The Abdus Salam International Centre for Theoretical Physics

2415-9

Winter School on Quantitative Systems Biology

26 November - 7 December, 2011

Topics in Theoretical Neuroscience

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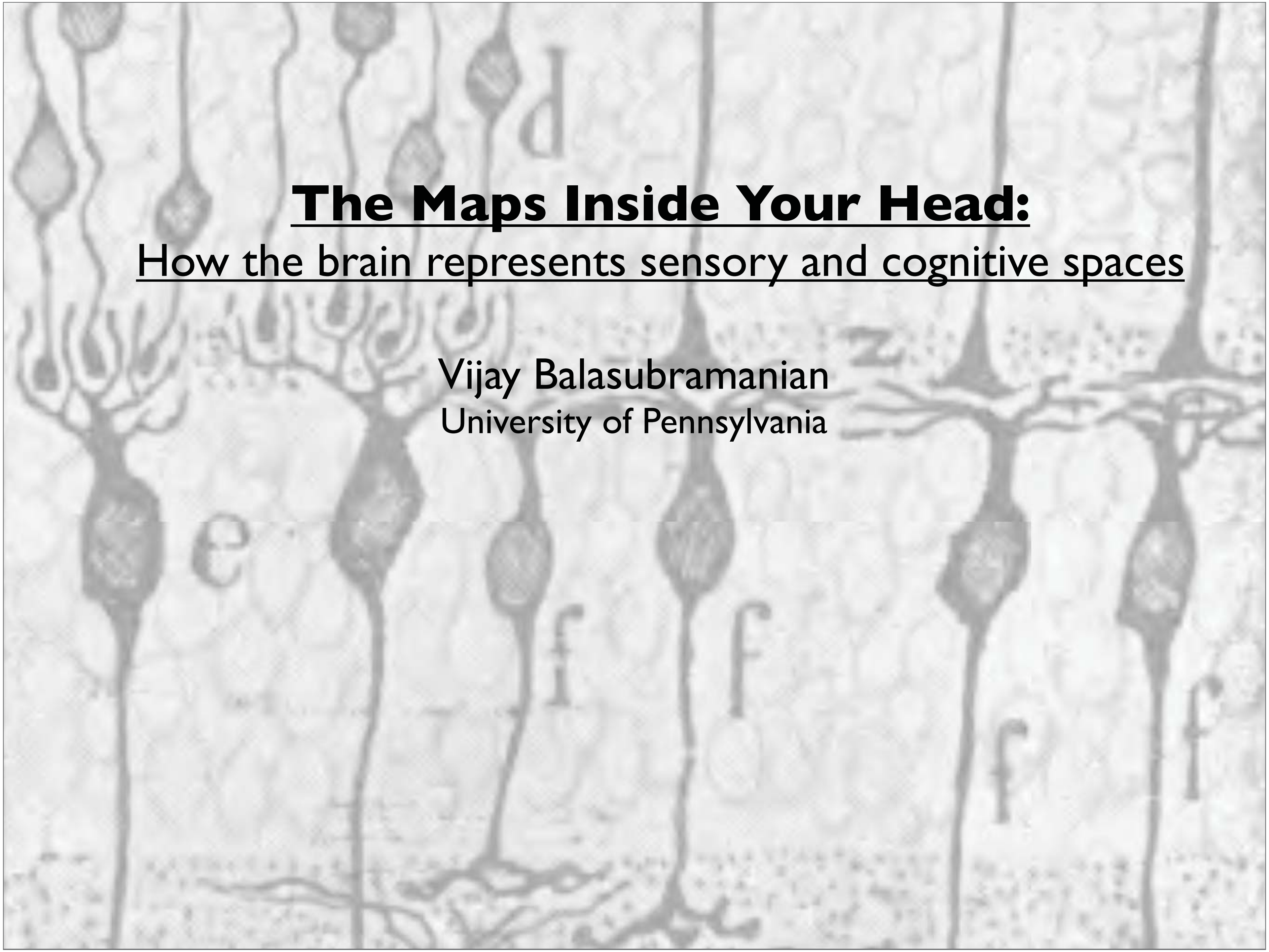


The Maps Inside Your Head:

How the brain represents sensory and cognitive spaces

Vijay Balasubramanian
University of Pennsylvania

Different kinds of Theory

- Modeling / description of data (summarize the data conveniently, discover empirical regularities; e.g. fit the responsiveness of a circuit as a function of enzyme concentration)
- Mechanistic models (reduce the phenomena to the interaction of elementary constituents -- e.g. cellular function from molecular dynamics
- Effective Models (describe dynamics in terms of "effective variables" -- i.e. collective variables that summarize microscopic information)
- Normative models ("why" things are the way they are, "principles" of organization", a conceptual frame for understanding)

Towards Physical "Laws" for Living Systems?

Obstacles to formulating principles of organization ("laws") for living systems

- Enormous range of scales (DNA to ecosystems) that can feedback
- Enormous complexity at each scale (e.g. diversity of structures from molecules to animal forms)

Why does evolution drive living systems towards complexity?

HYPOTHESIS: Because specialized systems use resources more efficiently, evolution drives the appearance of diverse specialized architectures that cooperate to achieve larger functions.

The brain is a good place to examine this idea. (We will use all four kinds of theory)

Big questions about the brain we want to answer?

- What is consciousness?
- How do we remember and learn things?
- How do you recognize your mother?
- How does personality arise?
- What are complex emotions like love?
- How do we make decisions?

- Can we wake people from coma?
- Can we make people smarter?
- Can we cure blindness & deafness
- Can we cure schizophrenia?
- Can we cure autism?
- Can we arrest mental decline in the old

Etc.

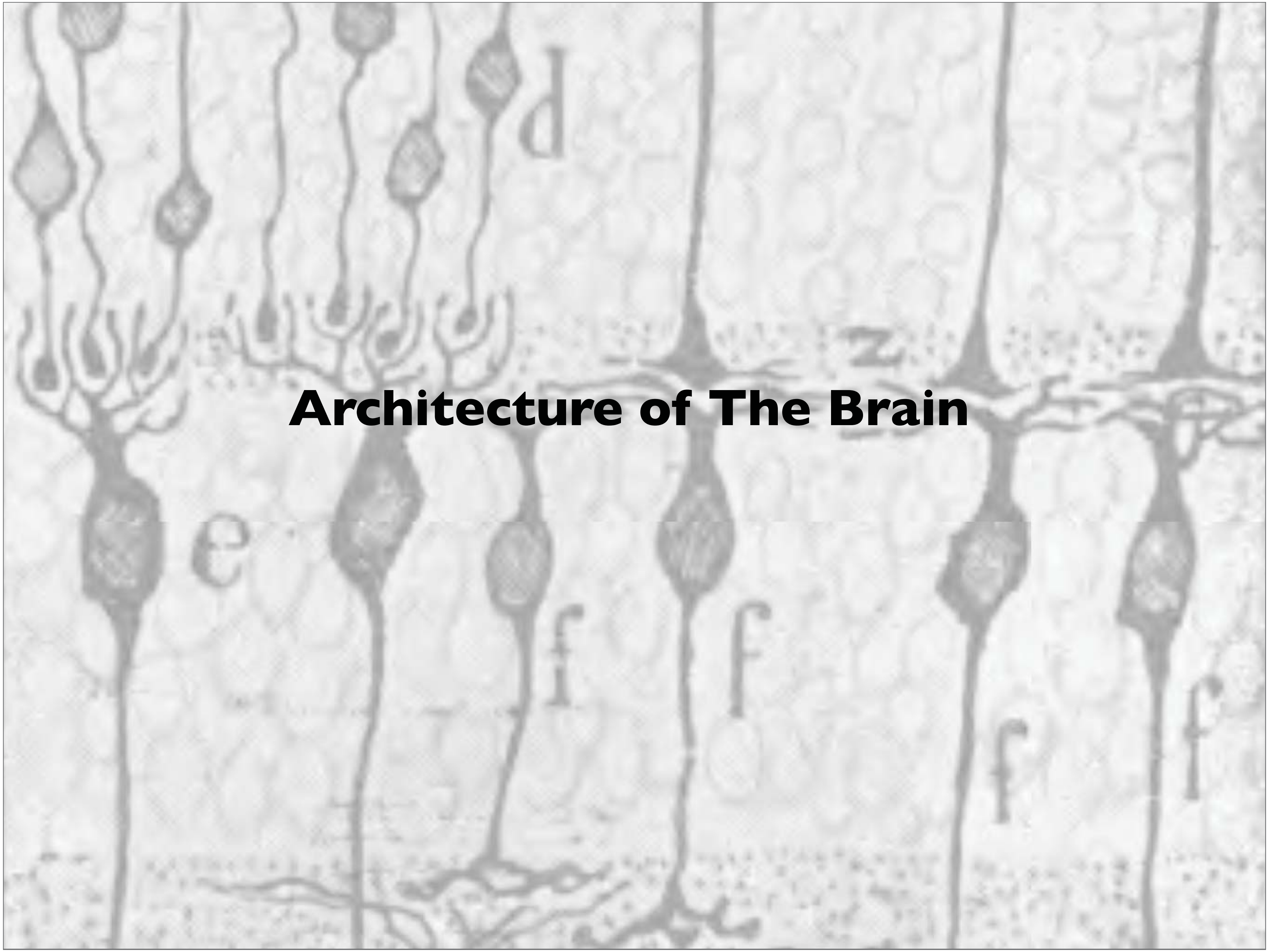
OUTLINE

• Introduction to the brain -- neurons, networks, specialization and functional maps

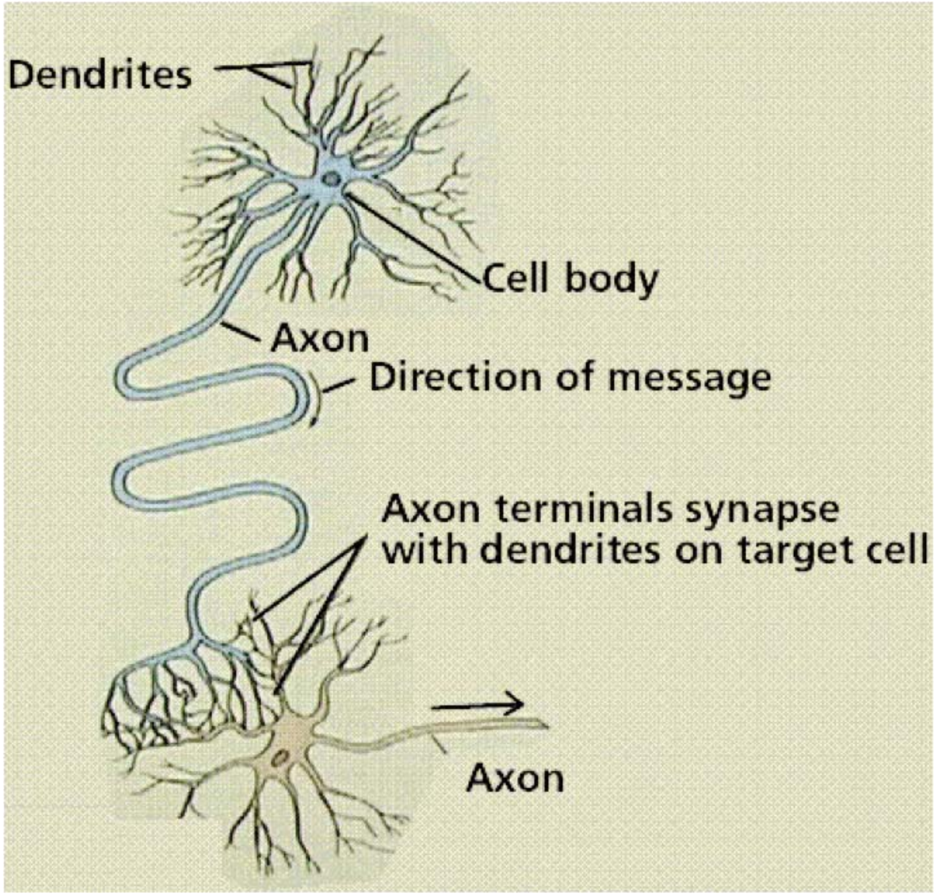
• Maps in the brain:
  Sensory systems: The early visual system
  Cognitive systems: The "sense of place"

• Interactions in neural populations:
  Sensory systems: The sense of smell
  Cognitive systems: Goal-directed navigation

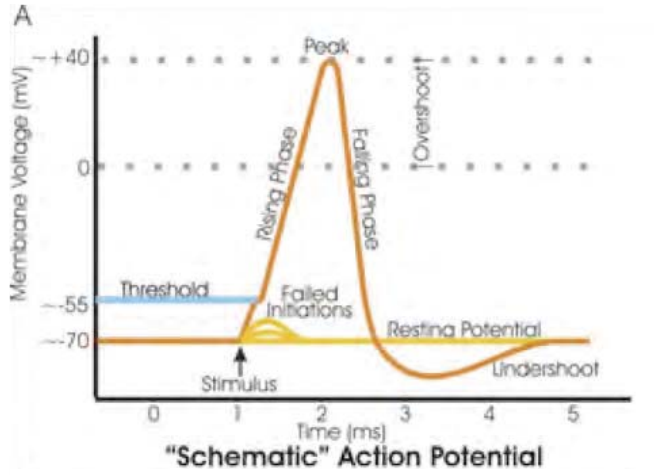
Architecture of The Brain

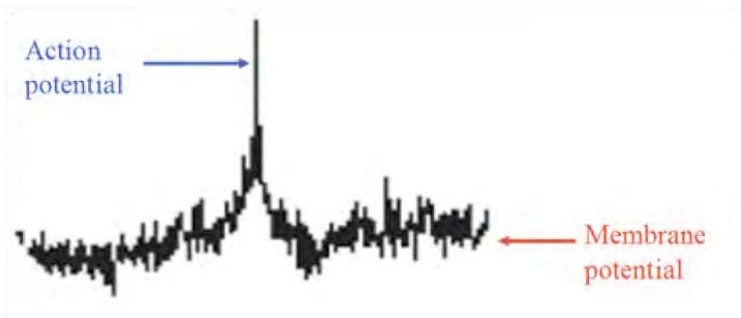


Neurons & Neural Communication



From Purves et al., *Life: The Science of Biology*





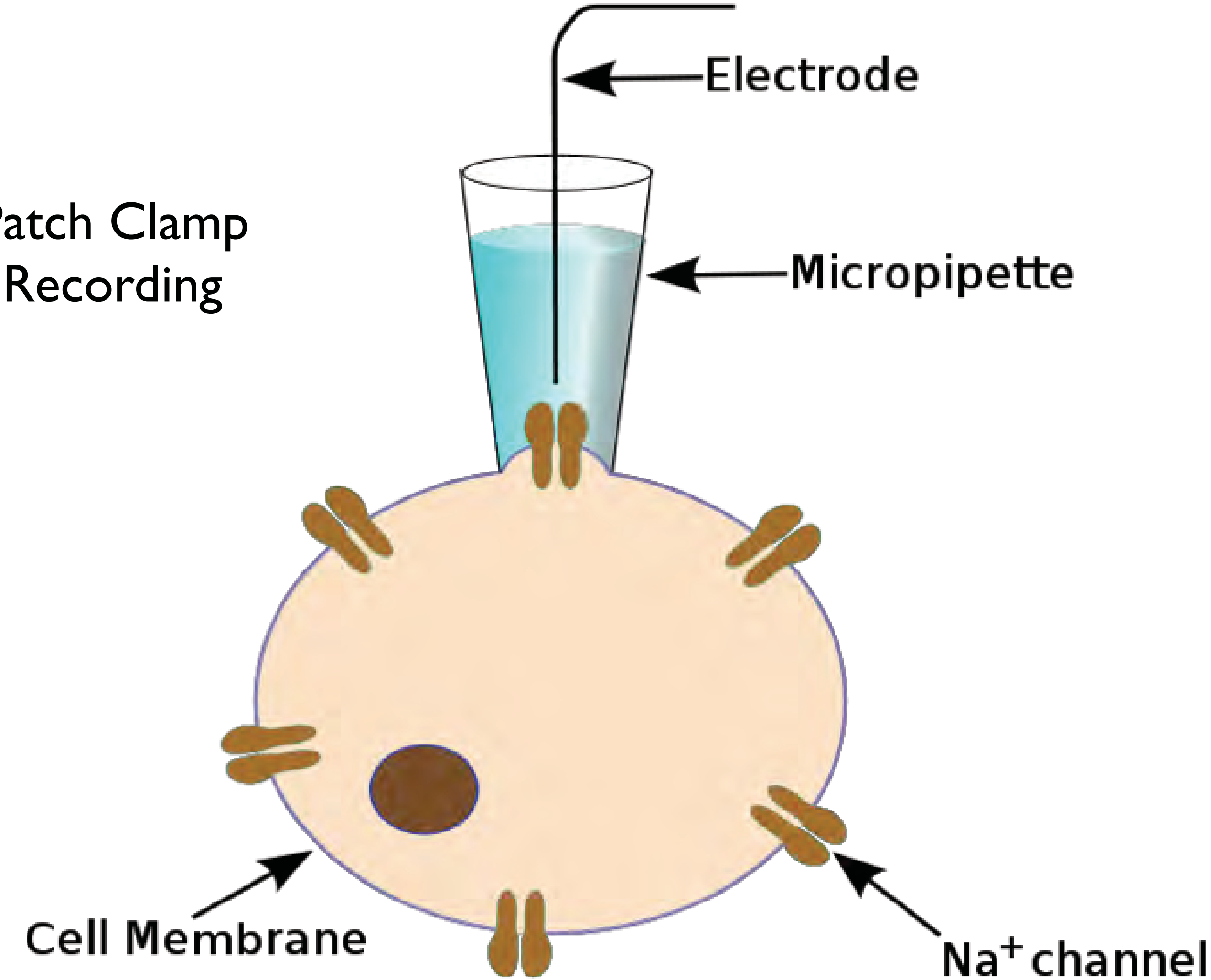
From Wikipedia article on Action Potentials

Models of response:

Hodgkin-Huxley vs effective models (LN models, reverse correlation)

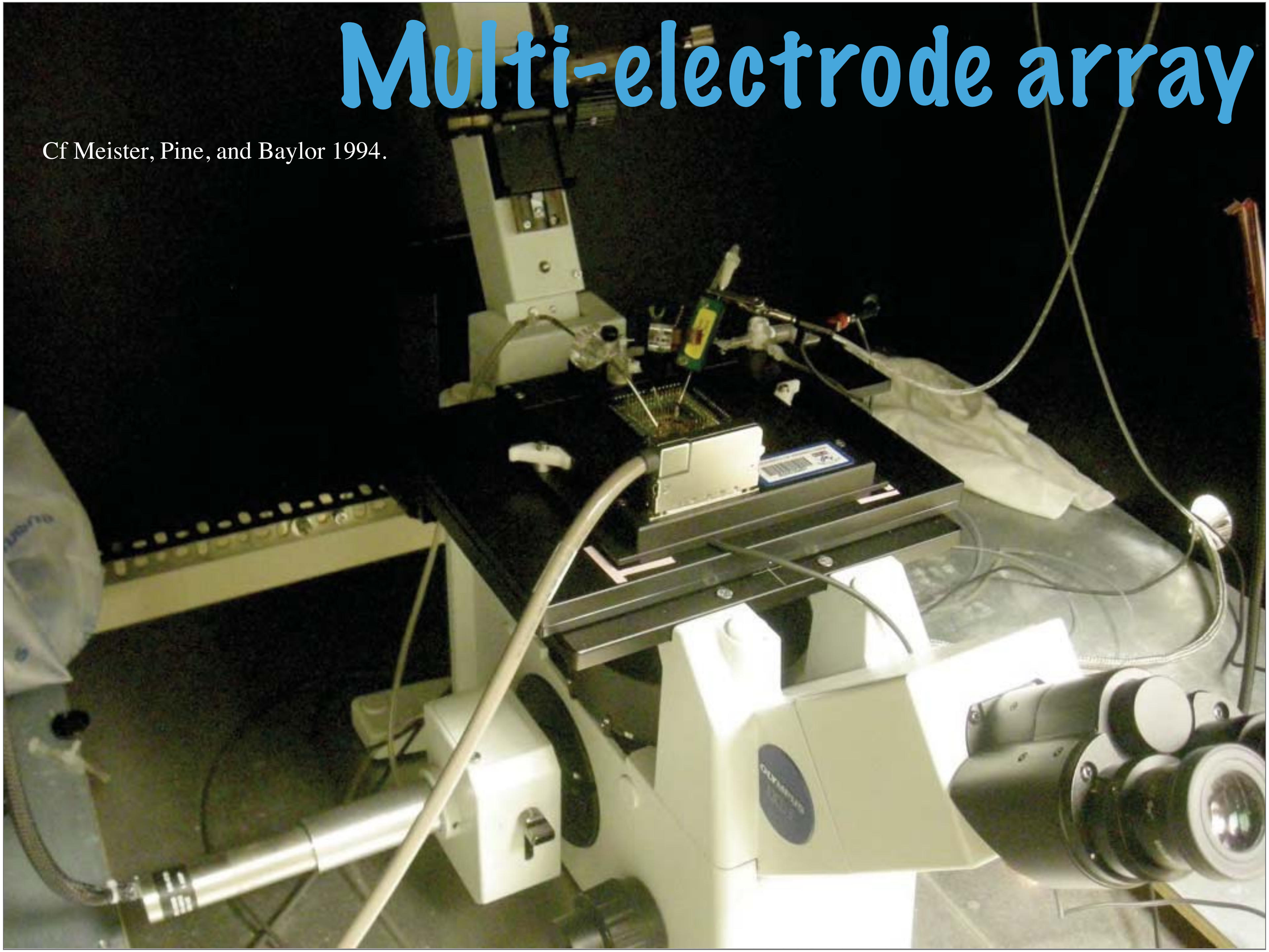
Interrogating the electrical activity of neurons

Patch Clamp
Recording



Multi-electrode array

Cf Meister, Pine, and Baylor 1994.



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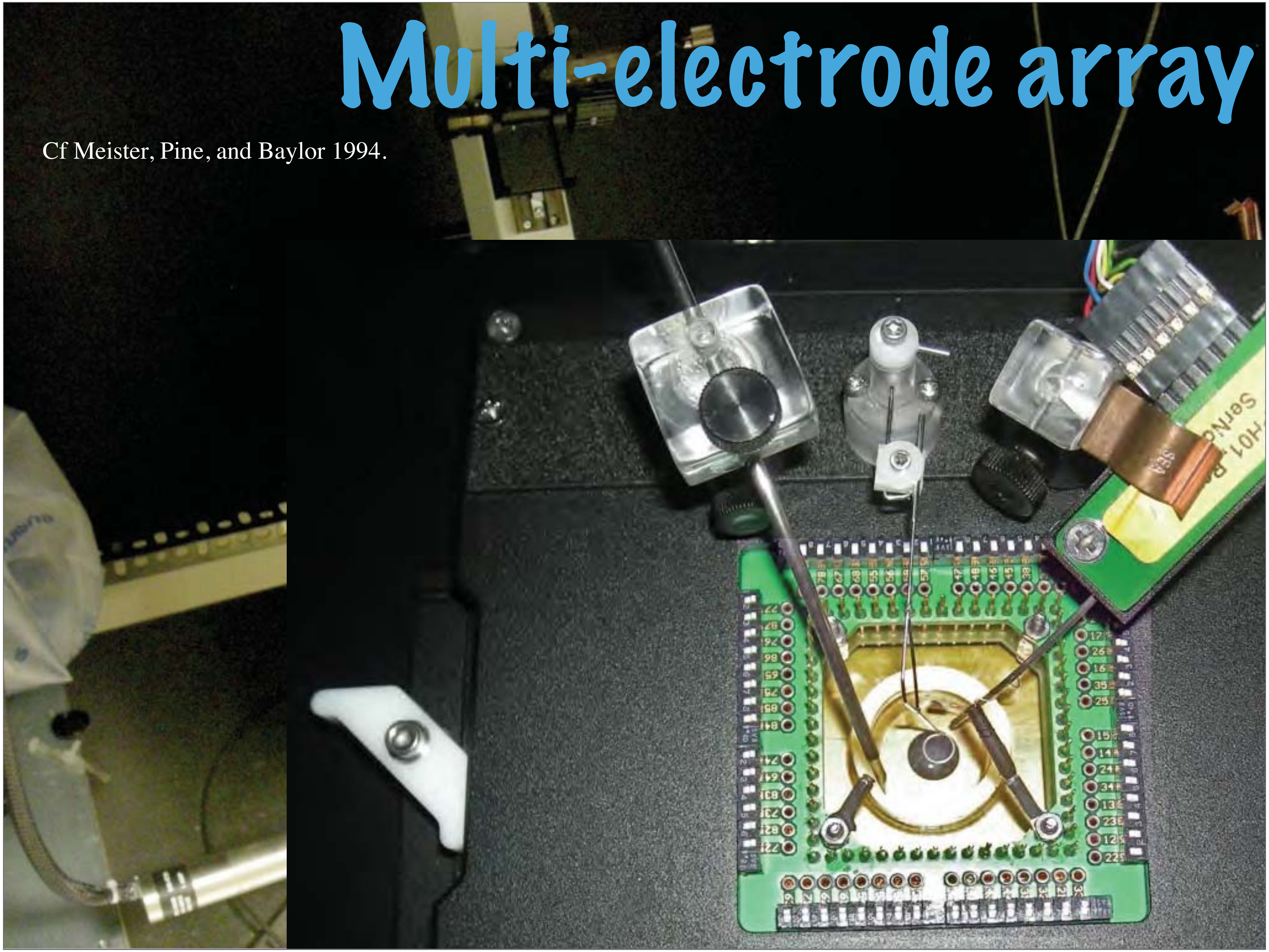
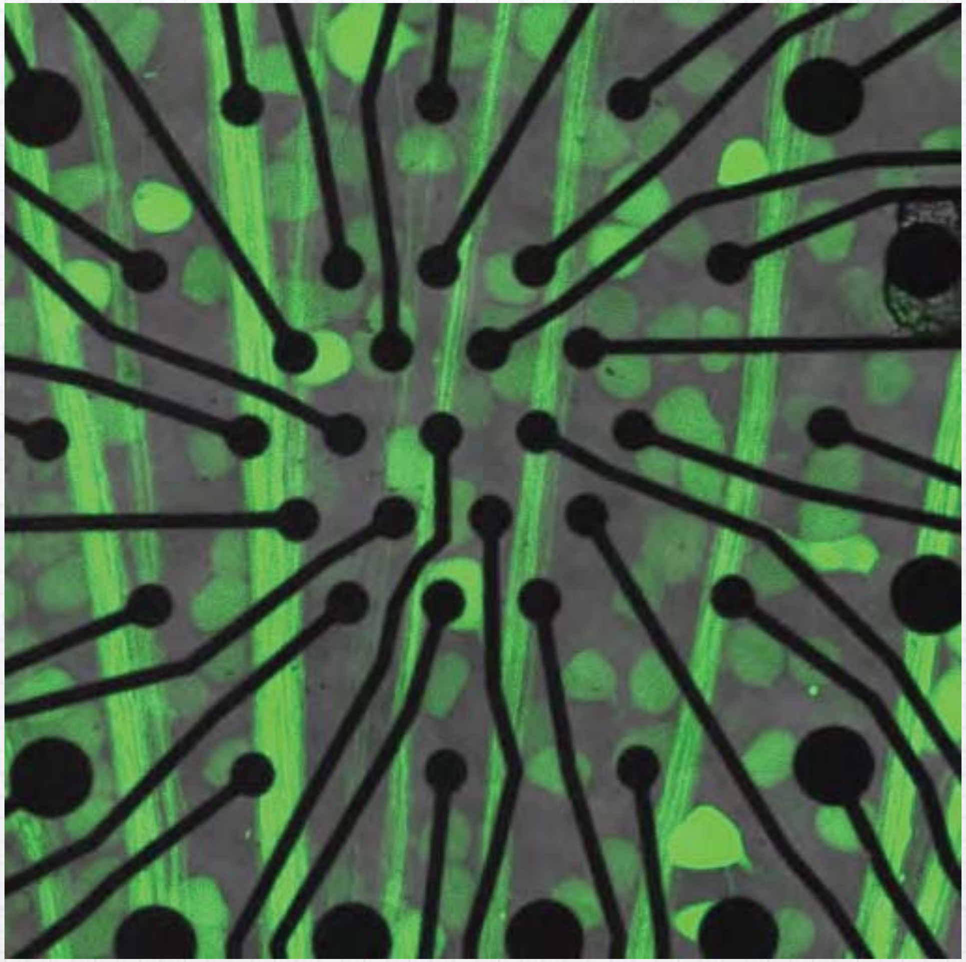


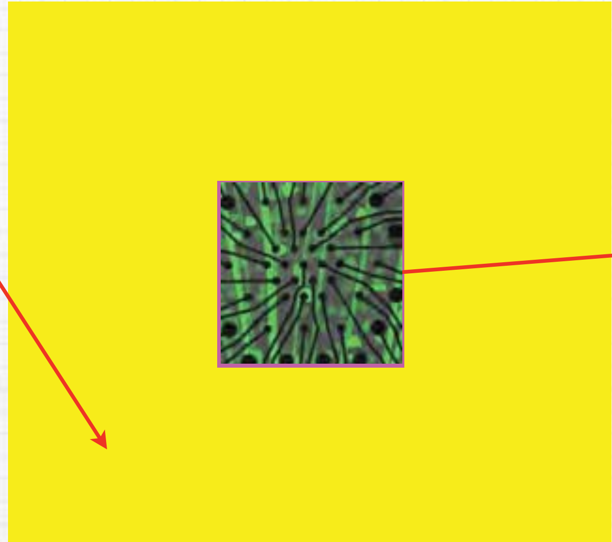
What's in the dish



Michael Berry, Princeton

Typical stimulus setup

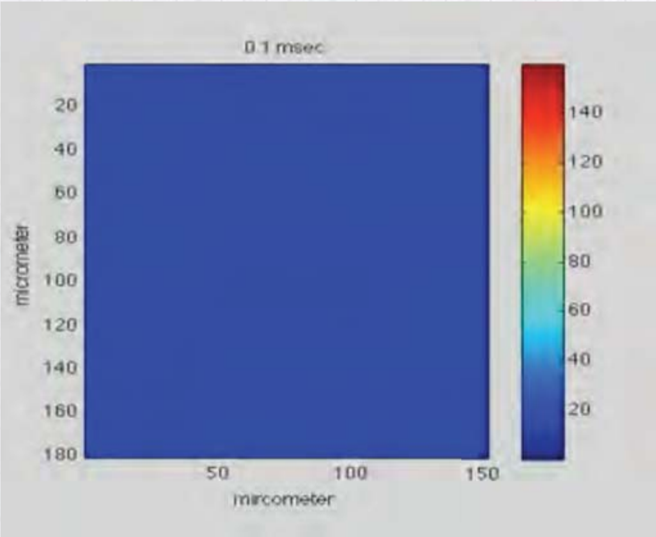
Field of illumination = e.g. 30x30 grid of stimulus checks, each 50μm on an edge.



Recording region = e.g., 5x6 array of electrodes spaced 30μm (similar to RGC spacing).

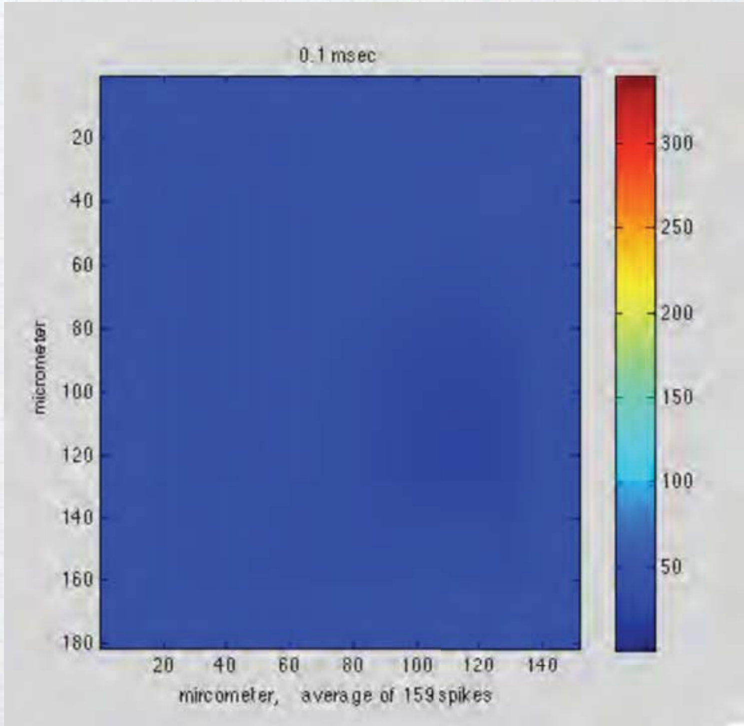
- Data taken at ~10kHz.
- Noise ~30μV. Big spikes ~400μV. Others go all the way down to the noise floor.
- Prior to analysis, filter out slow baseline drift. Also apply a spatial decorrelating filter, deduced from statistics of noise, to sharpen the “image” spatially.]

Simple events



67 ms of data,
viewed as a movie.
[data have been smoothed]

Some spikes move across the array:



The spike-sorting problem: Given raw data like these, convert to a list of discrete events (which cells fired at what times).

Not-so-simple events

Many complex events -- multiple overlapping spikes in many locations. And of course these may be the **most interesting ones!**

Mis-identifcation of overlapping spikes will lead to artificial correlations, errors in receptive field measurement etc.

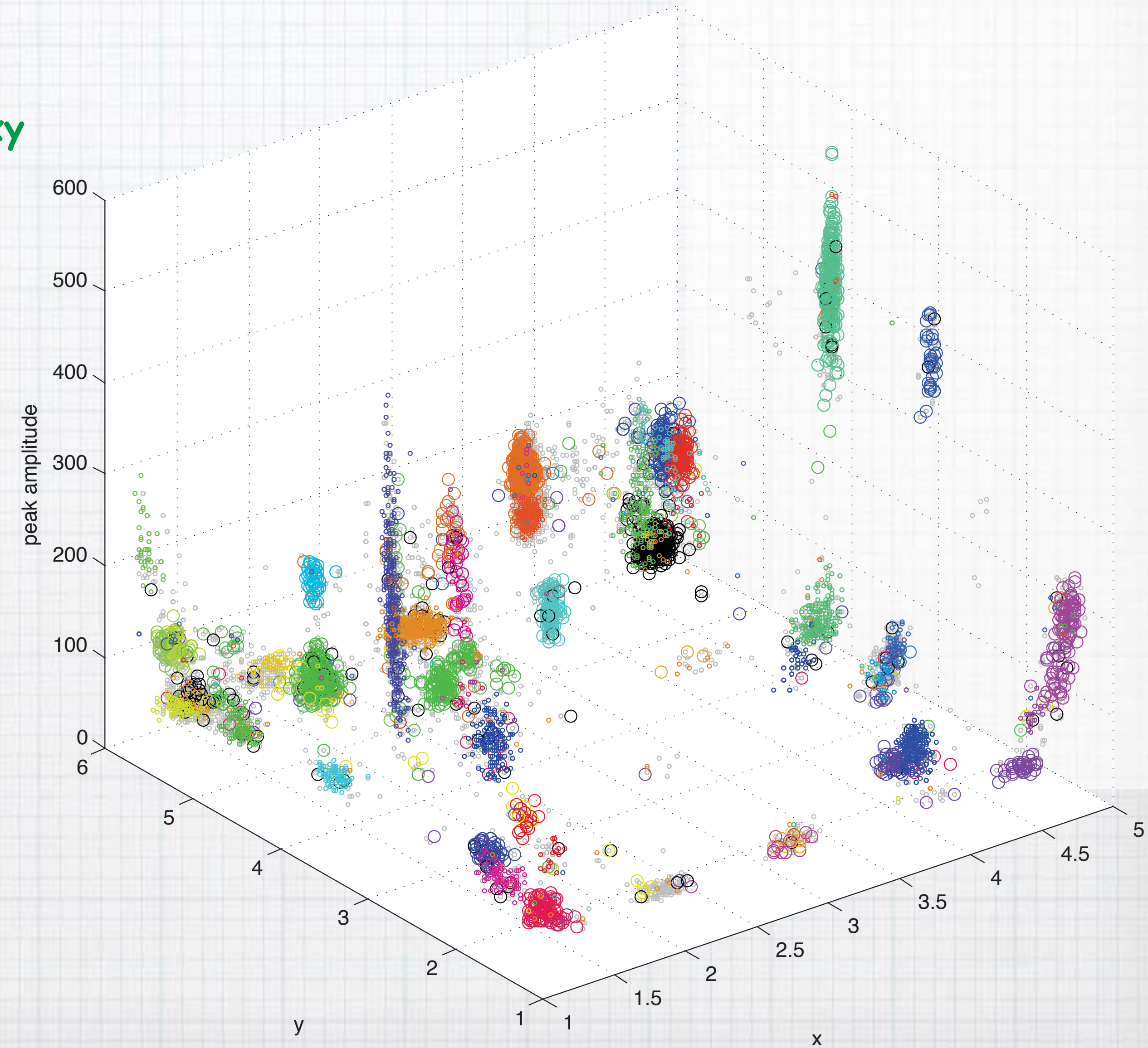
When we graduate to very large arrays, **nearly all** events will involve overlaps in space & time!!

JS Prentice, J Homann, KD Simmons, G Tkacik, V Balasubramanian, P Nelson, PLoS ONE 6(7): e19884 (2011).

Georaphical clustering

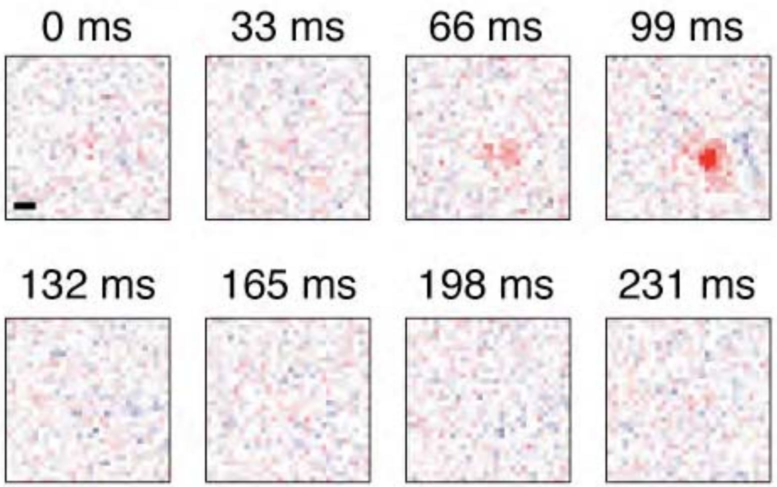
Feature 1: **weighted average xy location** for each event.

Feature 2: **amplitude on the highest-amplitude channel**



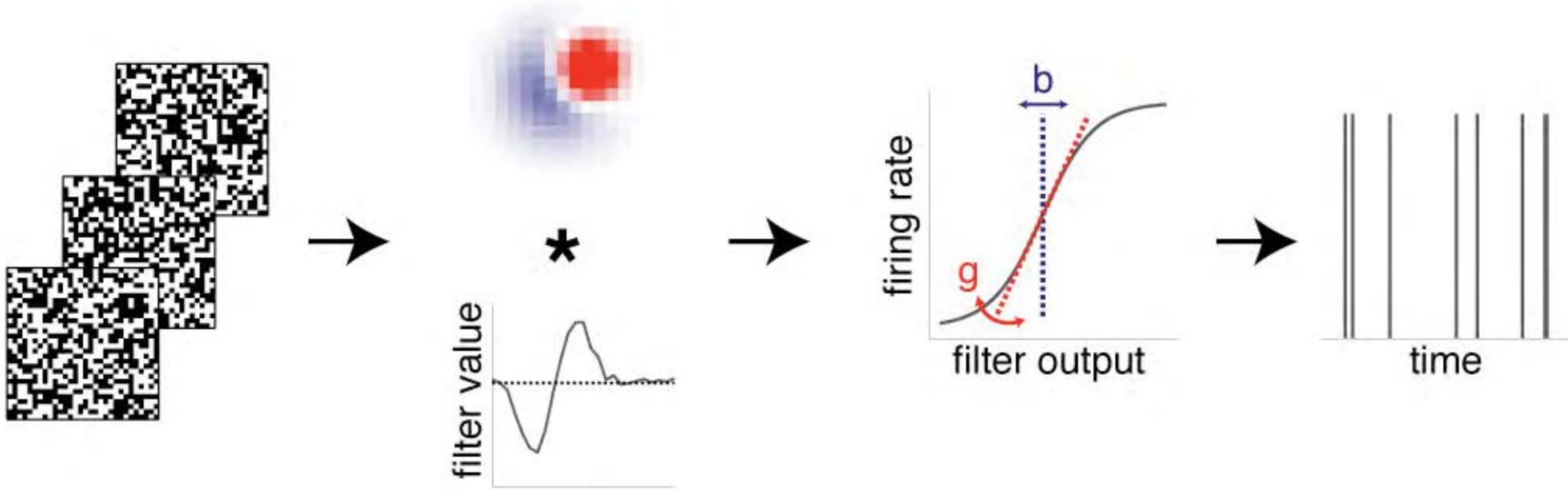
Cells have significantly different amplitude variability. We'll need to give each cell its own **amplitude profile** (i.e. prior probabilities of amplitudes) and then do statistical inference/

Effective model of neurons



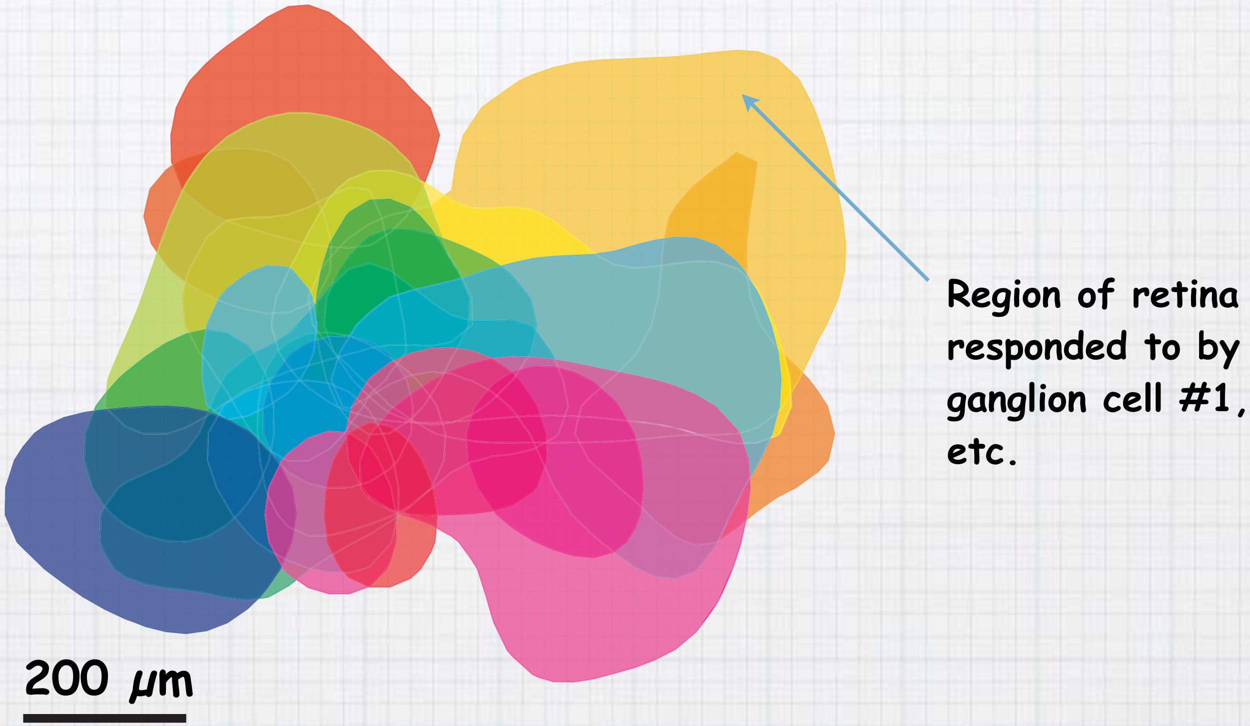
Spike triggered receptive field

Linear Nonlinear Model



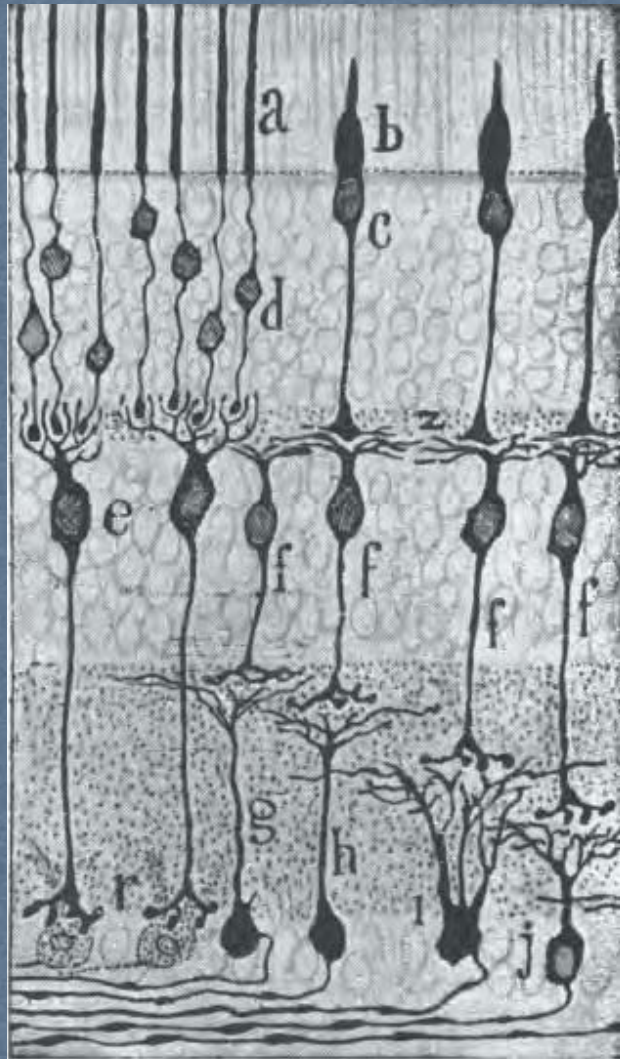
Receptive fields

... tile the visual field. Here: simultaneously recorded RF centers of ON cells.



Neurons compute in networks

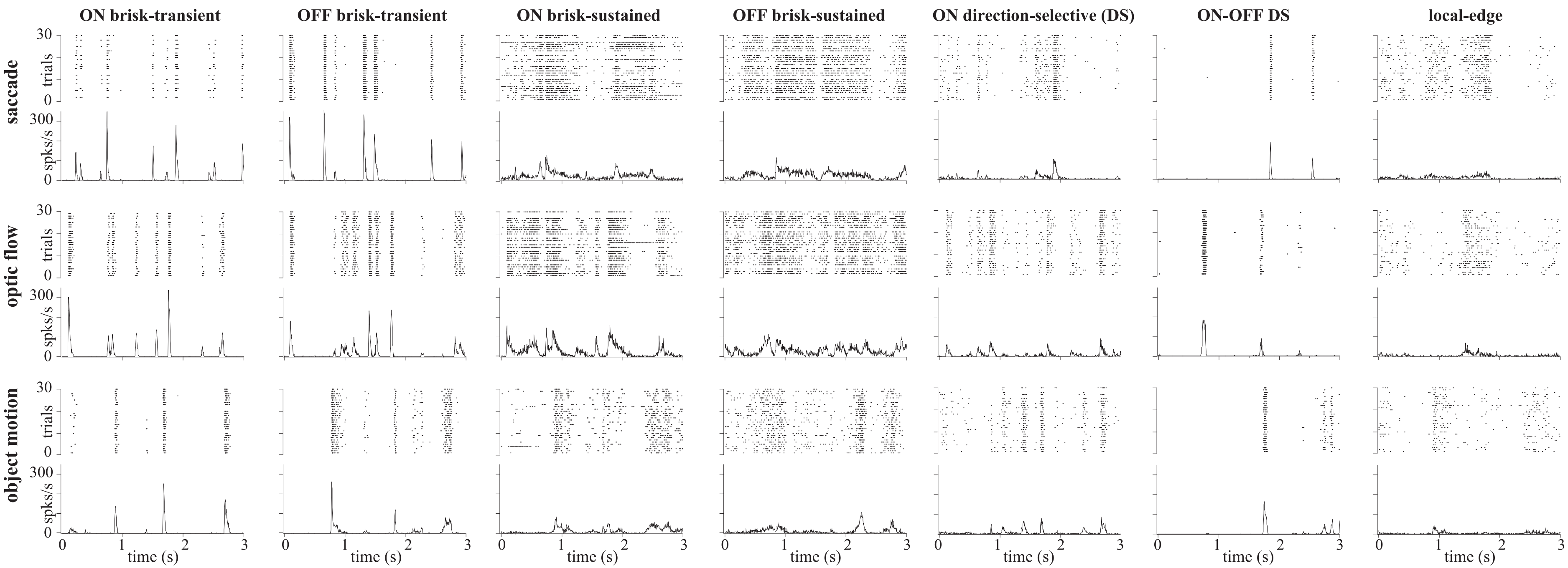
The Retina



Cajal 1917

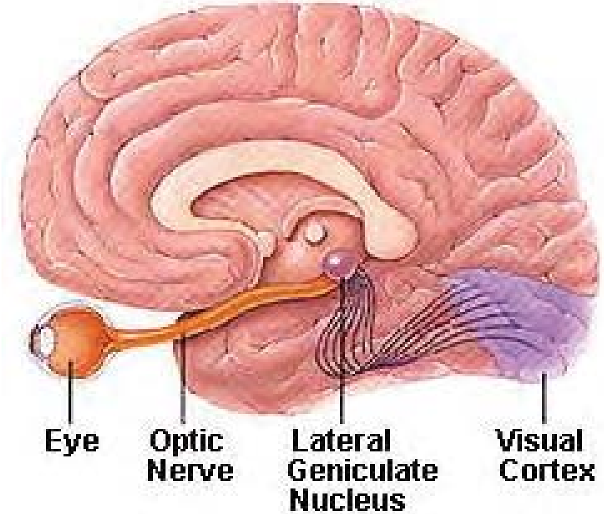
- Synapses: many neurotransmitters and receptors, excitatory & inhibitory
- Gap Junctions
- Many cell types

Retinal ganglion cell responses to natural stimuli



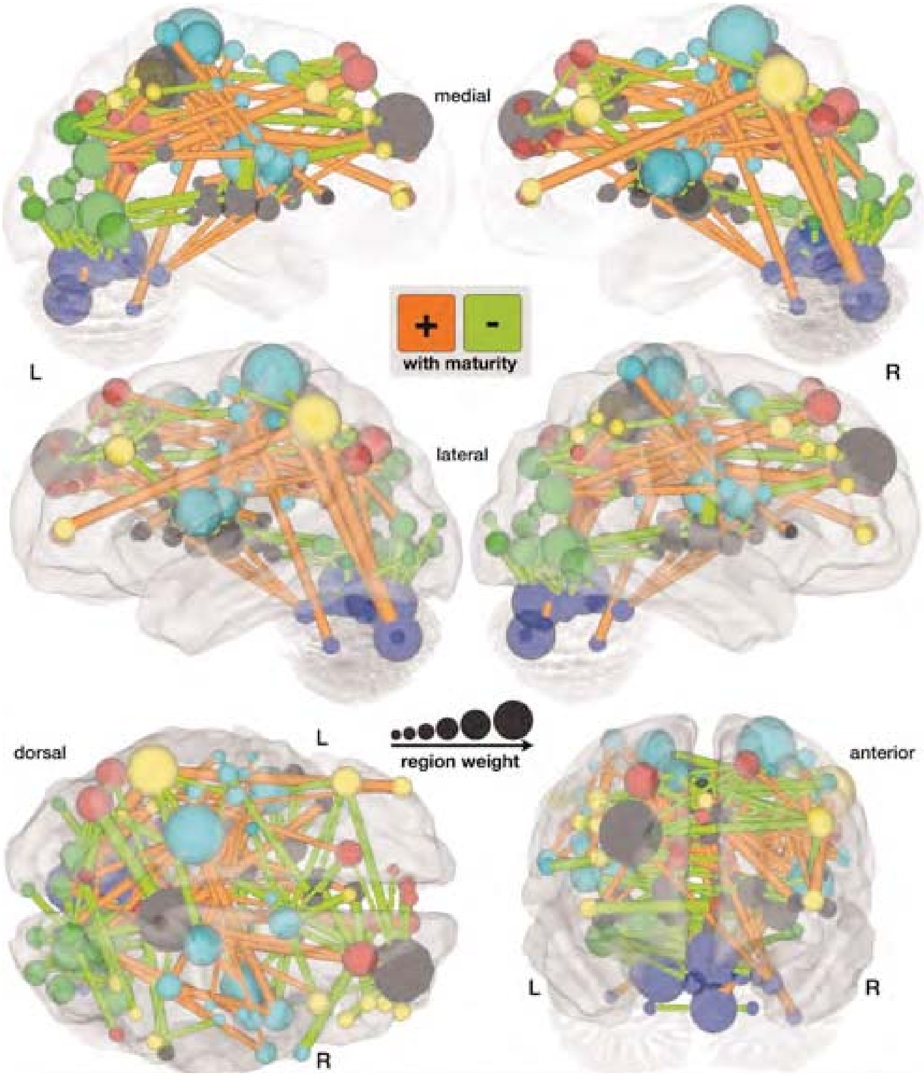
Guinea Pig (Koch et al., 2005; Koch et al., 2006)

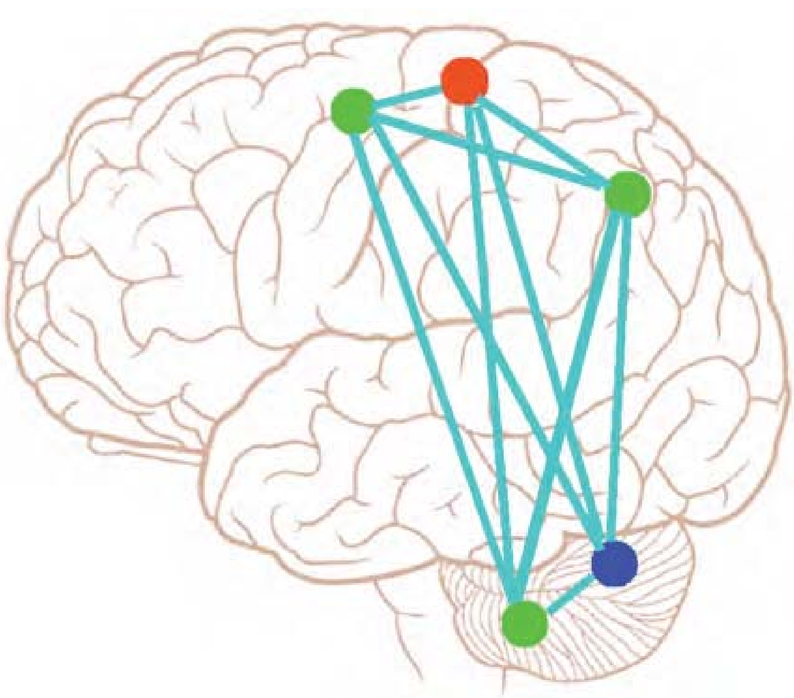
Multiple different cell types with overlapping sensitivities encode the visual world.



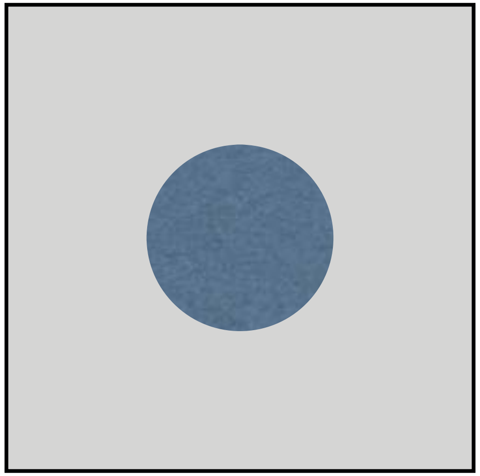
Glaucoma Research Foundation

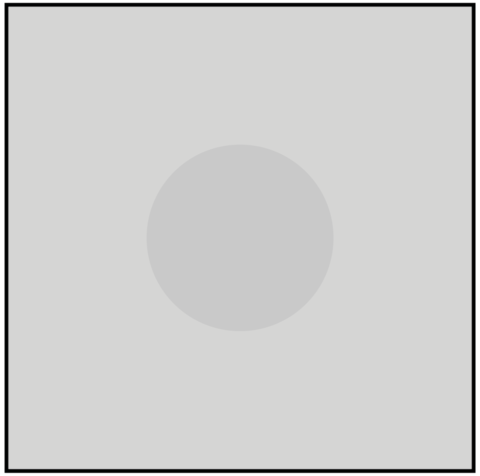
Can we get insight from abstract networks?

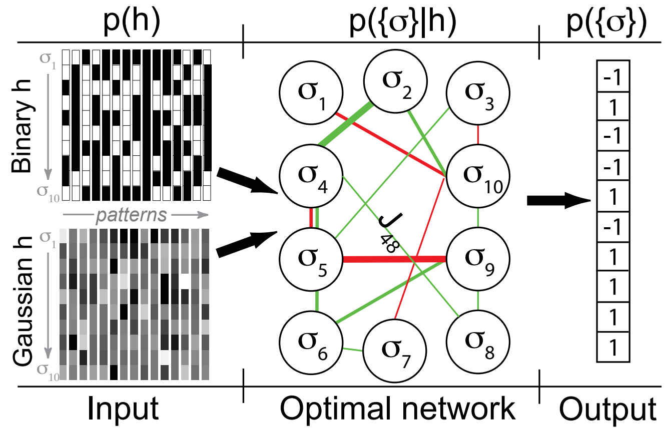




Neural networks: reasoning with uncertainty



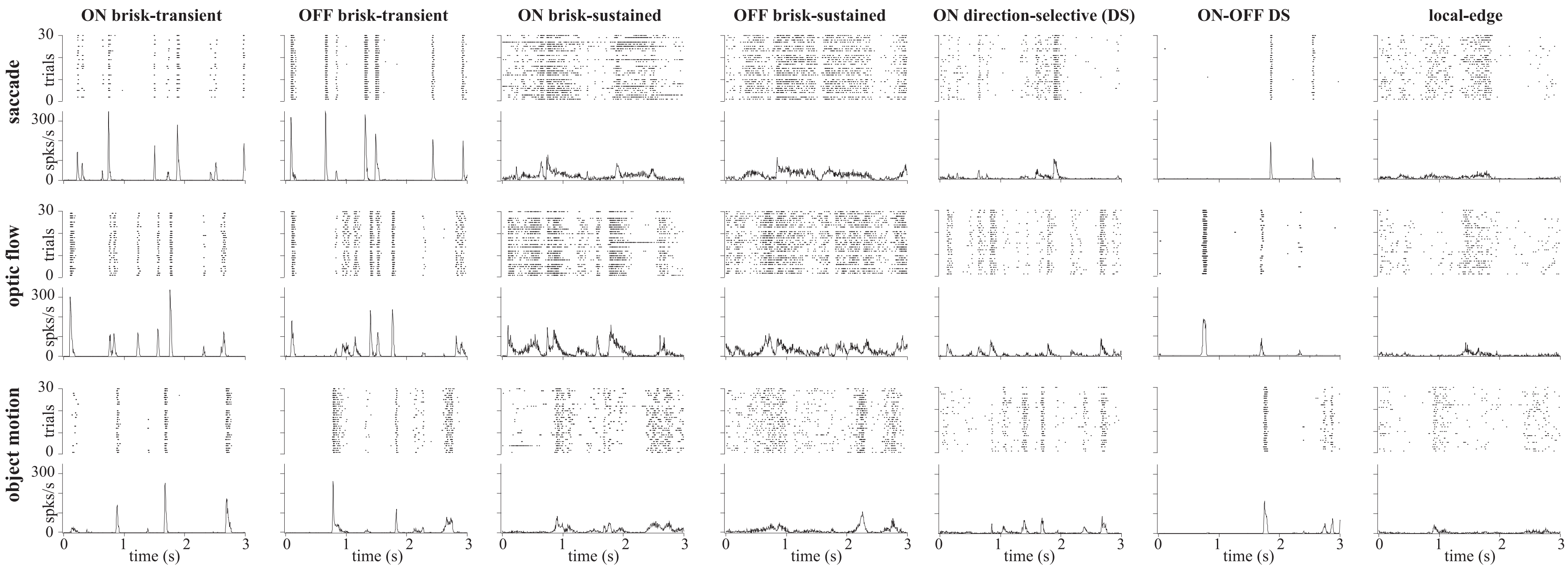




- Environmental inputs are ambiguous and noisy
- Neural responses are frequently unreliable

To achieve robust decisions and reasoning, neural circuits use redundancy in populations, clever encoding strategies, and a statistical approach -- i.e. make the best bet with the available evidence (e.g. Gold & Shadlen)

Retinal ganglion cell responses to natural stimuli



Guinea Pig (Koch et al., 2005; Koch et al., 2006)

Can we read this neural code? How does it achieve robustness?

Neural circuits consume resources efficiently

vs.

- Brain: 2% of body weight, but 20% of metabolic load.
- Brain: Every mm^3 contains 4 km of wire

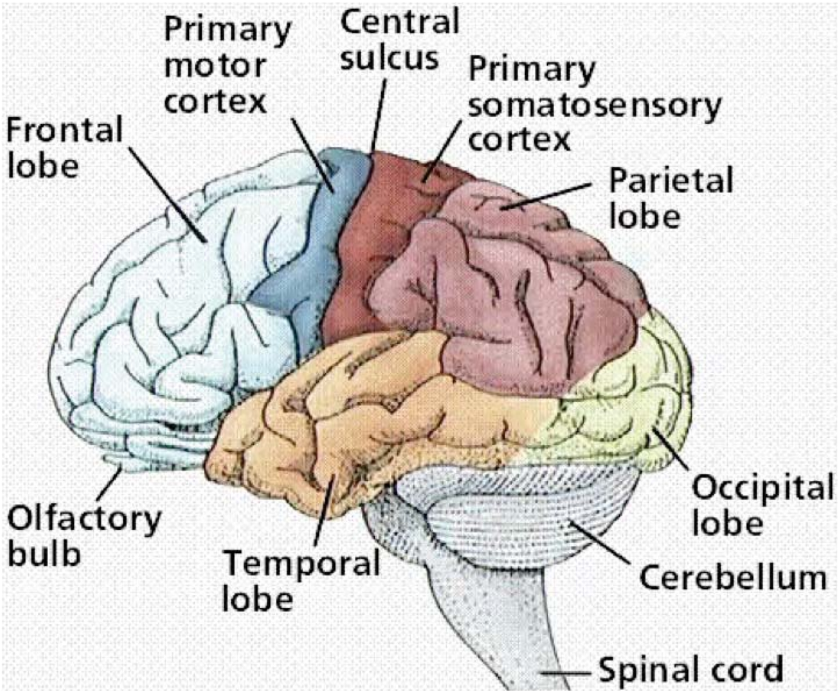
Power and space are major constraints -- (Attwell & Laughlin; Wen & Chklovskii)

- Brain consumes ~10W of power (refrigerator lightbulb)
- Packing seems to minimize wire length

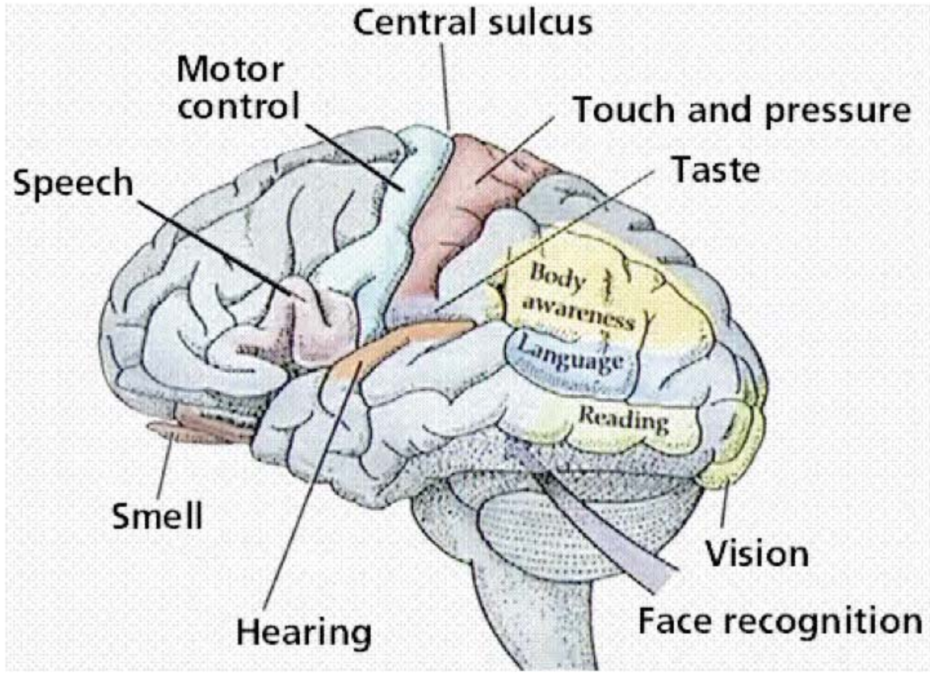
How does the brain achieve its efficiency?

One principle: specialization of structures and functions

Specialization of function: brain areas



From Purves et al., *Life: The Science of Biology*



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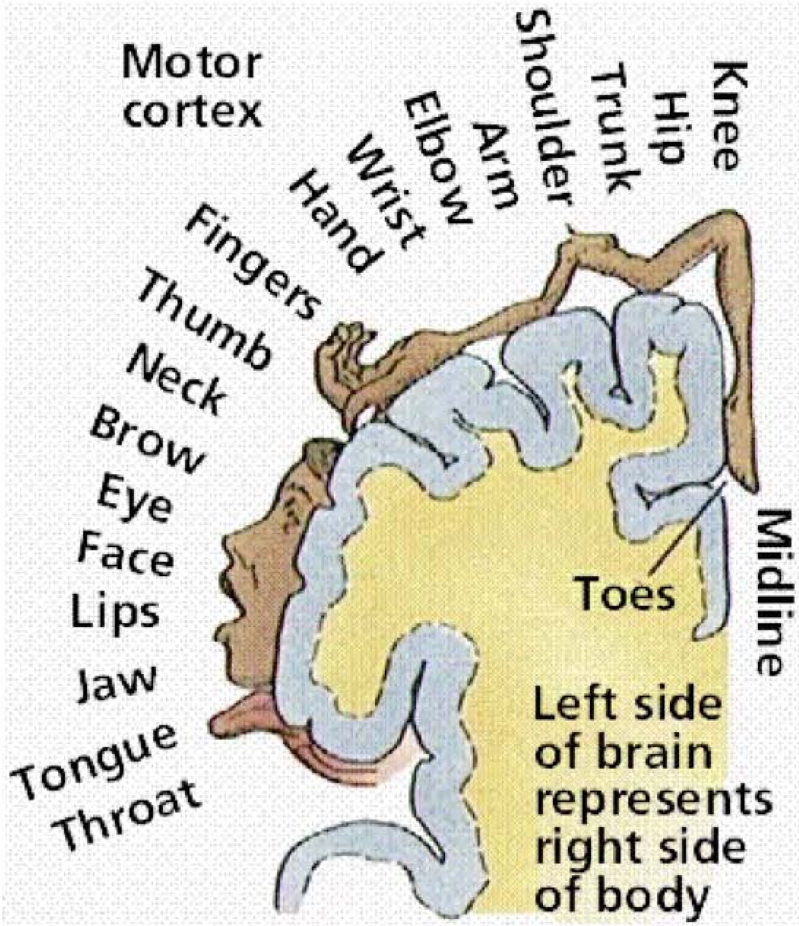
Specialization of function: layers within brain areas



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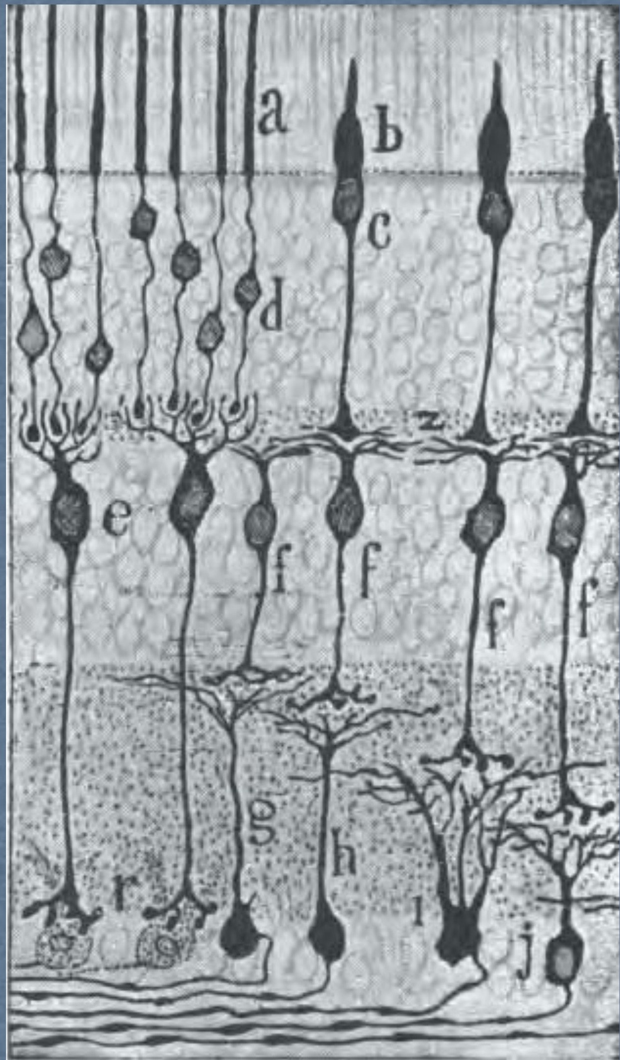
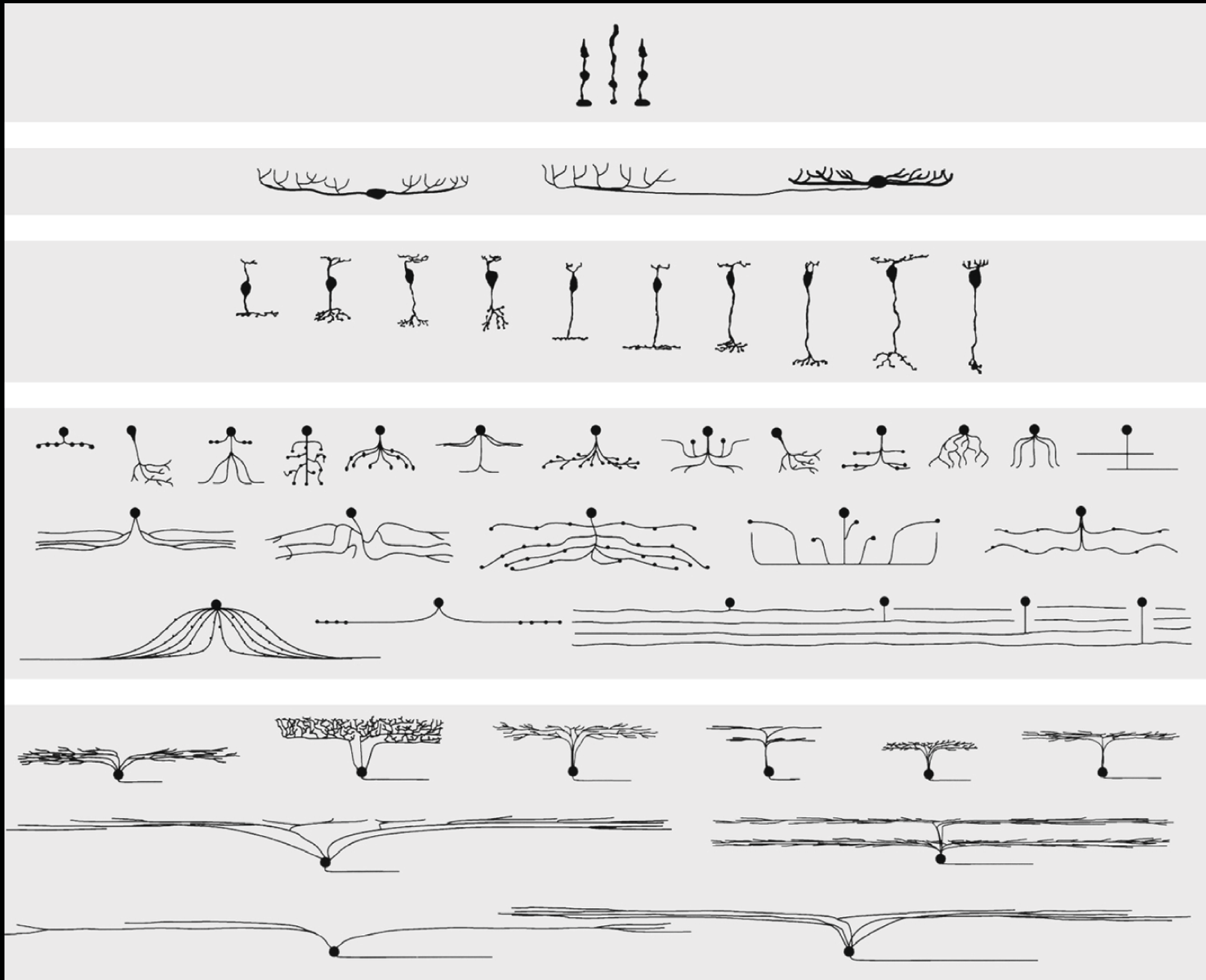
Specialization of circuits: the retina



Cajal 1917

Specialization: cell types



1 cone

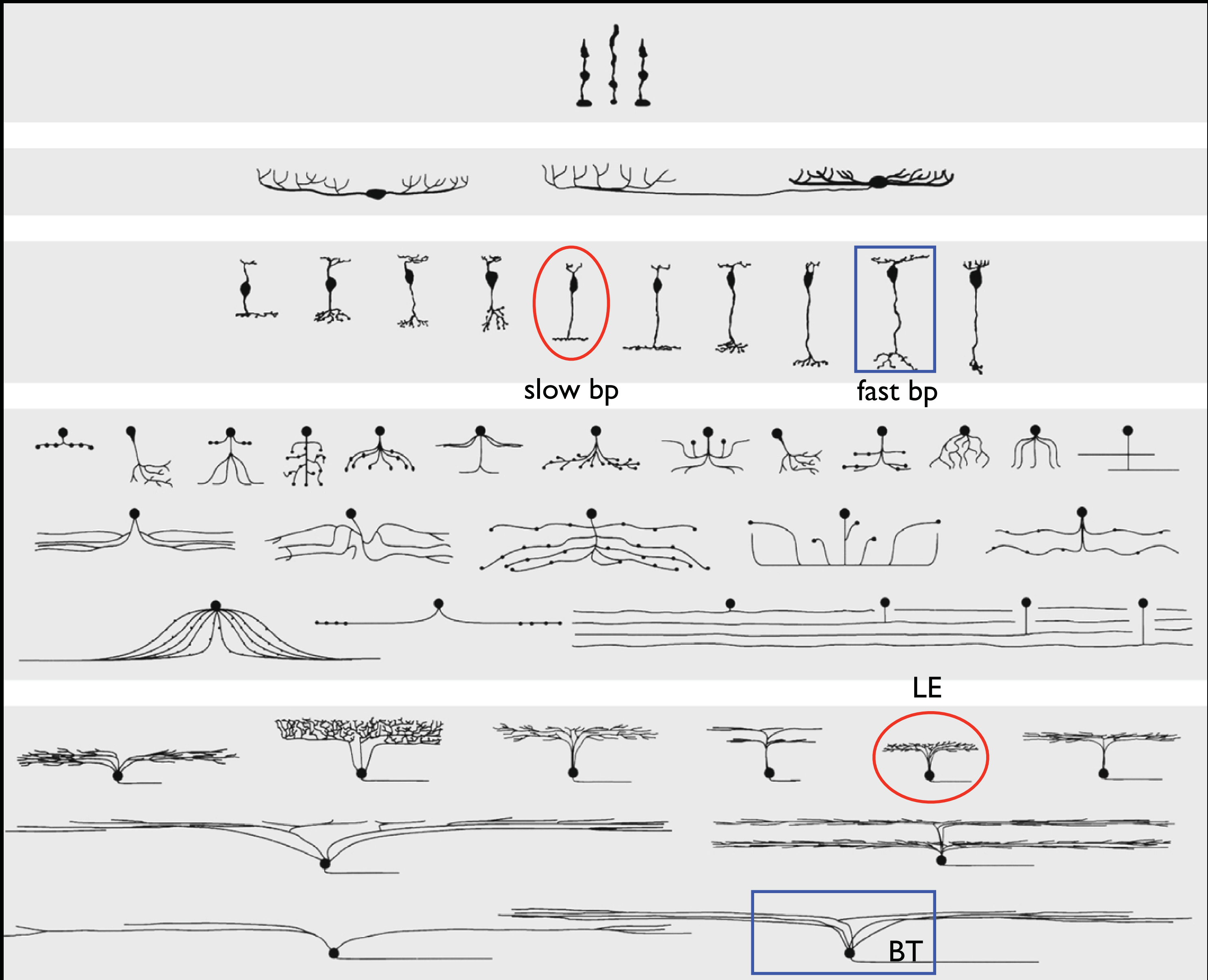
10 bipolars

30 interneurons

15 ganglion cells

Masland 2001

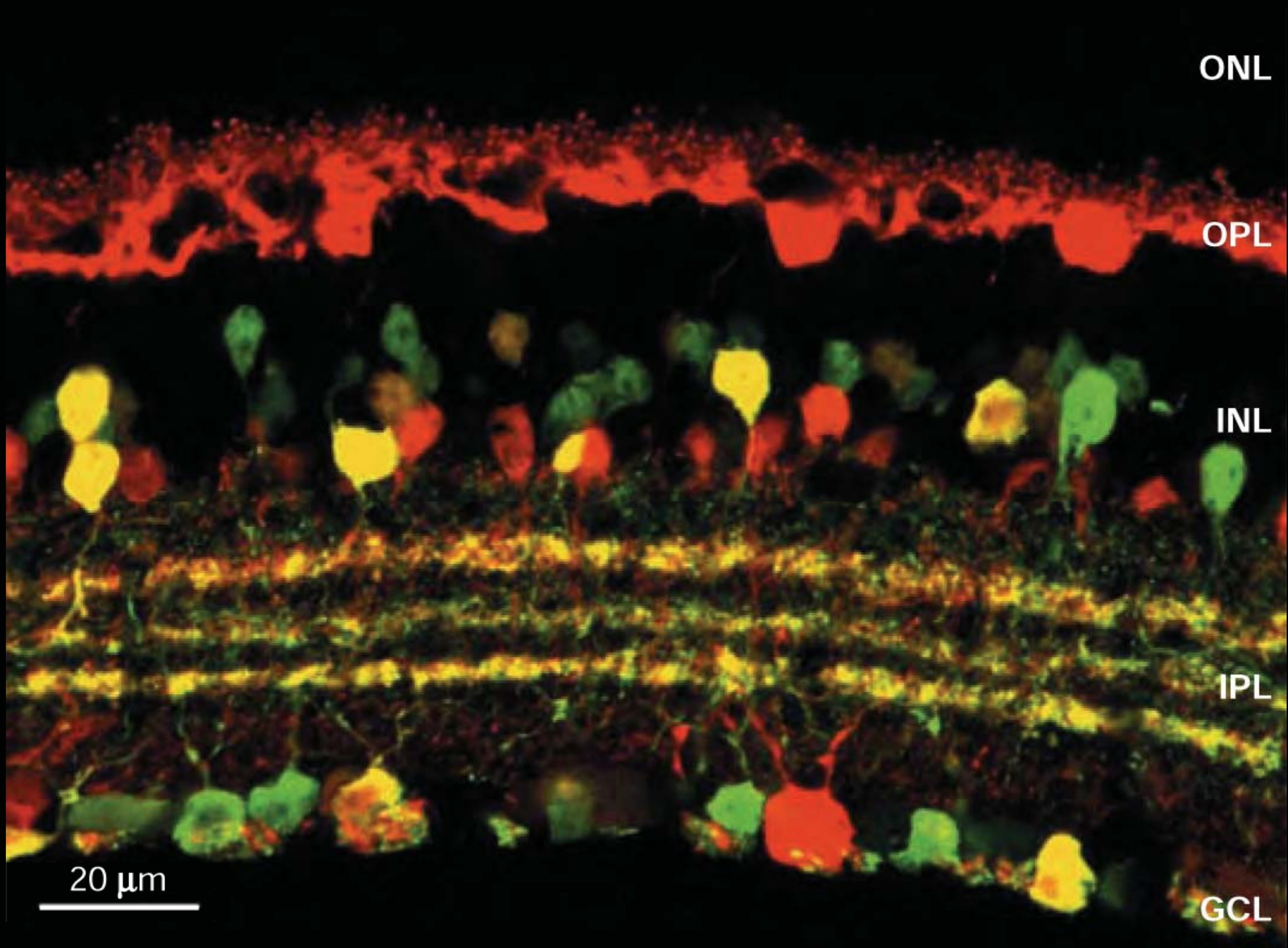
Specialization: Precise microcircuitry



slow bp → LE

fast bp → BT

Fine stratification of neuropil permits precise wiring

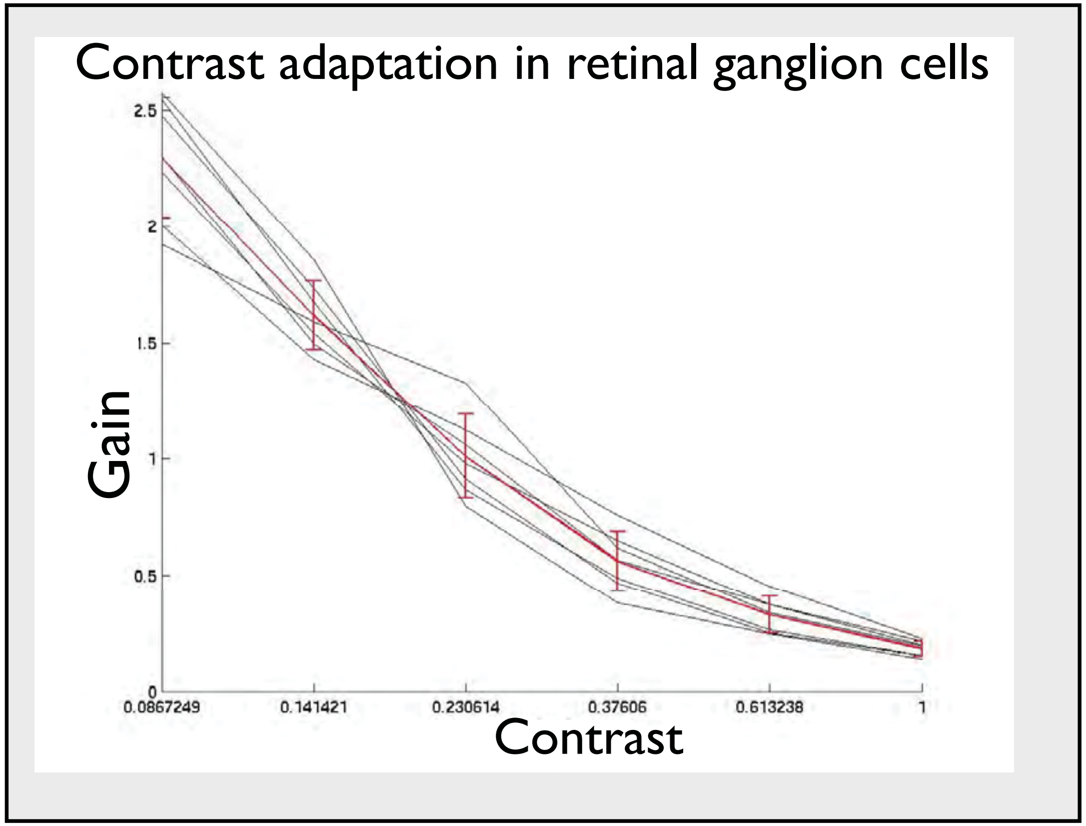


Wässle, 2004

Specialization: learning and adaptation of function

In the retina:

- Light adaptation
- Contrast adaptation
- Environmental statistics
- Omitted Stimulus Response
- Dynamic predictive coding



Can we develop a theory of specialization? Can efficiency of computation give a "theory of design"?

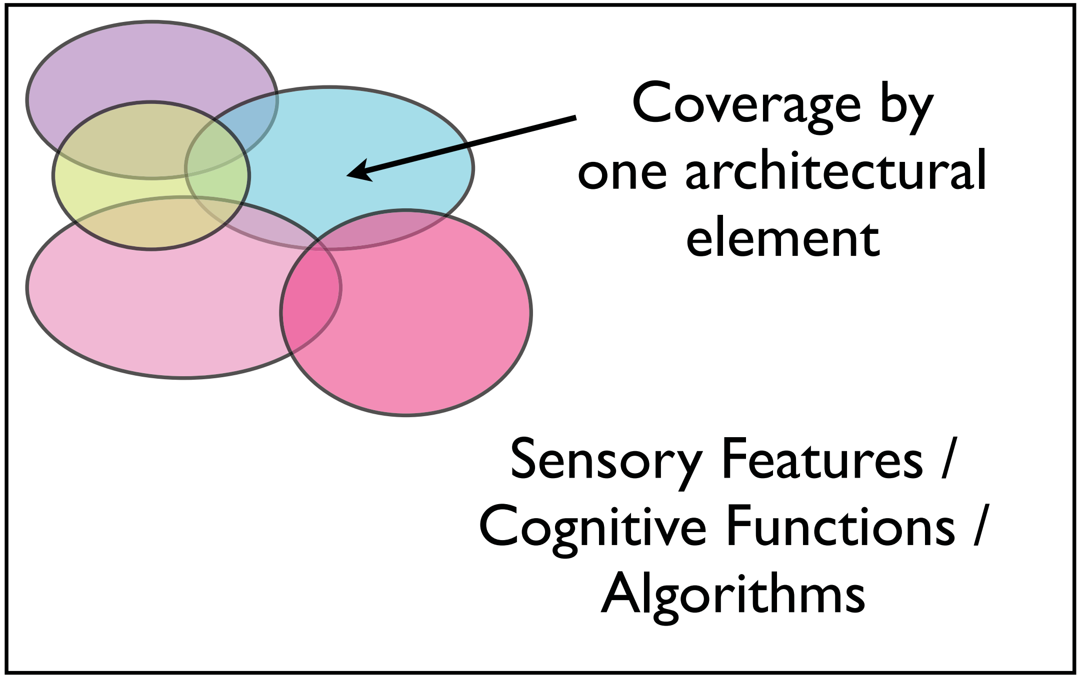
A theory of specialization & complexity?

HYPOTHESIS: Neural populations partition the tasks they perform to minimize resources while maximizing function

e.g Retina
(ganglion cells)

e.g. Entorhinal Cortex
(grid cells)

e.g. Whole Brain
(functional areas)



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