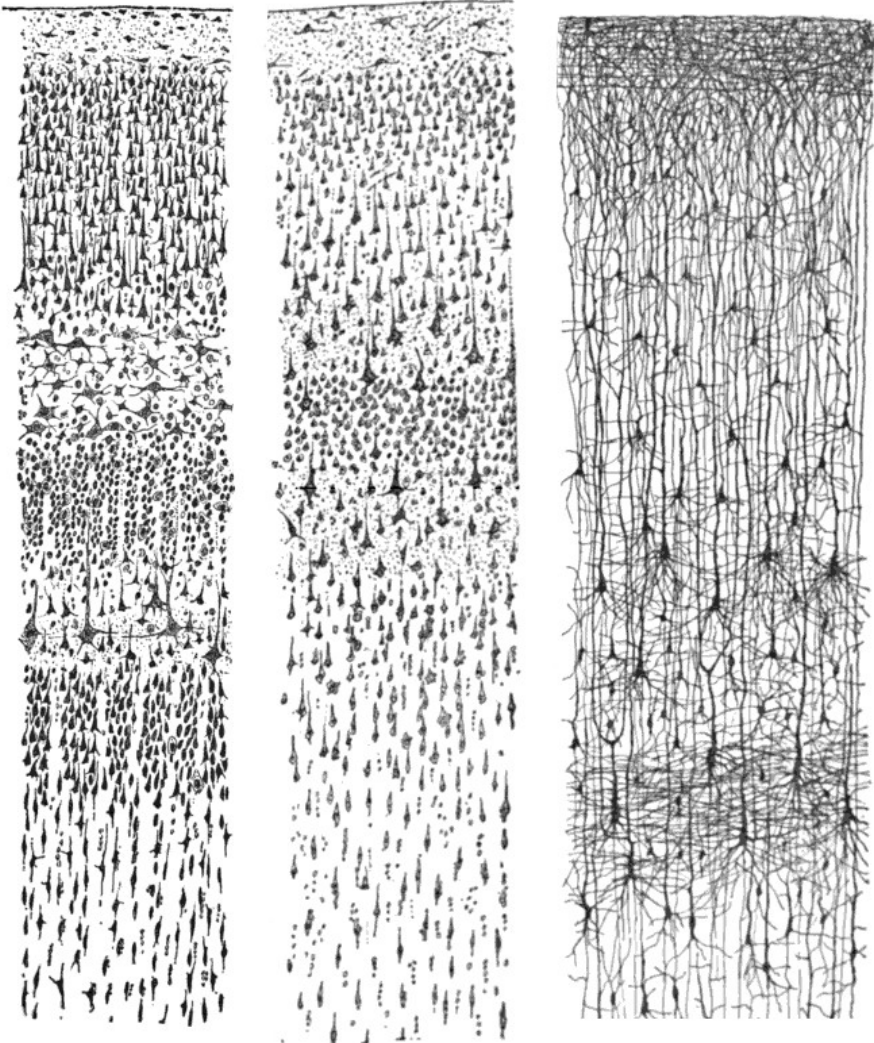


Describing the Action Potential

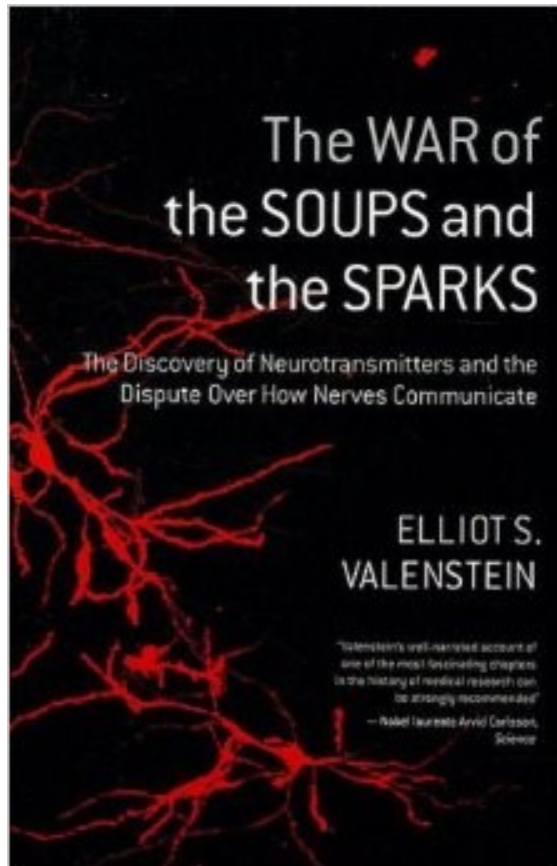
Dr. Santiago Ramón y Cajal (1852-1934)



From “Comparative study of the sensory areas of the human cortex” (1899)

- The father of modern neuroscience.
- Legendary medical artist and histologist.
- Used the Golgi Method to visualize individual neurons.
- Heavily involved in one of the great modern scientific debates: Neuronal Theory vs. Reticular Theory.
- Nobel Prize in Physiology or Medicine (1906).
 - Shared with Golgi, a stout reticularist.
- His drawings revealed a 20-40nm gap between neurons (the synapse).

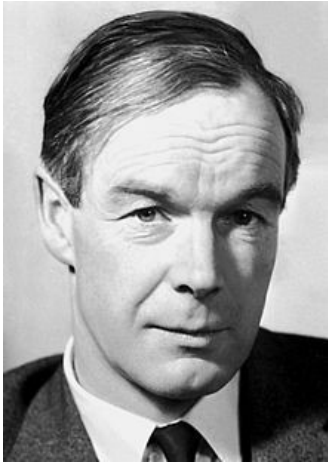
The War of the Soups and the Sparks



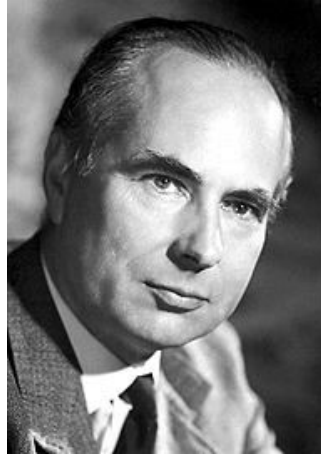
- Until Ramón y Cajal, neuronal communication was assumed to be entirely electrical.
- Work by Otto Loewi (1921) and others showed that chemicals impacted neural activity.
 - He is credited with the discovery of acetylcholine (ACh).
- *Another* great scientific “war” ensued.

The Authors (AL Hodgkin, AF Huxley, B Katz)

Sir Alan Lloyd Hodgkin
(1914-1998)



Sir Andrew Huxley
(1917-2012)



Bernard Katz
(1911-2003)



The Paper(s)

- “Measurement of current-voltage relations in the membrane of the giant axon of *Loligo*” (J. Physiol. 1952)
 - One of 5 papers published together...

Major Contributions of the 1952 *J. Physiol.* Series

- Development of “voltage clamping” technique.
 - Action potentials are fast. Voltage clamping uses a feedback system to hold the membrane potential at a desired voltage.
- Use of *Loligo* giant axon as a model.
 - Diameter allowed them to measure membrane potential from *inside* the axon.
- **Described key properties of ionic currents during an action potential.**

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Voltage Clamping

- Voltage clamping holds the membrane voltage at a steady level using a negative feedback system.

Results: *Stimulation with brief currents*

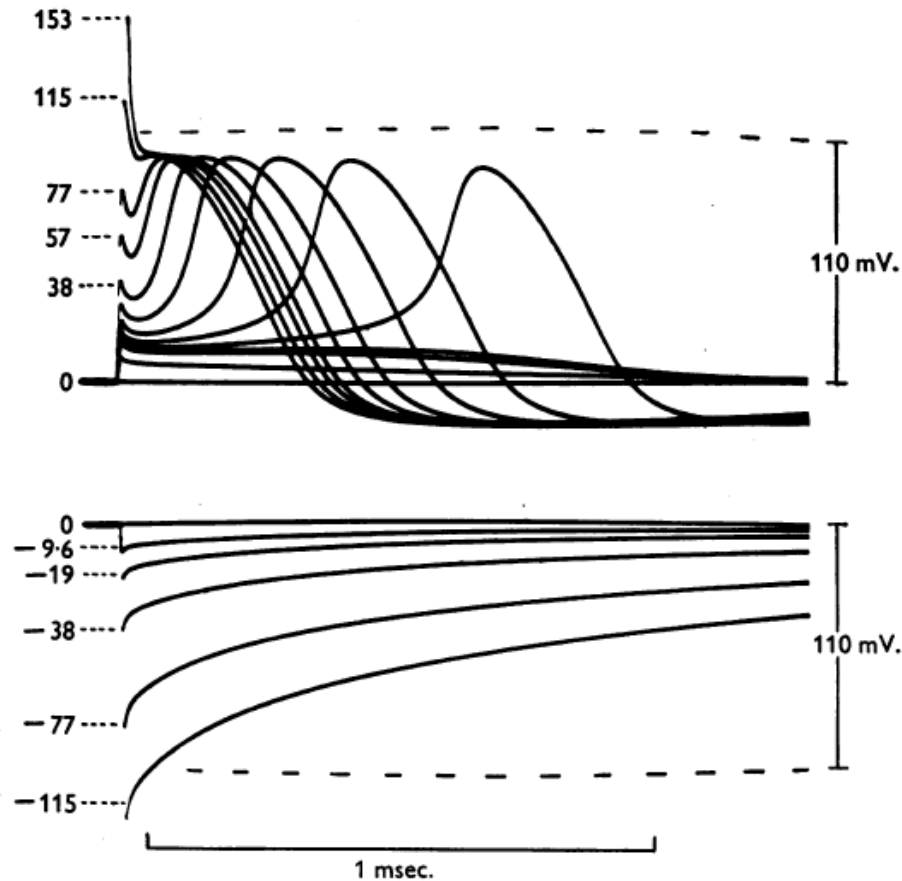


Fig. 8. Time course of membrane potential following a short shock at 23° C. Depolarizations shown upwards. Axon 18. The numbers attached to the curves give the strength of shock in $\mu\text{coulomb}/\text{cm}^2$. Shock strengths for unlabelled curves are 29, 23, 19.2, 17.3, 16.7, 15.3, 9.6.

- Before using the voltage clamp method, they had to show that these axons gave normal action potentials in response to brief stimuli.
- Shock above ~15mV triggered an AP of ~100mV.
- Stronger shocks cause membrane potential to reach the AP threshold faster.
- These giant axons give normal APs.

Results: *Membrane current under conditions of controlled potential*

- Using voltage clamp technique (and feedback system)
- Fig. 11 shows two representative records when the membrane potential is increased and decreased from rest by 65mV.
- Brief inward ionic current, followed by long outward phase. (sodium in, then potassium out)

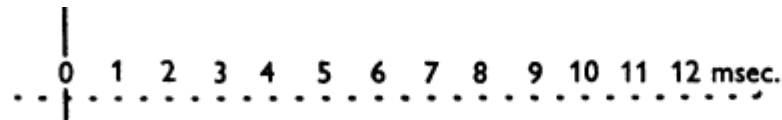
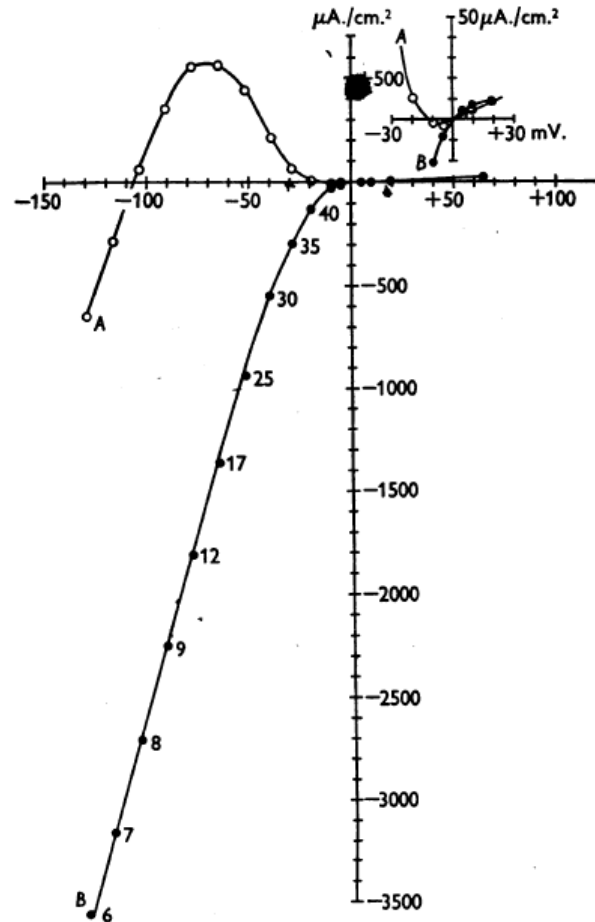


Fig. 11. Records of membrane current under a voltage clamp. At zero time the membrane potential was increased by 65 mV. (record *A*) or decreased by 65 mV. (record *B*); this level was then maintained constant throughout the record. Inward current is shown as an upward deflexion. Axon 41; diameter 585 μ . Temperature 3.8° C. Compensated feed-back.

X-axis: time

Y-axis: current density across the membrane

Results: *Membrane current under conditions of controlled potential*



X-axis: membrane voltage

Y-axis: current density across the membrane

- Using voltage clamp technique (and feedback system)
- Fig. 13 shows current density as a function of clamped membrane voltage.
- Curve A shows current SHORTLY after setting voltage (sodium influx).
- Curve B shows current several ms after setting voltage (potassium efflux).
- Brief inward ionic current, followed by long outward phase. (sodium in, then potassium out)

Fig. 13. Relation between membrane current density and membrane potential. Abscissa: displacement of membrane potential from its resting value in mV. Ordinate: membrane current density at 0.63 msec. after beginning of voltage step (curve A) and in 'steady state' (curve B). The numbers attached to curve B indicate the times in msec. at which the measurements were made. Inset: curves in region of origin drawn with a tenfold increase in the vertical scale. Inward current density is taken as positive and the membrane potential is given in the sense external potential minus the internal potential. Measurements were made from the records reproduced in Fig. 12 (3.8° C.).

Results: *The effect of temperature*

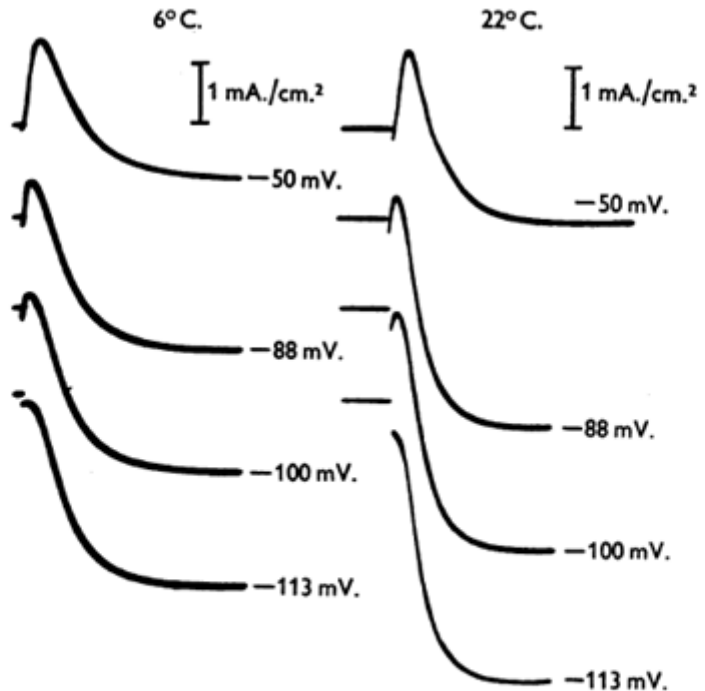


Fig. 15. Membrane currents at different temperatures. Axons 17 (6° C.) and 18 (22° C.), from the same squid. Inward current is shown as an upward deflexion. The numbers attached to each curve give the displacement of membrane potential. Uncompensated feed-back was employed.

- Two giant axons taken from the same squid and analyzed at different temperatures.
- Resting potential is the same at both temperatures.
- General form of the action potential is unchanged.
- The rate of change in membrane current is temperature-dependent.

What makes this work important?

- It showed, for the first time, that ionic current across the membrane was related to membrane voltage, time, and temperature.
- It showed that the intracellular voltage becomes *positive* during an AP (discrediting Bernstein's theory).
- It demonstrated the power of the voltage clamp technique.
- It demonstrated the power of the giant squid axon as a model system.

Looking ahead to Thursday...

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With 16 text-figures

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THE STATISTICAL
NATURE OF THE ACETYLCHOLINE POTENTIAL AND ITS
MOLECULAR COMPONENTS

BY B. KATZ AND R. MILEDI

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