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Gaspar Cano
University of Lisbon

Rui Dilão (✉ ruidilao@tecnico.ulisboa.pt)
University of Lisbon

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Action potential solitons and waves in axons

Gaspar Cano\textsuperscript{1,2}\textsuperscript{*} and Rui Dilão\textsuperscript{1,3}\textsuperscript{†}

\textsuperscript{1}\textsuperscript{*}Department of Physics, Nonlinear Dynamics Group, University of Lisbon, Instituto Superior Técnico, Av. Rovisco Pais, Lisbon, 1049-001, Portugal.

\textsuperscript{2}Department of Biology, Institute for Theoretical Biology, Humboldt-Universität zu Berlin, Berlin, 10115, State, Germany.

\textsuperscript{3}Institut des Hautes Études Scientifiques, 35, route de Chartres, Bures-sur-Yvette, 91440, France.

\textsuperscript{*}Corresponding author(s). E-mail(s): ruidilao@tecnico.ulisboa.pt; Contributing authors: gaspar.cano@hu-berlin.de;

\textsuperscript{†}These authors contributed equally to this work.

Abstract

We show that the action potential signals generated by the Hodgkin-Huxley cable model are reaction-diffusion solitons and waves. Action potential spikes travelling in opposite directions of the axon annihilate when colliding with each other or with the axon boundaries. Through numerical simulations, we characterise the properties of these action potentials, deriving their characteristic curves. We propose several tests to validate or falsify the Hodgkin-Huxley cable model.

Keywords: Action potential waves, Action potential solitons, Hodgkin-Huxley cable model, reaction-diffusion waves, reaction-diffusion solitons

1 Introduction

The electrophysiological states of cells and axons are characterised by an electric potential drop across the cellular membrane, maintained through the exchange of ions between the cytoplasm and the intercellular space, \cite{1}, \cite{2}, and \cite{3}. To describe the electrical properties of axonal signalling, in a sequence of papers, Hodgkin and Huxley (HH) introduced a mathematical model aimed
at describing the propagation of action potentials in the axoplasm, comparing their model results with voltage-clamp data taken from the axon of the squid *Loligo*, [4].

In current-clamp experiments, one of the electrodes is located in the extracellular space and the second one is a thin wire introduced longitudinally into the axon, [5], [6, p. 143]. When the axon is electrically excited away from the inner electrode, the measured electrical potential drop is a spiky (negative) signal that evolves in time, [7, p. 24]. In principle, this results from a longitudinally propagating signal — the action potential — measured by the inner electrode inside the axon.

The derivation of the HH mathematical model for the action potential phenomenon relies on the analogy between the potential difference measured on both sides of the cellular membrane and an electric circuit containing a variable resistance and a power source in series, both in parallel with a capacitor. This analogy is phenomenological, aiming to explain the gating mechanism of ion channels across a cellular membrane through a variable resistance. The power source and the capacitor describe a source of energy and a potential energy storage reservoir. The biological functions of the three electric components are unspecified, [5, p. 152].

In a synthetic form, the HH cable model equations are

\[
\begin{align*}
\tilde{D} \frac{\partial^2 V}{\partial x^2} &= C \frac{\partial V}{\partial t} + F(V, \vec{n}) + i(x, t) \\
\frac{\partial \vec{n}}{\partial t} &= \tilde{G}(V, \vec{n}),
\end{align*}
\]

where \(t\) is time, \(x\) is the position coordinate along the axon, \(V(x, t)\) is the potential drop across the cellular membrane, \(\tilde{D}\) is a diffusion coefficient of the potential drop along the axoplasm, \(C\) is the capacitance associated with the electric potential difference between the interior and the exterior of the axon wall, and \(i\) is a current density eventually describing an external forcing, as in current-clamp experiments, or simply a neuronal signal originated in the soma of the neurone. The vector function \(\vec{n}(x, t) = (n, m, h)\) contains gating variables specific to ion types. The functions \(F(V, \vec{n}) : \mathbb{R}^4 \to \mathbb{R}\) and \(\tilde{G}(V, \vec{n}) : \mathbb{R}^4 \to \mathbb{R}^3\) describe, respectively, the local response to the potential drop changes across the cellular membrane and the gating mechanisms of ion channels, [8]-[12].

Hodgkin and Huxley conjecture that the propagation properties of the action potential are analogous to those of a propagating elastic wave, [4, p. 522]. They assumed the existence of an unknown mechanism which would impose an elastic wave-type propagation inside the axon, such that the transmembrane potential would travel according to the wave equation

\[
\frac{\partial^2 V}{\partial x^2} = \frac{1}{\theta^2} \frac{\partial^2 V}{\partial t^2},
\]
where $\theta$ is an unknown ad hoc speed constant. Even though the solutions of equations (1) and (2) are generically incompatible (equation (1) is of parabolic type, and equation (2) is of hyperbolic type), Hodgkin and Huxley have substituted the first term in (1) by the second term in (2), obtaining

$$\left\{ \begin{array}{l}
\frac{1}{\theta^2} \frac{d^2V}{dt^2} = \frac{C}{D} \frac{dV}{dt} + \frac{1}{D} F(V, \vec{n}) + \frac{1}{D} i(x, t) \\
\frac{d\vec{n}}{dt} = \vec{G}(V, \vec{n})
\end{array} \right.$$  \tag{3}

which is an ordinary differential equation. Hodgkin and Huxley numerically integrated the ordinary differential equation (3) for guessed choices of the free parameter $\theta$ and compared the results with voltage-clamp data. Even though they obtained numerical results similar to their experimental data for some values of the chosen parameters, it is clear that an ordinary differential equation as (3) can’t correctly describe a time-dependent spatial phenomenon such as the propagation of an electric signal along the axon. Nevertheless, the merit of HH model equations (1) can be evaluated independently from the inconsistent simplification of assumptions (2) and (3). This paper aims to clarify what predictions equations (1) make so that HH’s model can be evaluated free of mathematical inconsistencies.

Beyond the mathematical inconsistency just described, there is a lack of the specific biochemical mechanisms that lead to the electric analogue of the model. Several authors, based on physical and chemical principles, provided plausible evidence of the inadequacy of the HH model, [13], [14], [15], and [16]. For a recent review of the discussion on the validity of the HH model, we refer to [17]. Despite its disputed biological and physical foundations, we can argue that the HH model is a heuristic approach to a plausible electric analogue of the ionic interactions in the axon. Understanding its solutions can still provide great insight into the mechanisms that govern action potential propagation.

The diffusion-free HH model ($\tilde{D} = 0$ in (1)) has been extensively analysed from the point of view of its bifurcations, [8] – [10], and [18]. In [18], it was shown that action potential spikes originated from a type I intermittency phenomenon ([19]) associated with a saddle-node homoclinic bifurcation of limit cycles. For the case with diffusion ($\tilde{D} > 0$), it was shown that, in the simplest case, action potentials are solitary spiky signals that propagate without attenuation along the axon.

Some propagation properties of action potential signals have also been studied in [20]. These authors have analysed localised high amplitude perturbations of the transmembrane potential in the HH equations (1). By manipulating the initial distribution of the membrane potential along the axon, they found that action potential fronts propagate as solitary waves, identifying the collisional annihilation of action potential spikes. This has been analysed for several values of the potassium Nernst potential $V_K^N$, with $i = 0$. These findings
are essential for understanding the fluctuation dynamics of the transmembrane potential but are challenging to observe in axons with voltage-clamp experimental techniques.

Due to the solitary characteristics of action potential signals observed by Hodgkin and Huxley, several authors attempted to explain the solitonic properties of the action potential with a non-linear elastic wave propagation mechanism ([21], [22] and [23]). These authors reported that action potential spikes travelling in opposite directions of the axon do not annihilate when colliding. With opposite conclusions, [24] reported that action potential spikes do annihilate at collision, and an HH-type compartment model supported these findings. In both cases, the experimental validation is not described in detail. Based on empirical observation, [25] suggested that action potential isolated spikes may annihilate.

Reaction-diffusion (parabolic) and wave-type (hyperbolic) equations may have oscillatory solutions in time and space and localised pulse-type solutions or solitons. However, the properties of the waves and solitons of the two types of equations can be distinguished by their behaviour at collision and spatial boundaries. As we will show below, the action potential signals generated by the parabolic HH model equations (1) are of reaction-diffusion type as in reaction-diffusion chemical kinetics models, [26] and [27]. Unlike those of hyperbolic equations, these waves and solitons are known to annihilate when colliding with each other and with spatial boundaries.

In this paper, we characterise reaction-diffusion waves and reaction-diffusion solitary waves or solitons. The qualitative properties of these results and the comparison with experimental data can be used to test the validity and falsifiability of the HH model.

The paper is organised as follows. In section 2, we review some of the results of the HH partial differential equation model (1) and some of the properties of its solutions, [18]. We also define the parameter settings of the model and summarise the numerical set of simulations. In section 3, we show that the HH model equations (1) have reaction-diffusion type solitonic and oscillatory solutions, behaving as solitary waves or as solitary wave packets in the intermittent dynamical regime of the diffusion-free equation (1). We derive the interaction properties of this type of reaction-diffusion waves and calculate wave speeds and dispersion relations of asymptotic regimes. Finally, in section 4, we propose several experiments to validate the HH model and summarise the paper’s main conclusions.

2 Action potentials propagate as reaction-diffusion waves

In [18], we have exhaustively analysed the solutions of the HH partial differential equations (1) in a one-dimensional spatial domain [0, L], with L < ∞, and with zero flux or Neumann boundary conditions. We have chosen the current density function: \( i(x, t) = i_0 \), for \( x = 0 \) and every \( t \geq 0 \), and \( i(x, t) = 0 \),
otherwise, and we have done the bifurcation analysis of the solutions of the reaction-diffusion equation (1), as a function of the diffusion coefficient $\tilde{D}$ and of the parameter $i_0$. This particular choice of the external function $i(x, t)$ simulates current-clamp experiments. For the calibrated parameters, propagating action potentials and action potential wave packets are generated near the left boundary of an axon. Some major conclusions derived from the HH model are important to recall:

1) For positive but small values of $i_0$, the shape of the action potential spikes is caused by a type I intermittent response of the HH equations associated with a saddle-node bifurcation of limit cycles of the diffusion-free system of equations ($\tilde{D} = 0$). This particular response is caused by a transient process that anticipates a transition from a dynamics with a unique stable steady-state to a dynamics with two limit cycles, one stable and the other unstable. These isolated spikes propagate without attenuation and therefore are solitary waves or solitons. Near the bifurcation, it is possible to obtain single action potential spikes or packets of propagating action potential spikes, depending on the intensity of the perturbation $i_0$.

2) For $\tilde{D} > 0$ and larger values of $i_0$ when compared with case 1), we found propagating periodic waves of action potential spikes. We have numerically measured the propagation speeds depending on the model’s parameters. This propagation speed is not an external parameter, as assumed in equations (2) and (3).

3) For $\tilde{D} > 0$ and larger values of $i_0$ when compared with case 2), we found solutions behaving chaotically and solutions with a long transient, which, as time passes, converge to a steady homogeneous state (chaotic or type III intermittency) — summarised in figure 1.

4) Action potential formation and propagation only occur if the current stimulus $i_0$ is large enough and persists long enough at some point of the axon. This requirement is essential for forming the action potential at the current injection point. Once this happens, even if $i_0$ is set to zero during the spatial propagation, the action potential will reach the right boundary of the axon without attenuation.

All these properties of the HH partial differential equation model (1) are predictions about the dynamics of action potentials and should be used to validate the HH model.
6  Action potential solitons and waves in axons

To test the above-mentioned dynamic features of the HH model, we use the following parameterisation of equation \((1)\)

\[
\begin{align*}
C \frac{\partial V}{\partial t} &= \tilde{D} \frac{\partial^2 V}{\partial x^2} - g_{Na} m^3 h (V - V_{Na}^N) \\
&\quad - g_K n^4 (V - V_K^N) - g_L (V - V_L^N) \\
&\quad - i(x,t) \\
\frac{\partial n}{\partial t} &= \alpha_n (V)(1 - n) - \beta_n (V)n = G_n (V, n) \\
\frac{\partial m}{\partial t} &= \alpha_m (V)(1 - m) - \beta_m (V)m = G_m (V, m) \\
\frac{\partial h}{\partial t} &= \alpha_h (V)(1 - h) - \beta_h (V)h = G_h (V, h),
\end{align*}
\]

(4)

where

\[
\begin{align*}
\alpha_n &= 0.01 \phi \frac{V + 10}{e^{(V+10)/10} - 1}, \quad \beta_n = 0.125 \phi e^{V/80}, \\
\alpha_m &= 0.1 \phi \frac{V + 25}{e^{(V+25)/10} - 1}, \quad \beta_m = 4 \phi e^{V/18}, \\
\alpha_h &= 0.07 \phi e^{V/20}, \quad \beta_h = \phi \frac{1}{e^{(V+30)/10} + 1}, \\
\phi &= 3^{(T-6.3)/10}.
\end{align*}
\]

(5)

\(V\) is the potential transmembrane drop, measured in mV, \(i\) is a transmembrane current density injected into the axon, measured in \(\mu A/cm^2\), and time is measured in ms. Positive values of \(i\) correspond to currents from outside to inside the axon. In equation \((4)\), the membrane potential is defined following the original HH paper, \([4]\), where the action potential voltage spikes are negative. The gating variables \(n, m\) and \(h\) describe the opening and closing of the channel gates, are specific to the ion type and are dimensionless. The ionic conductances across the cellular membrane are \(g_{Na}\) and \(g_K\), and \(g_L\) is a constant measuring “leak” conductance. \(C\) is the membrane capacitance, and \(\tilde{D}\) is a constant inversely proportional to the resistance (\(\Omega\)), measured along the axon.

The model equations \((4)-(5)\) have been calibrated for the squid giant axon at the temperature \(T = 6.3 ^\circ C, [4]\), and the values of the parameters are: \(C = 1 \mu F/cm^2, g_{Na} = 120 mS/cm^2, g_K = 36 mS/cm^2\) and \(g_L = 0.3 mS/cm^2\), where \(S=\Omega^{-1}\) (siemens) is the unit of conductance. The Nernst equilibrium potentials, relating the difference in the concentrations of ions between the inside and the outside of cells with the transmembrane potential drop, are \(V_{Na}^N = -115\) mV, \(V_K^N = 12\) mV and \(V_L^N = -10.613\) mV. The equilibrium electrophysiological state of the axon is the quantity \(p^*(i) = (V^*(i), n^*(i), m^*(i), h^*(i))\), obtained by equating to zero the equations \((4)\).

Hodgkin and Huxley have shown that the transmembrane diffusion coefficient is \(D = a/(2R_2)\), where \(a\) is the radius of the axon (considered as a cylinder) and \(R_2\) is the specific resistivity along the interior of the axon. For the case of the squid giant axon, \(a = 238 \mu m, R_2 = 35.4 \Omega cm\) and \(\tilde{D} = 0.336 mS\).
To validate the HH model predictions, we simulate the solutions of the reaction-diffusion equation (4) in a domain of length $L$, with zero flux (Neumann) boundary conditions. We use a stable explicit Euler-type numerical method that minimises the global error of the solution. The spatial region is divided into $M$ small length intervals $\Delta x$, such that $L = M \Delta x$. With $D = \tilde{D}/C$ as the renormalised diffusion coefficient, we take the stability condition $D \Delta t / \Delta x^2 \leq 1/2$, [28], and the minimisation condition $D \Delta t / \Delta x^2 = 1/6$, which ensures the error of the solutions is of the order of $\Delta x^6$ [29]. For all simulations, we use the diffusion coefficient suggested by Hodgkin and Huxley, $\tilde{D} = 0.336$ mS, and pick a small enough $\Delta x = 0.125$ cm. For this choice, the error minimisation condition imposes the time step $\Delta t = 0.007747$ ms and ensures the error of the solutions is of the order of $(3.8 \text{ cm}) \times 10^{-6}$. The code to reproduce all simulations is publicly available [30].

3 Results

3.1 Overall behaviour of the HH equations

If an axon is initially at rest $p^*(i = 0)$, it can be perturbed by injecting some transmembrane current. If this current is injected at the point $x = 0$, the transmembrane current density in (4) is $i(x, t) = I_0 \delta(x)/2\pi a$ for every $t \geq 0$, where $\delta(x)$ is the Dirac delta distribution, $I_0$ is the amount of current injected, and $a$ is the axon radius as measured by HH. In figure 1, we show a bifurcation diagram of the HH model as a function of $I_0$ for a chosen diffusion coefficient.

![Fig. 1 Bifurcation diagram of the solutions of the HH equations (4)-(5), for $\tilde{D} = 0.336$ mS, as a function of the parameter $I_0$, adapted from [18]. For this parameterisation, $I^*_1 = 1.087$, $I^*_2 = 5.510$, $I^*_3 = 5.721$, $I^*_4 = 6.533$ and $I^*_5 = 6.540$.](image)

For $I_0 < I^*_1$, the system responds with type I intermittency, generating a finite number of action potential spikes. For $I_0 \in [I^*_1, I^*_5]$, the system oscillates indefinitely, never returning to rest. For $I_0 \in [I^*_1, I^*_2] \cup [I^*_3, I^*_4]$, asymptotically in time, the oscillations converge to a periodic solution. For the small regions $[I^*_2, I^*_3]$ and $[I^*_4, I^*_5]$, the oscillations show chaotic behaviour with period bifurcations. The system shows chaotic intermittency for $I_0 > I^*_5$, generating a finite number of action potential spikes before returning to rest, [18].
3.2 Action potential solitary waves

In the HH model, the action potentials propagate without attenuation. Thus, we can define the characteristic curve of the action potential by the condition $dV = 0$. As $dV = \frac{\partial V}{\partial x} dx + \frac{\partial V}{\partial t} dt = 0$, then $\frac{dx}{dt} = -\left(\frac{\partial V}{\partial t}\right) / \left(\frac{\partial V}{\partial x}\right)$, implying that action potentials may have a well-defined speed. We can follow the action potential space-time evolution by taking the maxima of the functions $-V(x,t)$ as a reference point. We shall call the curves defined by the condition $dV = 0$ the characteristic curves of the solution of the HH equations (4)-(5).

In figure 2, we show the solution of the HH system of equations (4)-(5), responding to an injected current in the type I intermittency parametric region seen in figure 1. In this case, a single action potential spike is generated at the injection point, propagating along the axon and disappearing at the boundary $x = L$. The characteristic curve of the solutions of the HH equations shows a linear profile, and the isolated action potential spike propagates along the axon at a constant speed. The slope of the characteristic curve corresponds to the propagation speed $v = 12.07 \text{ m/s}$.

![Figure 2](image)

**Fig. 2** We show five time snapshots of the solutions $-V(x,t)$ of reaction-diffusion equations (4-5) in a spatial domain of length $L = 100 \text{ cm}$. The bottom snapshot was taken at $t = 5 \text{ ms}$, and the succeeding snapshots differ by time intervals $\Delta t = 25 \text{ ms}$. We have considered that the axon is initially at the rest state $p^*(0)$ and the injected current at $x = 0$ has the value $I_0 = 1.028 \mu A$ during the entire simulation. The system is in the type I intermittency region (figure 1), generating one spike. The dotted line shows a characteristic curve of the solutions of the HH equations. The propagation speed of the action potential spike is $v = 12.07 \text{ m/s}$. The action potential spike annihilates at the boundary $x = L$ without reflection.

In figure 3, we show the solution of the HH system of equations (4)-(5), in the region of type I intermittency, generating a total of three action potential sequential signals — packet of spikes. This figure has been obtained for a larger
value of $I_0$ compared with the simulations in figure 2. The speed of the first action potential spike is the same as in figure 2.

In both figures 2 and 3, the action potentials propagate without attenuation and annihilate at the boundary of the axonal domain. This effect is not observed with elastic waves. These action potentials propagate as solitary reaction-diffusion signals. After the annihilation of the action potentials at the boundary, the axon stays in a non-uniform and non-excitable state ($I_0 \neq 0$). For a signal to propagate again along the axon, the electric state of the axon must return to the rest state $p^*(i = 0)$ so that the neurone may again be excited with a current above the threshold.

In figure 4, we analyse the case where two current sources are injected into the interior of the axon at the longitudinal coordinates $x = L/3$ and $x = 2L/3$. At each injection point, one action potential spike is generated, and during propagation, each of them splits into two action potential spikes, moving in opposite directions. The four action potential spikes have the same amplitude as those in figures 2 and 3. Then, later, the two action potentials that travel towards the centre of the axon collide at $x = L/2$ and annihilate each other — another effect characteristic of reaction-diffusion waves [26], and [27]. The chosen injected current value is also within the type I intermittency region. After the collision at the boundaries, all the spikes disappear. The axon stays in a non-uniform and non-excitable state.
These numerical results show that the solutions of the HH equations do not propagate as elastic waves, as conjectured by Hodgkin and Huxley, but behave instead as reaction-diffusion waves. Moreover, it has been shown that the action potential signals are not reflected at the axon boundary. The dynamic behaviour observed in figure 4 is not compatible with that of elastic waves, where the amplitudes would be halved when the action potential splits in two, and the collision of two waves fronts would not result in annihilation.

3.3 Action potential waves

In this section, we have extended the spatial domain of the simulation to $L = 250 \, \text{cm}$, to perceive better how the action potential changes as it propagates along the axon. We measure the velocity $v$ of the action potentials along the axon, with $v_0$ and $v_L$ corresponding to the values measured at the beginning ($x \approx 0$) and end ($x \approx L$) of the axon, respectively. In figure 5, the axon is excited at $x = 0$ with large currents $I_0$ in three different oscillatory regions of figure 1.

In figures 5a, the neurone is excited with current $I_0 = 3.500 \, \mu\text{A}$, in the periodic oscillatory region (figure 1). The initial speed of the action potentials $v_0$ converges quickly to a fixed value, but the action potential spikes accelerate while propagating through the axon.

In figures 5b, the neurone is excited with current $I_0 = 5.570 \, \mu\text{A}$, in the chaotic oscillatory region $[I_2^*, I_3^*]$. The initial speed of the action potentials $v_0$ converges to a period-3 solution. However, as the spikes propagate along the axon, this period-3 disappears, giving a constant propagation speed.
**Fig. 5** In the first row, we show snapshots of the solutions $-V(x,t)$ of (4)-(5), for injected currents a) $I_0 = 3.500 \, \mu A$, b) $I_0 = 5.570 \, \mu A$, and c) $I_0 = 6.535 \, \mu A$, at $x = 0$ during the entire simulation. We also show some of the characteristic curves of the solutions. In the second row, we show the initial speed $v_0$ (for $x << L$) of the first 40 action potentials generated by the system. The horizontal axis is the spike number $N$. In the third row, we show the evolution of the speed $v$ of the first 40 action potentials as they propagate throughout the axon – dashed lines correspond to spikes 1 to 29 and full lines to spikes 30 to 40. In a) and c), we have an asymptotically oscillatory response and, in b), a chaotic response.

In figures 5c, the chosen current is $I_0 = 6.535 \, \mu A$, in the small chaotic oscillatory region $[I_*^4, I_*^5]$. This small region shows period bifurcations, which give way to a chaotic intermittency regime (as shown in [18]). However, the simulations show that initial velocities $v_0$ quickly converge to a fixed value after generating a few spikes. The speed of these asymptotic spikes is constant as the action potentials travel along the axon. The chaoticity of signals is present in the non-uniformity of the distances between consecutive action potential spikes.

In figure 6, we show the asymptotic velocity profiles $v_L$ for the oscillatory region $[I_*^1, I_*^6]$ for different values of current $I_0$.

The speed of the first action potential spike is the same ($v = 12.07 \, \text{m/s}$), regardless of the value of injected current. We had already observed the same value for the type I intermittency region in figures 2 and 3. On the other hand, the final speed of the later action potentials varies as the injected current increases. At first, the velocity decreases, reaching its lowest value around $4.5 \, \mu A$. Then, it increases until $I_*^5$, where transient chaos influences the period and speed with which the spikes are generated (as shown in figure 5b). In $[I_*^3, I_*^4]$, the final velocity of the system stabilises, only varying slightly as the current keeps increasing until it stops existing at the end of the oscillatory region.

The simulations just obtained with the HH model equations (1) invalidate the assumption made for the derivation of equations (3), supporting the calibration of the HH model.
Fig. 6 Action potential propagation speeds for the entire oscillatory region $[I^*_1, I^*_5]$, measured at the end of the axon ($x \approx L$). The dashed line represents the speed of the first action potential spike, which is always constant. The full line represents the final speed of the later action potential spikes ($N > 30$). The shaded grey region is the chaotic oscillatory region $[I^*_2, I^*_3]$.

In figure 7, we measured the velocities of the action potentials in the type I intermittency region. We also analysed their profile changes along the transition to the oscillatory region.

Fig. 7 Propagation speeds of action potential spikes in the vicinity of $I^*_1$. The horizontal line corresponds to the velocity of the first spike, which remains constant throughout the axon (see figure 5). In a), the speed of the action potentials is measured at the beginning of the axon; in b), it is measured at the end of the axon. All of the dots correspond to the measured velocities of the action potentials. The transition from type I intermittency to periodic oscillations occurs at $I_0 = I^*_1$.

For low current values ($I_0 \leq 1.034 \, \mu A$), only one action potential spike is generated. The speed of the first action potential spike remains constant during propagation, both in the intermittency and oscillatory regions. This is
consistent with what we have seen in figures 2, 3, 5, and 6. As the current increases (1.034 µA < I₀ < I₁*), we can see additional action potential spikes with different speeds. At I₀ = 1.073 µA, we can distinguish three different propagation speeds, corresponding to the three action potential spikes seen in figure 3, where the same current was injected. Whereas in figure 3, all of the characteristic curves seemed to be linear, the speed of the second and third spikes do not remain constant during the propagation, having different values at the beginning (figure 7a) and end (figure 7b) of the axon. As the current approaches I₁*, the number of spikes increases (an effect of type I intermittency [18]), and the velocity profile approaches the profile of the oscillatory region.

In figure 8, we have calculated the asymptotic dispersion relation for the oscillatory region [I₁*, I₄*]. To do this, we calculated the period and wavelength at the end of the axon (x ≈ L) between spikes 30 and 31 (in black) and between spikes 1 and 2 (delimited by the dashed lines).

![Figure 8](image)

**Fig. 8** Asymptotic dispersion relations for the oscillatory region [I₁*, I₄*]. The measurements were made in the last quarter of the axon. The periods (T = 1/ω) and wavelengths (λ = 2π/k) shown in black were calculated through spikes 30 and 31. Those calculated through spikes 1 and 2 are within the region delimited by the dashed lines.

4 Final remarks and conclusions

To test the predictions of the HH model (1) with patch-clamp data and without the Hodgkin and Huxley assumptions (2) and (3), the first requirement is to measure the current as a function of the spatial position along the axon. Due to the diffusive nature of the current propagation along the axon, the second requirement is to test if action potential spikes propagate without attenuation. Without fulfilling these requirements, the HH model can not be validated.

Another prediction of the HH model (1) about the propagation of axonal signals is the existence of the type I intermittency phenomenon associated with a saddle-node bifurcation of limit cycles. This bifurcation is tuned by the magnitude of the applied current I₀ to the axon.

Let I₁* be the I₀ bifurcation value. For I₀ < I₁*, and depending on the electrophysiological state of the axon (transmembrane potential, ionic concentrations, etc.), we may have no spikes at all, one spike or several spike
responses up to some maximum number $N$. This number $N$ relates with $I_1^*$ and $I_0$ through the relation $\ln N = C_0 - (\ln(I_1^* - I_0))/2$, where $C_0$ is a constant, characteristic of type I intermittency, [18]. This multi-spike phenomenon has never been reported in voltage-clamp experiments, [13]. Its observation would corroborate the existence of the bifurcation predicted by the HH model. If this behaviour is not observed, the HH model validity would be for values of $I_0$ below $I_1^*$. In this case, the HH model equations have a unique stable steady state associated with the equilibrium values of the Nernst potentials, and isolated action potential signals could not exist. According to the HH model, isolated action potential spikes are due exclusively to the type I intermittency phenomenon.

The importance of the existence of a saddle-node bifurcation of limit cycles implies that axonal signals may respond to external stimuli with asymptotically periodic or chaotic responses. Observing this response is an essential biological phenomenon predicted by the HH model. For $I_1^* < I_0 < I_5^*$, action potential responses are independent of the potential transmembrane drop.

Another consequence of the HH model is the possibility of the existence of propagating signals in both directions of the axon and their characteristic behaviour at collision and boundaries. This is the critical test for the validity of the HH model. If these interaction patterns fail, the derivation of a more detailed model for studying electric phenomena in cells and axons should be reconsidered.

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Competing interests

The authors declare that they have no competing interests.

Data availability

The code to reproduce all simulations is available in the GitHub repository https://github.com/gaspar-c/hodgkin-huxley-waves, [30].

References

References

[1] Oh, S. H., Clinical electromyography. Nerve conduction studies, Lippincott Williams & Wilkins, Philadelphia, 2003.
[2] Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., Lamantia, A.-S., McNamara, J. O., Williams, S. M., Neuroscience, Sinauer Associates, Inc., 3rd Edition, 2004.

[3] Phillips, R., Kondev, J., Theriot, J. and Garcia, H., Physical Biology of the Cell (2nd Edition), Garland Science, 2012.

[4] Hodgkin, A. L., Huxley, A. F., A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. 117 (1952) 500–544.

[5] Tasaki, I., Physiology and Electrochemistry of Nerve Fibers, Academic Press, 1982.

[6] Leuchtag, H. R., Voltage-sensitive ion channels, biophysics of molecular excitability, Springer, The Netherlands, 2008.

[7] Hill, B., Ionic Channels of Excitable Membranes, 2nd edition, Sinauer, Sunderland, 1992.

[8] Rinzel, J. and Miller, R. N., Numerical calculation of stable and unstable periodic solutions to the Hodgkin-Huxley equations, Mathematical Biosciences 49 (1980) 27-59.

[9] Hassard, B., Bifurcation of periodic solutions of the Hodgkin-Huxley model for the squid giant axon, J. Theor. Biol. 71 (1978) 401-420.

[10] Ermentrout, G. B., and Terman, D., Mathematical Foundations of Neuroscience, Springer, New York, 2010.

[11] Keener, J., and Sneyd, J., Mathematical Physiology, Springer, New York, 1998.

[12] Hoppensteadt, F. C., and Peskin, C. S., Modeling and Simulations in Medicine and the Life Sciences, Springer, New York, 2002.

[13] Clay, J. R., Excitability of the Squid Giant Axon Revisited, Journal of Neurophysiology, 80 (1998).

[14] Meunier, C., and Segev, I., Playing the devil’s advocate: is the Hodgkin-Huxley model useful?, Trends in Neurosciences 25(11) (2002) 558-563.

[15] Leuchtag, H. R., What’s wrong with the Hodgkin-Huxley model? An Exercise in Critical Thinking, Biophysical J. 112(3), supp. 1, 464A (2017), DOI: 10.1016/j.bpj.2016.11.2488.

[16] Bezanilla, F., Gating currents, J. Gen. Physiol. 150(7) (2018) 911-932, doi: 10.1085/jgp.201812090.
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[17] Peyrard, M., How is information transmitted in a nerve?, J. Biological Physics, 46 (2020) 327-341.

[18] Cano, G., and Dilão, R., Intermittency in the Hodgkin-Huxley model, Journal of Computational Neuroscience, 43 (2017) 115-125, DOI: 10.1007/s10827-017-0653-9.

[19] Pomeau, Y. and Manneville, P., Intermittent transition to turbulence in dissipative dynamical systems, Comm. Math. Phys. 74 (1980) 189-197.

[20] Aslanidi, O. V. and Mornev, O. A., Can colliding nerve pulses be reflected?, ETP Lett., 65(7) (1997) 579-585.

[21] Heimburg, T., and Jackson, A. D., On soliton propagation in biomembranes and nerves, Proc. Natl. Acad. Sci. U.S.A., 102 (2005) 9790.

[22] Appali, R., van Rienen, U., and Heimburg, T., A comparison of the Hodgkin-Huxley model and the soliton theory for the action potential in nerves, in Advances in Planar Lipid Bilayers and Liposomes, Iglic, A. (ed), vol 16 (2012) 275-299. Doi: 10.1016/B978-0-12-396534-9.00009-X.

[23] Gonzalez-Perez, A., et al., Penetration of Action Potentials During Collision in the Median and Lateral Giant Axons of Invertebrates, Physical Rev. X, 4 (2014) 031047(12).

[24] Follmann, R., Rosa, E, and Stein, W., Dynamics of signal propagation and collision in axons, Phy. Rev. E, 92 (2015) 032707.

[25] Tasaki, I., Collision of two nerve pulses in the nerve fibre, Biochimica et Biophysica Acta, 3 (1949) 494-497.

[26] Sainhas, J., and Dilão, R., Wave optics in reaction-diffusion systems, Phys. Rev. Lett., 80 (1998) 5216-5219.

[27] Dilão, R., and Volfor, A., Excitability in a model with a saddle-node homoclinic bifurcation, Discrete and Continuous Dynamical Systems - series B, 4 (2004) 419-434.

[28] Li, N., Steiner, J., and Tang, S., Convergence and stability analysis of an explicit finite difference method for 2-dimensional reaction-diffusion equations, J. Austral. Mat. Soc. Ser. B, 36 (1994) 234-141.

[29] Dilão, R., and Sainhas, J., Validation and calibration of models for reaction-diffusion systems, International Journal of Bifurcation and Chaos, 8 (1998) 1163-1182.

[30] Cano, G., and Dilão, R., Numerical integration of the Hodgkin-Huxley model, https://github.com/gaspar-c/hodgkin-huxley-waves.