

HST 750
Modeling Issues in Speech and Hearing
Spring 2003

Introduction to the Hodgkin and Huxley model:
Some personal notes while reading Cole and Hodgkin's recollections of
the events that led to the taming of the squid giant axon

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“A friendly biologist told me long ago that a physicist, who should know something about cables, ought to be interested in nerve if only because the two were built in somewhat the same way and both carried electrical messages”, Cole (1972)

Bernstein's membrane theory and the core conductor model of a nerve

1855: Lord Kelvin (1855) wondered if an electric signal could be sent across the ocean. From that emerged the cable theory.

1868: Julius Bernstein postulates the existence of a membrane

1902: Bernstein's membrane theory.

“Both the passive and the active electrical aspects of biology were considered by Bernstein in his membrane hypothesis. This consisted of three propositions: (1) Living cells are composed of an electrolytic interior surrounded by a thin membrane relatively impermeable to ions. (2) There is an electrical difference of potential across this membrane at rest. (3) During activity the ion permeability of the membrane increases in such a way as to reduce this potential to a comparatively low value”, Cole (1972).

1905: Hermann (1905) came up with the idea that propagation of current flow was in a cable-like structure and that current flow from an active region stimulated adjacent regions ahead.

1909: Lucas proves all-or-none concept for muscle and nerve (also Andrian, 1912)

1912: Involvement of potassium more explicitly stated. “At rest membrane permeability was that for potassium. When the membrane became active this permeability was lost as the membrane became permeable to all ions. The diffusion potential all but disappeared as the “excess negative ions inside the membrane joined with excess positive outside ions””, Cole (1972).

Hodgkin enters the field of electrophysiology (from Hodgkin, 1976)

- 1934: Recall: Blinks (1930): increase in membrane conductivity during the action potential in *Nitella* (plant)
Hodgkin started experiments to see if the membrane conductivity increased during the action potential in the animal nerve. Found no evidence for electrical transmission, no evidence for increase in membrane conductivity. Experiments seemed to agree with local circuit theory. *

Later that year: convinced from literature that axonologists were skeptical about the membrane theory and in particular the local circuit theory. He concluded that it would be worth while to see whether the transient increase of excitability beyond a localized block was an electrical effect.

- 1935: Hodgkin recorded the electrotonic potential produced by local electric circuits spreading through a blocked region of the nerve.
- 1936: Young introduces the squid preparation. Cole et al. attempted to use the axon with no success but were determined to continue trying (Cole, 1972).
- 1937: J Neuroph. papers "Evidence for electrical transmission in nerve" Part I, II

Goal: the way in which activity is transmitted in medullated nerve

Widely accepted theory: transmission depends on excitation by the action current. More precisely, each section of nerve is excited by the local electric circuits produced by the activity of adjacent parts.

Fundamental question: decide whether the local circuits set up by an active region of a nerve fiber are able to excite an adjacent part. Decide whether spread of electrotonic current is in fact the cause of the increase in excitability.

General conclusion: it is possible for nervous impulses to be transmitted by electrotonic currents → nothing to do with an increase in membrane conductivity mostly explained by electric circuit theory.

- 1937: Hodgkin soon interested in cable theory and the idea that it is necessary to excite a finite length of nerve in order to start an action potential. (further developed by Rushton – 1937) lead to idea of subthreshold response (explained data of Katz – 1937, Rushton – 1932). He makes no attempt to test these ideas, starts working on crab nerve, picks up a single axon (!) and see graded response. Later that year he joins Gasser (director of Rockefeller Institute) and his group. He is still interested in measuring conductance changes during the action potential and gets some preliminary results. He then visited Cole and Curtis at Columbia who had already obtained such data on *Nitella* and were planning on repeating them on squid, therefore Hodgkin abandons his efforts.

Evidence of conductance changes during an action potential

- 1936: Hill started talking about the two factor (local potential and the threshold) excitation hypothesis in an attempt to explain the electrically excitable properties of cells. Impulse conduction was entirely understood, as a physical process, except for the cause and effect of excitation which were complete physical mysteries!
- 1937: Rushton evolved a powerful theory for the initiation and propagation of an impulse. Sudden change of membrane emf at a critical membrane potential. (consistent with Bernstein) → imp conclusion was that a minimum length of axon had to be so excited before a sustained propagation could appear.
- 1938: Cole and Curtis report conductance increase during a propagating impulse on *Nitella*. The need for the value of resting conductance becomes obvious. Important questions: What was the nature of the membrane conductance change? What did it have to do with excitation and with its propagation in an axon? (could cable model give insight? Not really, the cable modes was inadequate for active characteristics (excitation and propagation).

Hodgkin met with Erlanger who was not convinced about subthreshold activity in myelinated axons and was skeptical about the local circuit theory: Hodgkin had an idea from Erlanger i.e. to alter conduction velocity by changing the electrical resistance outside the nerve fiber. That would be a good test of the local circuit theory:

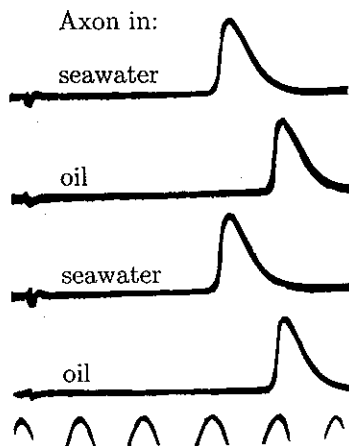


Figure 2.14 The effect of increasing the resistance of the extracellular solution on the conduction velocity of the action potential of an unmyelinated axon (adapted from Hodgkin, 1939, Figure 2). A crab (*Carcinus maenas*) axon of 30 μm diameter was immersed alternately in seawater and in oil and the action potential recorded 13 mm from the site of stimulation. The time scale is given by a simultaneously recorded sine wave of period 1 ms (lowest panel).

Weiss, 1996

1939: Cole and Curtis report conductance increase during a propagating impulse on squid. Cole and Hodgkin reported the squid axon resistance of 1000 Ohm cm^2 . Towards the end of this work Cole noticed that there appeared to be something like an inductance which showed up in the longitudinal impedance at low frequencies – later explained as being due to the delayed increase in potassium conductance which can make membrane current lag behind voltage provided the internal potential is positive to the potassium equilibrium potential. Hodgkin also performed experiments with Curtis: trying to push electrodes up the cut end of giant axon to try and record action potentials with an internal electrode. An interesting comment by Cole: "I was far from excited by the possibilities and even commented that an upside-down action potential would not be very interesting. But if it could be done it should".

Where is Hodgkin now?

By the fall of 1938 Hodgkin is back to Cambridge. Hodgkin : "I had worked hard the previous six years. The war in Europe was almost certain so I decided to choose a straightforward problem to work on. Decided to check how close the action potential came to the resting potential". **Andrew Huxley** joined in some experiments. **Result: found that action potential was much larger than the resting potential.** (using external electrodes)

Intracellular recordings of action potentials – Bernstein no longer adequate

1939: Hodgkin decided to continue the experiments at Plymouth (worked there off and on since a schoolboy in 1931). In a few weeks Huxley joined him and started measuring viscosity of axoplasm. He got negative results BUT Huxley thought it would be fairly easy to stick a capillary down the axon and record potential differences across the surface membrane. Result → absolute magnitude of action potential is at 90 mV (peak is at about 40 mV which exceeds the 0mV maximum predicted by Bernstein's theory. Started tests on effect of potassium ions on resting potential and action potential (later done nicely by Cole and Curtis 1942). Three weeks later Hitler into Poland **WW II**. Had to leave the technique for 8 years (!) until possible to return to Plymouth in 1947.

Where does the cable theory stand?

From Cole, 1972

Cable theory consideration and the known parameters of the squid axon required that the membrane perform as a **negative resistance**.

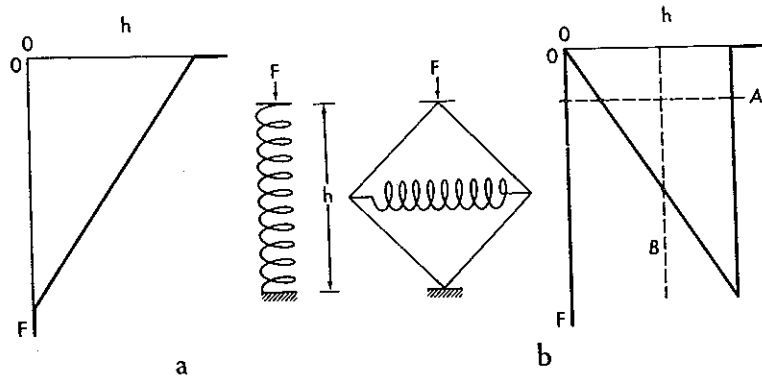


FIG. 2:73. (a.) The usual positive spring requires an increasing force as it is compressed. (b.) The negative spring linkage requires a decreasing force as it is compressed. A constant force, such as weight *A*, results in an unstable equilibrium but a very stiff spring *B* can provide a stable equilibrium anywhere in the negative spring region.

Cable theory had two obvious deficiencies (1) no good way to compute the time course of memb. potential (2) spatial distribution of alternating and direct currents in the electrode regions made the analysis difficult. Persistent question: how does an impulse start?

“A considerable variety of experimental and analytical approaches had produced at least as much variety of ideas and information. In fact, I felt that there must be enough available in the background to provide a simple concept of the workings of a nerve membrane if one but had that touch of genius that could ignore everything but the important” Cole, 1972

The sodium theory

1944: Hodgkin started thinking again about physiology (Cole had sent him his reprints till 1942). Finished paper on action potential and resting potential which he had started in 1939. Regretted the discussion in that paper – Sodium hypothesis not mentioned since results till then were not favorable although later those results were proven wrong.

1945: Hodgkin and Huxley meet again in Cambridge. Work on indirect measurements of potassium leakage in activity (1947 paper) **which got them thinking quantitatively** about ionic movements during the nerve impulse.

ideas start to trickle together to form theory, those ideas acting as a guide to the experiments

1946: Started speculating about the kind of system which might give rise to an action potential (unpublished work). Katz showed that crab axons became inexcitable in salt free solutions

1947: Huxley calculated a propagated action potential: model incorporated the main features later seen in voltage clamp experiments: rapid rise of sodium permeability followed by slower decay and a slow rise of potassium permeability (unpublished). Hodgkin was more doubtful but all other schemes were shot down by Huxley's calculations.

Hodgkin was doubtful of the theory though Huxley had some good data

Measured the effect of sodium deficient solutions on (1) external action potentials (2) longitudinal resistance of external and internal fluids in parallel. Showed that lowering the external sodium concentration reduced the action potential by the right amount. (Overton had suggested possible effect of sodium in 1902).

Support for Na⁺ theory

Energy crisis till end of March 1947 – stopped experiments. Stayed home writing, Huxley cranking a Brunsviga.

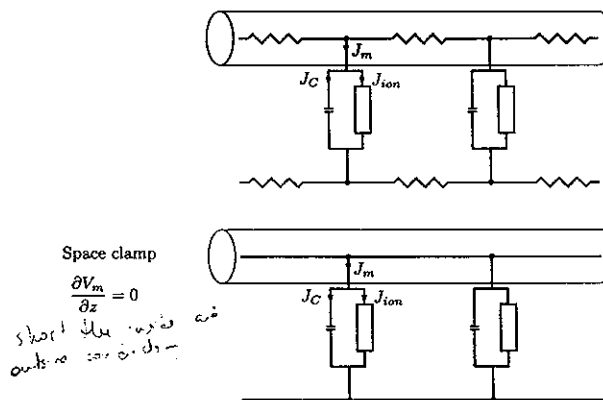
Summer 1947 – decided to do experiments properly at Plymouth using squid and an internal electrode. By July 1947 he did experiments providing strong support for the sodium hypothesis. Continue experiments again in September with Katz – (HHK paper 1949).

Taming the squid giant axon: Space and voltage control

1947: Hodgkin wrote to Cole about his results also perfusing axon and stimulating axon with diffuse electrode to excite 1-2 cm of axon uniformly, so no propagation or local circuit theory confusion. October 1947: Cole replies, internal electrode and voltage clamp in the making.

1947-1949:

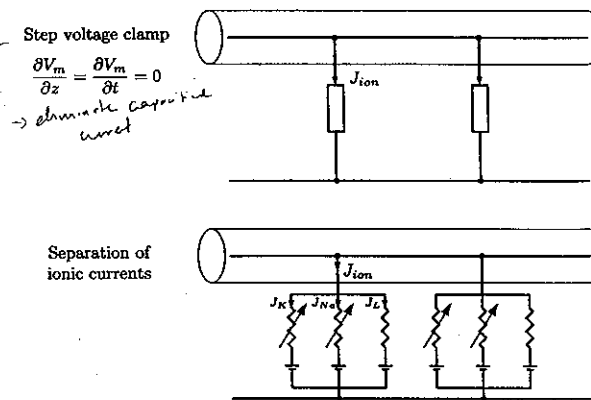
Marmont: long current-carrying electrode on the axis of the axon, a coaxial external measuring electrode with equipotential guards at each end and an electronic feedback membrane current control with direct measurement of the membrane potential. Now the axon is space clamped and the cable equation reduces to an ordinary dif. equation. (Feedback control concept was highly developed in world war II and widely applied under the name of cybernetics by Norbert Wiener (1948)).



An interesting note from Cole, 1972:

“Quite aside from the immediate possibilities, this approach has seemed to me to be a beautiful example of the interplay of experiment and theory. Much of the previous progress had been made possible by varied and usually rather elementary theoretical considerations. But a limit had been reached practically at which the appropriate theory was far too difficult – for us at least – to be useful. Since no way could be found to appreciably simplify the theory for existing experiments the impasse could only be broken by very considerably complicating the experiment; placing the axon in a highly nonphysiological situation, for which the theory was almost immeasurably simplified. This is no isolated example of a valuable strategy – if in experimental trouble look at theory and if in theoretical trouble look at experiment”.

Potential control: simplified even more the cable equation



1949: Cole and Marmont conclusions: there was no trace of a threshold or unstable behavior as a function of either time or potential. Early inward current, disappeared at larger depolarizations. The current late turned smoothly at all potentials to flow in the outward direction. This came earlier and the final current became larger as the potential step was further increased. Membrane no longer responded in its usual all-or-none fashion
 No theory to explain the early inward current. (remember sodium theory is still in the makings by Hodgkin and Huxley)



Where is Hodgkin and Huxley?

1948: Hodgkin visited Cole in America to exchange info and discuss future experiments. Heard about Cole and Marmont experiments voltage clamp and internal electrode, and Huxley and him anxious to test their carrier hypothesis. Before leaving America made a short double-spiral electrode – one for current one for voltage.
Return to Cambridge, built apparatus similar to Cole and Marmont but with changes.

July 1948: experiments with Katz try to perfuse squid axons – no success. Started making and inserting double spiral electrodes. Short shocks and constant currents with different external solutions obtained indirect evidence on permeability changes to sodium and potassium.

Mid-August 1948 Huxley arrives, feed-back amplifier work, made few voltage-clamp experiments (published in 1949). Realized needed guard electrodes, do exp. at low temperatures. Start improving equipment.

1949: Hodgkin returned to Plymouth for experiments. By mid-July Katz joined and in the next month obtained all voltage-clamp records published in 1952.

1949-1951:

Spent 2 years analyzing data, why so long? As analysis progressed realized that from the data could not deduce a mechanism. Carrier model could not fit certain results, had to be replaced by some kind of voltage-dependent gate. Begun to think about molecular mechanisms and realized that data would only yield general info about the class of system likely to be involved. Settled on finding mathematical equations, that was also hard as kinetics were complicated. Huxley came up with the m, n, h formulation. Difficulty computing the action potential from equations.

March 1951 – settled all the equations, hope to solve at the Cambridge U. computer but that would be down for about six months. Huxley solved equations numerically using a hand held Brunsviga.

And a last quote from Cole, 1972:

“.. Hodgkin and Huxley went ahead with amazing speed.... This speed of application has seemed to me a very powerful example of the benefits of rapid and free communication. Hodgkin and Huxley had not progressed to internal current electrodes, to guards, or to control systems. They had not developed or used the membrane potential control concept. I could not publish my work immediately or in appropriate detail but, by free exchange of methods and results, they were able within a year to repeat all my work with very considerable improvements. This may well have saved several years at the least!”