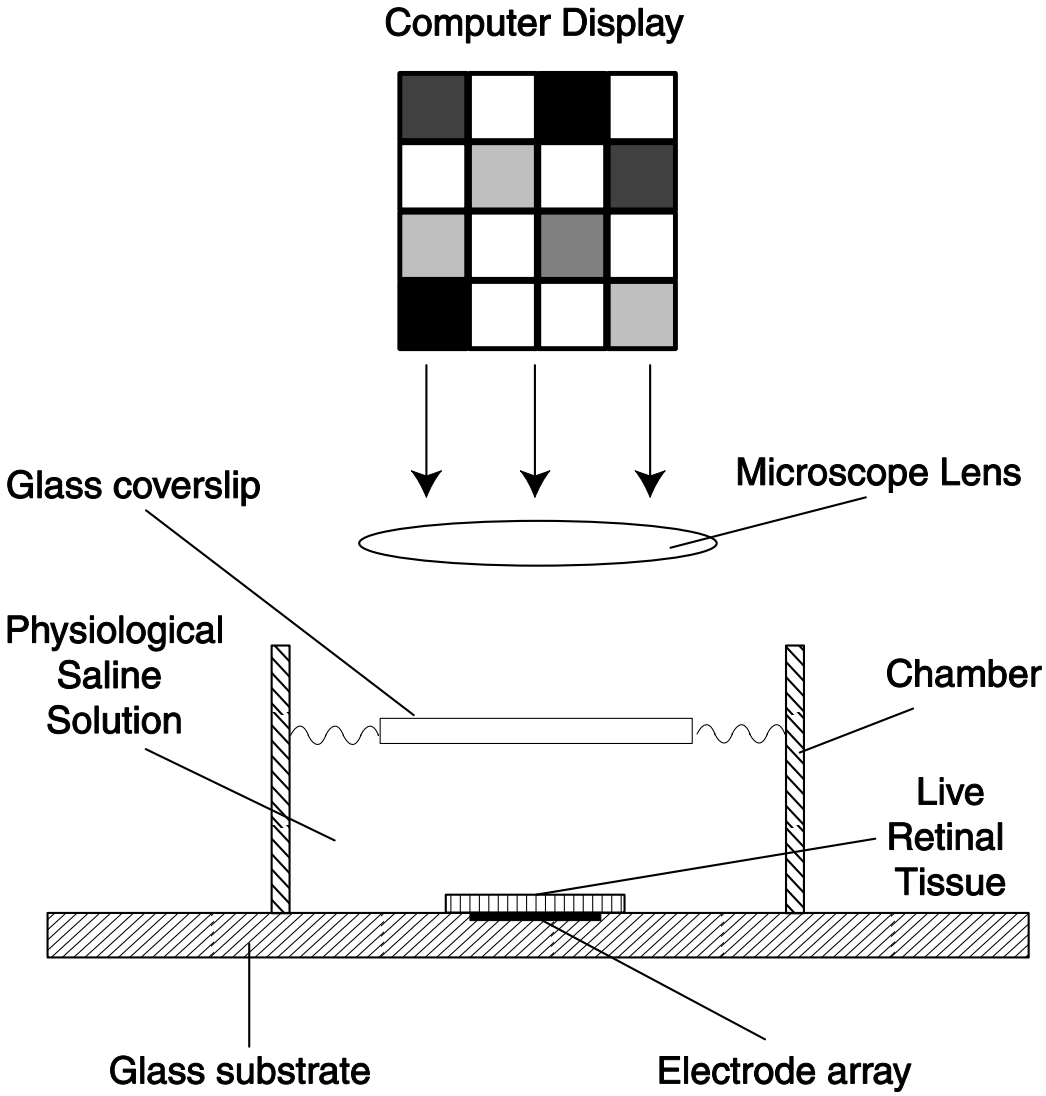

Spikes from live monkey retina
signal amplitude (adc counts)
time (seconds)
800
600
400
200
0
−200
−400
−600
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5

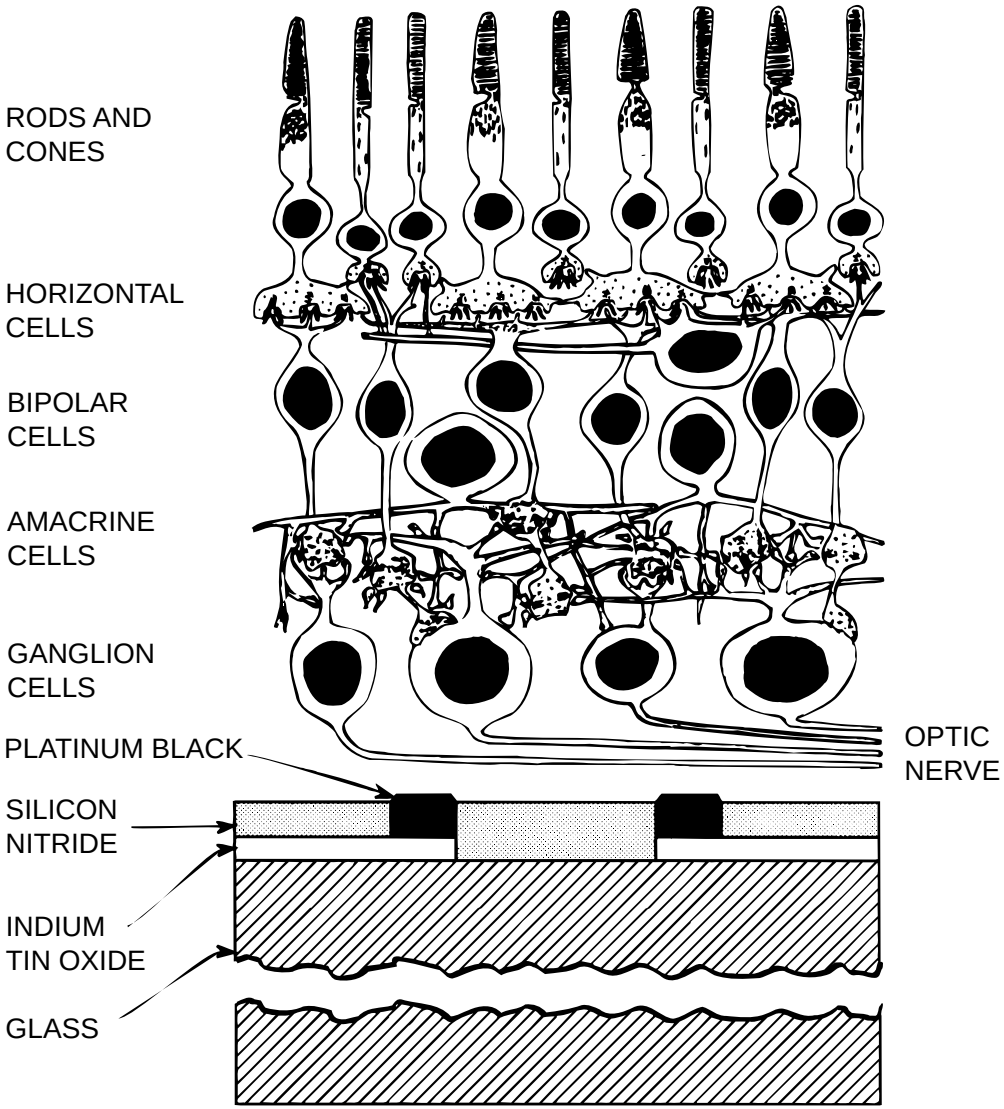
The Retina Project

- **Goal:** understand how the retina processes and encodes dynamic visual images
- **Method:** record the patterns of electrical activity generated by hundreds of retinal output neurons in response to a movie focused on the input neurons
- **Technology:** based on silicon microstrip detector techniques and expertise developed for high energy physics experiments – an example of the application of expertise in HEP instrumentation to neurobiology

Experimental Technique

(based on work by Meister, Pine and Baylor)




RODS AND
CONES
HORIZONTAL
CELLS
BIPOLAR
CELLS
AMACRINE
CELLS
GANGLION
CELLS
PLATINUM BLACK
OPTIC
NERVE
SILICON
NITRIDE
INDIUM
TIN OXIDE
GLASS

Species?

Monkey:

- closest to human visual system (medical applications)
- large body of experimental work on monkey vision (neurophysiology, behavior)
- But rare and precious tissue (guinea pig retina is also being studied)

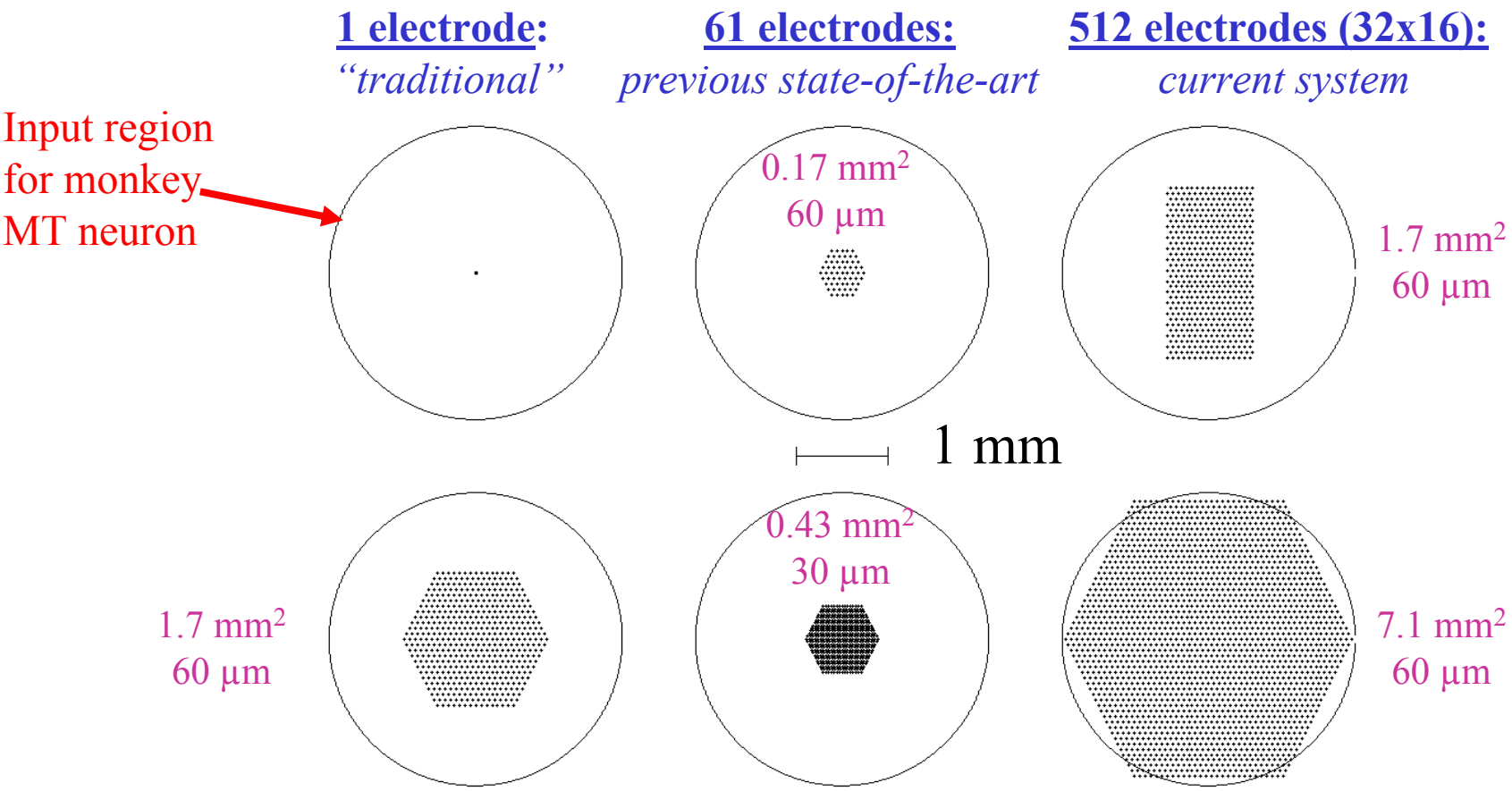
Scale?

- Record from a population of neurons approaching a scale of interest for neural computation
- order-of-magnitude improvement in state-of-the-art

$\Rightarrow$ Record simultaneously from hundreds to thousands of retinal ganglion cells in a single preparation

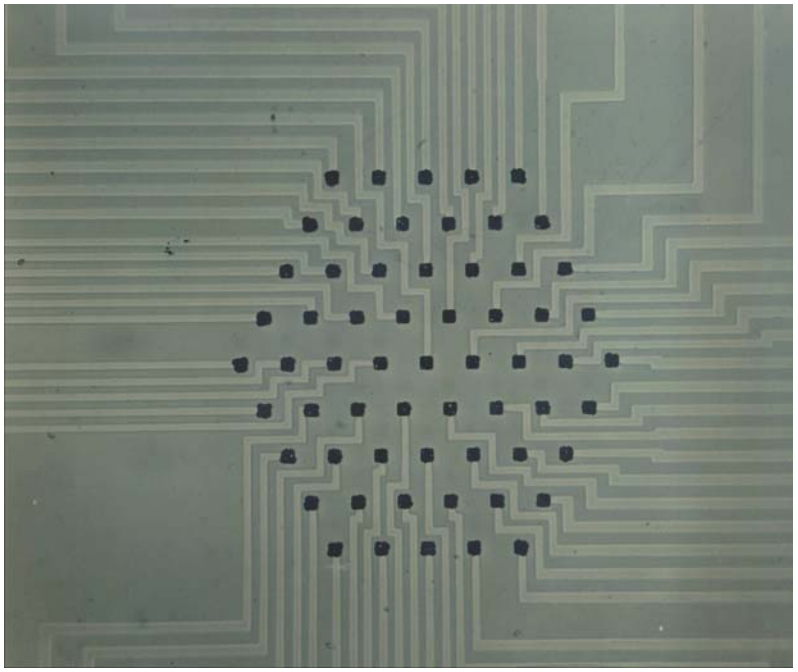
Electrode Array Geometries

(Electrode diameters = 5 μm; area and electrode spacing given below.)

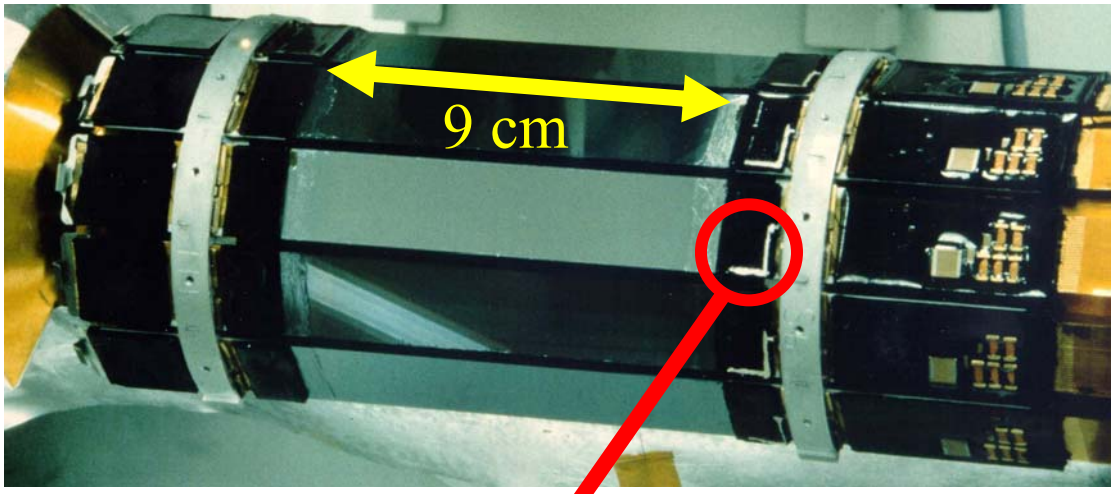


Previous state-of-the-art

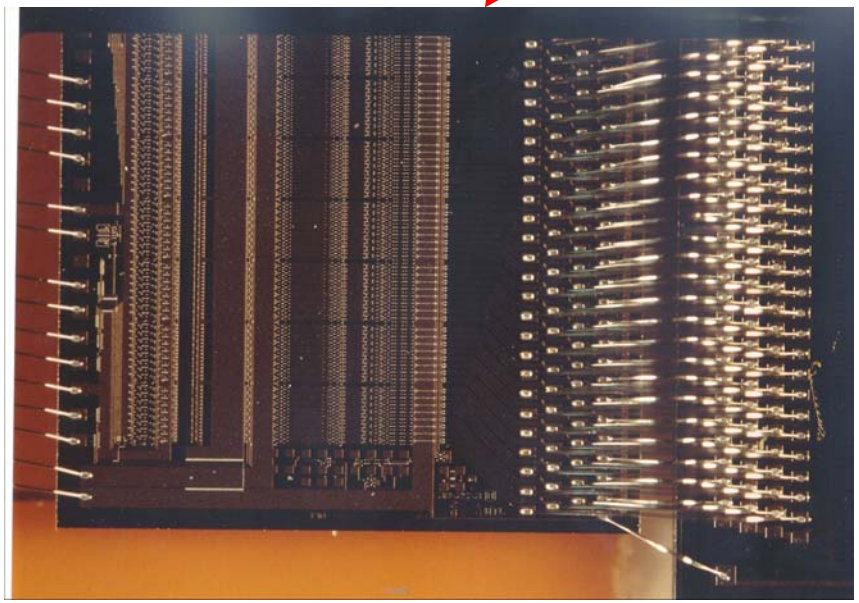
M. Meister, J. Pine, D. A. Baylor,
J. Neuroscience Meth. 51 (1994) 95.



61 electrodes, 60 μm electrode spacing,
conventional electronics, “zebra” interconnect,
tens of retinal ganglion cells simultaneously detected



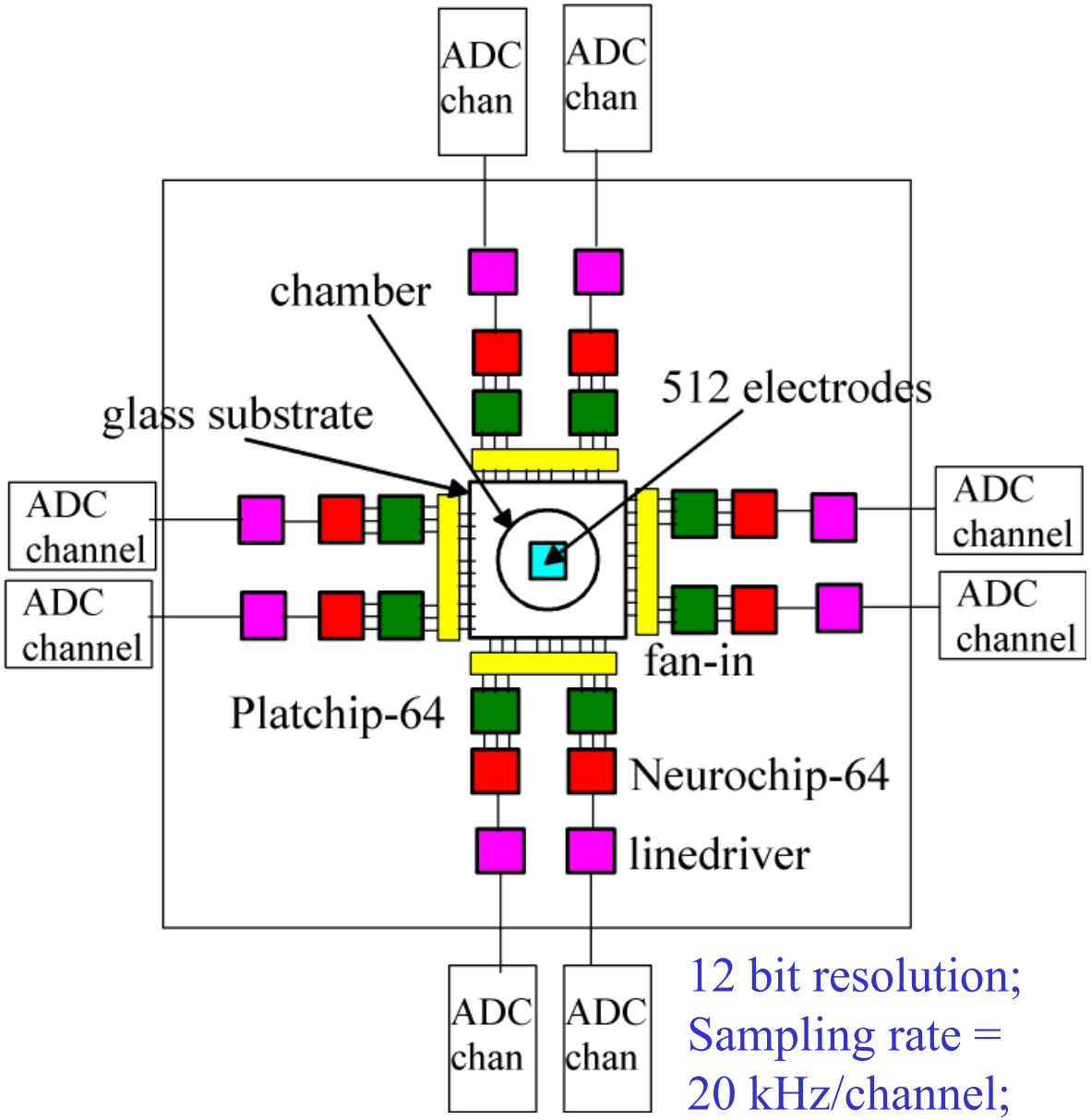
Silicon Strip
Vertex Detector:
MARK II experiment
at SLAC Linear Collider
(512 channels/module;
18K channels total)



Microplex readout chip
128 channels, 47.5 μm pitch
(Walker, Parker, Hyams)

Parallel efforts in ALEPH, DELPHI, OPAL at LEP and CDF at the Tevatron Collider

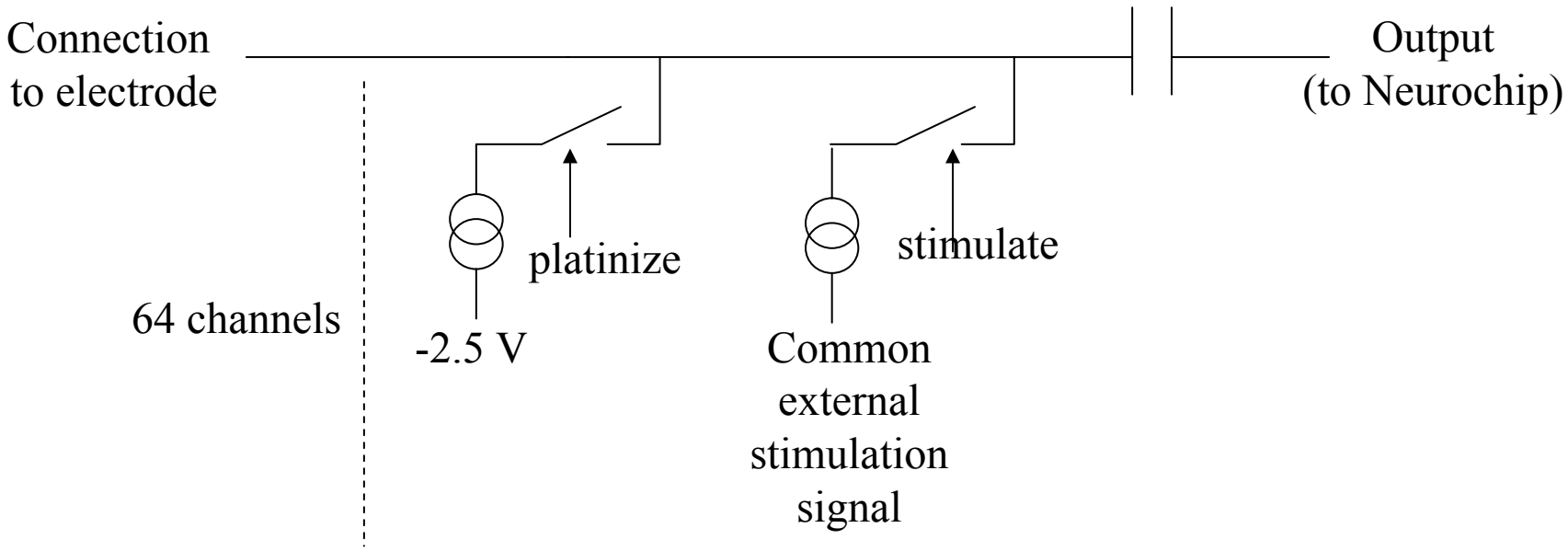
“Neuroboard” Block Diagram



12 bit resolution;
Sampling rate =
20 kHz/channel;

Platchip

- 64 channels; 120 μm pitch; die size = 3.3 x 7.8 mm^2
- AC coupling: 150 pF
- Platinization current: 0-1.2 μA (controlled by 5 bit DAC)
- Stimulation current: 0-150 μA (controlled by external analog signal with gain set by 5 bit DAC)



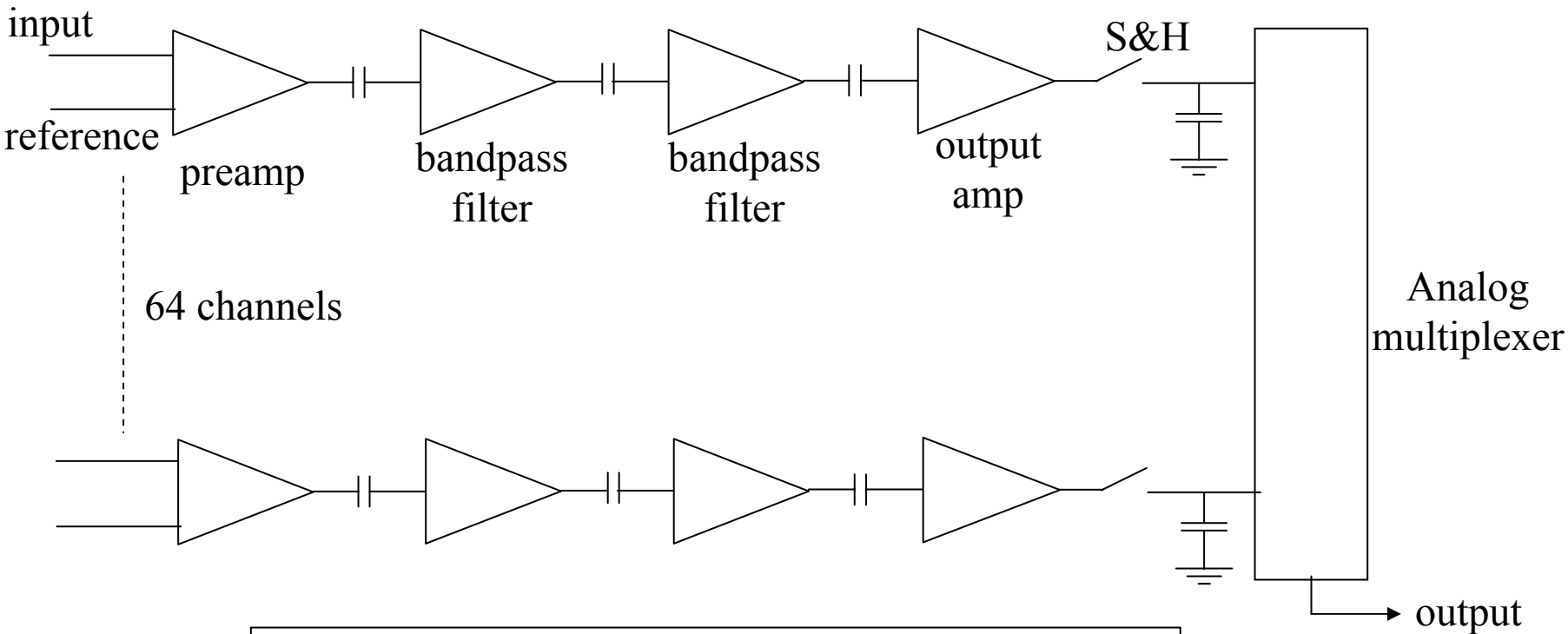
Design by W. Dabrowski et al., Krakow

Neurochip

•64 channels; 120 μm pitch; die size = 4.8 x 7.8 mm^2

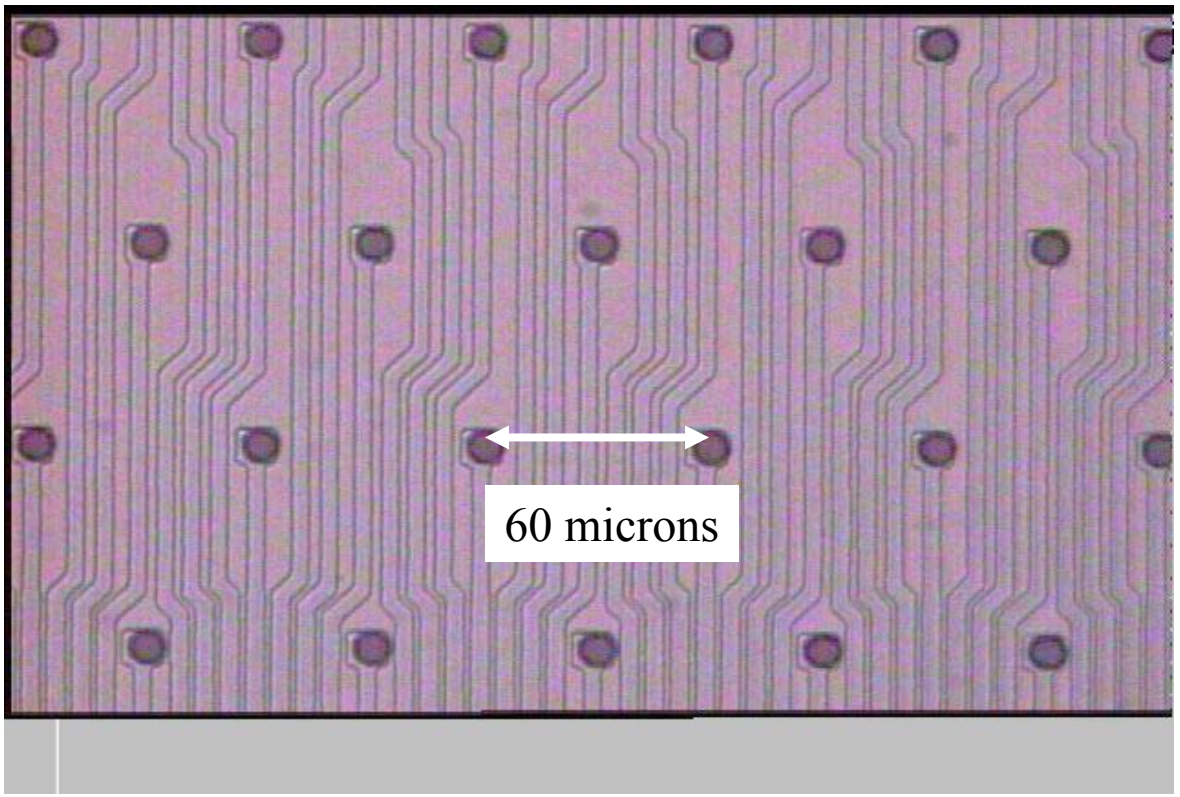
•bandpass filter: 80 - 2000 Hz (typical); equivalent rms input noise ~5 μV (~7 μV for complete system with saline; signal amplitude range = 50 – 800 μV)

• sampling rate/channel = 20 kHz (typical); multiplexer freq. = 1.3 MHz (typical)



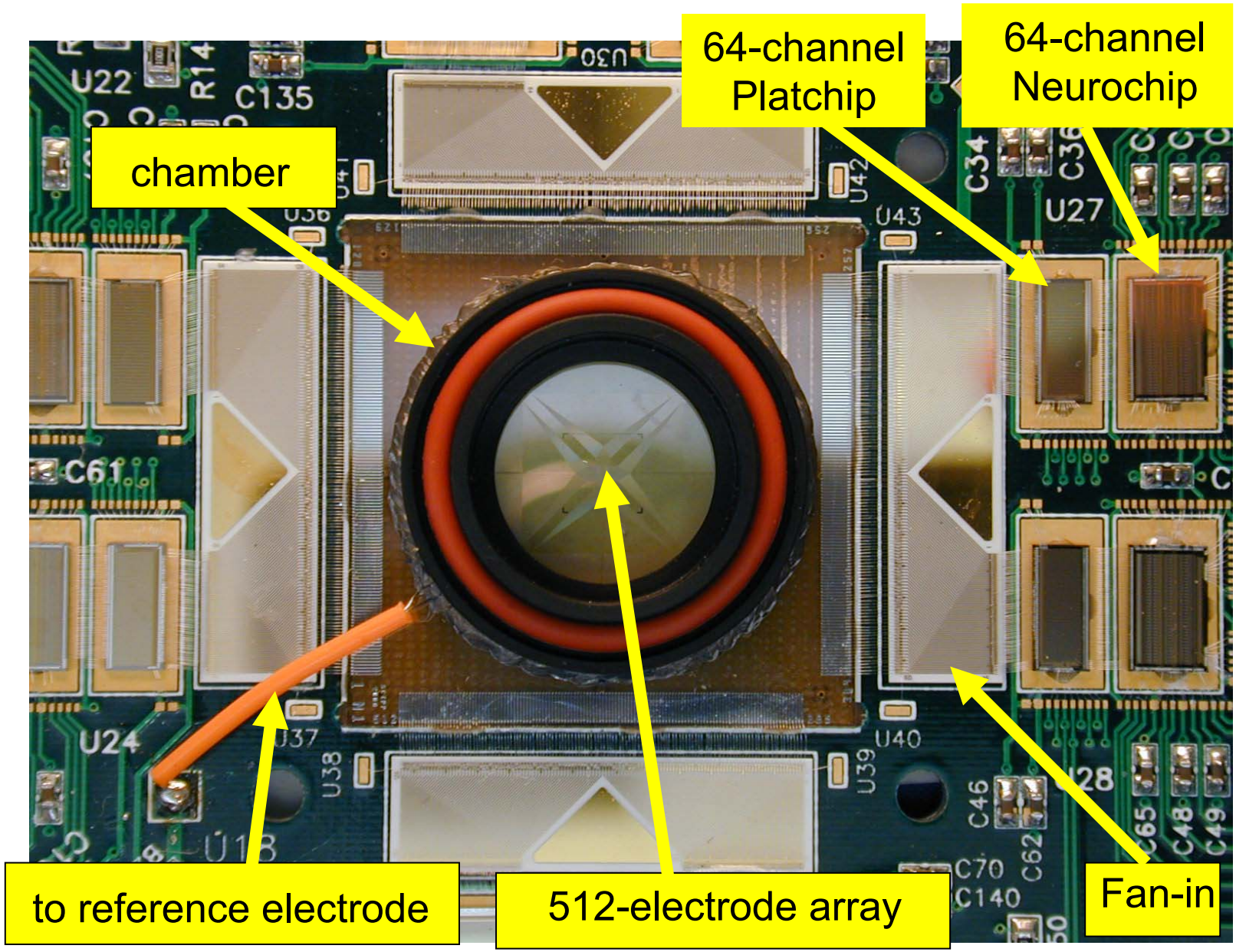
Design by W. Dabrowski et al., Krakow

Section of
512-electrode Array (32x16)

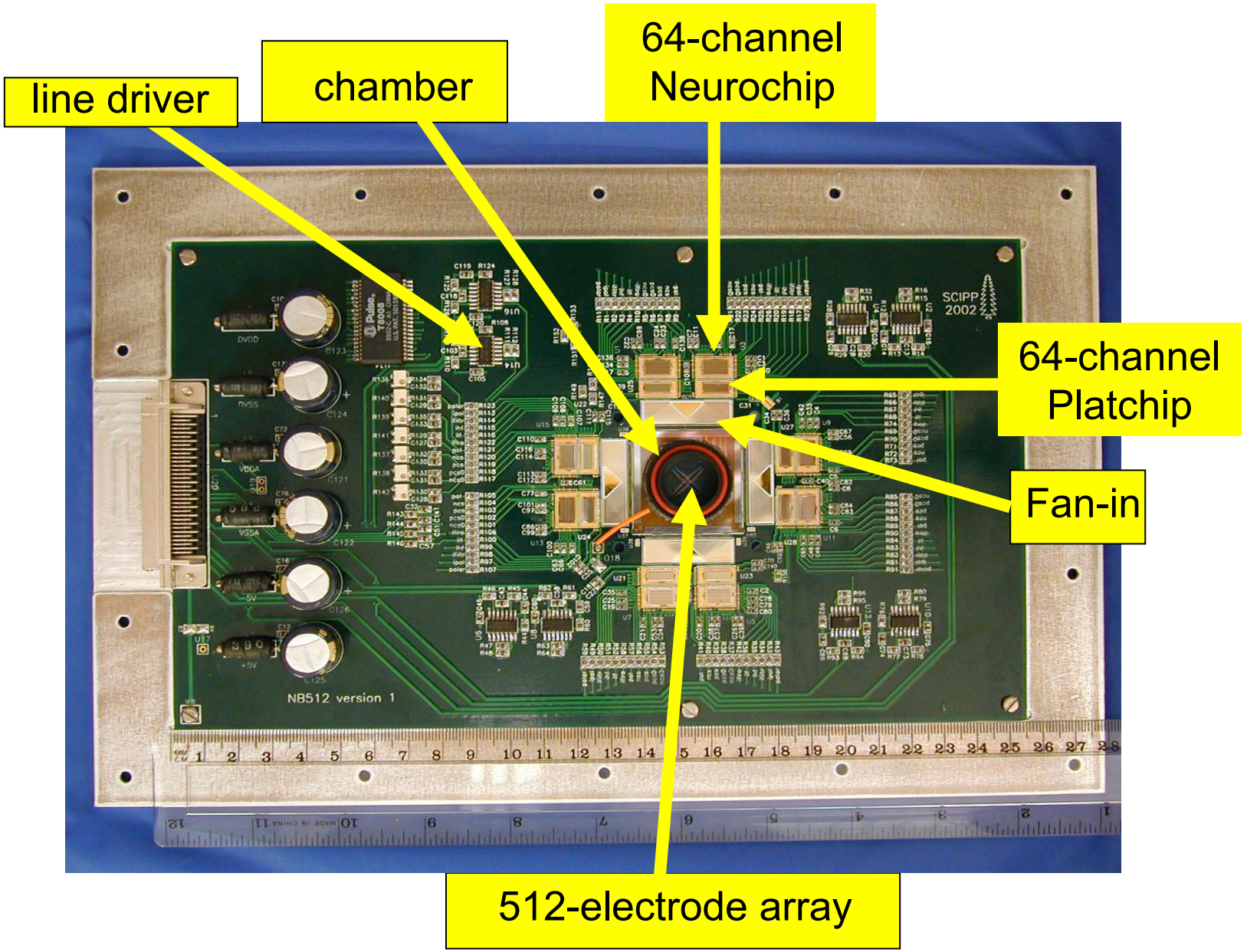


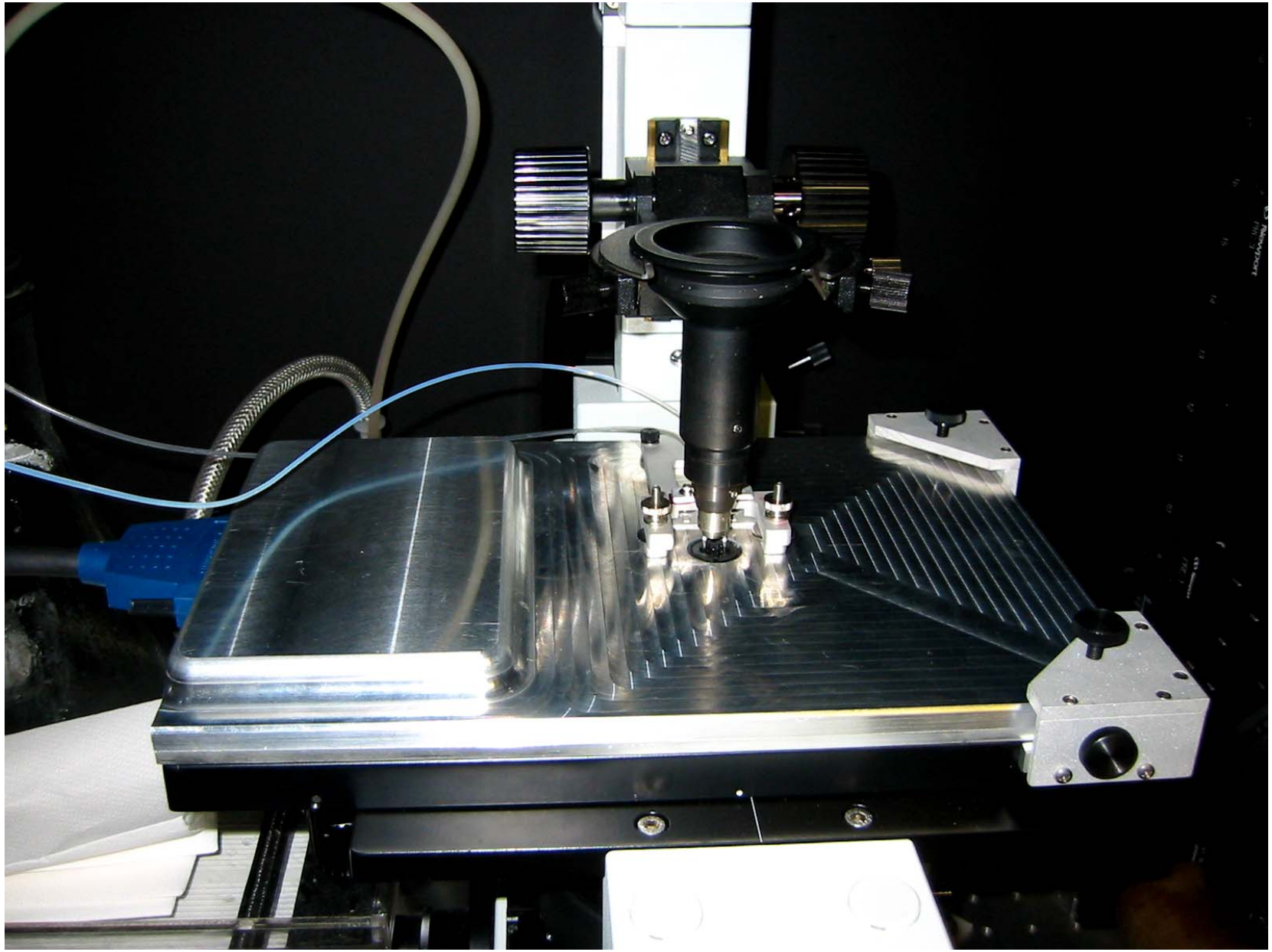
Electrode diameter = 5 μm

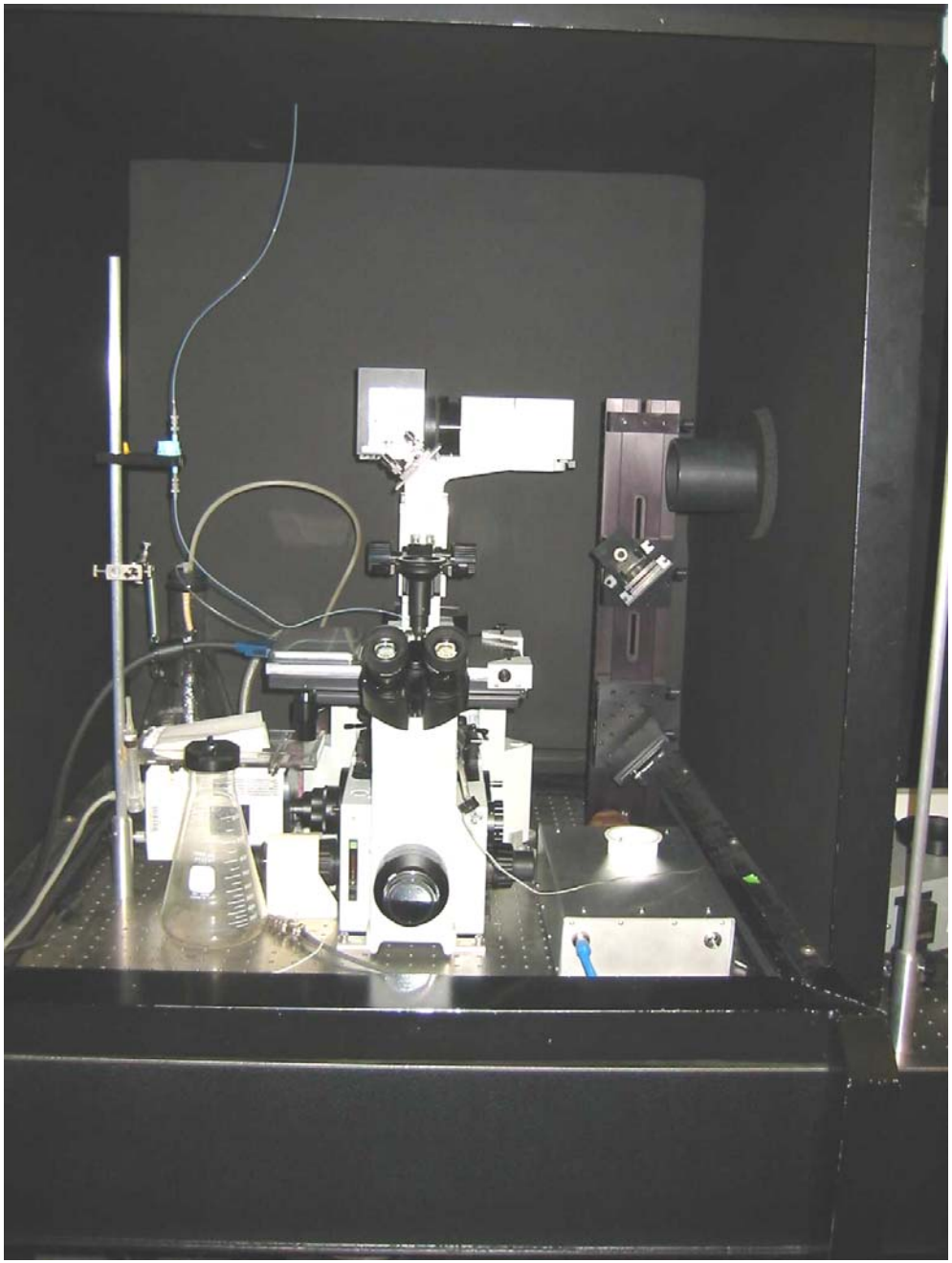
Section of 512-electrode “Neuroboard”

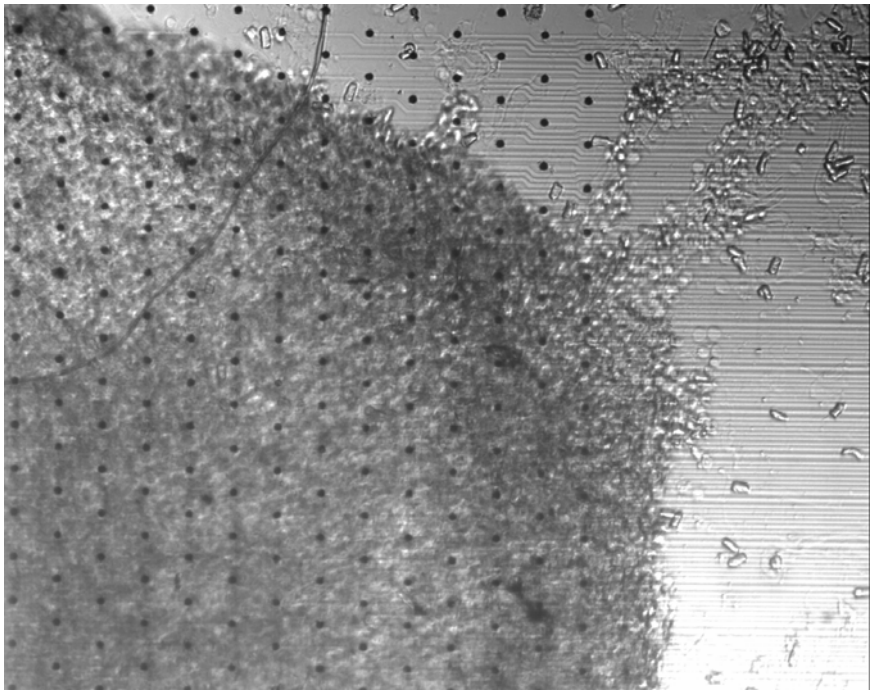


512-electrode “Neuroboard”

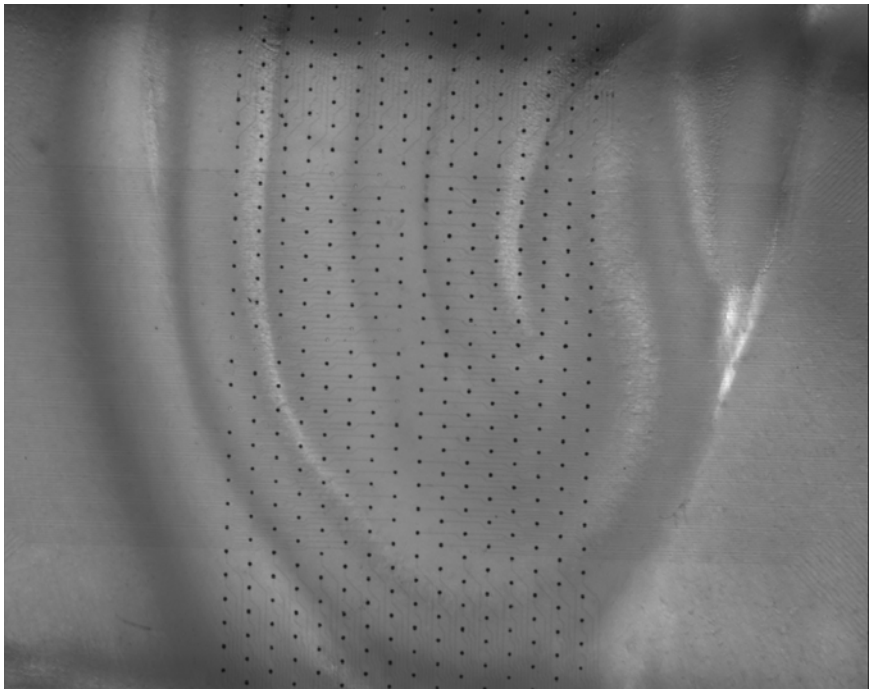






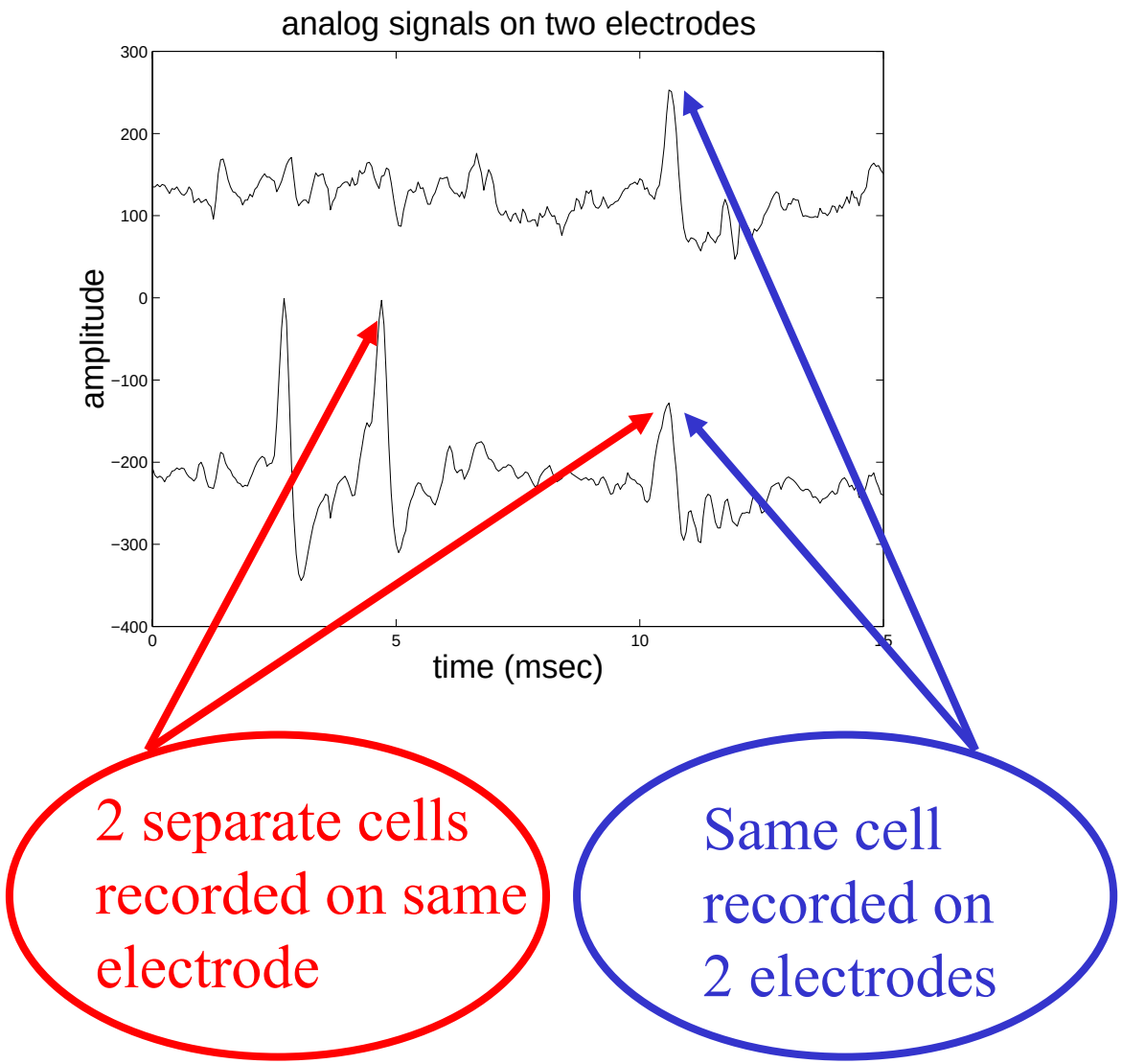


Salamander retina on
512-electrode array



Slice of hippocampal tissue
on 512-electrode array

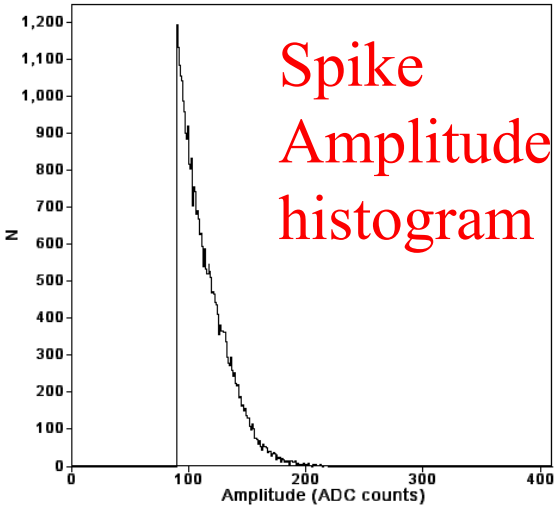
Spikes on electrodes ⇒ spikes from identified neurons

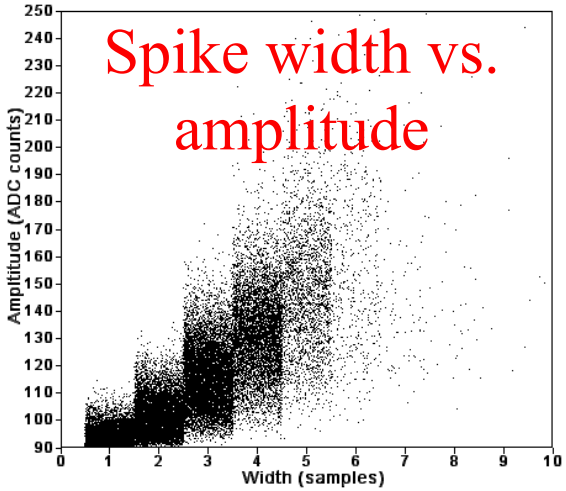


Neuron Identification

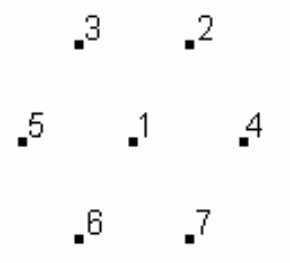
(signals on electrodes ⇒ spikes from identified neurons)

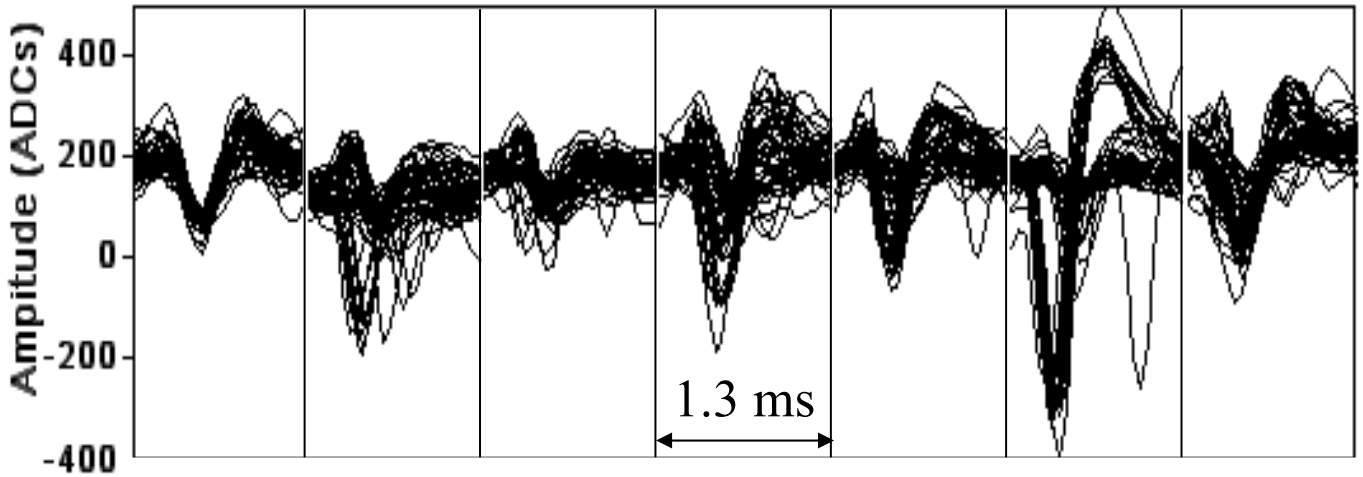
Single electrode
(electrode #1)





Multiple
electrodes

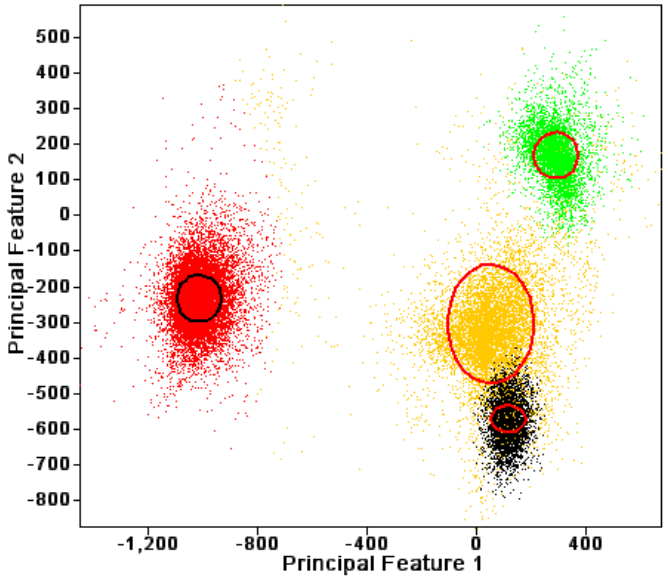




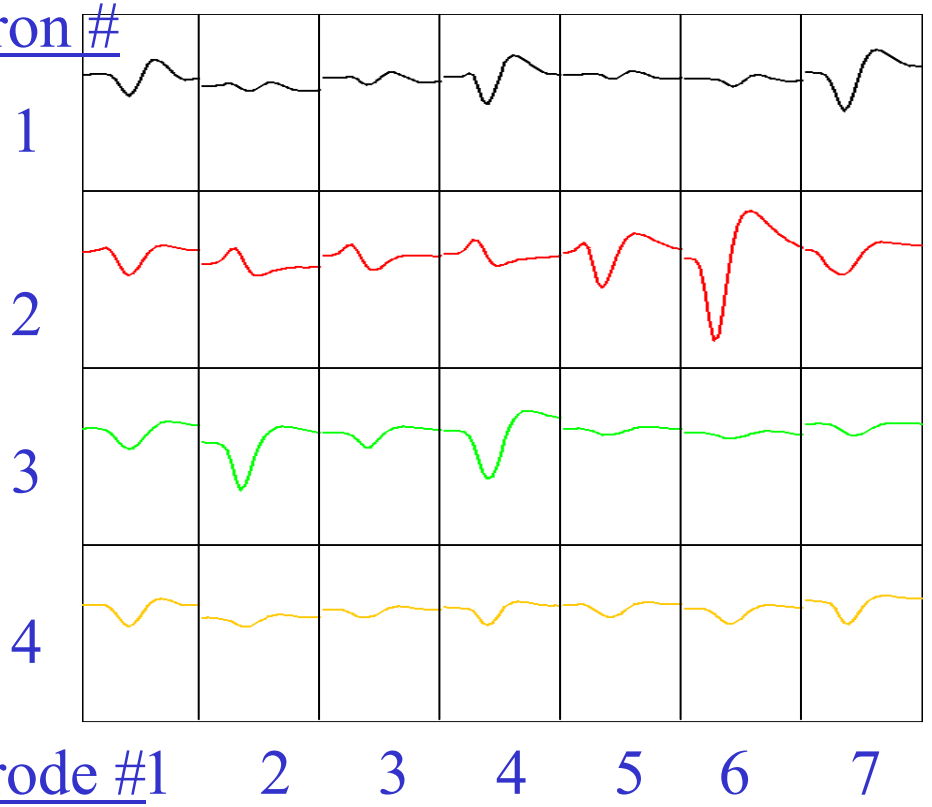
Electrode # 1 2 3 4 5 6 7

Principal Components Analysis; multidimensional clustering
⇒ 4 identified neurons

Multidimensional clustering



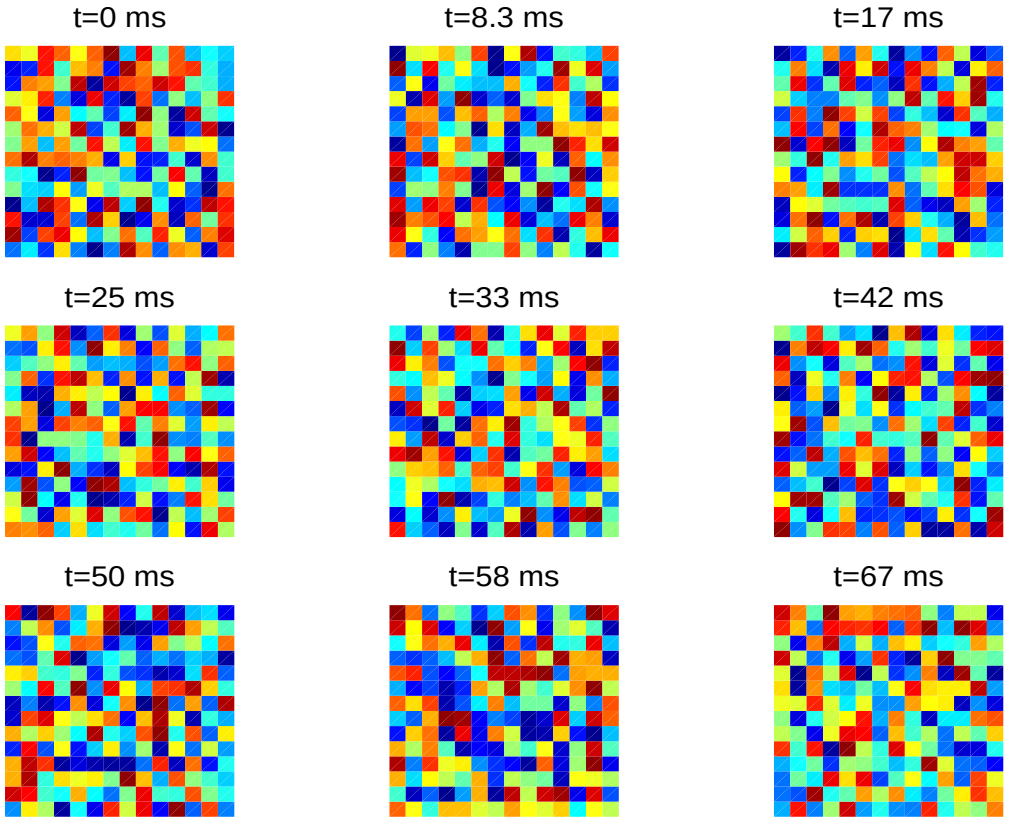
Average signal on each of the 7 electrodes for each of the 4 identified neurons



Neuron ID/analysis software: D. Petrusca, Santa Cruz

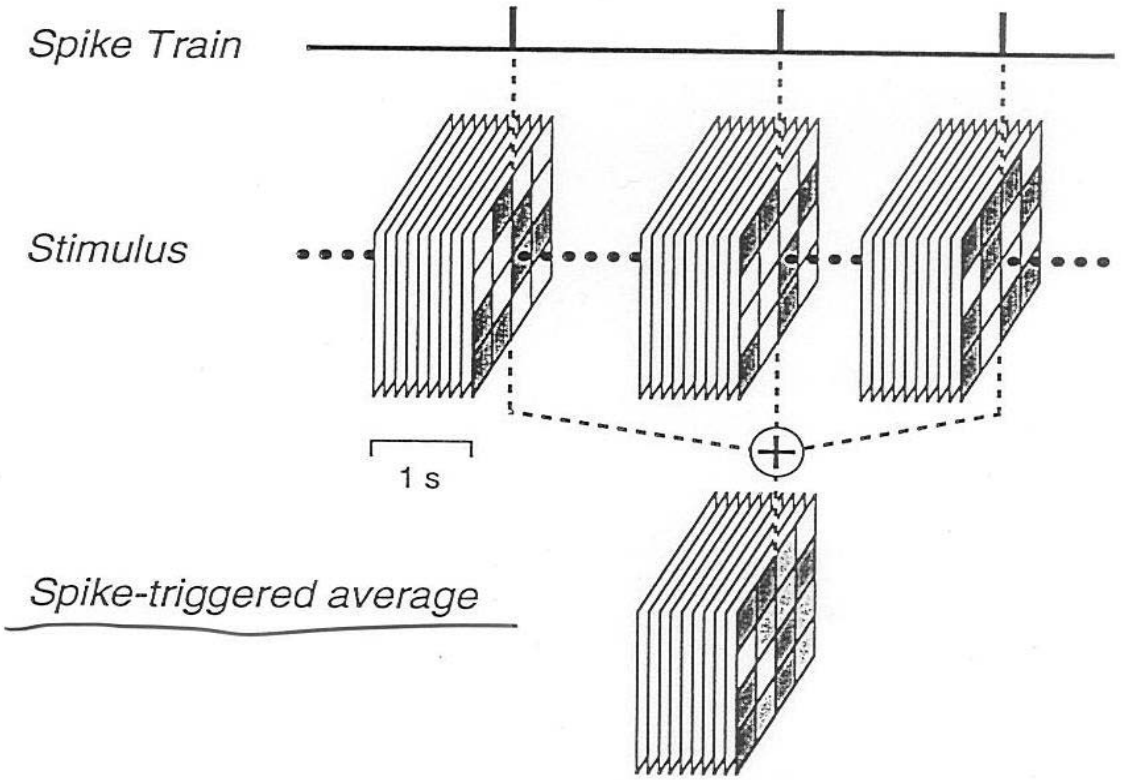
measure the response properties of identified neurons

⇒ white noise analysis: use time sequence of random checkerboard images



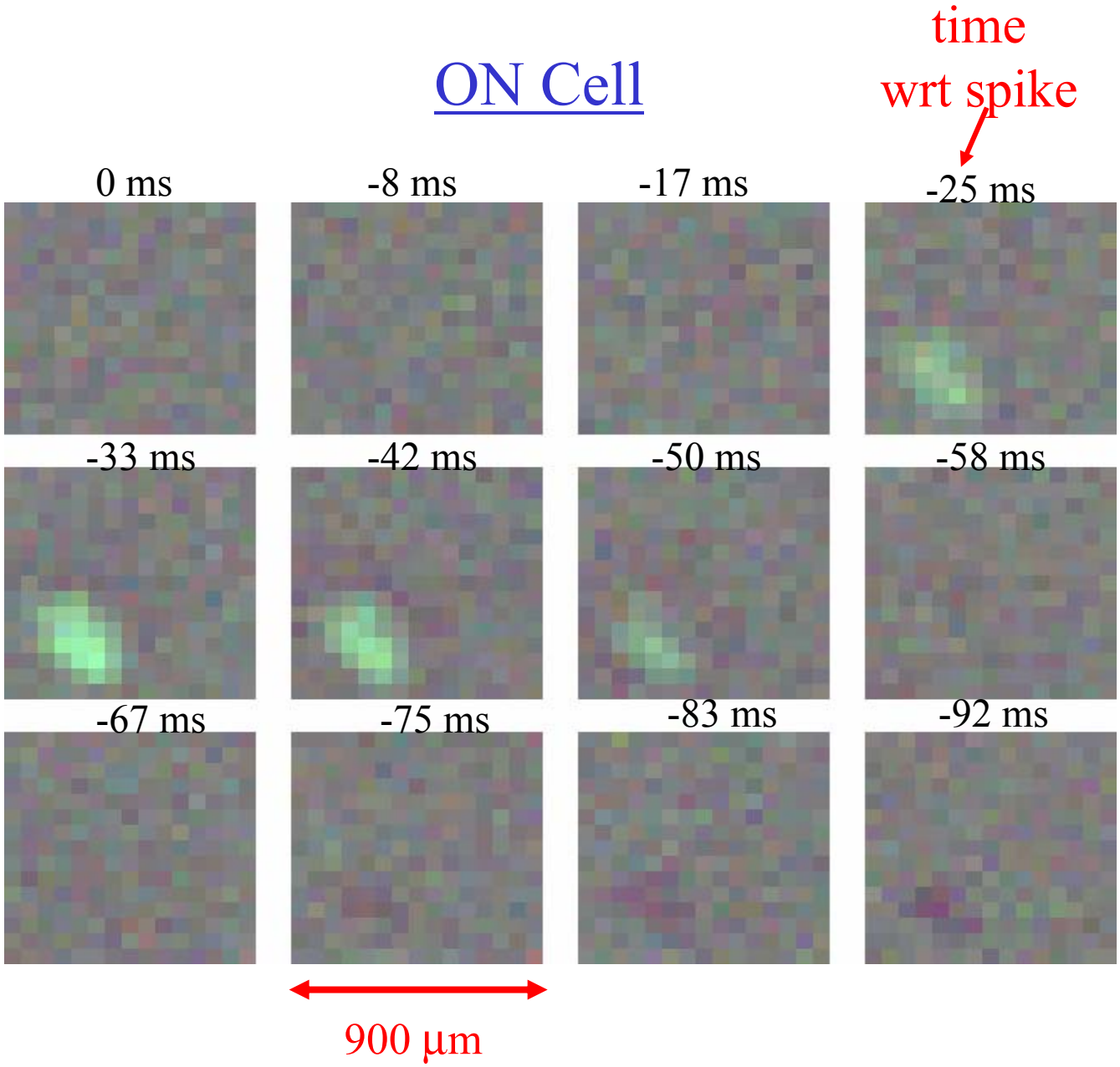
⇒ measure the "spike-triggered average" (sta) response for each neuron

Spike-triggered Average

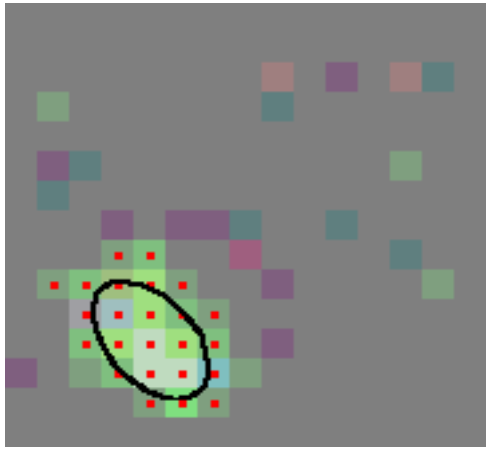


Monkey Retinal Ganglion Cell

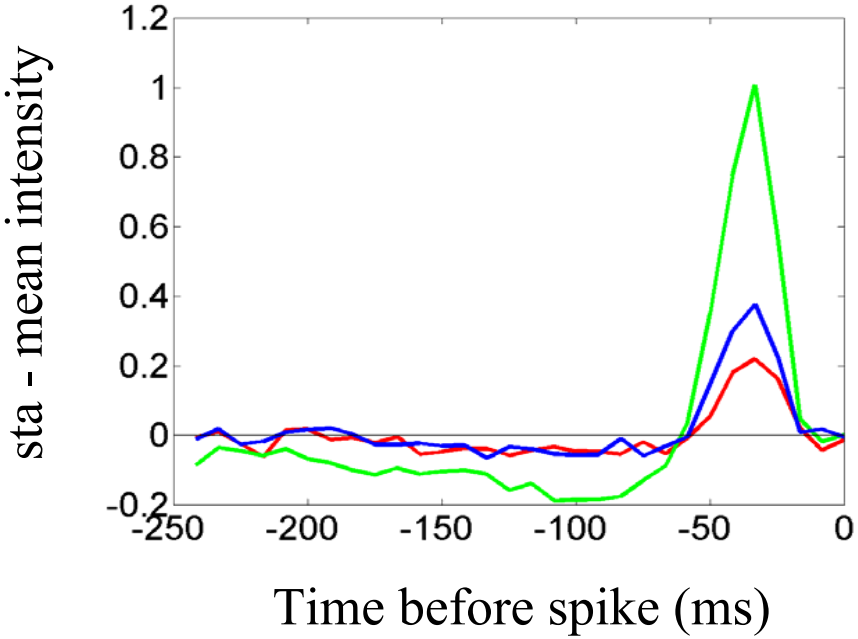
ON Cell

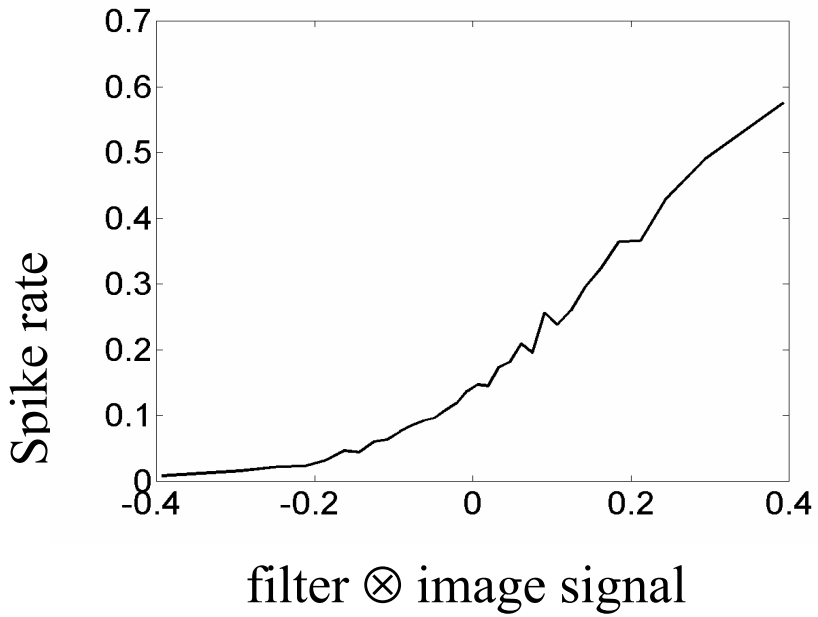


Spike-triggered
average image
at time of maximum
absolute intensity



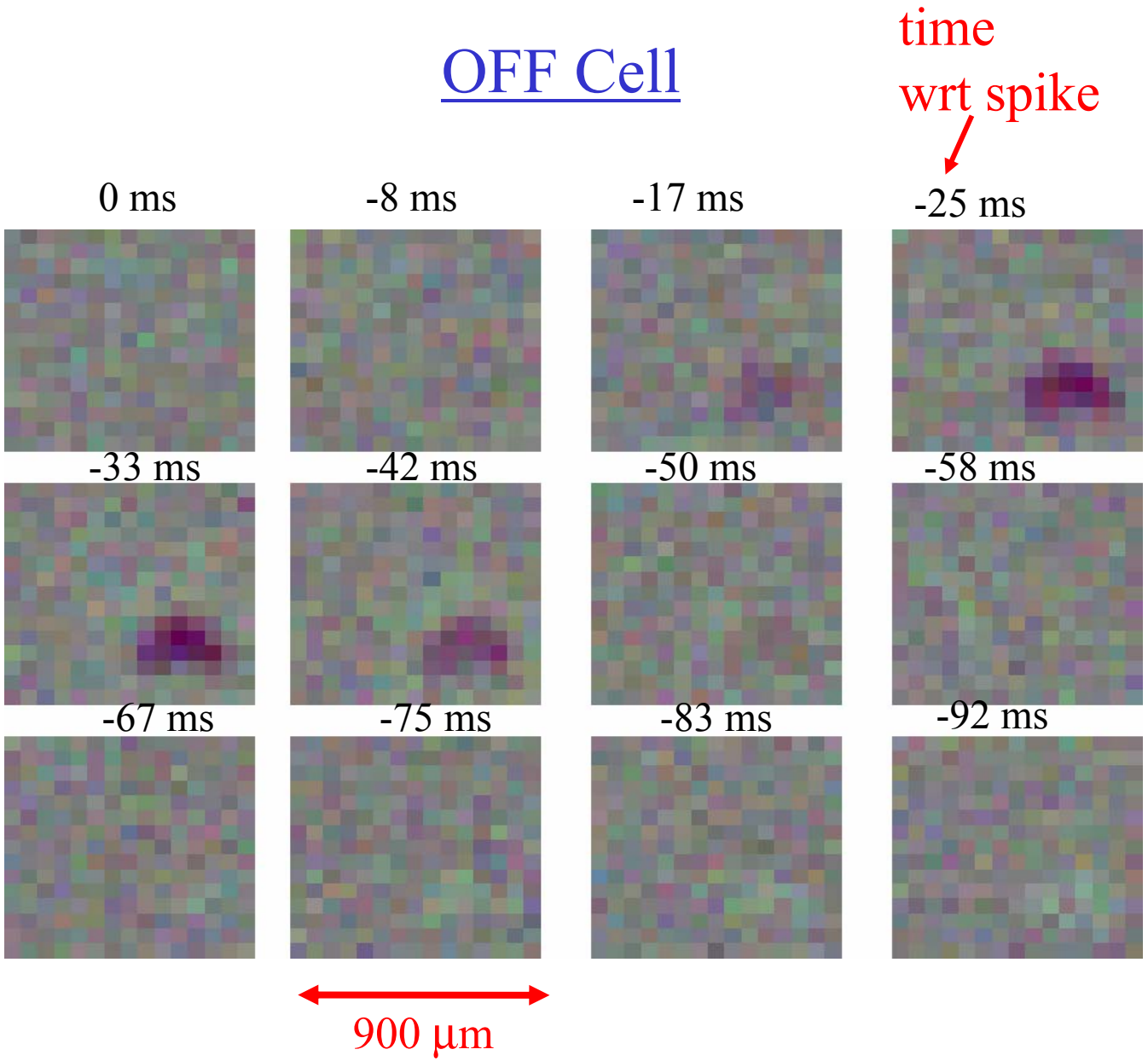
900
μm





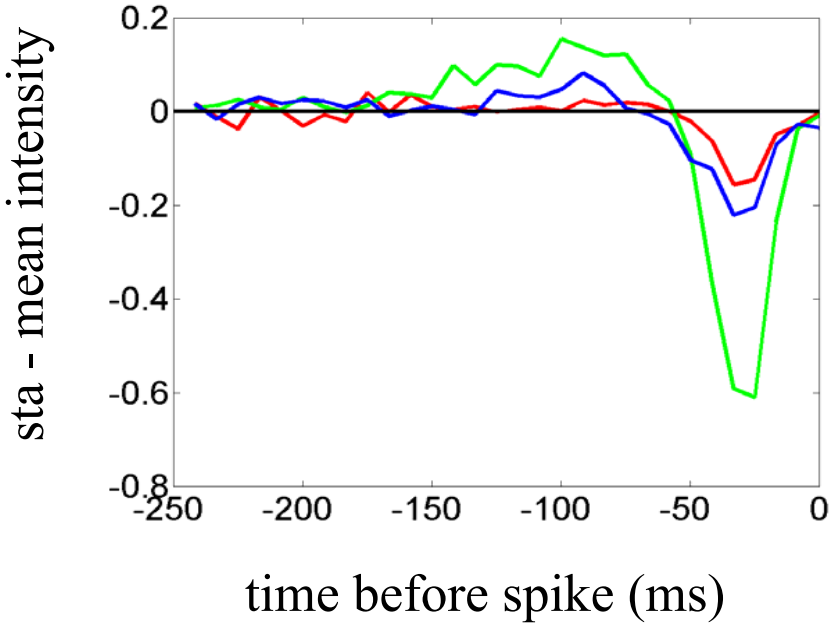
Monkey Retinal Ganglion Cell

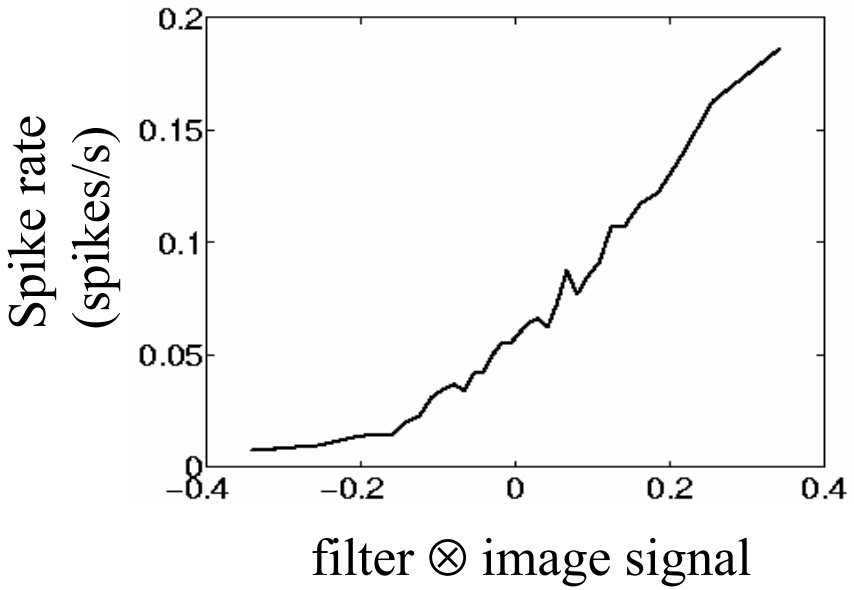
OFF Cell



Spike-triggered
average image
at time of maximum
absolute intensity

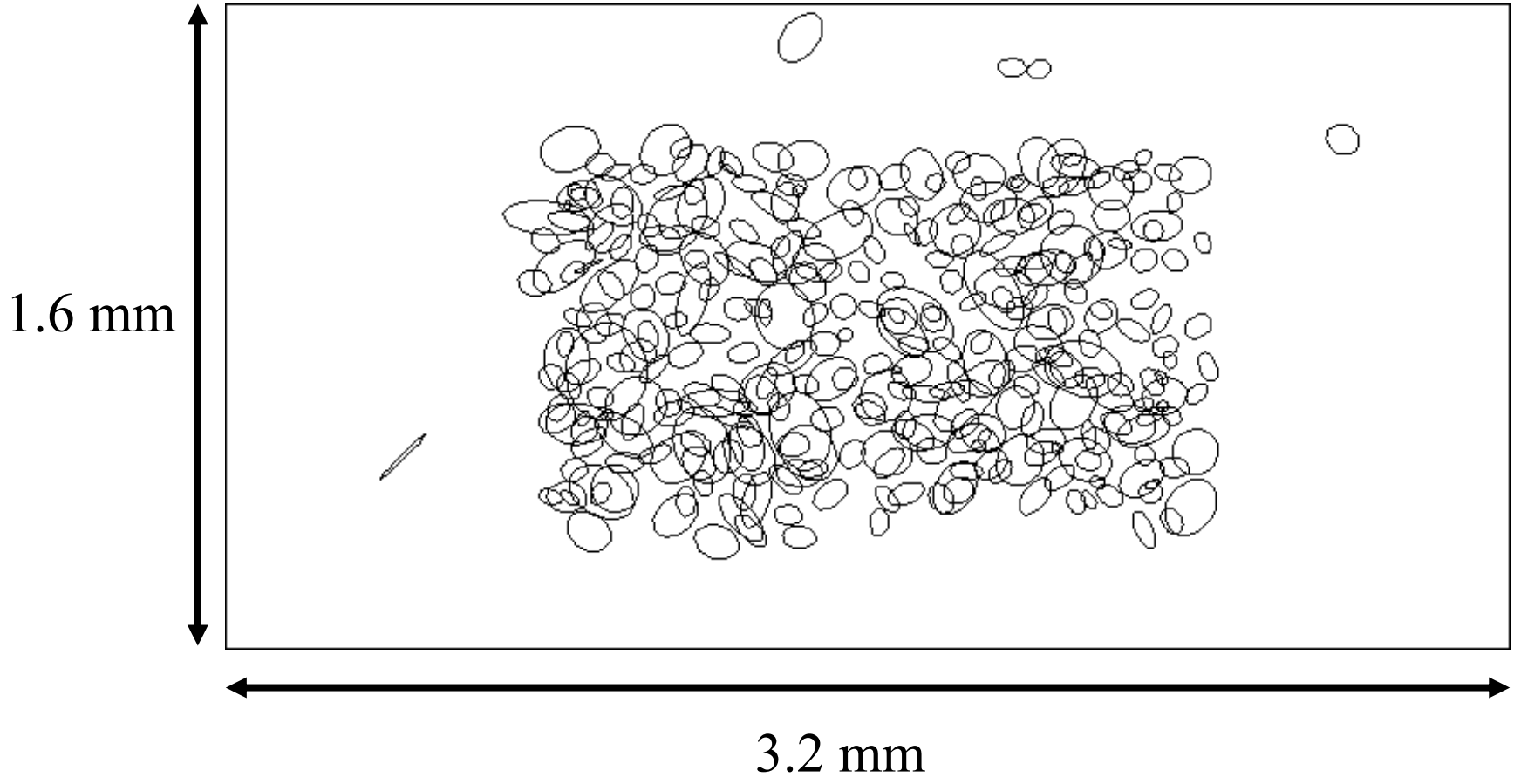
900
μm



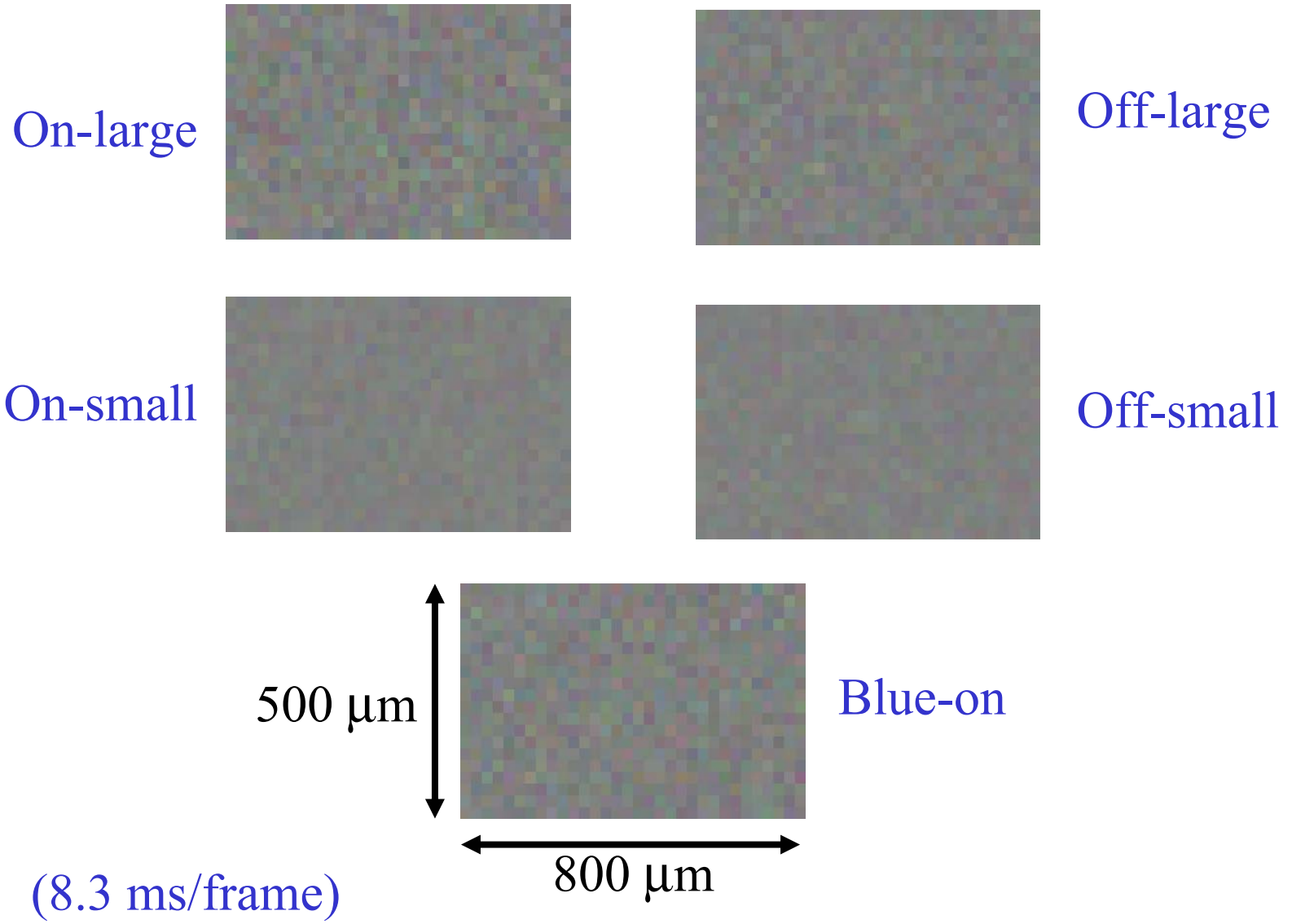


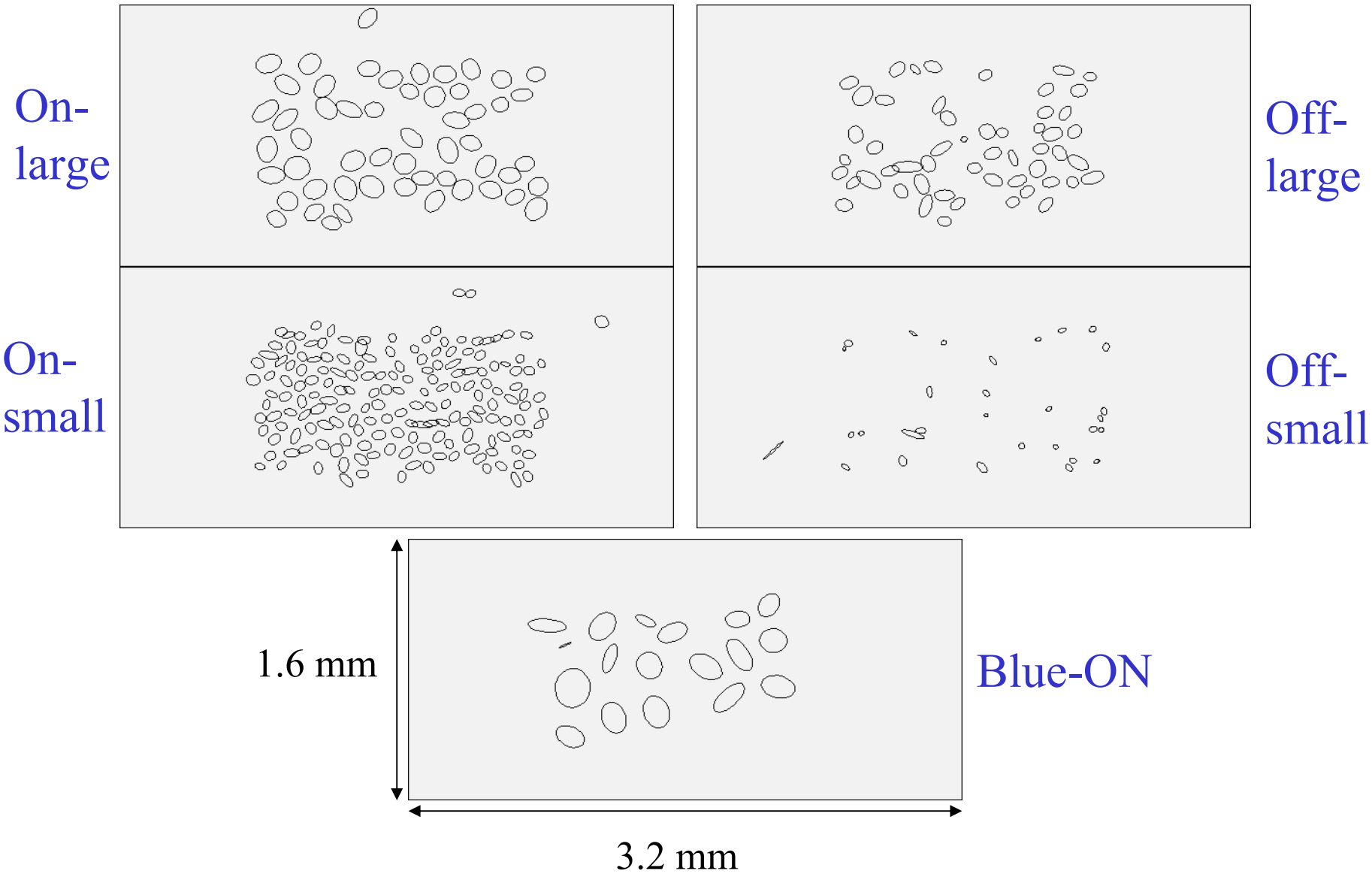
Some first (preliminary) results with monkey retina

Light-sensitive regions ("receptive fields") for 338 identified neurons



Spatial/temporal response properties of individual neurons ("spike-triggered average")

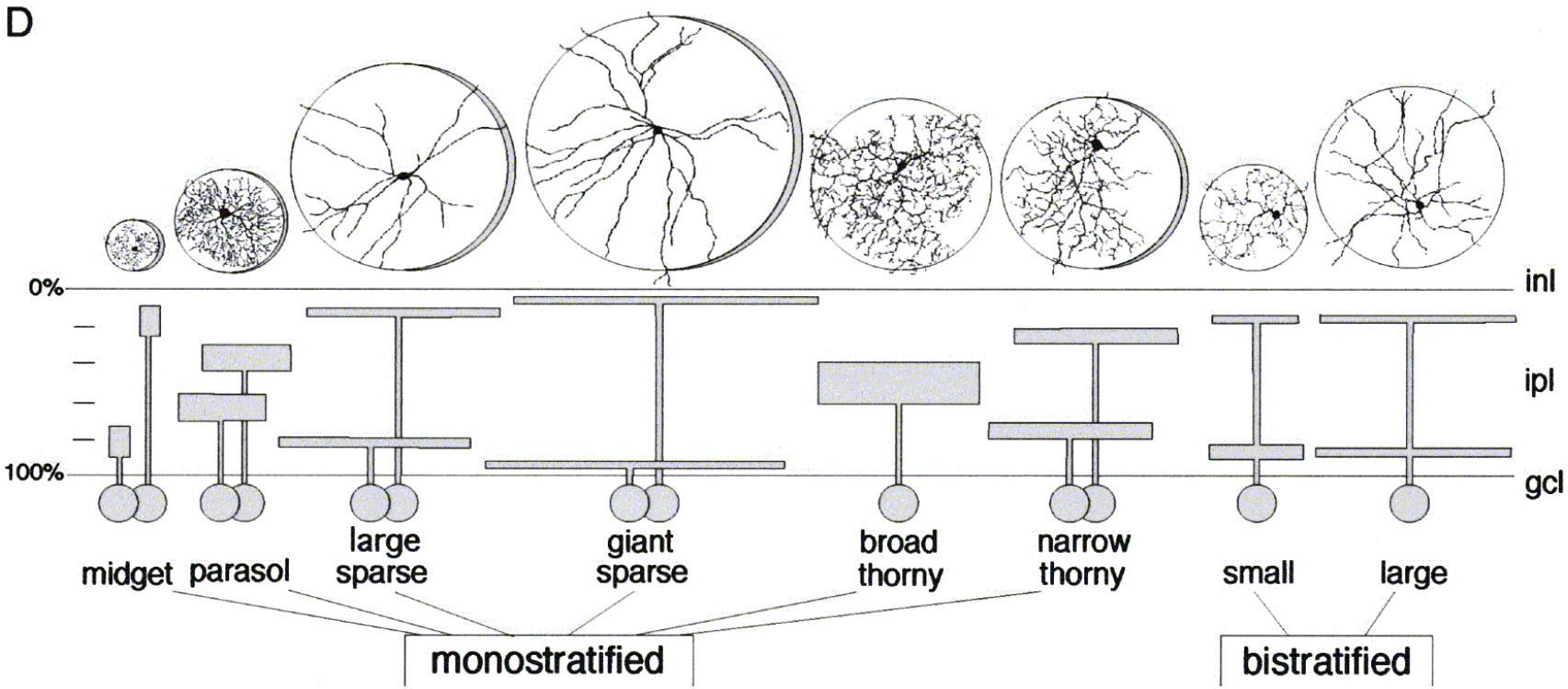



On-
large
Off-
large
On-
small
Off-
small
1.6 mm
Blue-ON
3.2 mm

Five identified monkey RGC classes (already well-known), but this is just the tip of the iceberg.

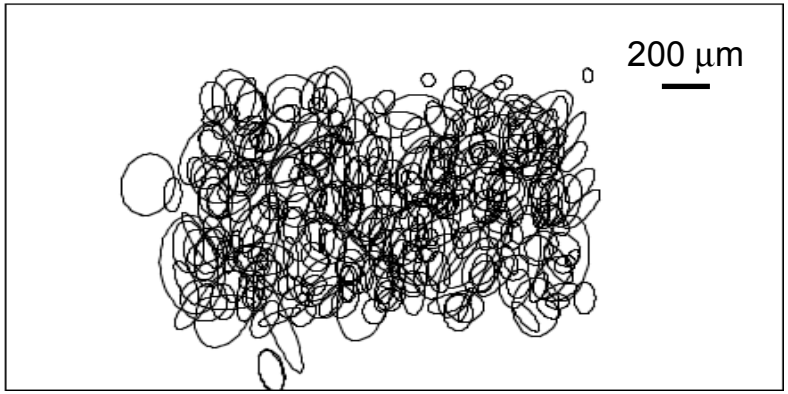
From anatomical studies, it is estimated that there are at least 22 distinct types of monkey RGCs.

Example: 13 cell types that project to the LGN (5 known + 8 new) (Dacey et al., Neuron 37 (2003) 15)

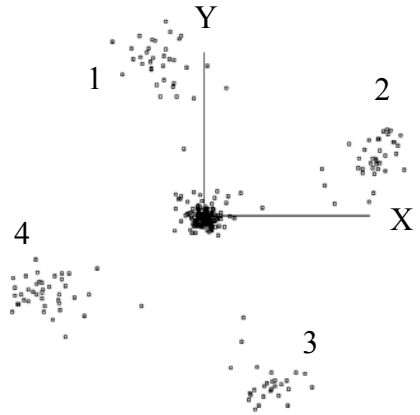


Guinea Pig Retinal Ganglion Cells: OFF cells

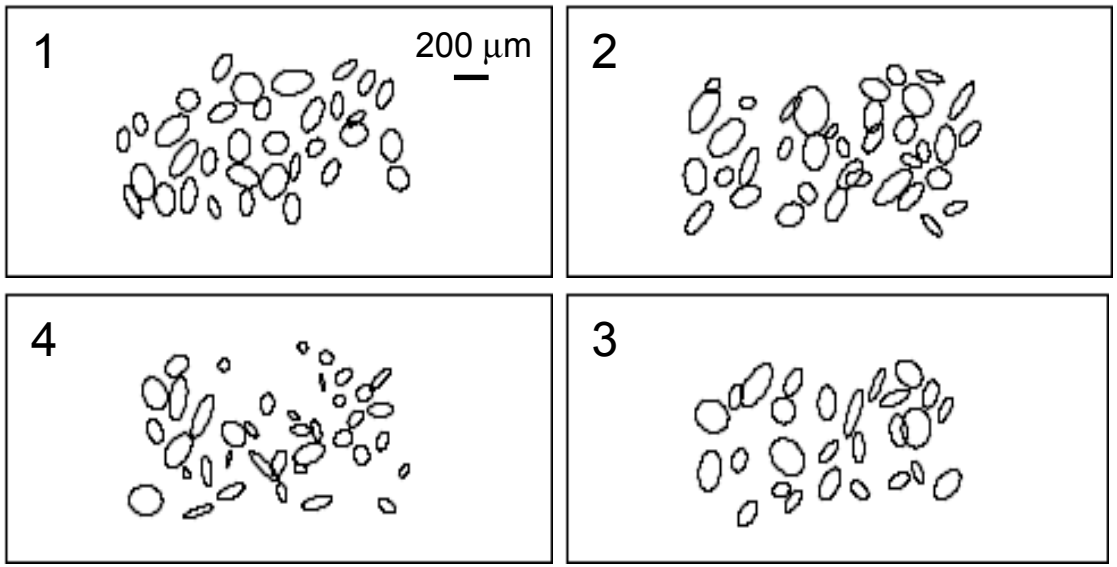
RF mosaic for 311 OFF cells



Direction selectivity for drifting sinusoidal gratings

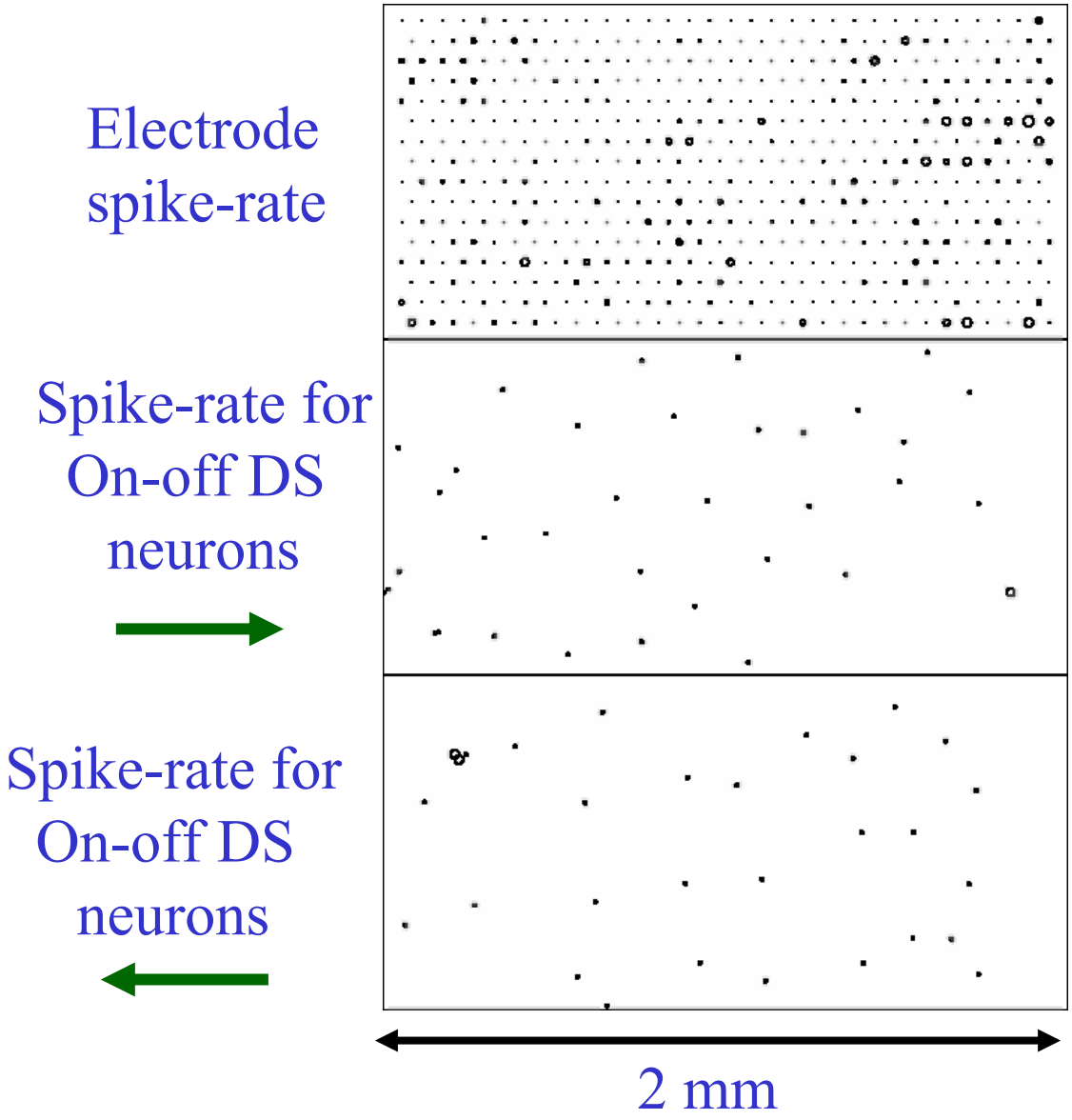


RF mosaics for clusters 1-4



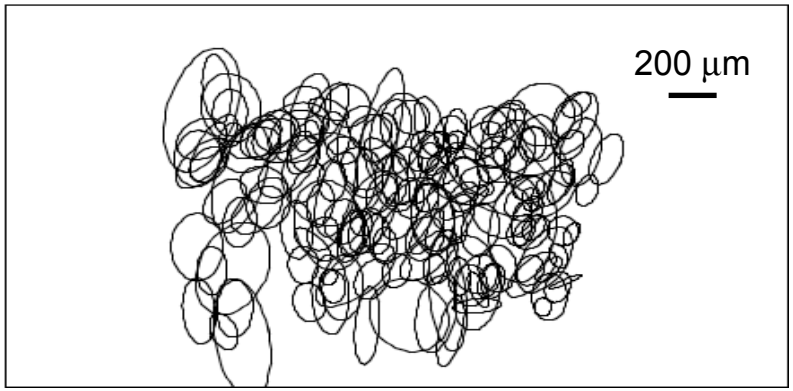
Neural activity recorded with 512-electrode system as image of vertical moving bar is focused on a section of guinea pig retina

(Animation repeats after 2 sweeps)

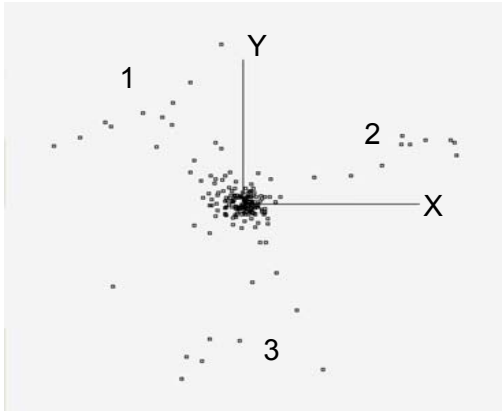


Guinea Pig Retinal Ganglion Cells: ON cells

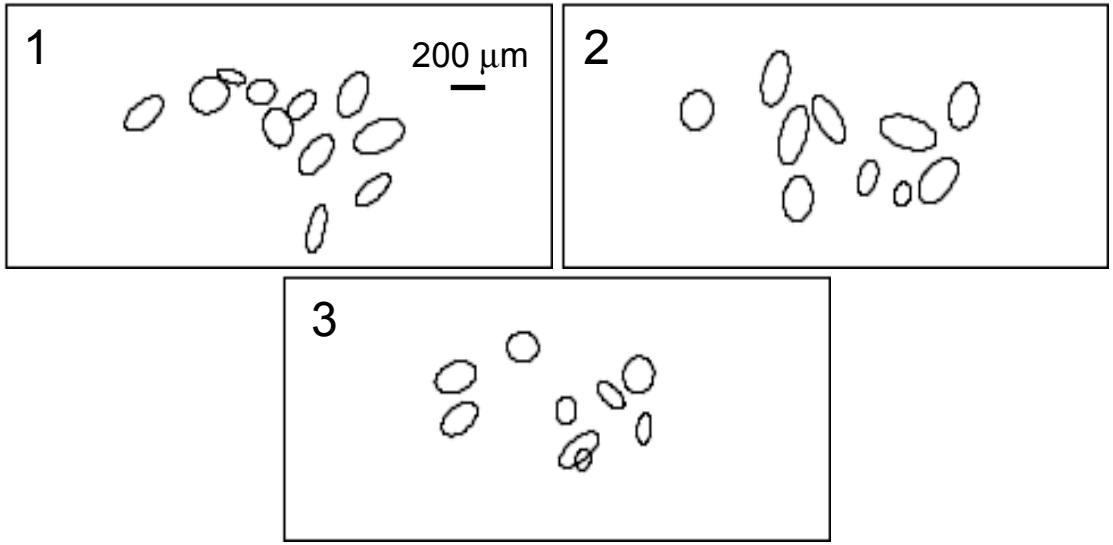
RF mosaic for 169 ON cells



Direction selectivity for drifting sinusoidal gratings



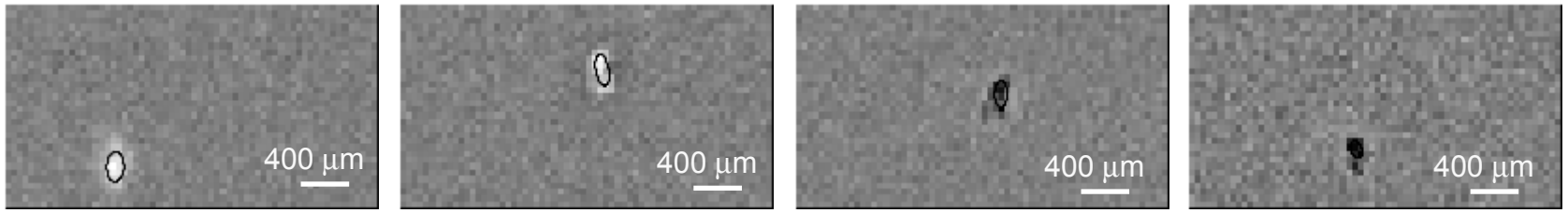
RF mosaics for clusters 1-3



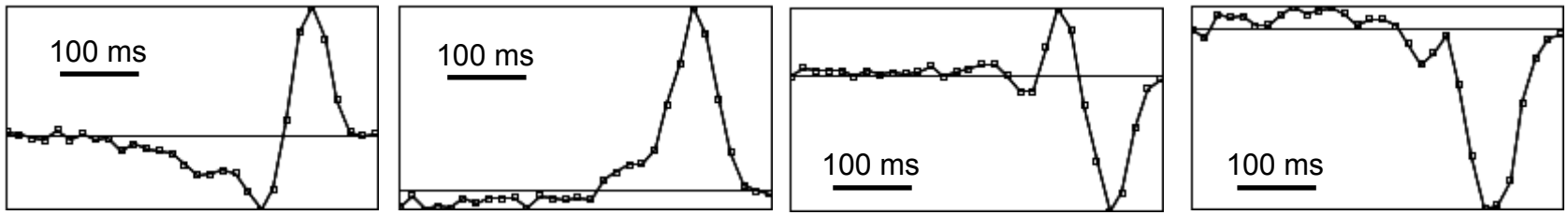
Non-DS Guinea Pig Retinal Ganglion Cells: Medium Sized

ON		OFF	
Transient	Sustained	Transient	Sustained

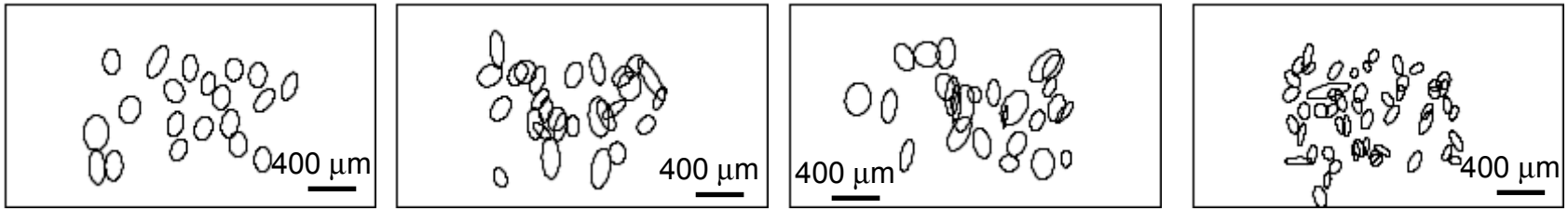
Receptive Fields



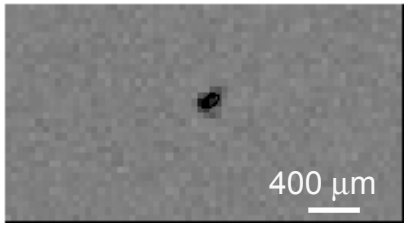
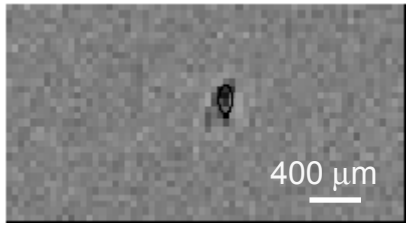
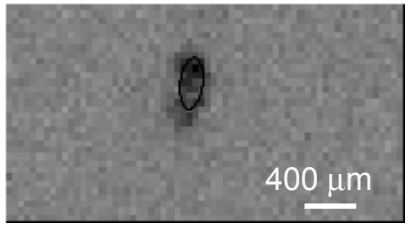
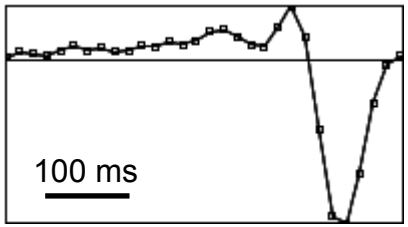
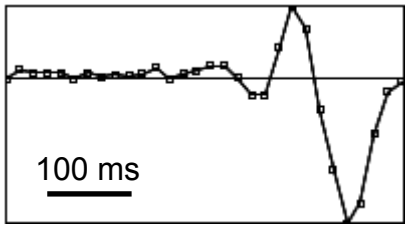
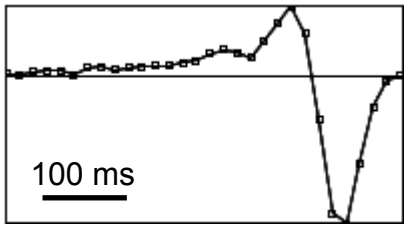
Timecourses



Mosaics



Non-DS Guinea Pig Retinal Ganglion Cells: OFF-Transient

Small	Medium	Large
Receptive Fields		
		
Timecourses		
		
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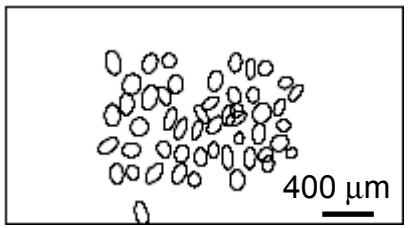
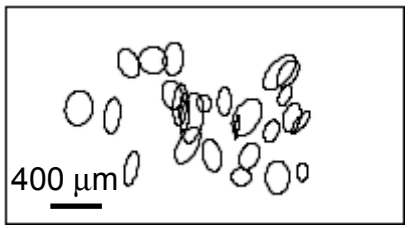
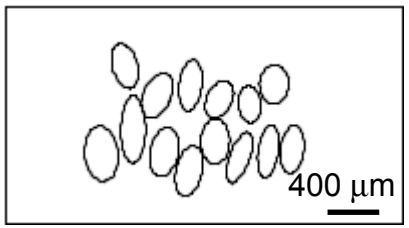
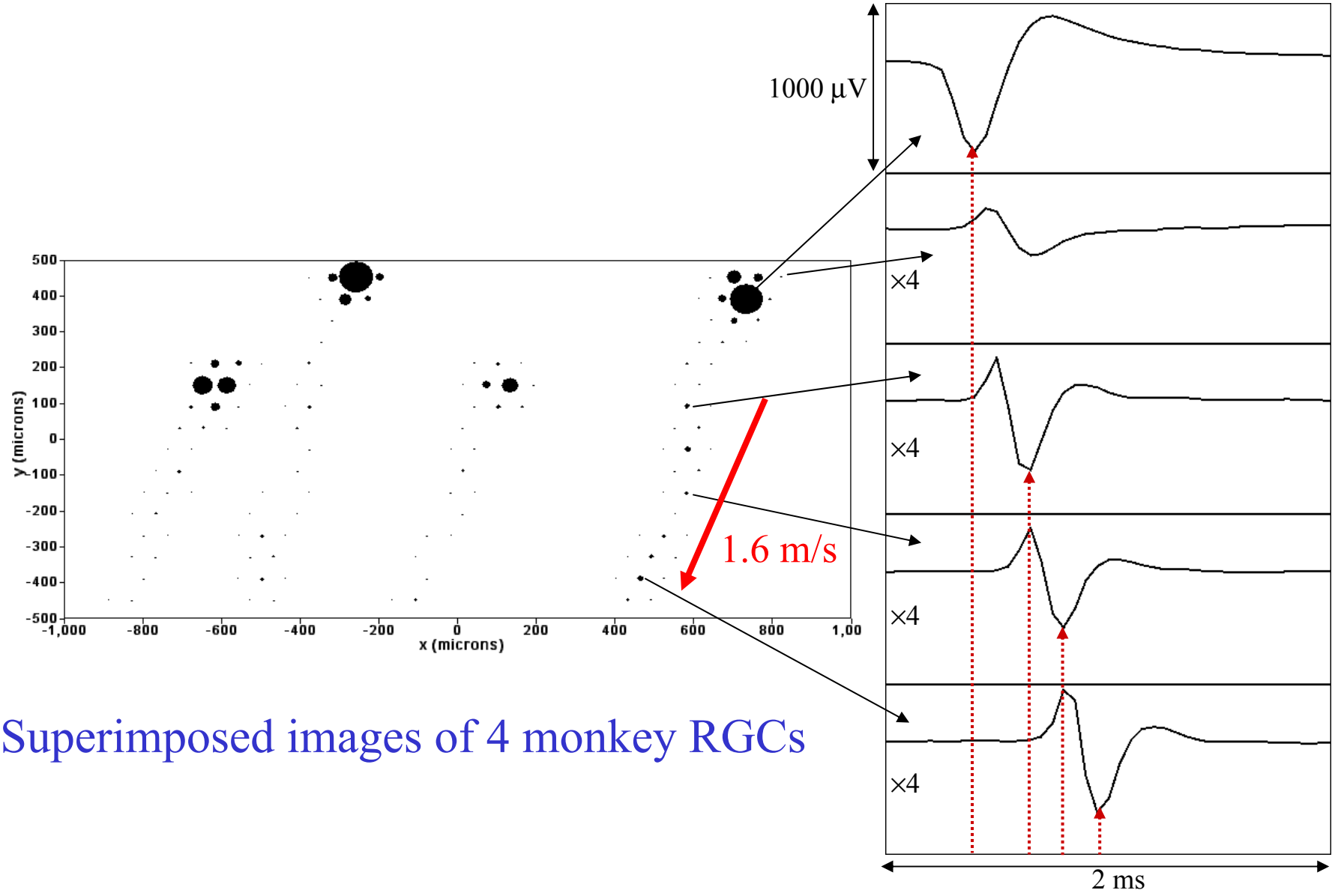
		

Electrophysiological Imaging

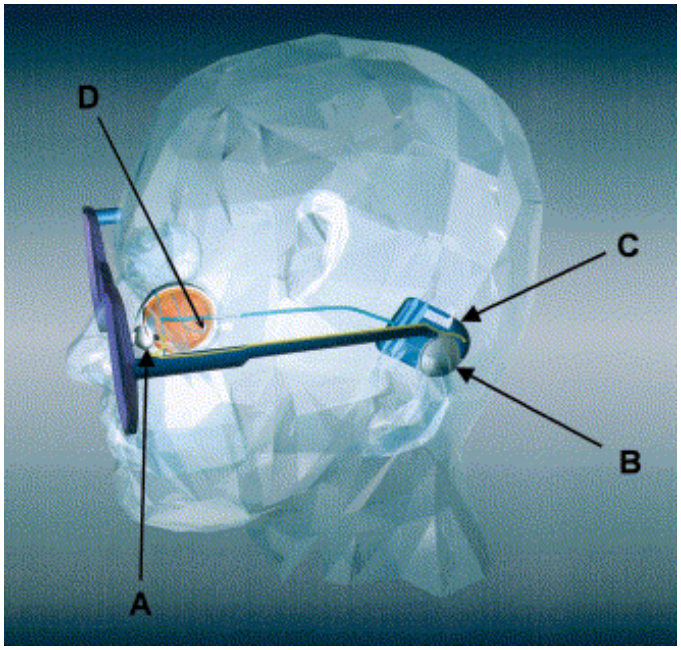


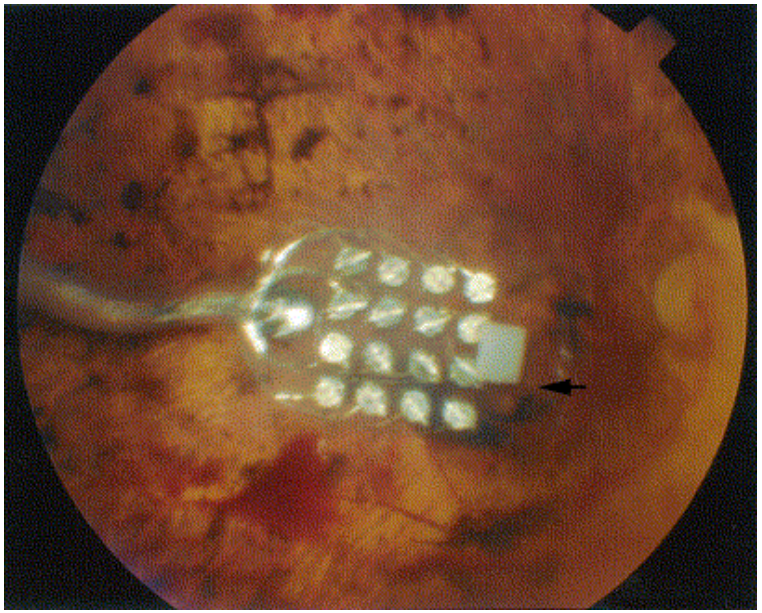
Superimposed images of 4 monkey RGCs

Future Activities and Directions

- Functional architecture/mosaic properties of monkey and guinea pig retina (with E. J. Chichilnisky, Salk Institute)
- Studies for Retinal Prosthesis (with E. J. Chichilnisky, Salk Institute)
- Retinal Development (with Marla Feller, UC San Diego)
- Cortical network dynamics in slices of brain tissue (with John Beggs, U. Indiana)

Retinal Prosthesis in Blind Subject





Implanted 4 x 4 electrode array;
electrode diameter = 520 μm,
electrode spacing = 720 μm

Humayan et al., Vision Research 43 (2003) 2573.

Summary

- We have developed a multielectrode system for the large scale recording of retinal ganglion cell activity
- Experimental data has been obtained with live guinea pig and monkey retinas
- For the first time, it has become possible to study image processing and encoding by the retina in terms of the correlated activity of hundreds of neurons
- There are numerous classes of retinal ganglion cells, each of which appears to tile the visual field, and each of which appears to send a separate image to the brain
- Potential additional applications include retinal prosthesis, retinal development, slices of brain tissue, and networks of cultured neurons