Fifty years of the Hodgkin–Huxley era

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Modern neuroscientists are accustomed to the detailed information on the structure and function of membrane ion channels that can be obtained by the combination of molecular biology, crystallography and patch-clamp recordings. It can be difficult for us to appreciate how hard it was for humankind to realize that physical events underlie nervous function and, moreover, to appreciate how long it took to devise a realistic model for the generation and propagation of the nerve impulse.

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In 1850, after congratulating his son Hermann for successfully measuring the speed of nerve-impulse conduction with a simple nerve–muscle preparation, August Helmholtz wrote that he nevertheless found surprising the existence of a delay between the psychical ideation of an act and its physical expression as a bodily reaction. This occurred despite the fact that, ~60 years before, Luigi Galvani (1737–1798) had proposed that nerve conduction is due to the flow of an electric fluid accumulated inside animal tissues in a condition of unbalance.

Nervous message: an anomalous slow-type electrical signal

The demonstration by Hermann von Helmholtz (1821–1894) that nerve signals propagate at a finite and measurable speed undoubtedly represented an epochal step toward a modern neural science based on physico–chemical principles. However, the measured conduction rate of ~27 m s^{-1} appeared to be too slow for an electrical event and, thus, seemed somewhat inconsistent with the electric hypothesis of nervous conduction. [This hypothesis had been proposed by Luigi Galvani and supported by the experiments of Carlo Matteucci (1811–1868) and Emile du Bois-Reymond (1818–1896), a few years previously.]

Following the model proposed by du Bois-Reymond, Hermann von Helmholtz assumed that nervous conduction involved electrical molecular rearrangements more complex than a passive current flow along a conducting cable – a view that might have accounted for the strong temperature-dependence of conduction speed. Among the possibilities envisaged by Helmholtz was that a nerve signal propagates in a way comparable to the progressive burning of a tube filled with an explosive mixture. Several years later, a similar analogy reappeared as the *leit-motiv* of the studies performed by Keith Lucas (1876–1916) and Edgar Douglas Adrian (1889–1977) to account for the non-decremental character of nervous conduction. In these studies, the idea that a nerve signal can progress like 'the firing of a train of gunpowder' came along with the demonstration of the highly non-linear 'all-or-none' character of nerve and muscle excitability. [This idea emerged from research carried out some years previously by Henry Bowditch (1840–1911) and Francis Gotch (1853–1913), although it was also anticipated by the 18th-century studies on 'irritability' by Felice Fontana (1730–1805)].

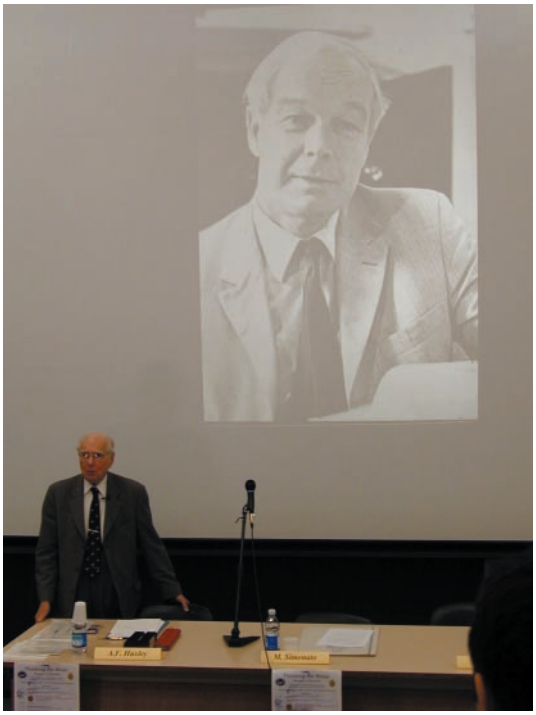

Fig. 1. Andrew Huxley commemorating, on 21 March 2002 at the University of Ferrara (Italy), 50 years of the Hodgkin–Huxley 1952 papers. The slide projection shows Alan Hodgkin. Photograph provided by L. Sbrenna.

Besides the identification of these important phenomenological aspects of nerve (and muscle) excitability, the main advancement of nerve physiology after Hermann von Helmholtz came from Julius Bernstein (1839–1917). Bernstein developed a mechanistic theory of bioelectric potentials, with reference to the electrochemical theory of Walther Nernst (1864–1941). Bernstein explained intracellular negativity as a consequence of the electrochemical equilibrium for K^+ to which membrane was selectively permeable at rest. A nerve impulse would originate from a sudden increase of membrane permeability to all ions ('membrane breakdown'), which would bring the potential difference toward zero.

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A complex route from 'overshoot' to the Hodgkin–Huxley model

The 40 mV overshoot of membrane potential that appeared in the first intracellular recording of the nervous impulse in the squid giant axon, published by Alan Hodgkin (1914-1998) and Andrew Huxley in 1939 [1], marked both the decline of Bernstein's hypothesis and the emergence of modern membrane electrophysiology. Subsequently, Hodgkin and Huxley (partially in collaboration with Bernard Katz) carried out an impressive series of studies. These led, in 1952, to a model for nerve impulse generation and propagation that is still a reference scheme for membrane physiology. This model was successful on both phenomenological and mechanistic grounds, in that it explained nervous excitation and conduction (including its non-linear characteristics and non-decremental signal progression) on the basis of mechanisms that have been largely supported by subsequent research. As we all know, the Hodgkin–Huxley model accounts for electric membrane events by the passive flow of ions along specific membrane structures, later identified as ionic channels that are opened by changes in membrane voltage. The model was formulated in a series of equations that 50 years ago were an elegant and sophisticated instance of mathematical modelling in biology, and that still maintain a strong impact on modern membrane biophysics. Claude Meunier and Idan Segev accurately discuss the model in this issue of *Trends in Neurosciences*.

Also in this issue is an article by Huxley, co-protagonist with Hodgkin in the extraordinary phase of research through which we have learned the nature of the basic units of the 'electric storm' that flows in our brain circuits, allowing us to hear a sound or music, see a landscape or the visage of a friend, and give the commands to move our hands, to speak and even to think (Fig. 1). Requested to commemorate these studies, Huxley, instead of writing a pompous celebration of the events, has provided a report of some apparently unsuccessful efforts as he and Hodgkin tried to account for generation of nervous impulses, before they finally set out on the path of discovery that led them to their 1952 papers.

Among the things that one can learn from this precious document, which reveals part of the story that has remained until now behind the scenes, is that even great science is not immune from difficulties and errors in its progression, which is much less linear than it appears from published papers. This is particularly true for highly creative research, as undoubtedly was the extraordinary Hodgkin–Huxley performance with the squid giant axon, which makes scientific endeavour both much more interesting and, moreover, rich in what Cajal called *humano aroma*.

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From overshoot to voltage clamp

Andrew Huxley

In 1939, A.L. Hodgkin and I found that the nerve action potential shows an 'overshoot' – that is, the interior of the fibre becomes electrically positive during an action potential. In 1948, we did our first experiments with a voltage clamp to investigate the current–voltage relations of the nerve membrane. Between those dates, we spent much time speculating about the mechanism by which ions cross the membrane and how the action potential is generated. This article summarizes these speculations, none of which has been previously published.

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I got to know Alan Hodgkin before World War II when we were both living in Trinity College, Cambridge. He finished as an undergraduate in 1935 and was a research scholar and, from 1936, a Junior Research Fellow; I came up as an undergraduate in 1935. In the summer of 1939, he went to the marine laboratory at Plymouth to do experiments on the giant nerve fibres of squid. He invited me to join him, which I did at the beginning of August; we left on 30 August because war was obviously imminent.

Finding the overshoot

We had been brought up on the theory of Bernstein [1], according to which the action potential is due to the membrane suddenly becoming permeable to all ions, so that the potential difference across the membrane would fall from its resting value to near zero. This permeability increase had been confirmed experimentally by Kacy Cole and Howard Curtis [2] (Fig. 1). Hodgkin had a hint, from experiments on single nerve fibres of crabs and lobsters, that the action potential might be larger than the resting potential, so that the membrane potential would actually reverse. However, this was uncertain (because it was based on recordings with external electrodes) and was not published until later [3]. At Plymouth, we pushed an electrode down inside squid fibres and found that this was true: at rest the interior was ~–45 mV but at the peak of the action potential it was ~+40 mV. We published this result in a short letter to *Nature* [4], with no explanation for this 'overshoot'.

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