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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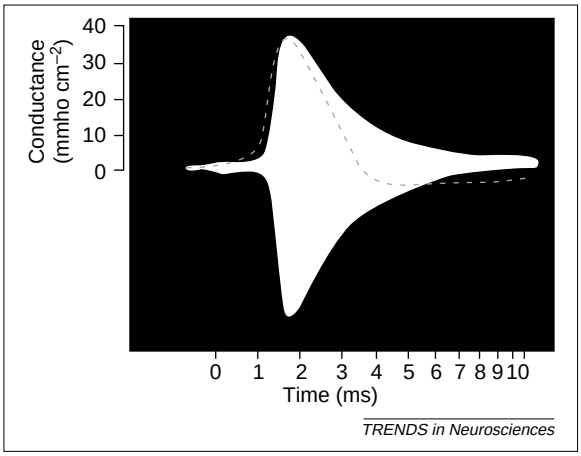

Fig. 1. The area below the solid line is the out-of-balance signal from a high-frequency bridge, representing increase in conductance during the action potential of a squid fibre. Reproduced, with permission, from Ref. [2], © (1939) The Rockefeller University Press. The superimposed dotted line shows the time course of membrane-potential change. Reproduced, with permission, from Ref. [9].

We met occasionally during the war and published a full paper in 1945 [3] with four possible explanations, all of which were wrong. We began discussing how ions might cross cell membranes in early 1945.

The Na^+ idea

Hodgkin and I joined forces again in Cambridge in January 1946. We had already begun to discuss the possibility that Bernstein's increase in permeability during the action potential might be specific for Na^+, so that the membrane potential would approach the equilibrium potential for Na^+, perhaps +60 mV inside. It was known that excitable tissues lose K^+ when active [5] and in 1946 Hodgkin and I used an indirect method to estimate the amount of K^+ lost per impulse by a nerve fibre. We found that the charge carried outwards by K^+ was enough to restore the resting potential after a spike, and in our paper we suggested that the rising phase might be due to entry of Na^+ [6]. This was shown to be correct by Hodgkin together with Bernard Katz in 1947 using squid fibres [7]; it had been impossible to do so earlier because the laboratory at Plymouth had been severely damaged by bombing during the war.

Although we were also engaged in experimental work, we spent a lot of time in 1946, 1947 and the first half of 1948 in speculative discussions about the mechanism by which ions cross membranes, and how an action potential might be generated by the currents carried by ions under the influence of membrane potential changes. I computed (by hand) several action potentials on the basis of these ideas. These speculations will form the substance of this article as nothing has been published previously about them, although Hodgkin drafted a full-length paper in early 1948.

The voltage clamp

Hodgkin realized that measuring the current–voltage properties of the membrane would require a 'voltage clamp' – that is, a feed-back system to control the potential difference across the membrane. Without such a device, the instability that causes the explosive character of the action potential would make such measurements impossible. Cole had also realized this, and in 1947 he used an apparatus of this kind on squid fibres [8]. He showed that there was no discontinuity in the current–voltage relationship, although there was a region of instability in which raising the internal potential increased the inward current.

It was in the summer of 1948 that Hodgkin, Katz and I did our first experiments with the voltage clamp. Hodgkin and I continued these experiments in 1949, altering the external Na^+ concentration so as to divide the recorded current into components carried by Na^+ and by K^+. We fitted equations to the time- and voltage-dependence of these components, and these were the basis of the reconstruction of the action potential that we published in 1952 [9] and that led to our receiving shares of the Nobel prize for physiology or medicine in 1963. Several of the features that we found experimentally confirmed ideas that we had reached in our speculations, but the actual mechanism by which ions cross the membrane was of a kind that we had not contemplated.

Penetration as free ions

At first, we made calculations on the assumption that free K^+ and Na^+ would enter the lipid phase of the membrane from one side and dissociate from the other. It was of course known that inorganic ions are insoluble in the bulk phase of lipids but it seemed possible that an appreciable number might cross the bimolecular lipid layer that forms the cell membrane. However, we did not see any prospect of finding a basis for a major effect of membrane potential on the rate of penetration, or of selectivity between Na^+ and K^+. Cole had made similar calculations, starting before the war, but these were not published until 1965 and later [10,11].

Penetration in combination with a carrier anion

We therefore switched to considering the possibility that ions (e.g. Na^+) cross the membrane in combination with a lipid-soluble molecule that has a large dipole moment. In the resting state, the membrane potential would hold its negative charge at the outer surface of the membrane but, if the internal potential was raised by a stimulus or by an approaching action potential, it would become free to turn round. Na^+ is more concentrated in the external fluid than inside the fibre so the rate of combination with the negative group will be higher at the outer surface of the membrane than at the inner one. The proportion of journeys across the membrane in combination with Na^+ will, therefore, be higher for inward journeys than for outward and there will be net inward flux of Na^+ down its concentration gradient. In our computations we

assumed that the molecule carried two negative unit charges at one end and one positive at the other, when not combined with Na^+. Equation 1 gives the resulting formula for the instantaneous Na^+ current in runs 1–11; for the later runs it is given by analogous equations.

$$I_{Na}/\text{mA cm}^{-2} = (10\exp{-0.02E} - \exp{0.02E})/(\cosh{0.06E}\,(11\exp{-0.06E} - 2\exp{0.04E})) \quad \text{[Eqn 1]}$$

where E is the internal potential in millivolts. We disregarded the current carried by re-orientation of the dipoles when the membrane potential changed.

We developed the theory further by assuming that the negative group could also combine reversibly with other ions. Combination with H^+ (more concentrated inside than out) with a moderate rate constant, when the internal potential was raised would reduce the Na^+ current ('inactivation'). Rapid combination with Ca^{2+} at the outer surface would provide a store of the carrier that would become available when the internal potential was raised ('buffering'). We published a version of this theory in 1949 [12].

We had shown that the falling phase of the action potential is due to exit of K^+ [6]. To explain the speed of the falling phase, it was necessary to assume that the outward flux of K^+ increased steeply when the internal potential was raised ('outward rectification'). A lag in this rectification would help by accelerating the falling phase without interfering with the rising phase; it would also reduce the amounts of K^+ lost and Na^+ gained in an action potential. A further reason for assuming a delay was that it would explain the inductive characteristic of the resting membrane described by Cole and Baker [13]. Cole [14] drew attention to the inductive characteristic of carbon-filament light bulbs and thermistors. Their electrical resistance falls with rise of temperature so, when a constant voltage is applied, current flows, temperature rises, resistance falls and the current rises – just as it does when a constant voltage is applied to an inductance in series with a resistance. Provided that there is a net outward flux of K^+, the same effect would be produced by a lag in the increase of K^+ current when the internal potential is raised and in the decrease when the internal potential is lowered.

For the first group of action potentials that we computed (runs 1 to 11), we arbitrarily assumed a linear conductance to K^+ that increased with a lag when the internal potential was raised, the steady-state current being given by:

$$I_K = a.\sinh b(E - E_K) \quad \text{[Eqn 2]}$$

where E is the membrane potential (internal minus external) and E_K is the value of E at which K^+ ions are in equilibrium. The value of b determines the steepness of the rectification.

For runs 12 to 36 we assumed that K^+ crossed the membrane in combination with a lipid-soluble univalent anion, leading to a formula for the K^+ current with analogous to that given in Eqn 1 for the Na^+ current. For the final group of runs (37–61), we assumed that K^+ crossed the membrane in an aqueous channel with uniform electrical field through the membrane, according to the theory of Goldman [15].

Computing the action potential

The computations include eleven 'membrane action potentials' – that is, action potentials in which the whole of the membrane area undergoes the same potential changes simultaneously – and three propagated action potentials. The equations for a membrane action potential are ordinary differential equations and I solved them using a hand-operated calculating machine, first by Adams' method [16] and later by the method of Hartree [17]. The main equation for a propagated action potential is a partial differential equation with both distance along the fibre (x) and time (t) as independent variables, and it would have been impracticable to solve this by hand. We therefore assumed uniform propagation at velocity u, so that E was a function of $(x - u.t)$ and $\delta E/\delta t = -u.\delta E/\delta x$. The equation therefore became an ordinary differential equation that could be solved in the same way as a membrane action potential, although the solution went towards plus infinity if the velocity was higher than the true value and towards minus infinity if it was lower. The next run was computed with an adjusted conduction velocity, and the true value was approached by successive approximation.

In all cases, we assumed a membrane capacity of $1\,\mu\text{F cm}^{-2}$ and a resting potential of –70 mV – about the value in squid fibres *in vivo*, although the resting potential of isolated fibres is usually –45 to –50 mV. For runs 1 to 36, we assumed that there was an Na^+ pump that brought the total Na^+ flux to zero at the resting potential, and the equilibrium potential for K^+ ions was also assumed to be –70 mV. For the final runs (37–61) we did not include an Na^+ pump, so the Na^+ influx at the resting potential had to be cancelled by an equal efflux of K^+ and the equilibrium potential for K^+ had to be given the value –84 mV. The ratio of external to internal Na^+ concentration was taken as 10 for the first group of action potentials (runs 1 to 11) and as 100 in all later runs.

Results

Table 1 summarizes the membrane properties assumed for each run and the outcome of the computations. In the first group of action potentials (runs 1 to 4), the membrane potential did not recover to its resting value unless we assumed both inactivation of the Na^+ current and a lag in the rise

Table 1. Membrane properties assumed for the computed action potentials and their outcomes[a]

Run number	Action potential type	Inactivation of Na^+ current	Buffering of Na^+ current	Type of K^+ current	Steepness coefficient (*b* in Eqn 2 of main text)	Lag in K^+ current (ms)	Series resistance (ohm cm^2)	Overshoot (mV)	Complete recovery	Underswing (mV)	Conduction velocity ($m\ s^{-1}$)	Na^+ concentration ratio (out/in)	Equilibrium potential for K^+
1	M	No	No	sinh	0.06	0.2	0	17	No	–	–	10	–70
2	M	Yes	No	sinh	0.04	0.0	0	15	No	–	–	10	–70
3	M	Rate/3	No	sinh	0.04	0.0	0	24	No	–	–	10	–70
4	M	Yes	No	sinh	0.08	1.0	0	25	Yes	0	–	10	–70
5–11	P	----------All as run 4----------						11	Yes	0	18.4	10	–70
12	M	Rate/10	No	Carrier	–	Yes	30	28	Yes	0	–	100	–70
13–32	P	----------All as run 12----------						27	Yes	0	28.0	100	–70
33	M	Faster	Yes	Carrier	–	No	30	---Unstable---		–	–	100	–70
34	M	Faster	Yes	Carrier	–	No	10	74	?	–	–	100	–70
35	M	Faster	Yes	Carrier	–	No	0	83	Yes	0	–	100	–70
36	M	Faster	No	Carrier	–	No	0	26	Yes	0	–	100	–70
37	M	Faster	No	CF	–	No	0	28	Yes	–9	–	100	–84
38–60	P	----------All as run 37----------						16	Yes	–8	29.0	100	–84
61	M	Faster	Yes	CF	–	No	0	81	No	–	–	100	–84

[a]The time constants for inactivation and for the lag in K^+ current when K^+ are carried by an anion are not given because they vary with the membrane potential. Abbreviations: CF, constant field; M, membrane; P, propagated.

of the K^+ current (run 4). I then computed a propagated action potential (runs 5 to 11) using the same parameters as in run 4. I did not carry the computation further than about half-way down the falling phase but it is clear that full recovery to the resting potential was in progress. There was an overshoot but it was only 11 mV and there would have no underswing because the K^+ equilibrium potential was assumed equal to the resting potential. In other respects, the shape of the action potential and the conduction velocity were similar to those recorded from real fibres. By the time the peak of the action potential was reached, the Na^+ current was reduced nearly to half by the inactivation.

For the next run (12; a membrane action potential), inactivation was ten times slower and we included a resistance in series with the membrane capacity, with the result that the overshoot was larger. The potential recovered fully to its resting value. A consequence of the resistance in series with the membrane capacity was that the rate of rise of potential was infinite over part of its range.

We then computed a propagated action potential (runs 13 to 32) with the same parameters as for run 12. The rate of rise did not become infinite, and the shape of the action potential was not unlike that recorded from real fibres, although the rate of rise and the conduction velocity were unrealistically large.

With the Na^+ carrier system fully buffered and with faster inactivation, but no lag in the K^+ current, the system was very unstable until we omitted the series resistance (run 35). Its overshoot was 83 mV, much greater than has been recorded in actual fibres, no doubt because the internal Na^+ concentration was given an unrealistically low value. For run 36, the Na^+ system was not buffered, and inactivation was made faster to compensate for the effect of the lower peak potential.

For run 37, we assumed that K^+ ions crossed the membrane through aqueous channels under the influence of the electric field, which was assumed to be uniform [16]. This gives strong rectification because the K^+ concentration is higher inside than out, but it provides no lag in the K^+ current. Because the Na^+ pump was omitted, the equilibrium potential for K^+ (–84 mV) was more negative than the resting potential (–70 mV). At the end of the falling phase, the Na^+ influx was reduced by inactivation, so the membrane potential fell to a level between these two values ('underswing'), as seen in real isolated squid fibres. We then computed a propagated action potential with the same parameters (runs 38 to 60, completed in April 1948). The result (Fig. 2) again showed an underswing but differed from real action potentials in that the overshoot was too small and the recovery was too slow. The velocity was also too high.

We did one more membrane action potential (run 61) with the same parameters, except that the Na^+ current was buffered and the inactivation was slower. As a result, the overshoot was much larger but the potential did not recover to its resting value.

In the spring of 1948, after our first experiments with the voltage clamp, I computed another action

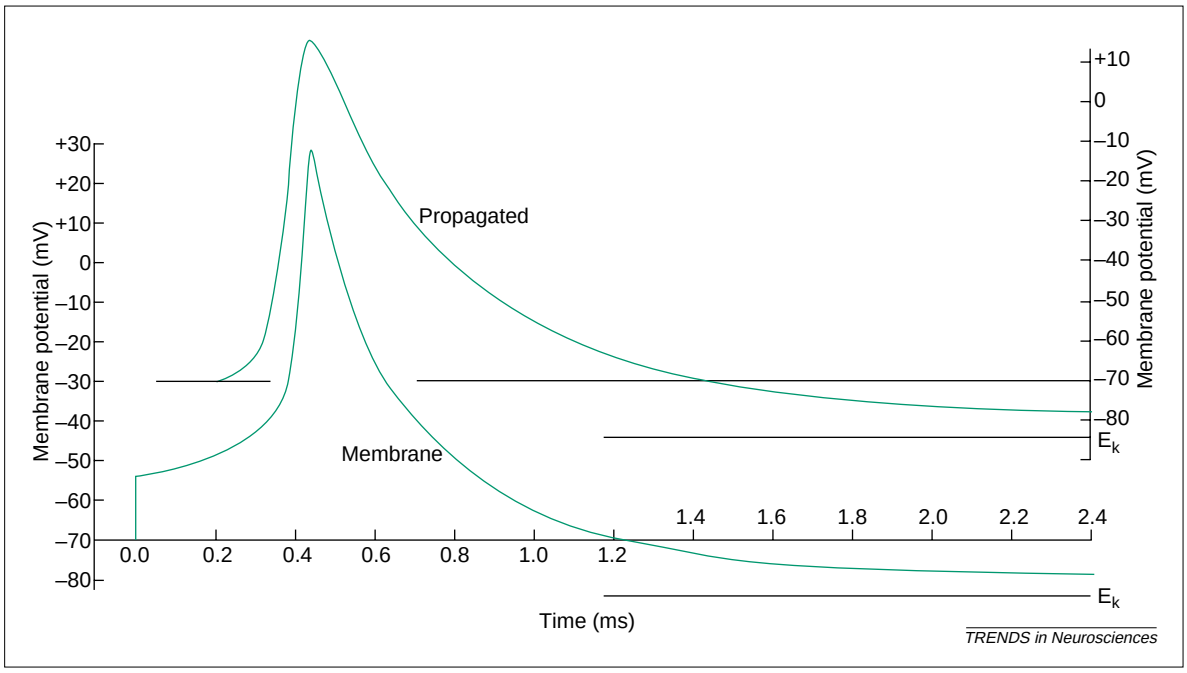

Fig. 2. Computed action potentials. Lower curve and left-hand scale: membrane action potential, run 37. Upper curve and right-hand scale: propagated action potential with the same membrane properties (run 60). The peak is lower in the propagated case because part of the net inward ionic current flows longitudinally inside the fibre ($\delta^2E/\delta x^2$ negative) and does not contribute to changing the charge on the membrane capacity.

potential on the assumption that Na^+ and K^+ ions crossed the membrane in combination with lipid-soluble anions. We adjusted the parameters for the ionic currents so as to match the time course of the total current measured with the voltage clamp at different membrane potentials. We included a lag in the K^+ current but no inactivation of the Na^+ current. The result, published in 1949 [11], was a good imitation of a real membrane action potential.

Discussion

The action potentials computed before our voltage-clamp experiments showed that we could obtain an action potential with roughly the right characteristics by assuming that the Na^+ current underwent inactivation, with or without a delay in the K^+ current – although when we did not include a delay the falling phase was much too slow. These conclusions certainly helped us in interpreting our voltage-clamp records. The action potential computed after our first voltage-clamp experiments showed that a delay in the K^+ current could be sufficient without inactivation of the Na^+ current, although without inactivation the loss of K^+ and the gain of Na^+ would be very much greater than with it. Our experiments in the following year showed that inactivation does occur, as well as a lag in the K^+ current.

By contrast, our final results with the voltage clamp showed clearly that the ions did not cross the membrane in combination with a lipid-soluble anion. We did not see the currents that would have been carried by movement of the uncombined anions, and the instantaneous current–voltage relations were linear both for Na^+ and for K^+ ions. We interpreted our results on the assumption that the ions crossed through channels that were opened or closed by alterations in the membrane potential. This has been amply confirmed, both by identifying the channel proteins through their genes [18] and by recording the currents through single aqueous channels [19,20]. But I do not believe that we considered this possibility at any time during our speculations in 1946–1948. There is no mention of it in Hodgkin's unpublished draft for a paper, written in early 1948.

Several of our systems, including the final ones, did not include a lag in the current–voltage relationship for K^+ ions. We ought to have realized that a substantial delay was clearly shown by the records of impedance change during the action potential published by Cole and Curtis in 1939 (Fig. 1). I do not remember discussing this point.

There are two morals that can be drawn from this story. First, showing by mathematical simulation that a theory leads to plausible results is not evidence that the theory is correct. Second, it is easy to fail to think of an idea that with hindsight seems very obvious. We felt stupid not to have considered that ions might pass through channels that are opened and closed by membrane-potential changes, just as we did for failing to think of the Na^+ theory until six years after finding the overshoot. Likewise, my grandfather T.H. Huxley, known as 'Darwin's bulldog', recorded that his response on making himself master of the central idea of the *Origin of Species* was: 'How stupid not to have thought of that!'.

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Playing the Devil's advocate: is the Hodgkin–Huxley model useful?

Claude Meunier and Idan Segev

Hodgkin and Huxley (H–H) model for action potential generation has held firm for half a century because this relatively simple and experimentally testable model embodies the major features of membrane nonlinearity: namely, voltage-dependent ionic currents that activate and inactivate in time. However, experimental and theoretical developments of the past 20 years force one to re-evaluate its usefulness. First, the H–H model is, in its original form, limited to the two voltage-dependent currents found in the squid giant axon and it must be extended significantly if it is to deal with the excitable soma and dendrites of neurons. Second, the macroscopic and deterministic H–H model does not capture correctly the kinetics of the Na^+ channel and it cannot account for the stochastic response to current injection that arises from the discrete nature of ion channels. Third, much simpler integrate-and-fire-type models seem to be more useful for exploring collective phenomena in neuronal networks. Is the H–H model threatened, or will it continue to set the fundamental framework for exploring neuronal excitability?

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It has taken three centuries to clarify the nature of the nervous impulse, from the questioning of Descartes [1] and Newton on 'animal spirits' and the discovery of 'animal electricity' by Galvani [2] to the final answer provided by the Hodgkin–Huxley (H–H) model [3]. Hodgkin and Huxley cleverly combined the voltage-clamp technique [4], manipulations of ionic concentrations and quantitative modeling [5] (Box 1) to demonstrate that spike generation is a nonlinear phenomenon arising from voltage-dependent membrane conductances. In this new conceptual framework, action potentials naturally appear as nonlinear solitary waves that travel at constant shape and velocity in a uniform axon.

Proving that the neuronal membrane behaved nonlinearly constituted a major breakthrough in science that is best appreciated in the historical perspectives presented by Hodgkin and Huxley themselves [5,6]. In 1952, the importance of nonlinearities was well recognized in chemical kinetics, reaction-diffusion equations and populations dynamics (e.g. the Lotka–Volterra equations). Nonlinear waves had also been known for a long time in hydrodynamics [7], but their nature was only understood in the 1960s. It was at that time too that nonlinear optics developed, with the discovery of harmonics generation in laser-illuminated materials, and that physics ceased to focus on the linear properties of materials.

Physics accounts for a wealth of experimental phenomena by establishing fundamental equations that govern the evolution in time of the relevant observable factors. An example is the Navier–Stokes equation that governs the flow of fluids and is successfully used in a range of contexts, from laboratory studies of convection to turbulence around the wings of airplanes. Are the H–H equations (Box 1) more than a good model of the action potential? And do they provide us with a 'natural law' of neuronal excitability that is useful extensively?

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