

The Hodgkin-Huxley theory of the action potential

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The Hodgkin-Huxley (H-H) theory of the action potential, formulated 50 years ago, remains one of the great success stories in biology, and ranks among the most significant conceptual breakthroughs in neuroscience. Together with the artificial neural networks of McCulloch and Pitts, the quantal theory of Katz, and the cable theory of Rall, all developed at around the same time, the H-H theory provided the foundation for modern computational neuroscience.

The theory was the culmination of an intense experimental and theoretical collaboration between Hodgkin and Huxley, from 1938 to the publication in 1952 of their five landmark papers in the *Journal of Physiology*. The stage was set by four key developments. First, Cole and Curtis demonstrated that the action potential is associated with a large increase in membrane conductance¹. Second, Hodgkin and Huxley² made the first intracellular recording of an action potential (Fig. 1a). This demonstrated directly that the action potential exceeds zero mV, rejecting Bernstein's hypothesis³ that the underlying increase in membrane permeability is non-selective. Hodgkin and Katz⁴ explained the overshooting action potential by showing that it results from an increase in sodium permeability (validating the neglected work of Overton⁵). Finally, Hodgkin, Huxley and Katz (following Cole and Marmont) developed a voltage-clamp circuit to enable quantitative measurement of ionic currents from squid axon.

Hodgkin and Huxley then showed that step depolarizations of the squid axon trigger an inward current followed by an outward current. Using ionic substitution, they demonstrated that this net current could be separated into two distinct components, a

rapid inward current carried by Na⁺ ions, and a more slowly activating outward current carried by K⁺ ions. From experiments using ingenious voltage-clamp protocols, they concluded that these two currents result from independent permeability mechanisms for Na⁺ and K⁺ with conductances changing as a function of time and membrane potential. This was a stunning conceptual breakthrough, later termed the 'ionic hypothesis,' a unifying framework for the field that triggered the search for the underlying molecular structures.

Their most remarkable achievement, however, was the empirical representation of the experimental data in a quantitative model⁶, the first complete description of the excitability of a single cell. They modeled the observed smooth current changes in terms of pores or channels that were either open or closed, and by using a statistical approach generated predictions for the probability of channels being open. They represented total ionic current as the sum of separate Na⁺, K⁺ and leak currents:

$$I = \bar{g}_{Na} m^3 h (V - E_{Na}) + \bar{g}_K n^4 (V - E_K) + \bar{g}_{leak} (V - E_{leak})$$

where separate equations for the gating variables m and h (for activation and inactivation of g_{Na}) or n (for activation of g_K) describe all the smoothly varying voltage and time dependence of the kinetics. Thus, the H-H model links the microscopic level of ion channels to the macroscopic level of currents and action potentials.

The model could reproduce and explain a remarkable range of data from squid axon, including the shape and propagation of the action potential, its sharp threshold, refractory period, anode-break excitation, accommodation and subthreshold oscillations. With minor parameter changes, the model

could describe many channel types, underlining the generality of their approach. Even today, most biophysical spiking models are based on the H-H equations.

Like any good theory, the H-H model inspired many new experiments. Armstrong and Bezanilla verified the prediction of gating charge movement. Hille and others confirmed that Na⁺ and K⁺ channels were separate molecular entities with different pore sizes. This was validated by single-channel recording of the behavior of individual Na⁺ and K⁺ channels, and by cloning of separate families of Na⁺ and K⁺ channels. Naturally, experiments over the last few decades also revealed phenomena incompatible with the original H-H model, such as the dependence of inactivation on activation (see ref. 7).

What have computational neuroscientists learned from Hodgkin and Huxley? First, they chose the right model system. The squid axon offered technical advantages due to its size and relative simplicity, with only two types of voltage-gated conductances. Second, the H-H model introduced the power of computers for solving quantitative problems in neuroscience. Third, they chose the right level of detail for the model. As Hodgkin and Huxley were careful to point out, the fits of the equations to the experimental data were not perfect, and could easily have been improved by adding more parameters. The H-H model thus compactly captured the essence of the behavior. Finally, perhaps their most important and intangible influence was the style of their discovery. The H-H model was so elegant and unprecedented in the quantitative and complete nature of its description that it provided an intellectual framework for biophysical and modeling work that would influence the field for decades. Moreover, their collaboration exemplified a balance between experiment and theory that has rarely been matched.

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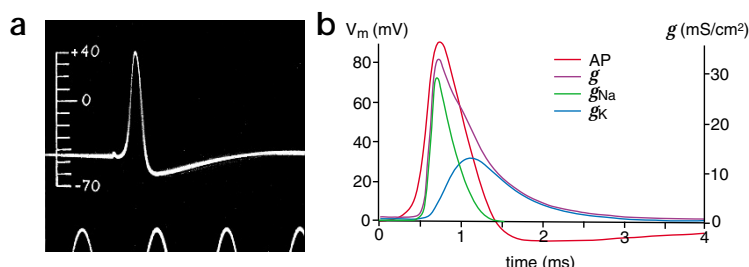


Fig. 1. The action potential: from experiment to theory. (a) The first intracellular recording of an action potential, from squid axon. Time calibration, 2 ms. Modified from ref. 2. (b) Separation of ionic conductances underlying the action potential (AP) in the H-H model. Modified from ref. 6.

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