Studying the Retina and Other Neurobiological Systems with a Physicist's Toolkit

or

What's a Physicist Doing in a Biology Lab?

Physics 10
7-Nov-2006

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SCIPP – UCSC

Focus of Talk

You may find this talk a little unusual compared to more typical class lectures.

The main focus is not so much on physics or neurobiology but on the potential commonality of investigating the two disciplines. In particular, the potential for applying research techniques and technologies from one discipline to questions in the other.

We will discuss some facts about physics and neurobiology but the emphasis will be on research techniques and problem solving and not on science facts, per se.

The Local Team plus Collaborators

Santa Cruz Institute for Particle Physics

Alan Litke (faculty)

Alex Grillo (research physicist)

Sasha Sher (post-doc)

Sergei Kachiguine (engineer)

Collaborators

neurobiologists at the Salk Institute (E. J. Chichilnisky et al.)

VLSI designers in Krakow (W. Dabrowski et al.)

microfabrication experts at U. Glasgow (K. Mathieson et al.)

biologists at UCSC (D. Feldheim et al.)

Biocomplexity Institute at Indiana U. (J. Beggs et al.)

What Does a Physicist Do?

In very general terms, physics is the study of matter and energy and how they interact with each other.

Particle physicists study sub-atomic particles and their interactions.

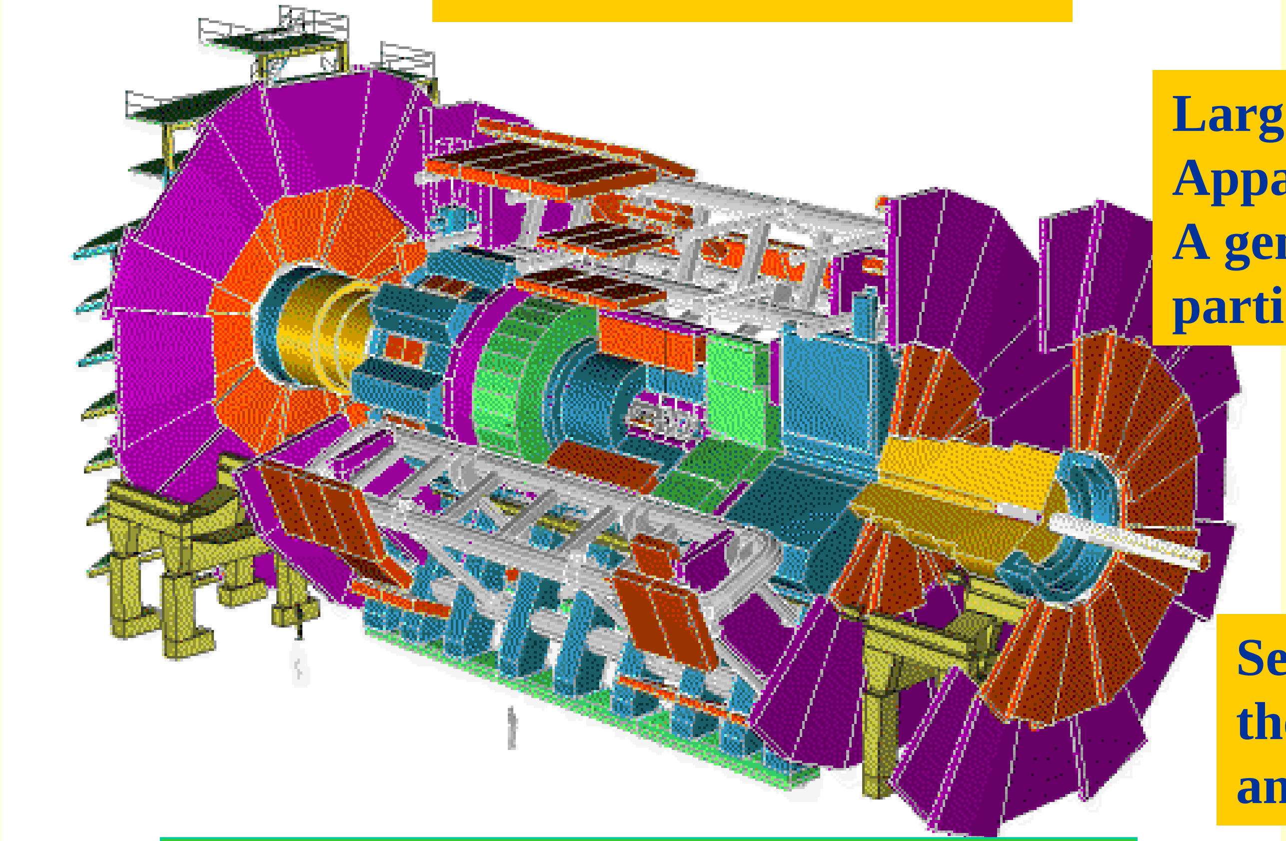
This requires very sophisticated equipment since these particles are not visible even with the most powerful microscopes and they often decay (or transform) into other particles within small factions of a second.

The development of new technologies to conduct such studies is often an important part of Experimental Particle Physics.

(See previous lecture by B. Schumm.)

A Brief Example

The ATLAS Detector



Largest Particle Physics Apparatus ever built - A general purpose particle spectrometer

Search for the Higgs particle and Super Symmetry

ATLAS eTour at http://atlasexperiment.org/

Some of the Challenges

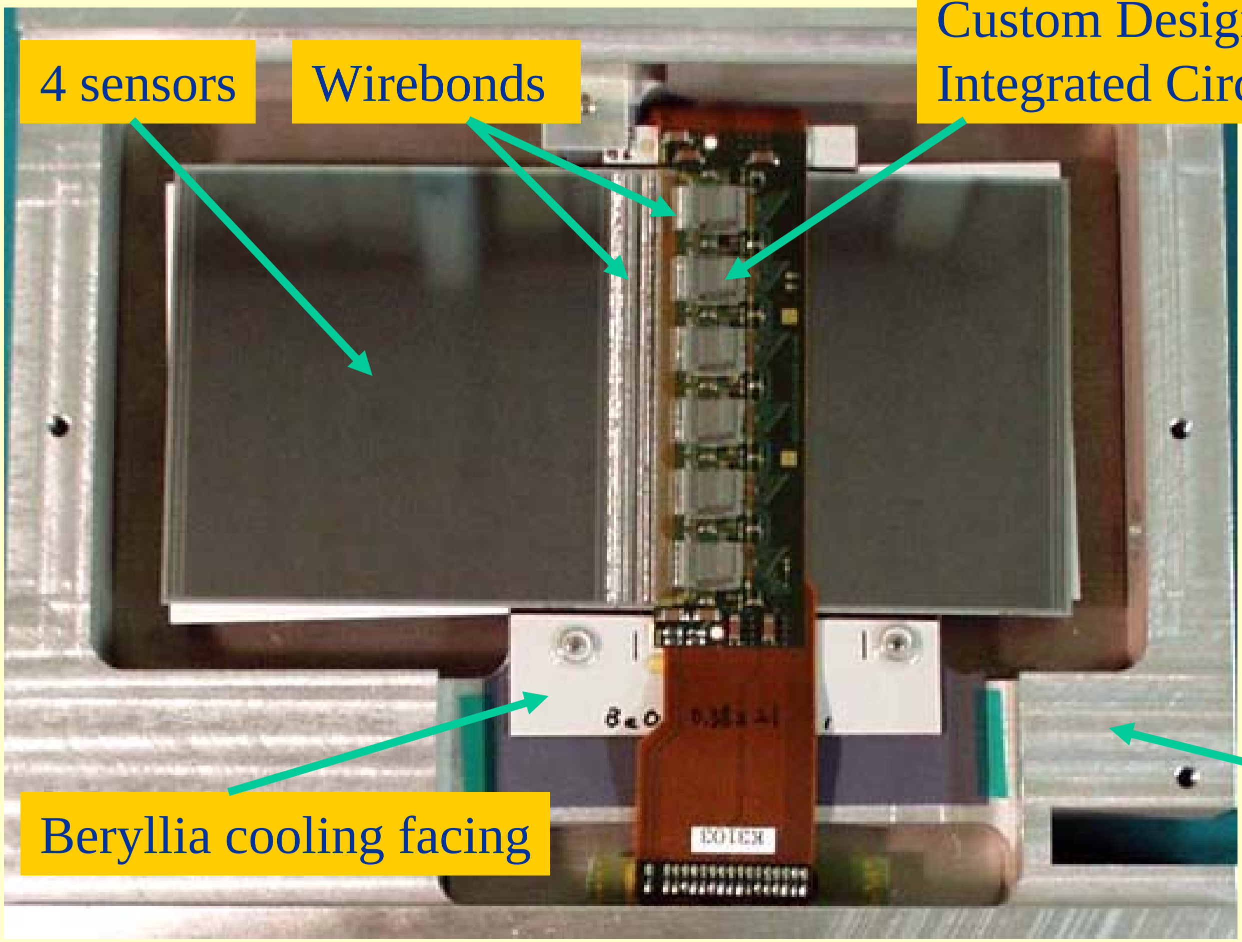
- Each interaction of the colliding beams of protons (occurring 40 million times per second) will produce hundreds of particles which must be detected and identified.
- This requires technology that can measure the position of particle trajectories to a few microns (10^{-3} millimeters).
- Requires electronics which has extremely low noise, uses low power but operates at high speed.
- Requires very fast data processing to manage ~ terabyte (10^{12} bytes) of data storage per day and sophisticated computer programs to analyze the data in a finite amount of time.

Silicon Microstrip Detectors

Here at Santa Cruz, we have developed a technology called "silicon micro-strip detectors" to fulfill these requirements.

- **Diode strips, with fine pitch, fabricated on silicon wafers (a la the microelectronics industry).**
- **Charged particles deposit charge inside the silicon.**
- **Novel integrated circuits sense the deposited charge and provide signals for computer recording.**
- **Particles traversing the detector can be located to within of a few tens of microns.**

A Silicon Microstrip Detector Module



Each module includes:

- **1536 diode strips in the sensor area.**
- **Strips spaced at 80 μm**
- **12 custom ICs**

ATLAS contains 4088 such detector modules

Can Any of This be Applied to Other Fields?

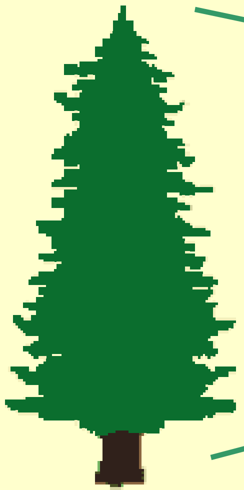
Are there other fields of science that could benefit from these technologies?

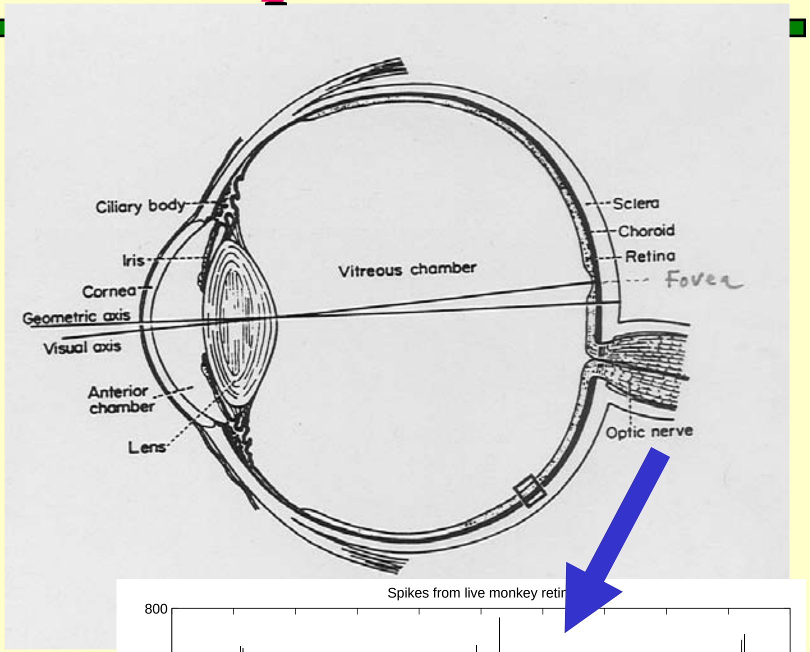
Possibly another question: are there puzzles in other fields of science that would interest a physicist?

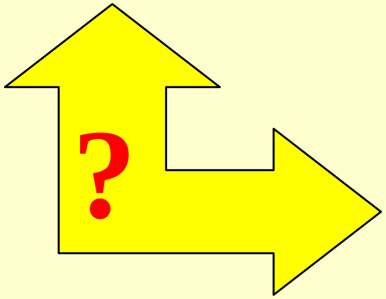
Neuroscience comes to mind (Hmm, interesting play on words.):

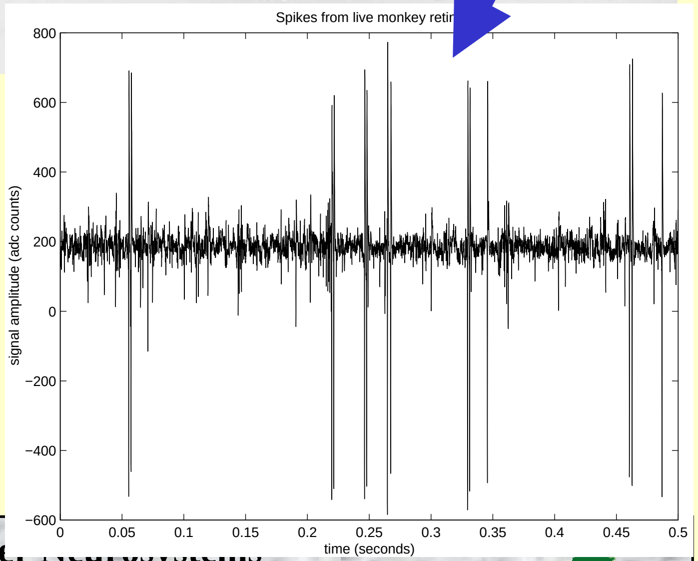
- Neurons manifest electrical activity which physicists know how to measure.
- Neuron spacing in tissue is on the order of microns, similar to the spatial resolution of particle detectors.
- Studying a large ensemble of neurons could be an interesting challenge with potentially big payoffs.

Vision: First Steps









The Retina Project

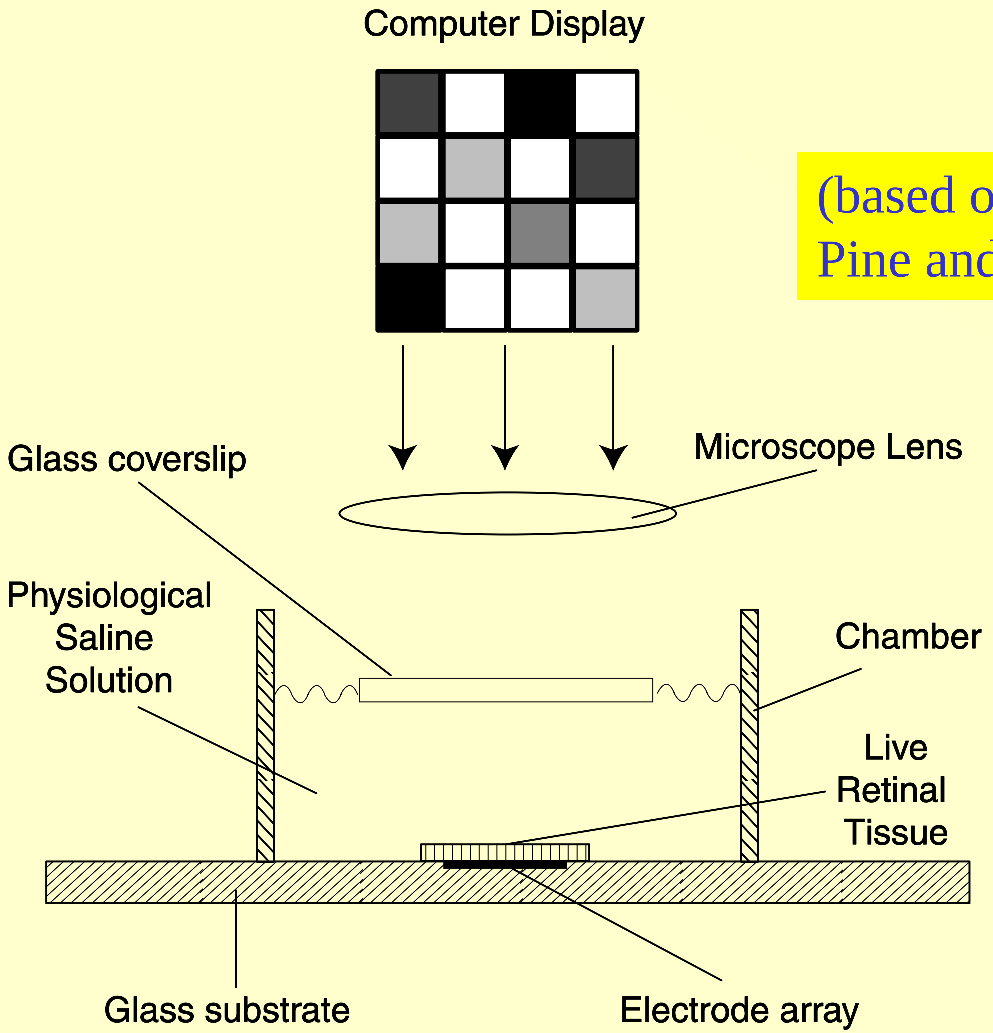
Goal: understand how the retina processes and encodes dynamic visual images.

Method: record the patterns of electrical activity generated by hundreds of retinal output neurons in response to a visual movie focused on the input neurons.

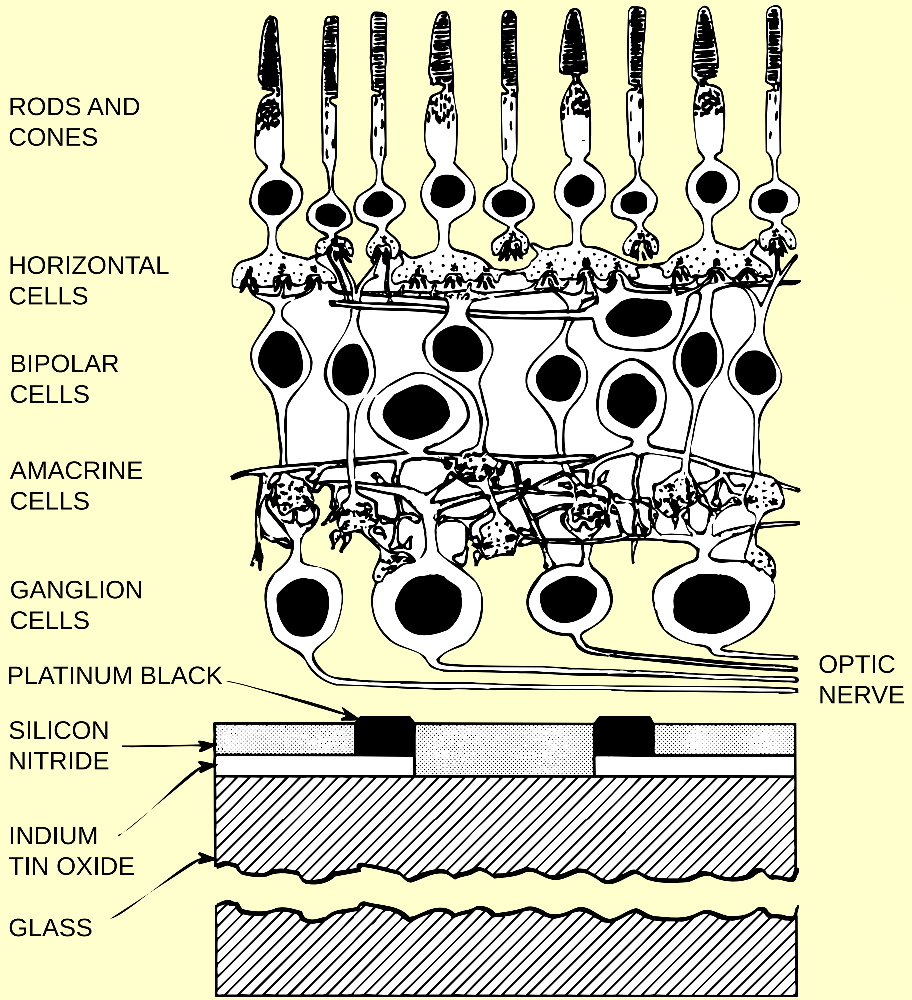
Technology: based on silicon microstrip detector techniques and expertise developed for particle physics experiments (including the search for the Higgs particle) – an example of the application of expertise in particle physics instrumentation to neurobiology

The Experimental Technique

(based on work by Meister, Pine and Baylor)



Cross Section of Retina on Electrode Array



Scale?

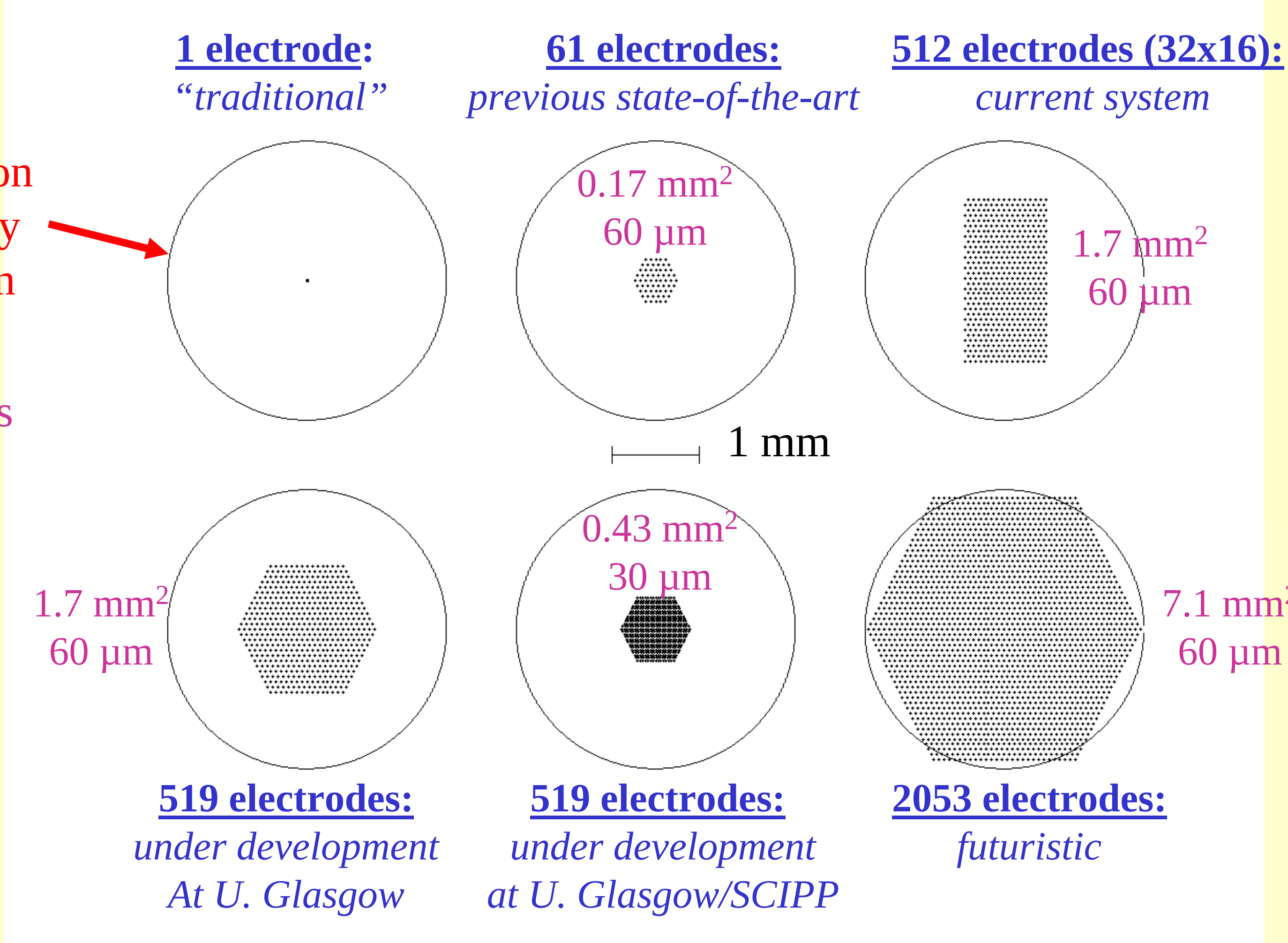
- Record from a population of neurons approaching a scale of interest for neural computation
- order-of-magnitude improvement in state-of-the-art

⇒ Record simultaneously from hundreds to thousands of retinal ganglion cells in a single preparation

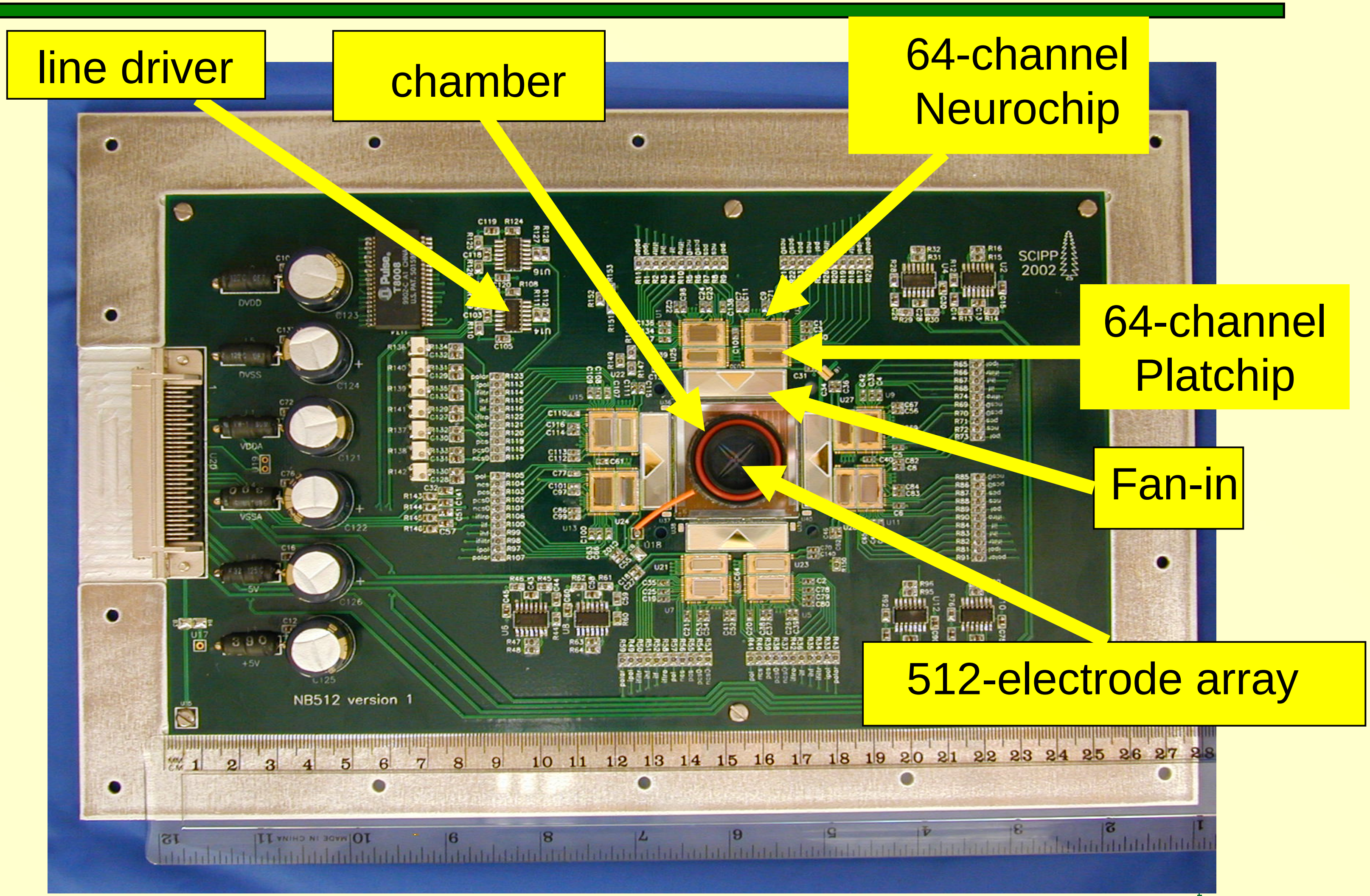
Electrode Array Geometries

Input region for monkey MT neuron

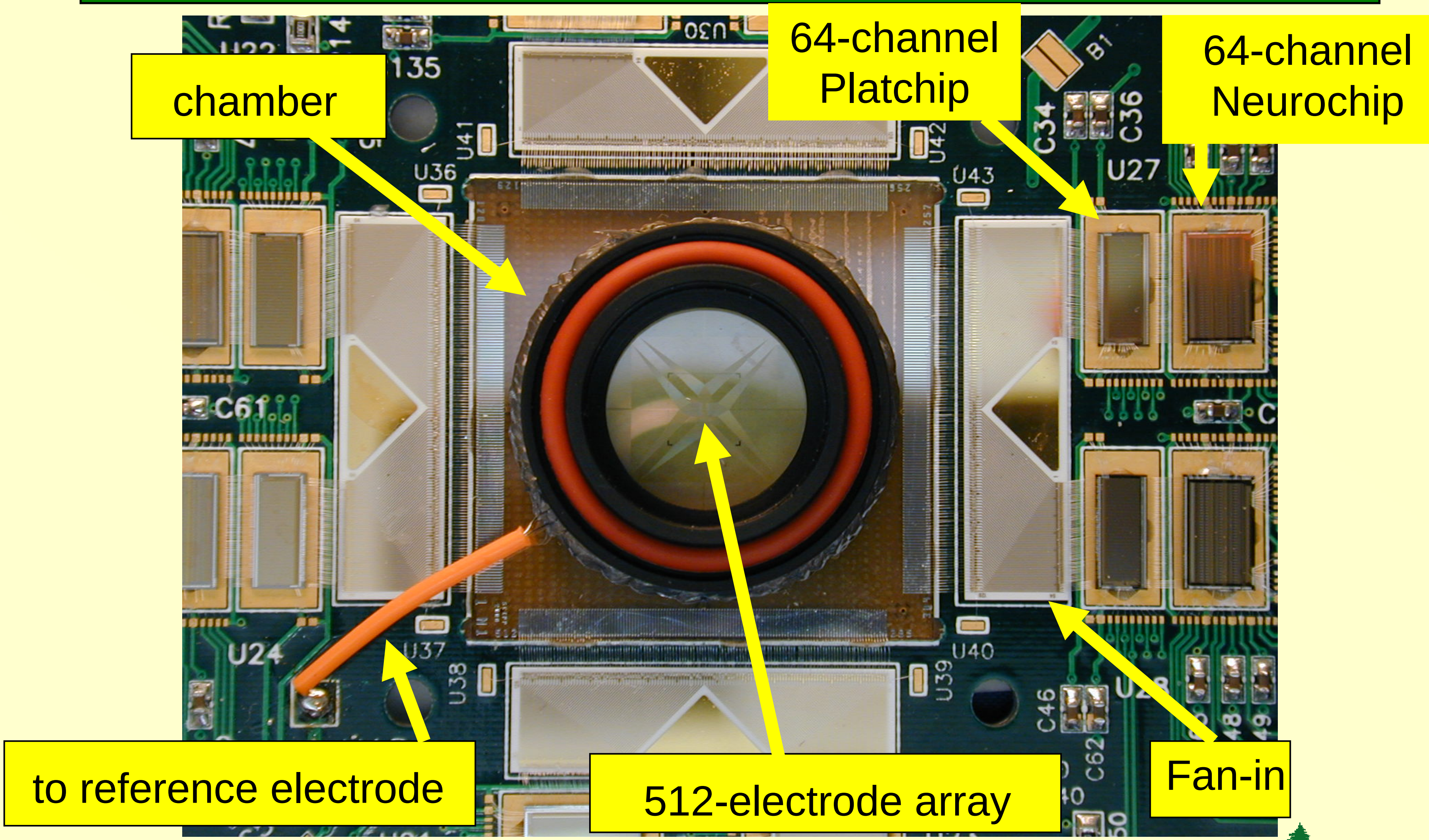
Electrode diameters are 5 µm; area and electrode spacing given by each array.



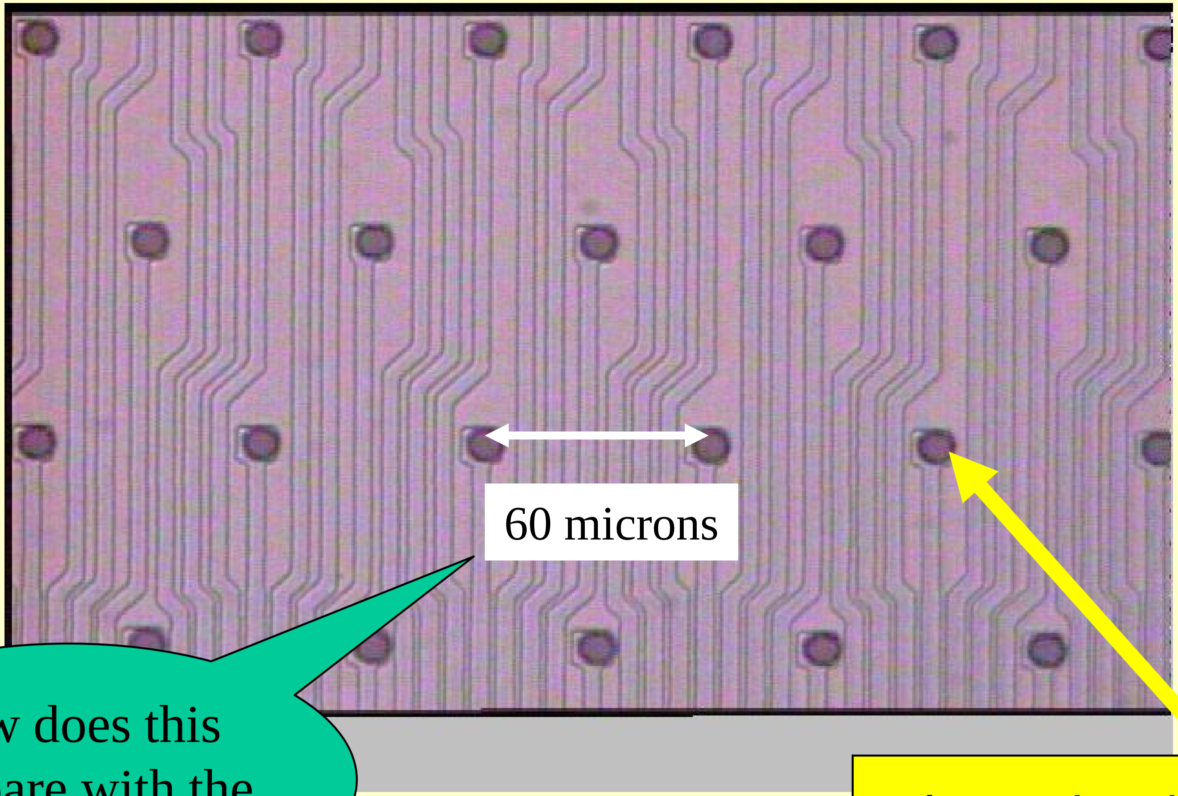
512-electrode "Neuroboard"



Section of 512-electrode “Neuroboard”

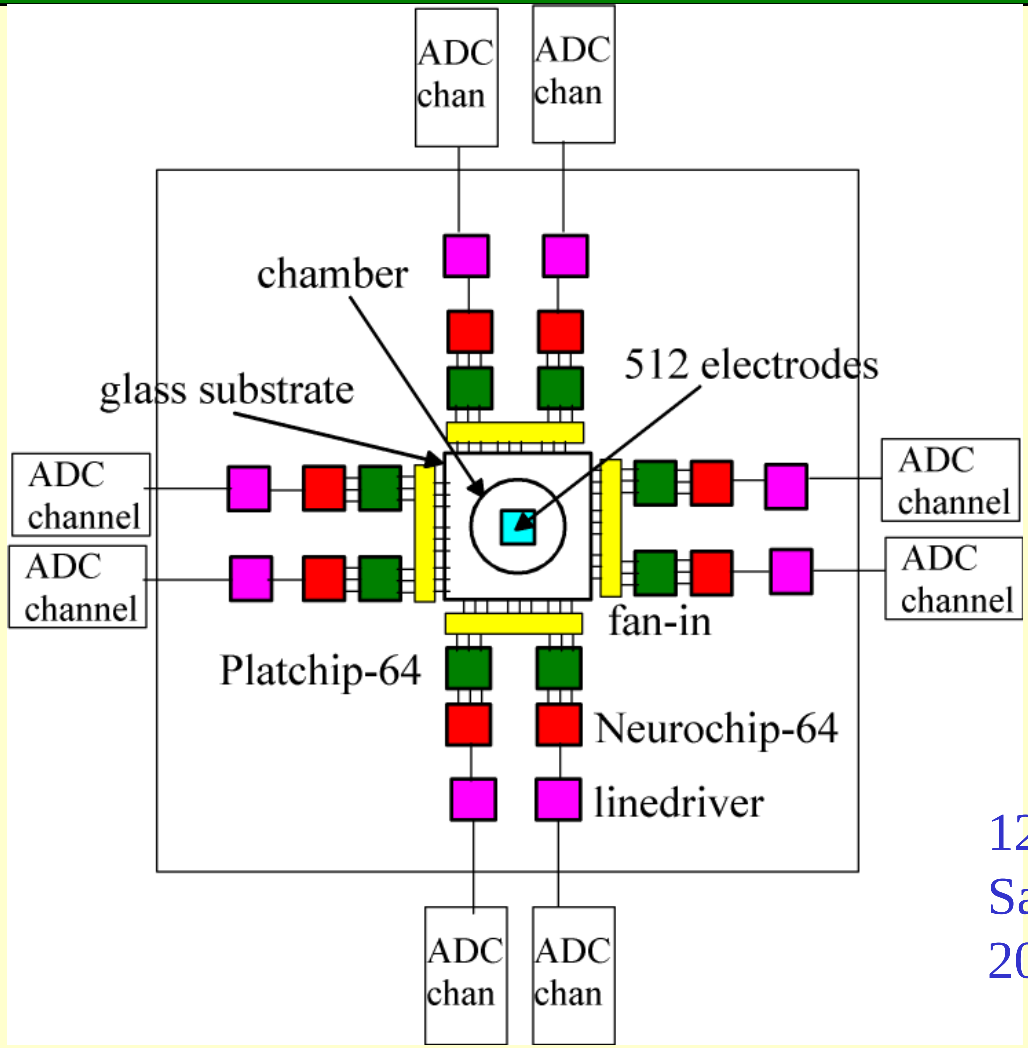


Section of 512-electrode Array (32x16)



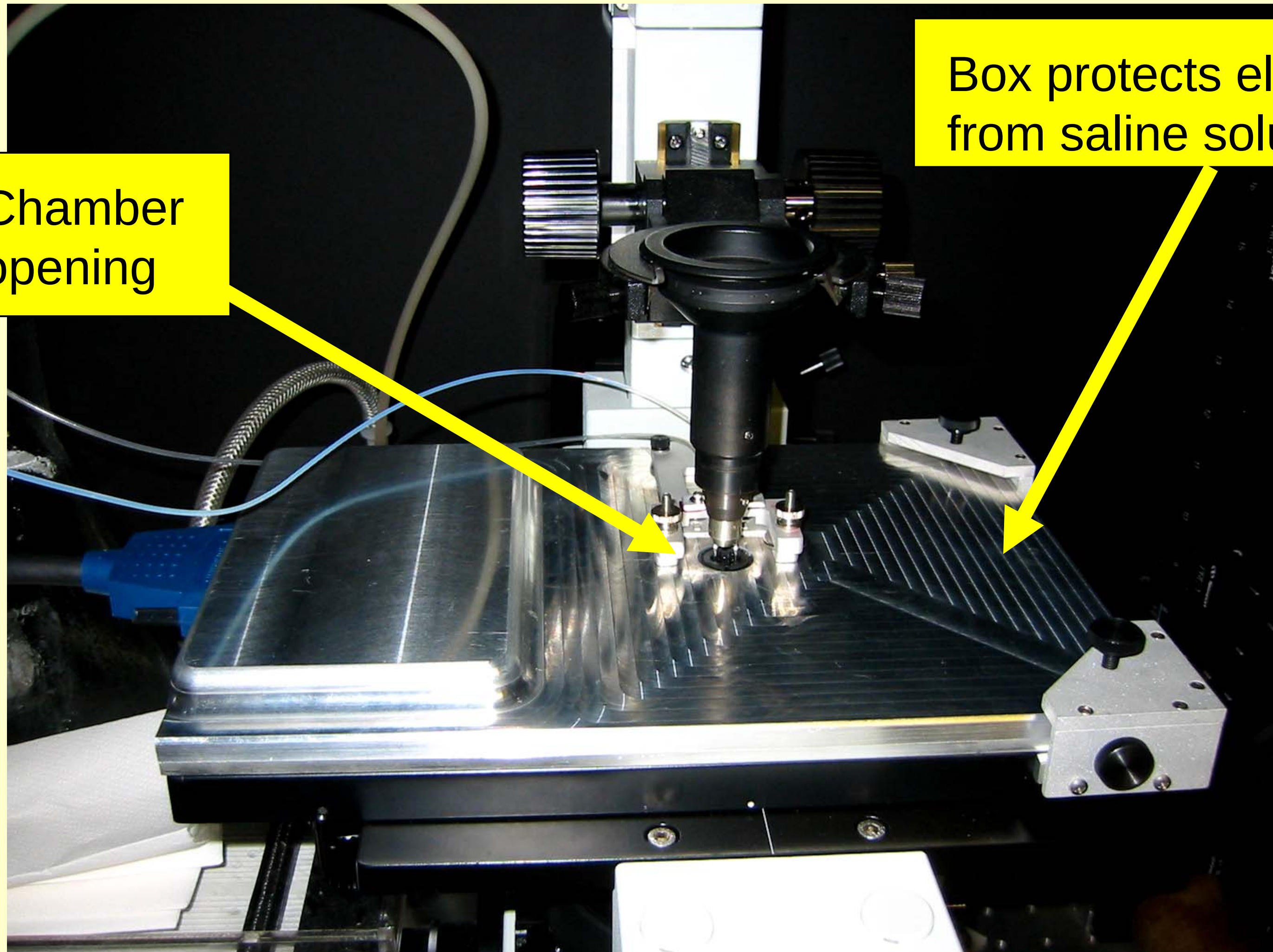
How does this compare with the silicon detector?

"Neuroboard" Block Diagram

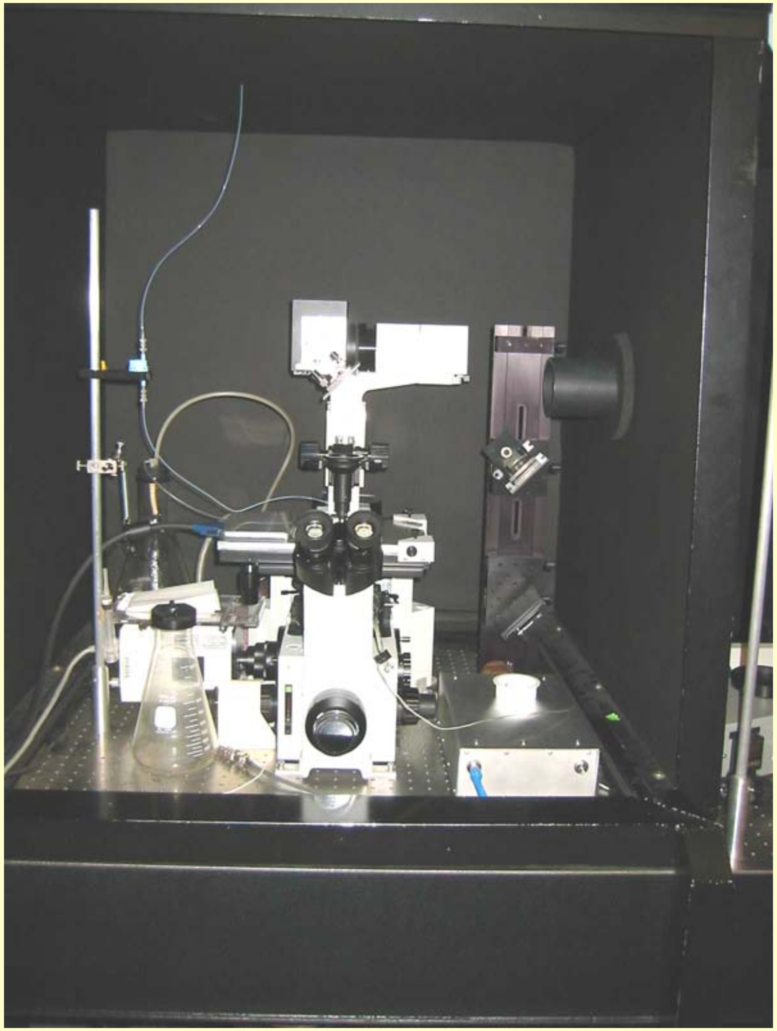


12 bit resolution;
Sampling rate = 20 kHz/channel;

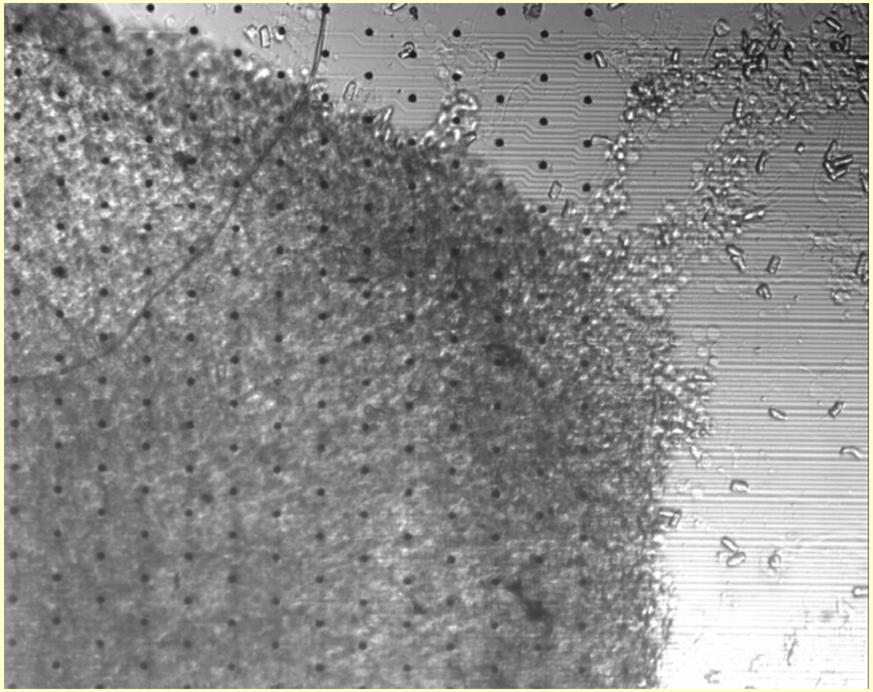
"Neuroboard" in Box on Microscope Stand



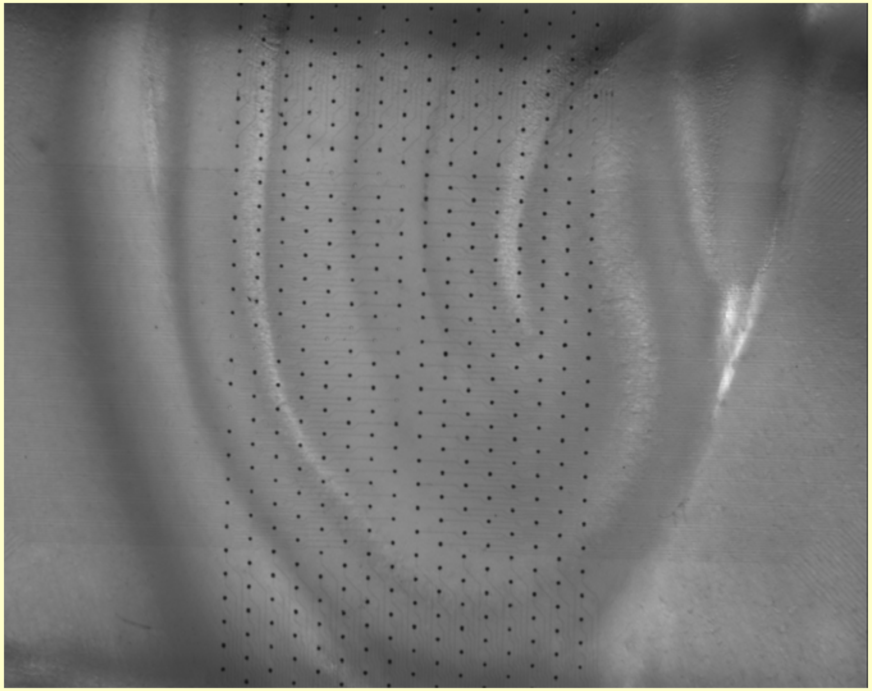
"Neuroboard" with Optical Setup



Some Sample Tissues

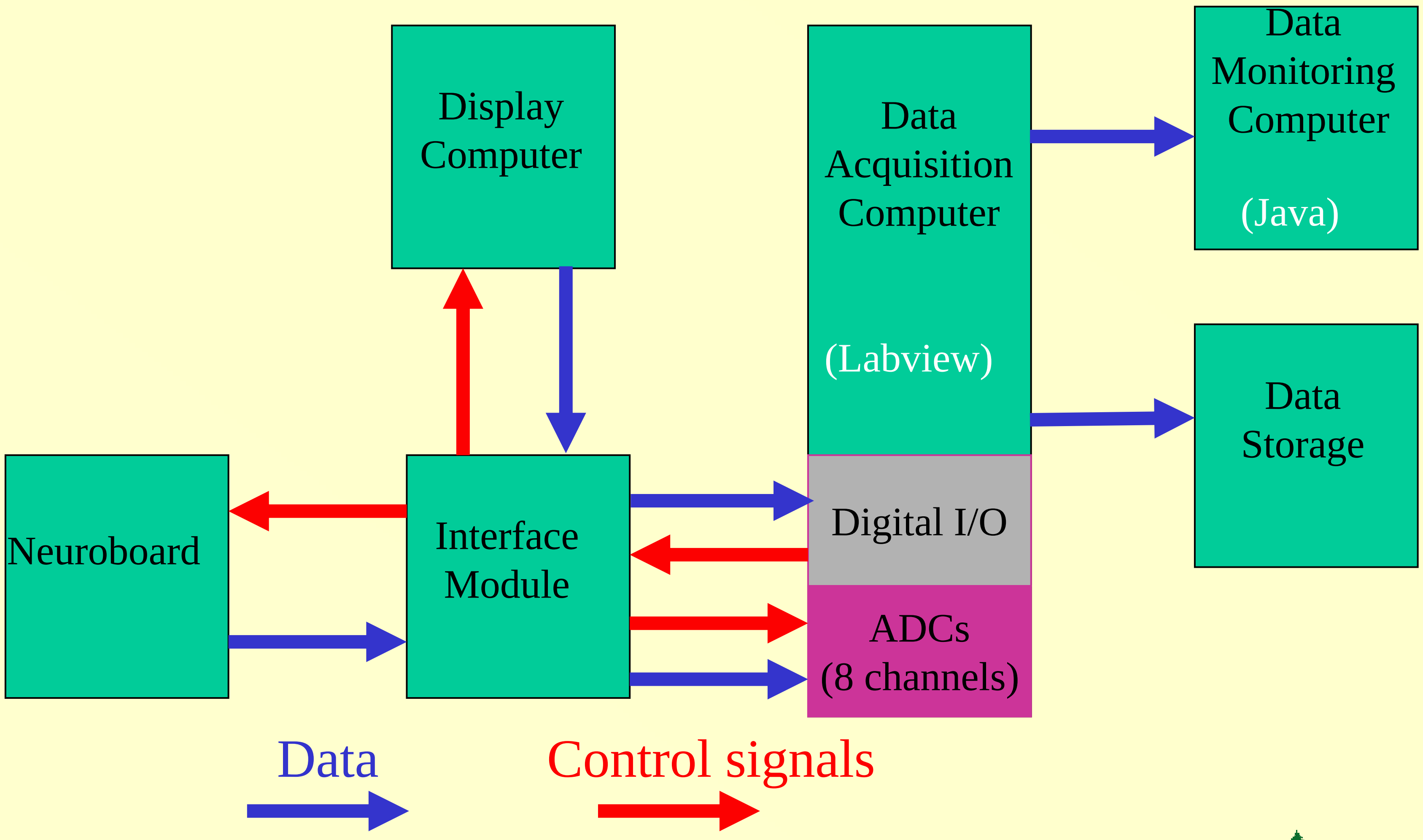


Salamander retina on 512-electrode array



Slice of hippocampal tissue on 512-electrode array

Data Acquisition System



So What Do We Do with All This?

The electrical signals from each electrode are fed to a computer for recording and analysis.

A typical experiment will record 0.3 terabytes in one day.

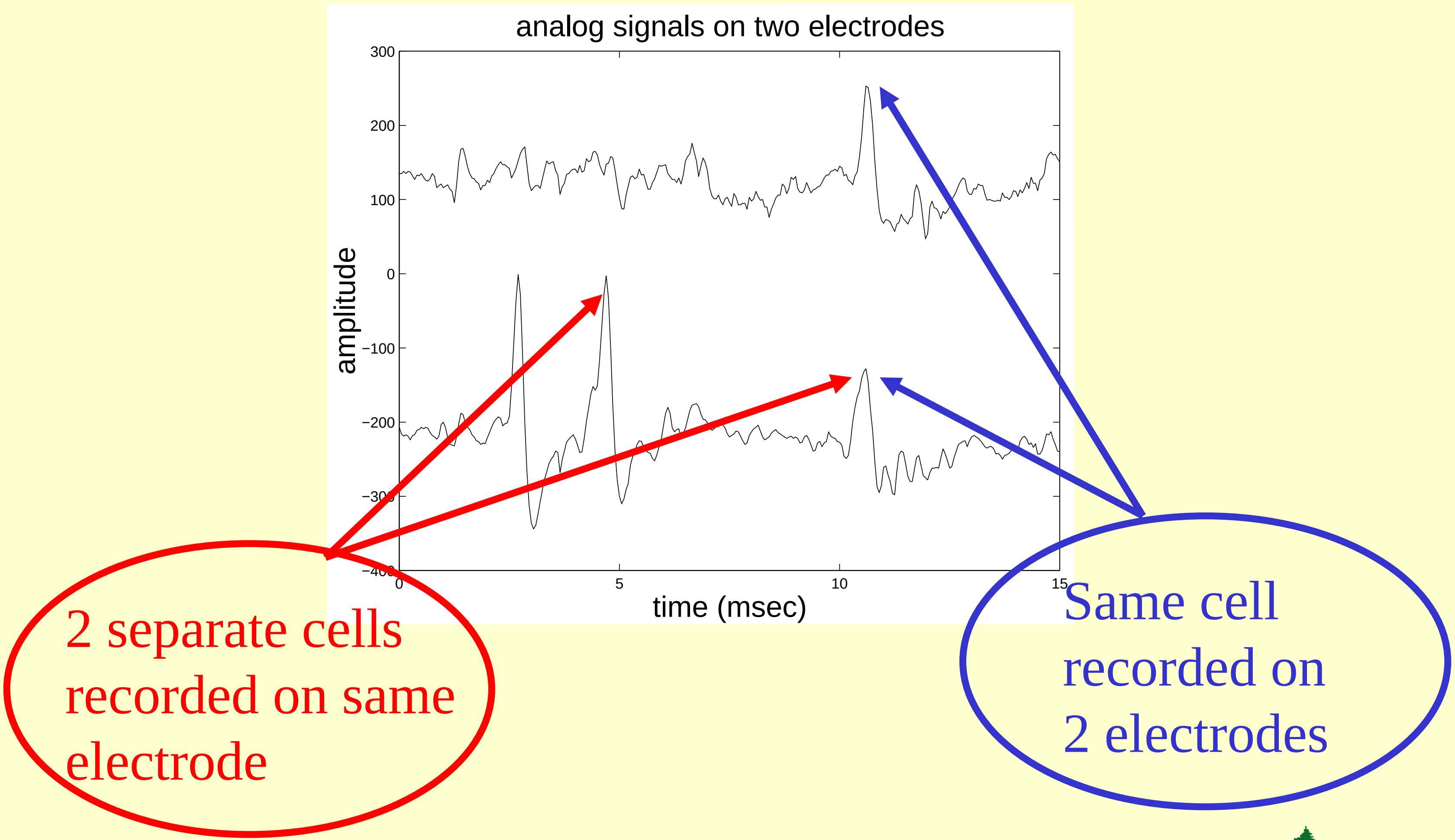
How does this compare to ATLAS?

Signals are associated with specific neurons.

The classification of each neuron is established.

Studies can be performed of neuron response to specific types of stimuli.

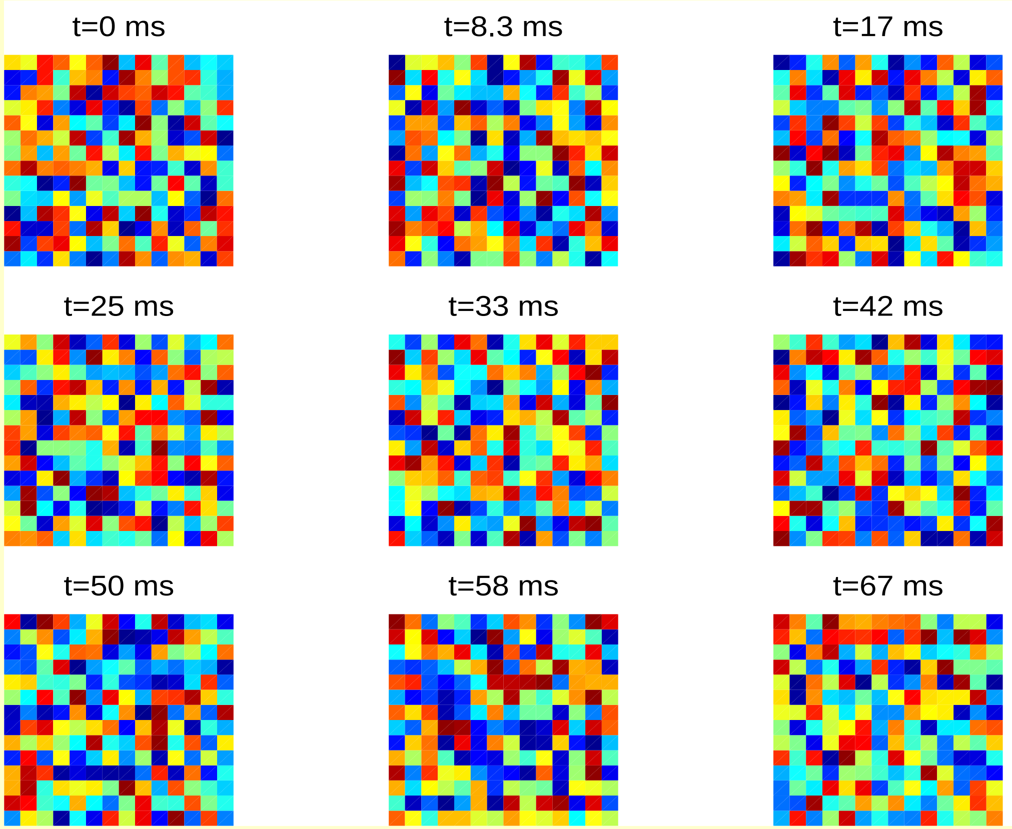
Identify Spikes from Different/Same Neurons



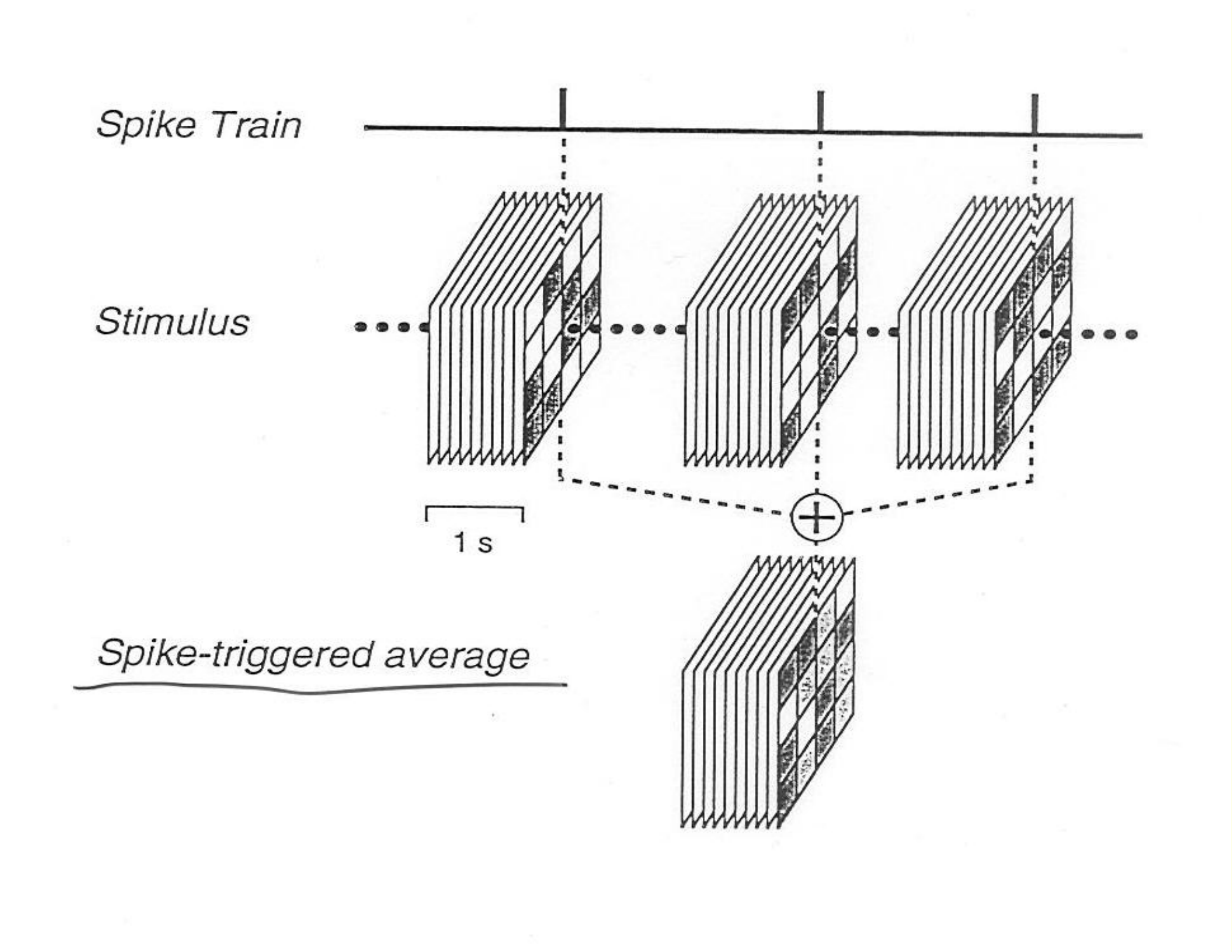
Measure the Response of Identified Neurons

White noise analysis: use time sequence of random checkerboard images.

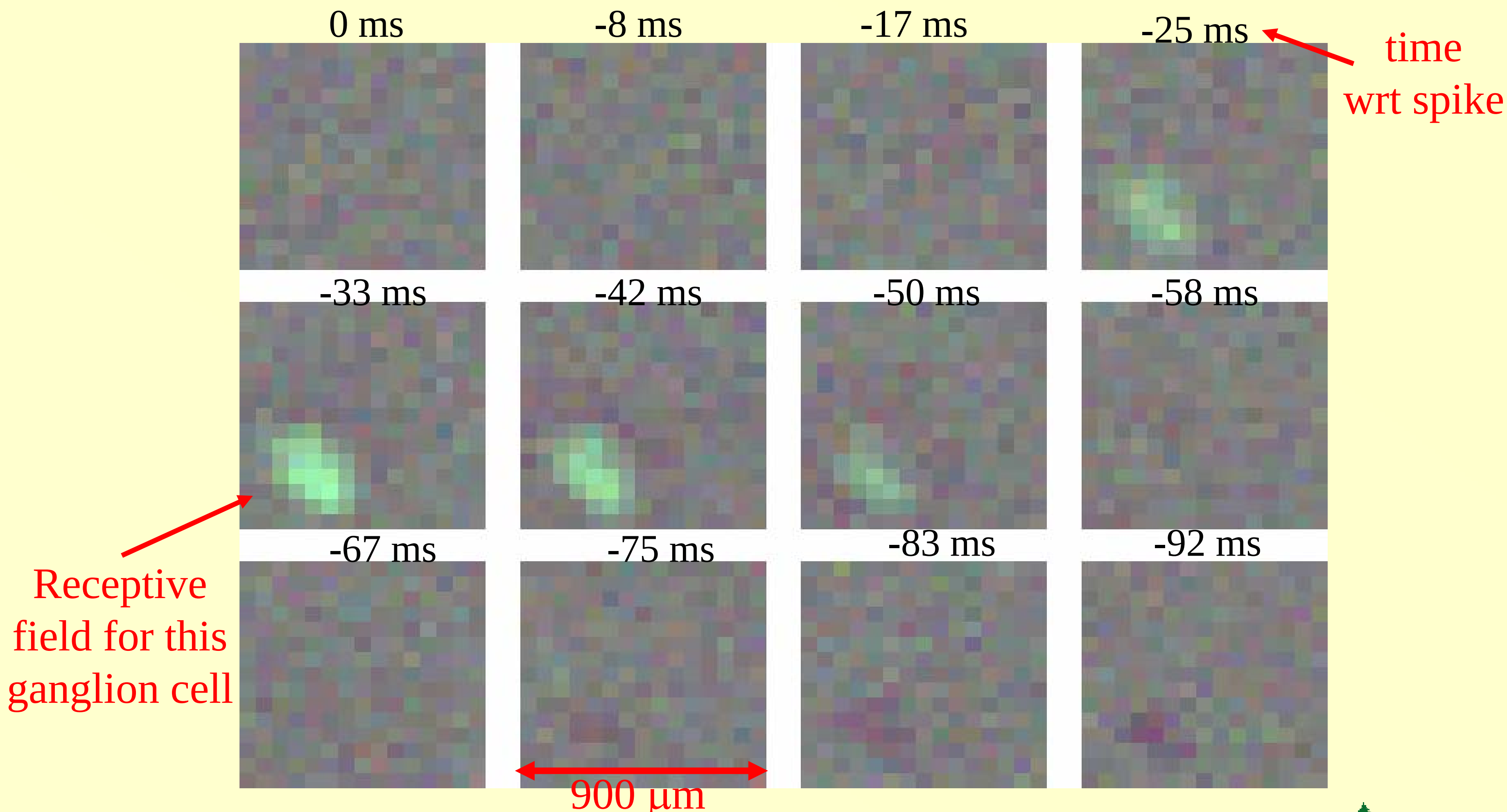
Measure the "spike-triggered average" (STA) response for each neuron.



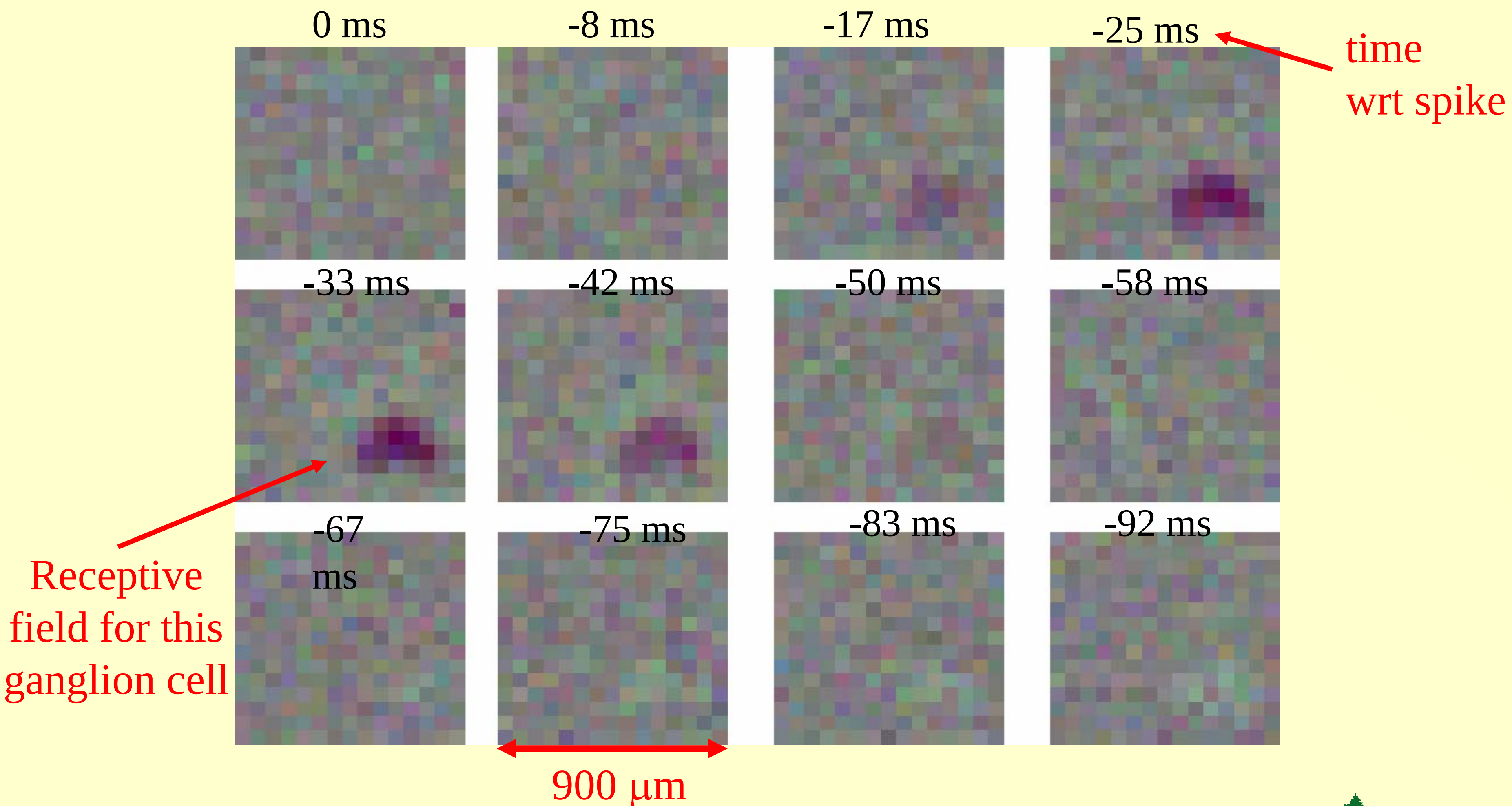
Spike-triggered Average



Monkey Retinal Ganglion "On" Cell

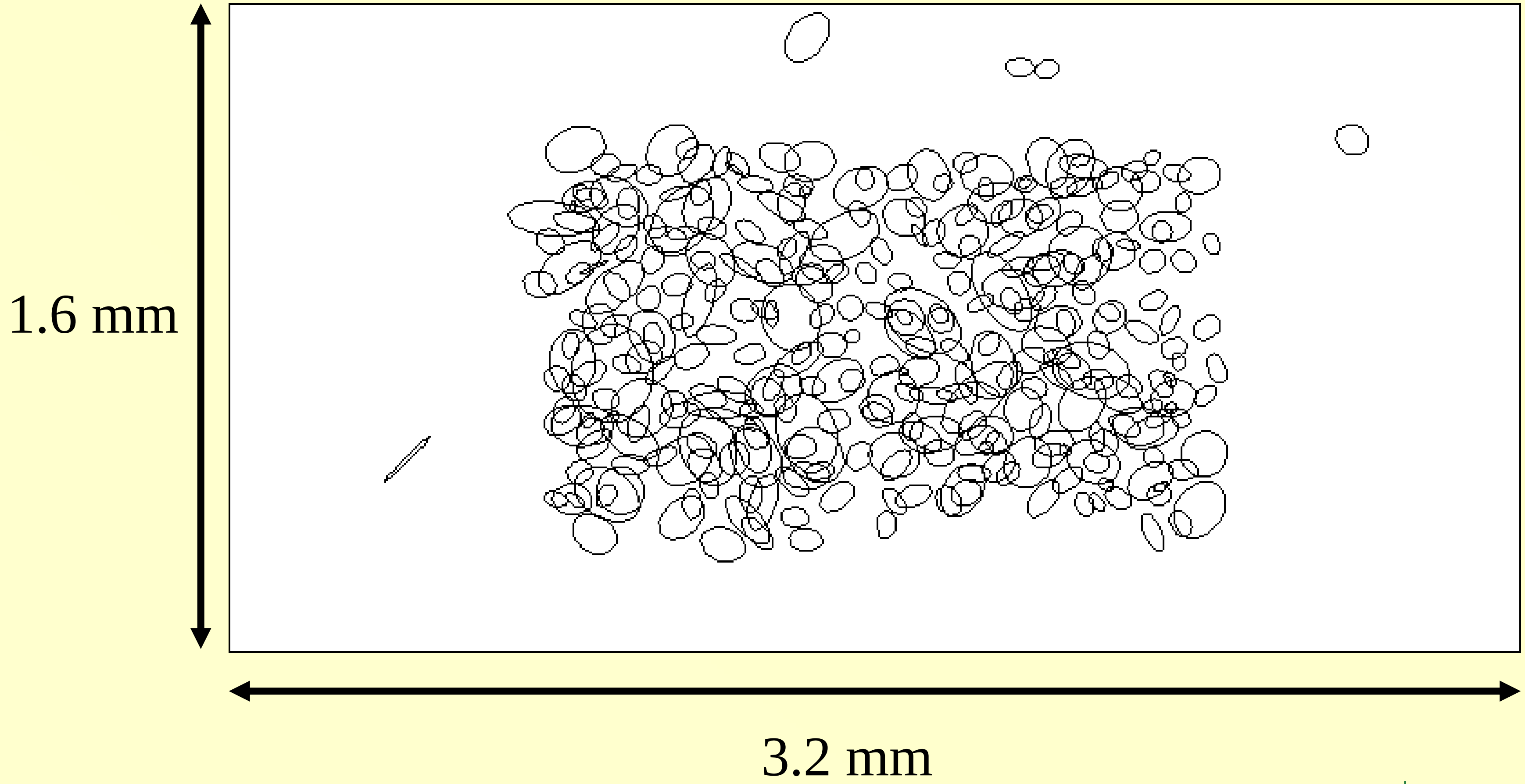


Monkey Retinal Ganglion "Off" Cell

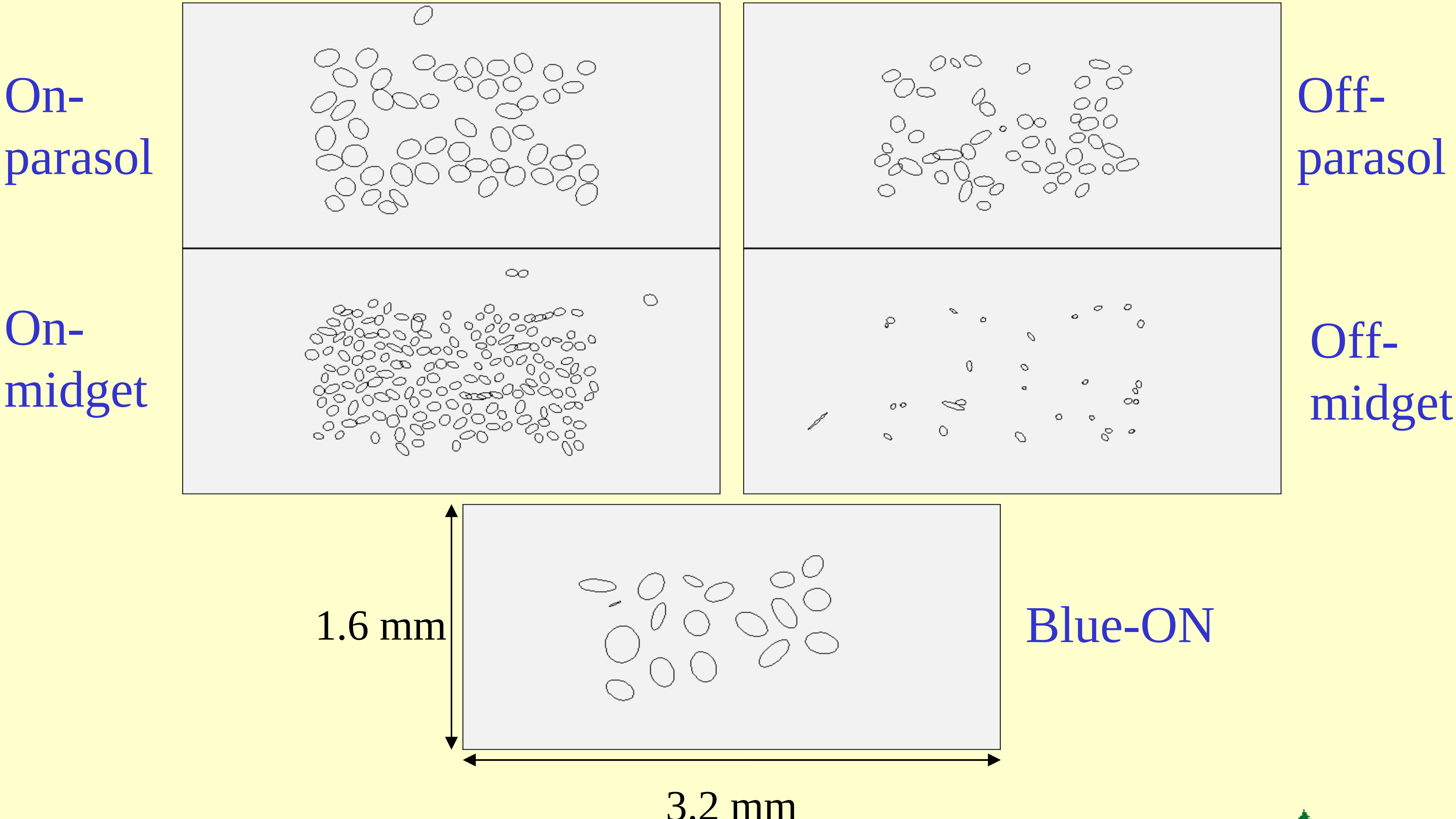


Some First Results with Monkey Retina

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



Separating Out Each Class Yields Overlapping Mosaics



Deciphering the Encoded Message

It is clear that the retina does not act like a simple digital camera, sending raw data to the brain about which photoreceptors have detected light and which have not.

The ganglion cells fire in response to processed information with different classes of ganglion cells processing data from overlapping receptive fields.

Could these overlapping mosaics be studied with single electrodes?

To understand the information sent over the optic nerve to the brain, the encoding of each class of ganglion cells must be understood.

What Else Can We Study in the Retina?

Functional architecture/mosaic properties of monkey and guinea pig retina (with E. J. Chichilnisky, Salk Institute)

- cell classes
- color response properties
- develop higher density arrays and large area arrays

Studies for Retinal Prosthesis (with E. J. Chichilnisky, Salk Institute)

- multielectrode electrical stimulation combined with multielectrode recording

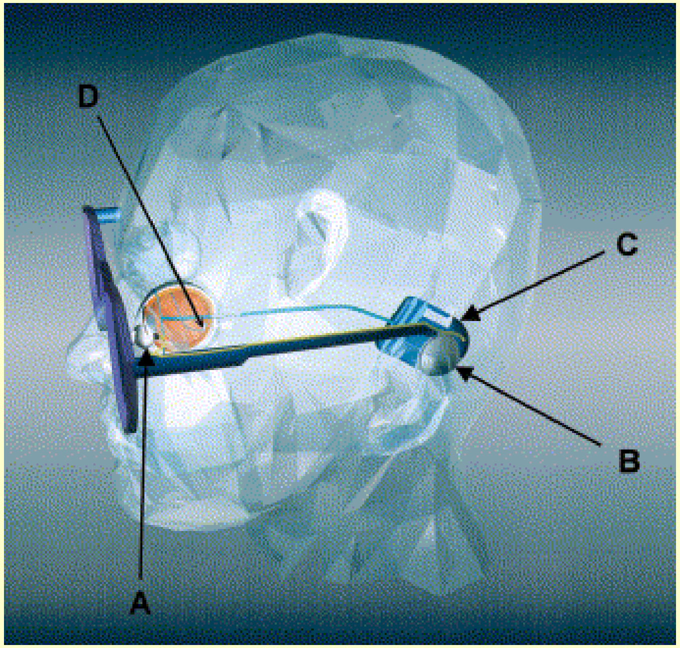
Retinal Development (with David Feldheim, UCSC and Marla Feller, UC San Diego)

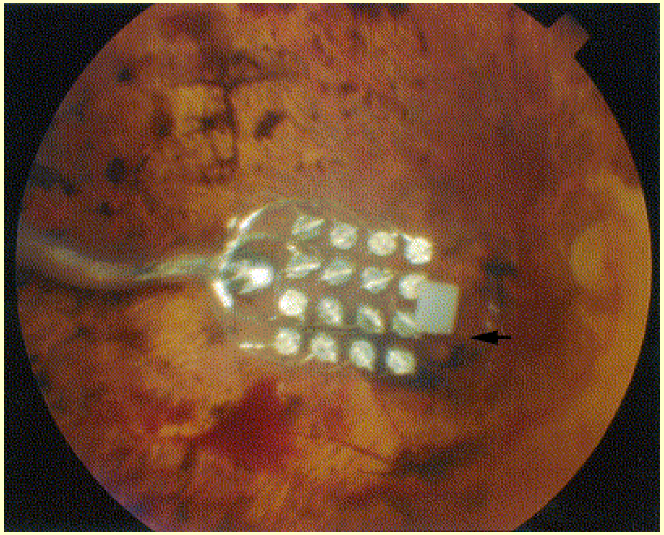
- transgenic mouse retina

Correlate retinal anatomy with physiology (with E. J. Chichilnisky, Salk Institute and P. Sterling, U. Penn.)

- match anatomical images with electrophysiological images and spatial receptive fields

Retinal Prosthesis in Blind Subjects





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

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

Key problems yet to solve:
- understand the encoding
- perfect electrical stimulation
- improve electrodes

What Are Other Areas We Can Study?

The Neural Systems Project: in-vitro studies

Cortical network dynamics in acute and cultured slices of brain tissue (with John Beggs, U. Indiana)

- multielectrode electrical stimulation combined with multielectrode recording
- develop bed-of-nails array

Neural Avalanches

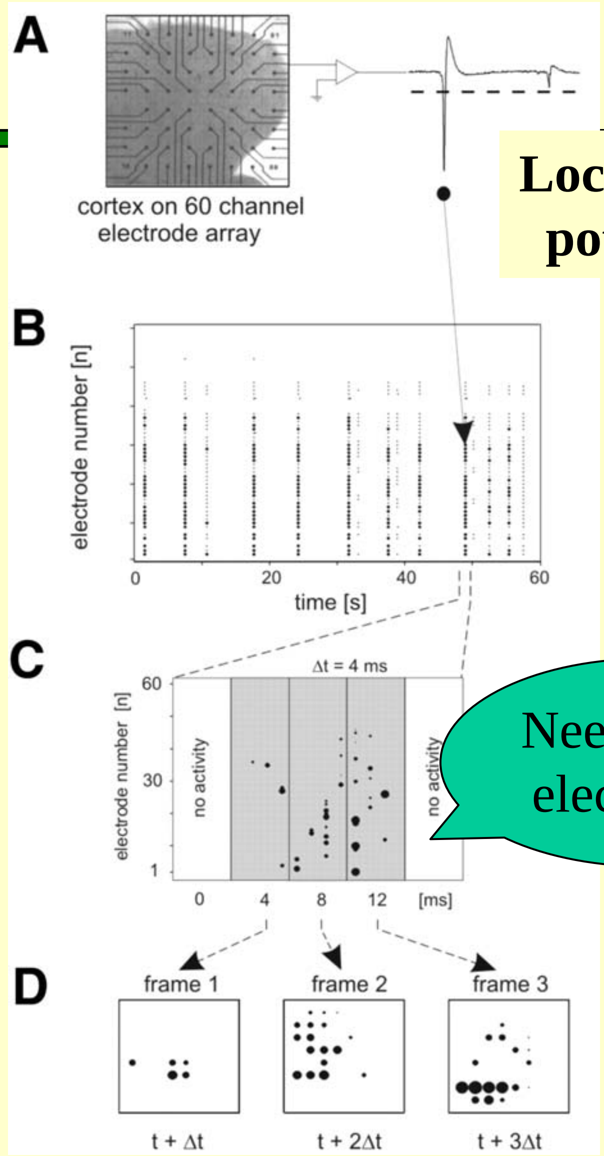
Previous studies using commercial 60-electrode array with 200 μm electrode spacing

John Beggs and Dietmar Plenz
J. Neuroscience 23 (2003) 11167;
J. Neuroscience 24 (2004) 5216.

Could they have something to do with memory formation or cortical connectivity development?

New studies with Beggs and SCIPP at UCSC will use 512-electrode array.

- More statistics
- Possibility for larger correlations



Local field potential

Need multi-electrodes!

Another Extension of the Technology

The Neural Systems Project: in-vivo studies

Study of brain activity of awake, naturally-behaving animals (with Markus Meister, Harvard and Thanos Siapas, Cal Tech)

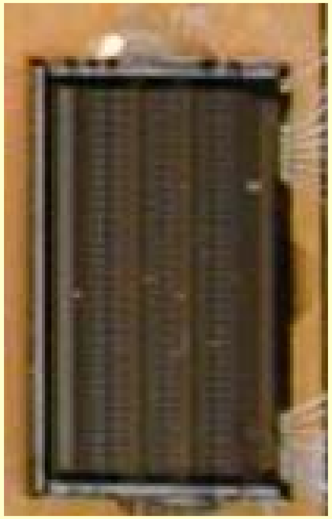
- develop Neurochip system for in-vivo recording and stimulation with multiple tetrodes (including a wireless telemetry system that can be carried by a rat)

In-vivo Wireless Recording System

28 tetrodes
with microdrives

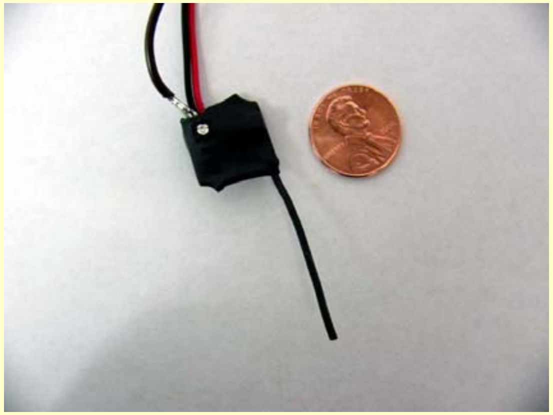
(Neuralynx/Siapas)

Neurochip



(Krakow/SCIPP)

Spy Transmitter



(Meister)