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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?

Published online: 23 September 2002

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?

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



Box 1. The Hodgkin–Huxley equations

Action potential conduction on the squid axon is governed by the partial differential equation

$$-\frac{d}{4R_i} \frac{\partial^2 V}{\partial x^2} + C \frac{\partial V}{\partial t} + G_{leak}(V - V_{leak}) + G_{Na} m^3 h (V - V_{Na}) + G_K n^4 (V - V_K) = 0$$

where C is the capacitance per unit area of the axon (of diameter d and axoplasmic resistivity R_i); G_{leak} , G_{Na} and G_K are the maximal conductances per unit area of the leak, transient- Na^+ and delayed-rectifier- K^+ currents, respectively, and V_{leak} , V_{Na} and V_K are the corresponding reversal potentials. In the space-clamped condition, where an electrode is inserted longitudinally along the axon, the first term (corresponding to the axial current) disappears and the partial differential equation above becomes an ordinary differential equation. An extra term must also be added to the right-hand side to account for the current flowing through the electrode.

The presence of the voltage-dependent variables m (Na^+ -current activation), h (Na^+ -current inactivation) and n (K^+ -current activation) make the partial differential equation above nonlinear. These gating variables satisfy first order kinetic equations of the form

$$\tau_x (V) \frac{dx}{dt} = x_\infty (V) - x$$

where the sigmoid function x_∞ gives the level of (in)activation achieved in voltage clamp, and τ_x is the relaxation time constant of variable x ($x = m, h$ or n). These kinetic equations can be rewritten as

$$\frac{dx}{dt} = \alpha_x (V) (1 - x) - \beta_x (V) x.$$

The rate functions α_x and β_x are now interpreted as mean transition rates of ionic channels from closed to open state and vice versa. Values of all parameters involved – obtained by fitting voltage-clamp data – can be found in Ref. [a].

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The H–H model suffers from several weaknesses. First, researchers seldom use the original H–H equations, which only incorporate two voltage-dependent ionic currents, but rather, they use H–H-like models, adding new currents as required by the specific membrane that is modeled. This makes the universality of the H–H equations questionable. A more serious objection is that the macroscopic H–H equations are not derived from a microscopic description of the neuronal membrane grounded on the opening and closing of ionic channels. Most notably, this led to an incorrect prediction of the inactivation kinetics of the Na^+ channel [8,9]. Moreover these deterministic equations cannot account for ionic ‘channel noise’ [10–12]. Finally, theoretical investigations of collective phenomena in neuronal networks, such as collective synchronization of neuronal activity, often rely on much simpler and more tractable models of the single neuron than that used by Hodgkin and Huxley. Here, we address these issues in turn, with little reference to experiments and a strong bias toward theoretical studies, reflecting our backgrounds.

A general framework for neuronal excitability?

The studies of Hodgkin and Huxley provided the appropriate conceptual framework for understanding

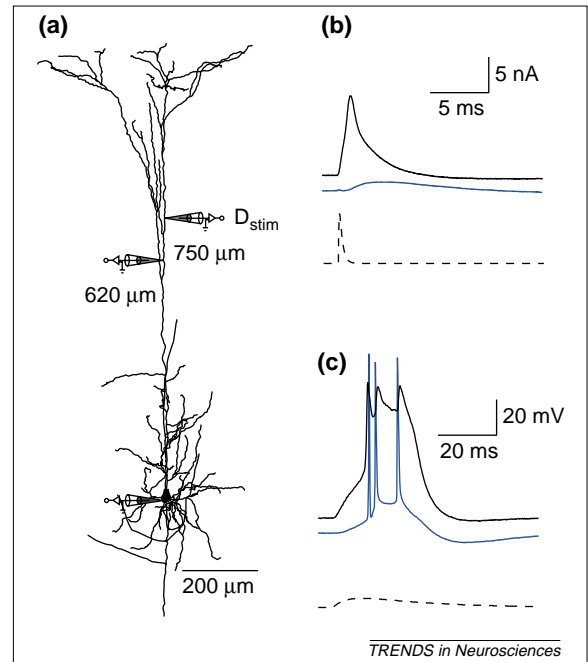


Fig. 1. Dendritic and axo-somatic action potentials.

(a) Reconstruction of a biocytin-filled L5 pyramidal neuron showing the sites of current injection (D_{stim} , 750 μm from soma) and recording (620 μm from soma and at the soma). (b) Brief current injections (dashed trace) elicited an all-or-none event in the dendrite (black trace) that did not propagate to the soma (blue trace), but appeared there as a ‘boosted EPSP’ (excitatory postsynaptic potential). (c) Longer current injection elicited a complex dendritic action potential (black trace) with three corresponding Na^+ action potentials at the region of the soma and/or axon (blue trace). Traces shown in (b) and (c) correspond to threshold current injection. Adapted, with permission, from Ref. [49].

spike propagation in axons: uniform and saltatory conduction, as well as the impact of geometrical heterogeneities (e.g. branching and varicosities) and presynaptic inhibition on spike propagation [13], could be understood from that framework. Further electrophysiological experiments extended the H–H approach to somata, showing that a variety of voltage- or Ca^{2+} -dependent currents regulate the firing pattern of motoneurons [14] and pyramidal cells, and underlie sub-threshold membrane voltage oscillations [15] and resonance properties [16,17]. In recent years, it has become clear that dendrites are equipped with a wealth of voltage- or Ca^{2+} -dependent channels [18]. These can give rise to local spikes in dendrites and dendritic spines (Fig. 1) and support backpropagation of action potentials from the axo-somatic region into the dendrites [19,20]. Membrane nonlinearities and action potentials now pervade our view of neurons and this forces us to reconsider their operating principles. The original H–H model, with its two voltage-dependent currents, cannot account for all of the phenomena observed, although appropriate models can be constructed within the same general framework by adding other ionic currents.

In addition to demonstrating voltage-dependent membrane currents, the H–H model for the

Claude Meunier
Laboratoire de
Neurophysique et
Physiologie du Système
moteur (UMR 8119 CNRS),
Université René
Descartes, 75270 Paris
cedex 06, France.

Idan Segev
Dept of Neurobiology,
Institute of Life Sciences,
and Interdisciplinary
Center for Neural
Computation, Hebrew
University, Jerusalem
91904, Israel.

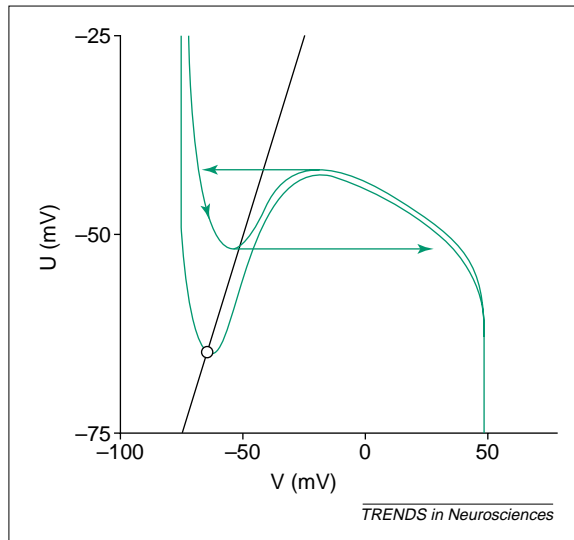


Fig. 2. Onset of firing in a two dimensional model derived from that of Hodgkin and Huxley. Na^+ current activation is assumed to be instantaneous and the variables h (Na^+ -current inactivation) and n (K^+ -current inactivation) are replaced by voltage-like variables U_h and U_n , which are combined into a single slow variable, U . Nullclines – on which the derivative of one variable vanishes – and asymptotic trajectories are displayed in the phase plane (V , U) for two values of the injected current: $I = 0$ and a value above the current threshold for firing. The first nullcline – on which dV/dt vanishes – is N-shaped and quite sensitive in the hyperpolarized voltage range to the amount of current injected. The second nullcline – on which dU/dt vanishes – is simply the straight line $V = U$. For $I = 0$ (lower curve) the nullclines intersect at a stable fixed point (circle) and the neuron is quiescent. For values of I greater than the threshold (upper curve, $I = 10 \text{ nA}$) the fixed point is unstable and the neuron displays periodic oscillations (arrows) on a stable limit cycle. The study is straightforward in the unrealistic but useful limit where recovery becomes infinitely slow. The limit cycle (arrows) then consists of epochs of slow evolution along the left or right branch of the first nullcline separated by jumps (at constant U) from one branch to the other. The analysis can be extended to more realistic conditions by using singular perturbation theory, an appropriate approach for studying systems involving several time scales. Reproduced, with permission, from Ref. [23].

space-clamped squid axon (Box 1) paved the way for the mathematical analysis of neuronal excitability. Applying the concepts and methods from the theory of differential equations provides us with a strong qualitative handle on the origin of the large firing repertoire of neurons [21]. Thus, one can investigate the ‘geometry of excitability’ by ‘reducing’ the H–H model to simple relaxation oscillators [22,23] that preserve the nonlinear character of the original model, but that involve only two variables: the membrane potential and a slower ‘recovery’ variable. One can then perform a phase-plane analysis that reveals the geometric nature of the solutions (Fig. 2; fixed points correspond to a steady state of the membrane and limit cycles correspond to the regular firing of spikes). Phase-plane analysis shed light on the behavior of excitable membranes near to their threshold for spiking [24], demonstrating how firing at very low frequencies could occur. Its extension to higher-dimensional systems involving slow ionic currents (multi-parameter singular perturbation theory) allowed applied mathematicians to

understand the basic scenarios that lead to bursts of firing activity [25].

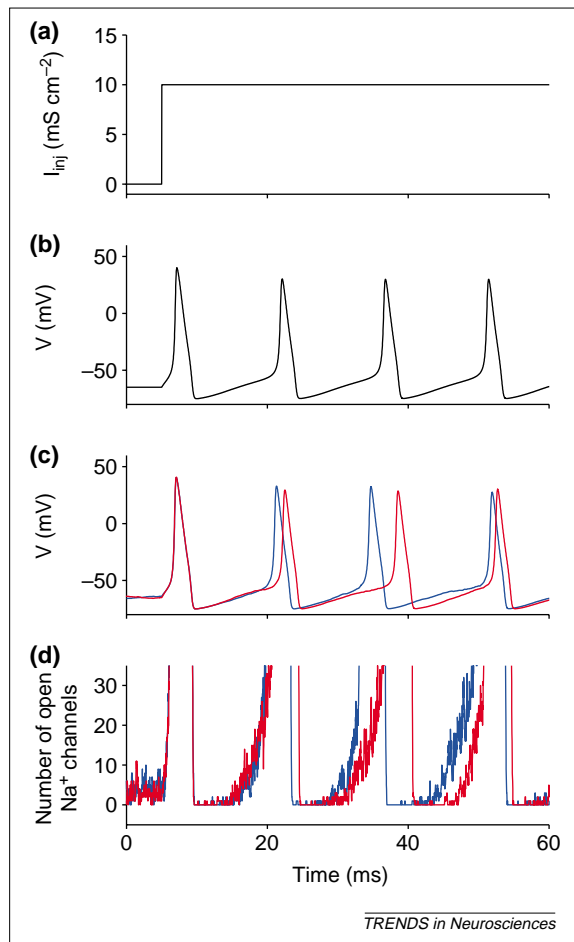
An alternative approach with which to explore mathematically neuronal excitability in the vicinity of the current threshold is bifurcation theory [26]. This theory unravels why and how a fixed point of a differential system (the resting state of the neuronal membrane) becomes unstable when a control parameter (e.g. the injected current) changes. This clarifies the relationship between the fixed point and the stable-limit cycle (regular spike firing) that emerges at the bifurcation point (current threshold). It relies on a linear and nonlinear analysis of the behavior of the system near to the fixed point, completed when needed by a qualitative investigation of the global dynamics of the system. The application of bifurcation theory to neurons clarified the interplay between the panoply of membrane currents, the current–voltage curve, the minimal firing frequency and the shape of the current frequency curve near the threshold for spike firing.

Levels of description: microscopic versus macroscopic

The H–H equations share one important feature with the laws of classical physics: they provide a simple macroscopic and deterministic description of a phenomenon that ultimately arises from the microscopic and random behavior of the system. Thus, the H–H model squeezes into just four macroscopic variables (the membrane voltage, V , together with three gating variables, m , h and n) the random openings and closings of a myriad of ion channels – in much the same way as Fick’s law provides a macroscopic description of the diffusion of a chemical in terms of its concentration without explicitly considering the underlying Brownian motion of innumerable molecules.

In physics, macroscopic laws generally predate microscopic descriptions. The Navier–Stokes equation, for instance, was never derived from a kinetic model of molecular dynamics. Similarly the H–H equations were written on an empirical basis and were not built on a microscopic description of the excitable neuronal membrane. Nonetheless, Hodgkin and Huxley laid the basis for gating theory by suggesting that charged ‘particles’ moving inside the membrane controlled its permeability to Na^+ or K^+ [3], although they did not interpret their results in terms of voltage-gated ionic channels [5,27]. This is hard to believe in retrospect, because the kinetic H–H equations are now readily interpreted [28] as describing a set of ion channels switching randomly between two states (open and closed). Actually, the very notion of ionic channels remained debated [27,29] until 1980, when single-channel recordings became possible [30]. This new technique largely substantiated H–H views, and it could be said that the H–H equations predicted the tetrameric nature and gating properties of the K^+ channel. This demonstrates well the power of macroscopic

Fig. 3. Deterministic versus stochastic models. The behavior of a Hodgkin–Huxley model of an excitable membrane patch of $600\ \mu\text{m}^2$ with 10 800 K^+ channels and 36 000 Na^+ channels is compared to the behavior of a corresponding microscopic model. Responses to a depolarizing current pulse (a) are shown for the deterministic model (b) and for two implementations of the corresponding stochastic model (c, in blue and red). Note the jitter in spike firing times in the stochastic model, which results from fluctuations in the small number of ion channels that are open below threshold for spike firing (d).



approaches and illustrates the general fact that equations always contain much more than it first seems. However, gating current measurements and single-channel recordings also revealed important discrepancies between the H–H model and the actual behavior of neurons: most notably, the inactivation kinetics of the Na^+ channel turned out to be voltage-independent [8,9]. This, in turn, illustrates the difficulty in deriving a microscopic model from a macroscopic description, and shows that the original H–H model should be modified to fit the microscopic reality. Nonetheless, it introduced the appropriate concepts (activation and inactivation) with which to understand the role of voltage-dependent currents, it accounted for the main features of action potentials and it unraveled the biophysical mechanisms underlying action-potential generation and propagation.

Macroscopic descriptions are always, to some extent, approximate. Plasmas, for instance, display kinetic instabilities of microscopic origin that are not predicted by the macroscopic magneto–hydrodynamic equations. Are there similar limits for the use of the original H–H equations and, more generally, of H–H-like models? Over the past decade it has become clear that the random opening and closing of membrane ion channels can give rise to substantial fluctuations in the number of open membrane ion

channels ('channel noise') and lead to a random spike jitter (Fig. 3). This was both demonstrated using stochastic variants of the H–H model [10–11] and observed experimentally in cortical pyramidal cells *in vitro* [12]. The stochastic nature of voltage-gated ion channels probably has little impact on the response of neurons to stimuli in physiological conditions where synaptic noise dominates. Nonetheless, this shows that the deterministic H–H model is valid only within the limit of a large number of open ion channels. This is certainly the case in axons but does not necessarily hold in weakly excitable dendrites.

Simple and complex models: H–H-like models versus integrate-and-fire models

The H–H model cannot be solved analytically and Huxley had to integrate numerically the nonlinear differential equations with just the help of a desk calculator [5] to compare the voltage evolution predicted by the model with the current-clamp data in the squid axon [3,6,31]. Numerical simulations of H–H-like models were required to study action propagation in axons displaying morphological or electrical heterogeneities, including myelinated axons [32,33]. This required that the axon be regarded as a set of discrete compartments, setting the basis for the now very popular 'compartmental modeling' approach [34], whereby the modeled neuron is subdivided into small isopotential membrane compartments, each described by an H–H-like model and coupled to its neighbors via the cytoplasmic resistance.

Owing to the tremendous increase in computing power, the design of improved numerical algorithms [35] and the availability of simulation packages (e.g. NEURON, GENESIS, SurfHippo), it is now customary to simulate model neurons composed of several hundreds or thousands of compartments. Nevertheless, even state-of-the-art numerical models cannot incorporate the detailed microstructure of neurons. For example, dendritic spines are often so numerous (e.g. 100 000 per Purkinje cell) that they cannot be all modeled individually. As a consequence, they are accounted for by globally changing the electrical properties of the modeled dendrites [36]. When necessary, a few spines that receive direct synaptic input are modeled in detail. In spite of this limitation, 'realistic' models, which take into account the morphological and nonlinear electrical properties of neurons at the spatial scale of $10\ \mu\text{m}$, are now feasible.

Much of our understanding of dendrites still comes from the linear cable theory [37] but several important insights were gained from nonlinear compartmental models for dendrites. For example, using a compartmental model of an unbranched dendrite, Rall [38] showed that shunting inhibition is most effective in vetoing the excitatory synaptic input when the inhibition is placed more proximally than the excitatory input. Conditions that give rise

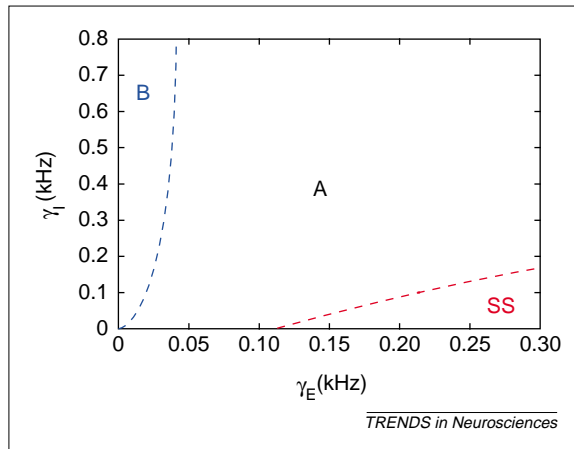


Fig. 4. States of synchrony in large networks of neurons. The network comprises both excitatory and inhibitory neurons, all interconnected and described by a quadratic integrate-and-fire (I-F) model, with parameters randomly varying from neuron to neuron. Stable states of synchrony – asynchrony (A), spike-to-spike synchrony (SS) or synchronized bursts of activity (B) – depend on the decay rates γ_E and γ_I (in kHz) of excitatory and inhibitory synapses, as shown on the phase diagram. Within the formal limits of an infinitely large network, these rates can be determined entirely analytically, without relying on numerical simulations. Adapted from Ref. [44].

to a local action potential in dendrites and dendritic spines, and to an active (but attenuated) back-propagation of the action potential from the soma to dendrites in the weakly excitable apical dendrite of cortical pyramidal neurons, were also highlighted using detailed H–H-like compartmental models [20].

In contrast to their certain usefulness at the single-cell level, detailed compartmental models of neurons have not, until now, been very fruitful for providing new insights into the collective behavior of large networks. For instance, the roles of excitation, inhibition or intrinsic cellular properties like after-hyperpolarization (AHP) on network synchronization was largely clarified by analytical or numerical studies of much simpler models: integrate-and-fire (I–F) type models (linear, quadratic, or with slow current) [39] or phase-oscillator models of conductance-based neurons [40]. Some enlightening studies on network dynamics use merely binary neurons [41] or threshold-linear rate models.

The usefulness of I–F-type models might seem surprising, because the model introduced by Louis Lapicque [42] in 1907 on the basis of extracellular recordings of nerves (now known as the ‘linear integrate-and-fire’ model) does not incorporate the biophysical substrate of neuronal excitability. It describes the neuronal membrane merely as a leaky integrator, as long as the voltage does not reach a preset level at which the firing of a ‘schematic’ spike occurred. This linear model is not a limiting case of the H–H equations [23,43] and it behaves very differently from H–H-like models in many aspects. For instance, the voltage remains close to the spike threshold during a large part of the interspike interval at low firing rate, which makes the Lapicque

model extremely sensitive to changes in the injected current near to the current threshold.

The interest in I–F models stems from the complexity of the model of Hodgkin and Huxley. The original space-clamped H–H model already involves 16 parameters that specify membrane capacitance, maximal ionic conductances, reversal potentials and kinetics of the two voltage-dependent currents involved. When extra currents are added or the morphology of neurons is taken into account, the number of parameters becomes huge. As a consequence, most numerical studies of ‘realistic’ neuron models rely on a parameter-tuning strategy to replicate experimental results. In general, this provides much less insight into the nature of network effects and on the key parameters that govern the observed behaviors than do analytical studies of simple models. In particular, analytically tractable models allow theoreticians to establish phase diagrams where the stability domains of the possible solutions and the transition lines between these solutions clearly stand out (Fig. 4).

Therefore, I–F models constitute a good choice for determining the stable states of activity of large networks when only the basic features of neurons seem important, and complexities such as the detailed morphology are deemed irrelevant. But, even then, the modeling of neuronal dynamics still pivots around H–H models. It is customary to check *a posteriori* that results derived for linear I–F models are still valid for H–H models. The impact of neuronal discharge properties on network synchronization can be investigated by adding to the Lapicque model features such as AHP borrowed from conductance-based models [44]. Nonlinear I–F models can also be chosen on the criterion that they behave quite similarly – qualitatively and quantitatively – to conductance-based models. This is the case in several recent studies on synchronization [45,46] and persistent activity [47] in large neuronal networks that make use of the quadratic I–F models [48]. Generalized multidimensional I–F models are also useful for investigating resonance properties of neurons and their impact on network synchronization (N. Brunel, unpublished).

Conclusion

The original H–H equations not only provide a good model for spike generation and conduction in the squid axon, but also incorporate the important features of neuronal excitability, activation and inactivation of voltage-dependent currents taking place at different time scales. H–H-like equations are powerful in that they capture compactly and mathematically a physical system – the neuron – that exhibits highly nonlinear properties. The proper biophysical level of abstraction used by Hodgkin and Huxley enables direct experimental assessment of model parameters, as well as the natural extension of the model to more complicated excitable membranes than that of the squid giant axon. It is, thus, unequivocal that the

Acknowledgements

We would like to thank Philippe Ascher, Nicolas Brunel, David Hansel, and Daniel Zytnicki for careful reading of the manuscript and for their many useful comments. We are also indebted to Mickey London for generating Fig. 3.

H–H model set the fundamental framework for exploring neuronal excitability.

Even so, theoreticians often prefer to use simpler ‘phenomenological’ models that are more tractable and that appear sufficient for investigating important aspects of the collective dynamics of networks. Interestingly, the H–H conductance-based approach still ‘sneaks’ into these models because many features of neuronal firing (e.g. adaptation, bursting and resonance) crucially depend on the activation of currents at the sub-threshold voltage regime.

So, avoiding modeling of the full action potential does not mean rejecting the H–H model and its descent. It is, rather, the happy marriage (with natural tension) between phenomenological and H–H-like models that provides the ‘model for all seasons’: from synaptic integration on dendritic trees to collective dynamics in large networks. The success of the H–H model in holding stable over all these seasons, including the recent years of exciting findings on membrane excitability in axons and dendrites, tells us that the H–H model is here to stay.

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