Outward Sodium Current, Fine-structure Constant, and Ferroelectric Hysteresis Regimes in the Giant Squid Axon Propagating Action Potential: a Phase Space Approach

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A phase space cable equation for the propagation of the functioning action potential is derived. Plots of the ionic current in the recovery region reveal the presence of two outward currents with quasilinear segments. The first one has never been detected with voltage clamp experiments. The plot of currents in the action potential frame of reference reveals that the modulated Ohm’s current determines the reversal of the ionic current from incoming to outward in the recovery region. We show that this current is sodium’s current caused by Ohm’s current buildup of the electrostatic gradient across the membrane opposing and overwhelming sodium’s concentration gradient. Fits of fractions of open sodium channels with the Avrami equation reveal the continuous phase changes of the sodium channels lattice at the inception and at the peak of the action potential. The correlation between the Avrami parameter A and the ionic channel’s time rate reveals the role of the fine-structure constant in the passage of ions through channels with activation energies of the same order as the rate-limiting biochemical reactions. The optimum sodium channel density is calculated that is close to the observed one. It is shown that action potential traverses a heat releasing ferroelectric hysteresis loop with sodium channels traversing two states with different symmetries. Presented results provide the framework for further analysis of excitability, channel’s lattice structure, thermodynamic phase behavior, and the role of quantum mechanics in biochemical reactions mediating the flow of ions through channels. The role of ferroelectric sodium channels behavior has implications for encoding and storing of memories.

I. INTRODUCTION

The initiation and propagation of the action potential in the giant squid axon has been described by the Hodgkin-Huxley [20, 21] empirical equations in terms of sodium, potassium and leak currents traversing the membrane. They reconstructed the action potential using the charge conserving cable equation and individual ionic currents obtained by separate voltage clamp experiments.

The reconstructed HH action potential is somewhat inaccurate in the recovery region, the value of its velocity of propagation doesn’t match the observed one and it yields the incoming sodium current with a peculiar wiggle. In his 1997 article J. Patlak [40] lists a number of comparisons between HH equations and voltage clamp experimentally observed facts. The most significant discrepancy ideals with inactivation. The HH’s inactivation variable h is independent of activation while experiments have established that inactivation follows activation.

A 2018 review by Drukarch et al. [12] describes alternative models that include non-electrical phenomena accompanying nerve impulse propagation and calls for a multidisciplinary approach to tackle the nerve impulse behavior. A description of the squid axon behavior based on first-principles physics has not been achieved with HH equations.

The success of the HH equations regarding the excitation and the propagation of the action potential has been accompanied over the years by a relative neglect of the recovery region of the action potential. The action potential is a paramount nonlinear phenomenon where any part of the process affects the whole of it. While descriptions of linear phenomena are also adequately linear, the descriptions of nonlinear phenomena must be recursive just as are the phenomena themselves. Understanding or modeling these phenomena requires approaches that involve iteration or self-reference, reflecting the complexity and interconnectedness inherent in nonlinear systems. What happens during the rising edge of the action potential affects the recovery region and vice versa. By comparison, Hodgkin and Huxley reconstructed a non linear action potential by incorporating sodium and potassium currents from independent voltage experiments, added a leak current and omitted the easily measured velocity of propagation into the cable equation.

In the present work, we analyze the Rosenthal-Bezanilla [42] experimental data for the steady propagation of the fully functioning action potential over a range

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of temperature from 1 to 30 °C.

The steady propagation of the action potential is simpler to analyze in Phase Space [33, p. 2]. The first and second time derivatives of the fully functioning action potential and its velocity of propagation, the capacitance of the axon and its radius, and the resistivity of axoplasm, yield the total capacitive, ionic and membrane currents of the charge conserving cable equation. While the action potential is measured as a function of time, the steady propagation currents can also be drawn as functions of the potential revealing other properties not obvious when plotted as function of time.

In the first part of our work, ANALYSIS - Part 1, we have rewritten the cable equation directly in Phase Space [33, p. 2]. The Phase Space cable equation yields several simple results. It shows that all three currents are proportional to $\Phi(V) = dV(t)/dt$ while the membrane current is independent of capacitance $C_m$. It also reveals the role of the propagation constant in the two crossings of the zero current axis by the total ionic current.

Our first significant result, obtained without any additional assumption, are the plots of currents vs. potential displaying quasilinear segments for all three currents, revealing physically relevant parameters such as the ionic maximum conductance and time rates associated with the capacitive current. These plots reveal fundamental properties required by any comprehensive theory of action potential propagation. During the recovery phase, beside the known potassium current $J_K$ we identify an additional ionic current that we name $J_H$. This current crosses the zero-current axis from incoming to outgoing shortly after the recovery begins (See Fig. 8 and Supplemental Material (SM) Fig. 23b). The quasilinear crossing of the zero current axis by the ionic current $J_H$ suggests a segment with most channels open implying that the ion involved is sodium ion since it is known that the incoming current is sodium current. However, since the pioneering work of Hodgkin and Huxley it has been accepted unlogically that "if the current is not seen by the voltage clamp, it doesn’t exist" [25].

In what follows we shall present additional arguments and eventually identify this additional outward current as the sodium deactivation current $J_H$, a previously undetected component of the action potential.

We take it, as usual, that all ionic activation currents $J_X$, driven by ionic concentration density gradients, are described by three factors: maximum conductance $g_X$, reversal potential $V_X$ and fraction of open channels $X_0/X$. Phase space graphs of activation currents should reveal quasilinear segments and approximate values of reversal potentials, the corresponding maximum conductance (all channels open) and the time rates associated with the capacitive currents. We confirm the simple relationships between the propagation constant $k$, the maximum conductance $g_X$ and the corresponding time rates $\mu_X$ for the activation currents driven by the $X$ ionic density concentration gradients at the foot of the action potential and for the potassium current. Significantly, the graphs reveal an additional quasilinear segment of the outward current $J_H$ in the recovery region of the action potential. This current doesn’t have the simple relationships between the parameters as those of the activation currents and we conclude that there is an additional driving force competing with the driving force of the ionic density gradient. In addition, the graph of the incoming sodium current doesn’t display an obvious reversal potential nor a quasilinear behavior associated with all channels open. Hodgkin and Huxley accounted for this inactivating behavior with the parameter $h$ that effectively decreases the fraction of open channels and thus competes with the driving force of sodium’s density gradient. We argue and demonstrate that in both cases this competing force is the electrostatic charge gradient caused by the accumulation of positive charges by the modulated Ohm’s law current. We conclude that the outward current $J_H$ is sodium’s deactivation current.

Quoting Patlak in the 1997 paper [40]: "... in the age of molecular biology the studying of the sodium current kinetics moved to studying the kinetics of sodium channel molecule itself." Unexpectedly, our analysis of current kinetics has detected a structural change in the sodium channel at the inception and at the AP peak. And, unexpectedly, the phase space analysis of macroscopic currents has revealed the sodium outward current in the recovery region.

The second part of our work, ANALYSIS Part 2, is based on the single assumption that the fractions of open ionic channels are given by the Avrami equation that was originally derived to describe the fraction of completed crystallization in metals as a three dimensional nucleation process [1], [2].

Hodgkin and Huxley constructed their empirical equations for the excitation and propagation of the action potential by describing the fraction of open potassium channels with an empirical S curve given by $n^4$ and the sodium S curve given by $m^3$. These exponents are interpreted as the number of structural sequential concurrent steps necessary to open the ionic channel. Since the steady propagation of the action potential ignores the initial excitation we assume instead that the fraction of open channels for all activation currents during the steady state action potential propagation in the lab is given by the Avrami S curve equation [18]. The Avrami equation was derived to describe the isothermal phase change in solids and crystallization processes. The particular value of the dimensionless exponent $\theta = 4$ comes from from three dimensions of growth and one representing a constant nucleation rate.

Our preliminary fittings of the incoming sodium current with the Avrami equation revealed two remarkable facts. First, inclusion of experimental points beyond the start of the negative resistance region leads to a fast divergence of the Avrami exponent beyond the value of 4. We conclude that in addition to the sodium concentration gradient driving force there is an additional component to the total ionic current beyond this point that is due...
to other driving forces. Eventually, we show that this additional driving forces are responsible for the inactivation. Second, the preliminary fitting of the experimental data reveals a remarkable correlation between Avrami parameters $A_X$ and $\theta_X$ and ionic current’s time rates $\mu_X$: $A_X \approx \alpha_X (\mu_X)^{\theta_X}$, where $\alpha_X$ are dimensionless constants. See also Eq. (19) and Fig. 6. We conclude that all $\alpha_X$ are equal to the fine-structure constant from quantum electrodynamics and consequently fit the experimental data with the so modified mAvrami equation Eq. (20).

We parse the total ionic, capacitive and membrane currents into ionic activation/deactivation currents and polarization currents. Ionic currents traversing channels are driven by gradients of ionic concentration across the membrane. Polarization currents are caused by the motion of dipole charges within the membrane opening and closing the channels; or caused by modulation of the charge concentration throughout the axoplasm by the membrane current that is proportional to the product of Ohm’s current and its derivative; or caused by structural continuous phase symmetry change of the channel. We call these currents mAvrami polarization currents and identify their physical cause and also fit them with mAvrami equations with effective reversal potentials and time rates.

We have also fitted fractions of open sodium and potassium channels directly as functions of potential. Fig. 18 displays phase space open channels fractions fits of Equations (27), for Sweep170 at 4.5 °C. The fractions of open channels at a given potential and temperature are interpreted as the fraction of time that the corresponding single channel is stochastically open.

Further, we develop a phenomenological theory that includes elements of thermodynamics such as first order and continuous phase transitions, heat release and Boltzmann’s kinetics.

Fits of polarization ionic currents reveal continuous phase transitions at the inception of incoming sodium current and its reversal at the peak of the action potential involving symmetry change of sodium channels lattice/domains. The resulting ferroelectric hysteresis loop is described in terms of sodium’s effective reversal potential in the rising edge of the AP and the effective reversal potential during recovery. The estimated heat released at 19.8 °C is about twice the heat released at 4.5 °C (See Fig. 19).

The role of continuous phase transitions of sodium channels domains in the propagation of the action potential suggests their role in excitation in general and in optical phenomena, heat release and raises questions of their pharmacological implications.

Plots of ionic time rates as Boltzmann’s kinetic rates yield ionic activation and inactivation energies of the same order as the average of 0.65 eV rate-limiting metabolic biochemical reactions.

The existence of sodium channels domains with two different symmetries, albeit only one being stable in squid axon, suggests the possible existence of neurons with more than one stable state. This is a necessary condition for storage and retrieval of memories. J. J. Hopfield in his paper [22] ”Neural networks and physical systems with emergent collective computational abilities” writes the following: ”A study of emergent collective effects and spontaneous computation must necessarily focus on the nonlinearity of the input-output relationship. The essence of computation is nonlinear logical operations.” and ”Thus, we consider a network of “on or off” neurons, …”. ”On or off” neurons implies neurons with two different stable states. The last reference in Hopfield paper is ”Kandel, E. R. (1979) Sci. Am. 241, 61-70". Over a period of many years Eric Kandel and collaborators experimented with the sea slug Aplysia californica and showed that short-term memory is created by strengthening existing synapses and that long-term memory is stored by the creation of new synapses. These processes require morphological changes in neurons and synapses. See Kandel’s Nobel Lecture ”The Molecular Biology of Memory Storage: A Dialog Between Genes and Synapses” [25].

Ultimately, our study suggests that the ferroelectric dynamics of action potential propagation may have broader implications for furthering the understanding of neural computation and memory storage foundations by J. J. Hopfield and E. R. Kandel, and echoing their ideas regarding the role of neuronal states in cognitive functions [23, 24].

II. ANALYSIS - PART 1

Is the propagating action potential a thermodynamic system with an equation of state? A thermodynamic system in equilibrium is described by a functional relationship, called equation of state, among Temperature and pairs of intensive and extensive thermodynamic parameters: Pressure, Volume; Magnetic Field, Magnetic Susceptibility; Electric Field, Polarization; etc (See [24]).

The steady state propagating action potential is described in the laboratory by the charge conserving cable equation. See [26] for an example of its derivation:

$$C_m \frac{dV}{dt} + J_I(t) = - \frac{R}{2} \frac{dJ_z(V)}{dz}$$

(1)

where $J_z$ is the Ohm’s current:

$$J_z(V) = - \frac{1}{R_i} \frac{dV}{dz}$$

(2)

and the cable equation is:

$$C_m \frac{dV(t)}{dt} + J_I(t) = \frac{R}{2v^2R_i} \frac{d^2V(t)}{dt^2}$$

(3)

where the experiment provides the action potential $V(t)$ as a function of time (See Fig. 1). $C_m$ is the membrane capacitance, $R$ is the axon radius, $R_i$ is the temperature
dependent resistivity of the axoplasm and $v$ is the temperature dependent velocity of propagation for the action potential. The first and the second term of Eq. (1) are the capacitive current and the total ionic current across the axon’s membrane respectively. The third member is the so-called membrane current loosely defined in the literature as the total current across the membrane because it is equal to the sum of the capacitive and ionic currents. In the context of the charge conserving cable equation derivation [26] for the propagated action potential in the Laboratory Frame (LF), the membrane current:

$$J_m = -\frac{R}{2} \frac{dJ_z}{dz} \tag{4}$$

is the explicit derivative of the Ohm’s current $J_z$ within the axon’s axoplasm and is independent of capacitance $C_m$. According to Eq. (1) the total ionic current is equal to the membrane current minus the capacitive current. Thus, the total ionic current $J_I$ is determined by the first and the second derivative of the action potential data and by the propagation constant $k$ of a fully functioning axon.

$$k = 2C_mRi_v^2/R \tag{5}$$

By contrast, the total ionic current in the HH approach is the sum of empirically fitted sodium and potassium currents obtained from separate voltage clamp experiments plus a leak current. The reconstructed HH action potential is somewhat inaccurate, particularly in the recovery region, and its value of the velocity of propagation doesn’t match the observed one. In his 1997 article J. Patlak [40] lists a number of comparisons between Hodgkin-Huxley equations and voltage clamp experimentally observed facts. The most significant discrepancy deals with inactivation. The Hodgkin-Huxley’s inactivation variable $h$ is independent of activation while the experiments have established that inactivation follows activation. In what follows, our analysis implies that inactivation follows activation. In other words, inactivation kicks in only after a certain stage of activation is reached.

The steadily propagated action potential appears at rest in the frame of reference moving with velocity $v$ along the axis of its motion and it is independent of time. Furthermore, the potential $V$ and the total ionic current $J_I$ are invariant under Galilean transformation connecting the two frames. The action potential propagating with constant velocity is interpreted as a thermodynamic system in equilibrium. The induced polarization is function of electrical field $E$ which is proportional to the potential $V$ measured across the thickness of the axon’s membrane. The ferroelectric equation of state for the propagating action potential takes the form of $f(Temperature, Electric Field, Polarization) = 0$. The two-dimensional nature of the axon membrane renders the ferroelectric equation of state to be a function of temperature and electric potential.

All three terms of Eq. (1) are time dependent in the Lab. However, since there is the one to one relationship between time and potential, the propagating steady state is conveniently described in Phase Space [33, p. 2] without explicit time dependance. In other words, the capacitive current can be written as a function of potential: $C_mV/dt = C_m\Phi(V)$ and the cable equation Eq. (1) can be rewritten as (see also Eq.13 of reference [27]):

$$J_I(V) = C_m\Phi(V)(\frac{1}{k}\frac{d\Phi(V)}{dV} - 1) \tag{6}$$

All three currents and also the Ohm’s current

$$J_m(V) = -(1/vR_i)\Phi(V) \tag{7}$$

are proportional to $\Phi(V)$. Also note that the membrane current is independent of capacitance $C_m$ and that the ionic current has one contribution dependent and one contribution independent of the capacitance. Eq. (6) shows that the ionic current crosses the zero current axis when the capacitive current is equal to the membrane current, which happens when $d\Phi(V)/dV = k$. The first zero ionic current happens after the inception of the action potential in the rising edge region and the second one happens in the recovery region just after the peak of the action potential.

Plots of currents ($C_m\Phi, J_m, J_I$) vs. Potential (Fig. 2) show that capacitive current is positive during the fast charging of membrane’s capacitor and negative during the slow discharging of the capacitor in the recovery regions of the action potential. In the rising edge and immediately after the AP peak the incoming ionic current is sodium current driven mostly by sodium’s concentration gradient across the membrane. After the AP peak the ionic current crosses the zero current axis and turns outward. We shall later argue that this outward current is sodium’s deactivation current that starts with all channels open that close as the recovery proceeds with all potassium channels opening as potassium’s reversal is reached. The trajectory of the membrane current is more complex. At the foot of the action potential, the Ohm’s law factor determines its quasilinear growth that closely builds the quasilinear capacitive current since the ionic current is small and outward. It crosses the zero current axis at the inflection point of the rising edge of the action potential and approaching the peak of the action potential it follows the fast ionic (sodium) current making the capacitive current small. After the AP peak everything slows down. Recovery is much longer in extension and it takes much longer in time than the rising edge. The recovery starts with the negative membrane current discharging the membrane’s capacitor despite the still incoming decreasing ionic current, known to be sodium incoming, current. As it turns outward, the ionic current, later to be shown to be outward sodium current, takes on the discharge of membrane’s capacitor. As the outward sodium current deactivates, potassium channels open and the outward potassium current driven by the potassium concentration gradient starts to discharge the membrane capacitor until reaching potassium’s reversal potential. As the capacitor is discharged by the out-
FIG. 1. The experimental data $V(t)$ vs. time is presented as colored segments corresponding to sodium and potassium ionic currents $J_M, J_H, J_N, J_K$, a sodium ionic polarization current segment. The time $t = 0$ is set at the peak of the action potential separating the rising edge and the recovery regions.

ward potassium current the quasilinear membrane current reaches the zero current axis closing it’s extension in space and time.

Since the capacitive current depends on the dipole charges across the membrane and the ionic currents depend on availability of open ionic channels and are driven mainly by ionic concentration gradients across the membrane during the rising edge and by the slow discharge during the recovery the so-called membrane current enforces the charge conservation during the propagation of the action potential and puts constraints on both the capacitive and ionic currents. It keeps the shape of the traveling action potential by acting as an arbitrator between the capacitive and ionic currents enforcing the charge and current conservation.

In what follows, we shall use alternatively the terminology of Eq. (1) or Eq. (6) since there is a one to one correspondence between potential $V$ and time $t$ for the propagating action potential.

Fig. 2 and Fig. 3 exhibit the complex behavior of the modulated axoplasmic axial Ohm’s current, the so-called membrane current. Plots of currents $k(C_m\Phi, J_m, J_I)/C_m\Phi$ vs. Potential (Fig. 3) show explicitly that all three currents are proportional to $\Phi(V)$ and that the ionic current crosses the zero current axis when $d\Phi(V)/dV = k$.

To advance the understanding of the physics of competing sodium’s concentration gradient inward force and the general ionic electrostatic gradient outward force driving positive ions through open channels resulting in the total ionic current across the membrane we plot in Fig. 4 the total ionic current and the axial current in the action potential frame (APF) where the action potential is at rest. This plot is an update of Fig. 2 from reference [27] using HH axon’s data.

For the pulse traveling to the left, the laboratory frame (LF) and the action potential frame (APF) are related through a Galilean transformation along the z axis: $z^* = z + vt$, $t^* = t$, where $v$ is the velocity of the laboratory frame as seen from the action potential frame. See ref [27] for detailed Galilean transformations of other electrodynamic quantities. In the APF, where the symbols have asterisks, the charge conservation expression equivalent to Eq. (1) is

$$J^*_z(V^*) = -\frac{R}{2} \frac{dJ^*_z(V^*)}{dz^*} \tag{8a}$$

and

$$J^*_I(V^*) = -\frac{R}{2v} \Phi(V^*) \frac{dJ^*_z(V^*)}{dV^*} \tag{8b}$$

where $J^*_z$ is the axial current in the APF that transforms as:

$$J^*_z(V^*) = J_z(V) + 2\frac{v}{R} C_m V \tag{9a}$$

and also

$$\frac{dJ^*_z(V^*)}{dz^*} = \frac{d}{dz}[J_z(V) + 2\frac{v}{R} C_m V] \tag{9b}$$
FIG. 2. The experimental data for currents $C_m \Phi(V)$, $J_m(V)$ and $J_I(V)$ vs. $V$ are presented as trajectories in time. The rising edge and the recovery of the action potential are defined respectively by the positive and negative capacitive current $C_m \Phi(V)$. Note that the total ionic current $J_I(V)$ is zero when the capacitive current is equal to the membrane current. Note that ionic current deals with specific ions traversing specific ionic channels while the membrane current deals with the net motion and distribution of charges in the axoplasm. At the foot of the AP, the bulk of the positive membrane current $J_m$ charges the membrane’s capacitor and the minor portion contributes to the outward ionic current first increasing and then decreasing with the potential. As the ionic current crosses the zero current axis from outward to incoming, driven by the ionic concentration gradient (known to be sodium’s), it starts sharing the charging of the membrane’s capacitor and takes over completely as the membrane current crosses the zero axis current from positive to negative while in the axoplasm the membrane current pushes positive charges down the potential gradient in the direction of the AP propagation. The charging of the capacitor continues up the AP peak where the capacitive current decreases to zero and the ionic current is equal to the membrane current. The membrane current starts discharging the capacitor immediately after the AP peak pushing the positive charges in the axoplasm down the potential gradient in the opposite direction of the AP propagation. The charging of the capacitor continues up the AP peak where the capacitive current decreases to zero and the ionic current is equal to the membrane current. The membrane current starts discharging the capacitor immediately after the AP peak pushing the positive charges in the axoplasm down the potential gradient in the opposite direction of the AP propagation despite the still decreasing incoming ionic current. At the same as the AP propagates all the charges associated with it appear to propagate as well. Afterwards, the outward ionic current takes the lead to discharging the membrane.

\[
\frac{dJ_I^*(V^*)}{dV^*} = \frac{d}{dV}[J_z(V) + \frac{2v}{R}C_m V] \tag{9c}
\]

and since the ionic current traversing axon’s membrane is invariant under the Galilean transformation:

\[
J_I^*(V^*) = J_I(V) \tag{9d}
\]

In the APF the three current problem is reduced to a two current problem: total ionic current and the total axial current. The total axial current has two components: the Ohm’s component and the motion of capacitive charges with $v$, the velocity of AP propagation. When the derivative of the total axial current is zero the total ionic current is zero crossing the zero current axis. The graph Fig. 4 shows that the total axial current, initially negative and very small up to the inflection point of the AP has a shallow minimum at the potential where the
FIG. 3. The experimental data Currents/$C_m \Phi(V)$ vs. $V$ are presented as time trajectories. Note that the total ionic current $J_I$ is zero when $d\phi(V)/dV$ is equal to the propagation constant $k$. Note that ionic current deals with specific ions traversing specific ionic channels while the membrane current deals with the net motion and distribution of Ohm’s charges in the axoplasm. There are four distinct segments of $d\phi(V)/dV$, alternating positive and negative. The first segment is positive. It anticipates and feeds the capacitive current and it is responsible for advancing the foot of the AP. This segment extends up to the inflection point of the AP rising edge (about 70 mV for Sweep 425) and it is mostly dedicated to the initial charging of the membrane’s capacitor at the foot of the AP allowing a small outward ionic current until $d\phi(V)/dV = k$ when the outward ionic current crosses the zero current axis turning to incoming. In this segment the membrane current pushes axoplasmic positive charges in the direction of the AP motion down the AP rising edge slope. The second segment is negative, it extends up the AP peak, and it corresponds to the decreasing rate of capacitive charge accumulation by the membrane current and it coincides with the first part of inactivation and the decrease of ionic conductance. It effectively flattens the potential across the membrane up to the AP peak. The third segment is positive, it starts from null at the AP peak and grows very large as the action potential enters recovery and then decreases slowly practically to zero for a long stretch and then turns negative at about 30 mV. This behavior indicates further accumulation of positive charges in the axoplasm immediately after the AP peak leading to the potential at which the derivative $d\phi(V)/dV = k$ and at which the ionic current turns from incoming to outgoing. The electrical gradient of positive charges across the membrane eventually overwhelms sodium ion’s concentration gradient by pushing positive ions outward, to be later shown to be sodium ions traversing through open sodium channels. The fourth segment is negative and it extends up to the end of the action potential as the other outward ionic current (potassium current) decreases to zero by reaching its reversal potential. It corresponds to the membrane current retracting of the AP by decreasing the accumulation of axoplasmic positive charges to zero.
FIG. 4. Time trajectories of the total ionic current \( J^*_I = J_I \), the total axial current \( J^*_z \) and its parts, the Ohm’s current \( J_z = -1/(vR_i)\Phi(V) \) and the "transport" current \( (2v/R)C_mV \) are plotted vs. \( V \). Note that the axial current \( J^*_z \) has three segments: a decreasing one to a minimum, then an increasing one to a maximum after the AP peak followed by a decreasing one. The ionic current \( J^*_I = J_I \) is outgoing as the axial current \( J^*_z \) decreases from its inception to its shallow minimum; the ionic current \( J^*_I \) is incoming as the axial current \( J^*_z \) increases with potential from its minimum to its maximum; and it is outward as \( J^*_z \) decreases from its maximum. There is a strong correlation between the two behaviors, indicating cause and effect. The minimum and the maximum of the axial current \( J^*_z \) correspond to potentials at which the total ionic current crosses the zero current axis. At the foot of the action potential the total axial current and its derivative are negative up to the axial’s current minimum resulting in outward ionic current. As the derivative of the axial current turns positive the ionic current turns inward. Later we shall parse the total ionic current into sodium’s activation current driven by the sodium concentration gradient and a concurrent incoming polarization current. At the action potential peak \( V_p \) the axial current is \( J^*_z(V_p) = (2v/R)C_mV_p \). As the action potential decreases from its peak \( V_p \), the decrease of \( (2v/R)C_mV \) is smaller than the increase of the Ohm’s current \( J_z(V) = -1/(vR_i)\Phi(V) \) which has turned positive and \( J^*_z \) keeps increasing while the incoming ionic current \( J^*_I \) is decreasing until the axial current peaks at the potential \( V_H \) and \( J^*_z \) crosses the zero current axis. As axial current \( J^*_z \) starts decreasing from its maximum, the total ionic current turns positive (outward). In sum, Ohm’s current determines that the ionic current during the descent must be outward. In particular, as the potential starts to decrease from its peak \( V_p \), Ohm’s current turns positive and positive (negative) charges start descending (climbing) the potential. In either case there is an increase of positive charge density that is relieved by an outward ionic current through already open ionic channels. We shall later argue that this outward current is sodium current with a smaller effective reversal potential \( V_H \) than sodium’s reversal potential \( V_{Na} \) defined by sodium’s concentration gradient. The effective reversal potential \( V_H \) is a result of competitive sodium concentration gradient and electric charge density gradient across the membrane. As the potential starts descending from \( V_p \), the electrical gradient of positive charges across the membrane eventually overwhelms sodium ions concentration gradient at the potential \( V_H \) and it selectively starts pushing sodium ions outward through already open sodium channels.
total outward ionic current crosses the zero current axis and turns incoming. After the inflection point the axial current is positive growing large and it peaks after the AP peak at the potential where the total ionic current crosses the zero current axis and turns outward. The axial current $J^*_Z$ of the HH version doesn’t have the shallow minimum. It follows then that the total ionic current crosses the zero current axis at potentials where the derivative of the axial current Eq. (9c) is zero. The axial current $J^*_Z(V)$ shown in Fig. 4 displays a minimum and a maximum at potentials corresponding to potentials at which $d\Phi(V)/dV = k$. We conclude that at the potential $V_H$ the driving force proportional to sodium concentration gradient $(V_H - V_{Na})/D$ is equal to the driving force proportional to the opposing electric gradient $V_H/D$ where $D$ is the thickness of axon’s membrane. As axial current $J^*_Z$ starts decreasing from it maximum, the total ionic current turns positive (outward). Furthermore, if Ohm’s current is turned off (made null) during this descent the outward ionic current is null as well. In sum, Ohm’s current determines that the ionic current during the descent must be outward. In particular, as the potential starts to decrease from its peak $V_p$, Ohm’s current turns positive and positive (negative) charges start descending (climbing) the potential. In either case there is an increase of positive charge density that is relieved by an outward ionic current through already open ionic channels. We shall later argue that this outward current is sodium current with a smaller effective reversal potential than sodium’s reversal potential $V_{Na} = V_M$ defined by sodium’s concentration gradient. The effective reversal potential $V_H$ is the result of competitive sodium concentration gradient and electric charge density gradient across the membrane through open sodium channels that have gone through a continuous phase change at the peak of the action potential.

The phase space trajectories represent the time evolution of the system and their shape exposes properties of the system such as quasilinear portions that might not be obvious otherwise. Differently colored regions of the action potential in Fig. 1 correspond to specifically identifiable regions in the phase space of currents vs. potential $V$. In particular we shall identify and describe the diverse colored segments of $V(t)$ vs. $t$ from Fig. 1 in the phase space graphs Figures 2,8 and 9. Fig. 19(b) and Fig. 19(d) show the AP hysteresis phase space trajectory. The colored segments of the action potential graph in Fig. in 1 correspond to:

1. At the foot of the action potential there is a quasi linear membrane current moving charges down the potential gradient feeding the growing capacitive current and resulting in a small increasing ionic current consisting of an unresolved combination of potassium K, chloride and sodium-potassium exchange transport Keynes. According to Eq. (6) all three currents are proportional to $\Phi(V)$. At the foot of the action potential the capacitive current is proportional to the potential $V$ (See Fig. 7 and Supplemental Material (SM) Fig. 21) and so are the membrane and ionic currents:

$$C_m\Phi_K(V) = C_m\mu_KV \quad (10a)$$

$$J_{mK} = C_m\frac{\mu_K^2}{k}V \quad (10b)$$

$$J_K = C_m\mu_K(\frac{\mu_K}{k} - 1)V = g_KV \quad (10c)$$

where

$$g_K = C_m\mu_K(\frac{\mu_K}{k} - 1) \quad (10d)$$

is the maximum conductance and $\mu_K$ is the time rate of the $K$ ionic channel. The ionic current at the foot of the action potential is a very small current equal to the difference between the membrane and capacitive currents. The membrane current given by Ohm’s current and its derivative is responsible for the advancing of the leading edge of the action potential and it is larger than the two other currents.

2. As the potential at the foot of the action potential increases so does the dipole polarization within the membrane. The sudden, all or nothing, excitation of the nerve impulse requires a sudden, all or nothing, morphing of the sodium channel manifested by the jump (discontinuity) of the capacitive polarization current causing the inception of the inward sodium current accompanied by the inception of the corresponding capacitive and membrane currents as dictated by the charge conserving cable equation. The value of the action potential $V$ is determined by the dipole of free charges across the membrane. Any morphing inside the membrane creating a polarization dipole layer inside the membrane doesn’t change the potential across the membrane. However, when the capacitive polarization morphing opens the sodium channels the charge conservation of the three cable currents and sodium’s reversal potential come into play maintaining the potential across the membrane continuous. The continuous (second order) phase transition changes sodium channel’s symmetry at the inception potential $V_o$ into the excited state sodium M-channel symmetry while keeping the total cable currents continuous. The continuous phase change results in the inception of the three charge conserving mAvrami currents: incoming sodium’s activation current, capacitive current and membrane current starting from zero, and the three corresponding charge conserving polarization currents (See Fig. 7 and SM Fig. 21). The capacitive polarization current accompanying the inception of the action potential is the result of motion of charges associated with the
morphing of sodium channel structure that opens sodium channels. The capacitive polarization current corresponds to the gating current that was detected in 1973-1974 (See \[2, 3\] and \[31\]). The simultaneous inception of the incoming sodium current and the capacitive polarization current (gating current) is consistent with the conclusion reached with experiments as reported by Armstrong and Bezanilla \[3\]: "Gating Current is Associated with Na Activation". The surface under the capacitive polarization current vs. time is the so-called gating charge, \(Q_p \approx 10\times10^{-9}\) Coulomb/cm\(^2\) at all temperatures (See Fig. 11 and SM Fig. 24). By comparison, the total gating charge deduced from Fig. 8 of reference \[8\] is approximately 8.5\(\times\)10\(^{-9}\) Coulomb/cm\(^2\), although the two distributions with potential differ. In our phenomenological theory the dependence of the gating charge with potential is instantaneous while in direct experimental measurements the gating charge is obtained by averaging potential segments. While the inception of the six currents is simultaneous, the capacitive polarization current (gating current') precedes in size the total incoming ionic current (See Fig. 11 and SM Fig. 24). In other words, a sizable 'gating' charge moves before a detectable ionic current is developed (See also Fig.12 of reference \[8\] with data for potassium channel gating current). The inception of the action potential is triggered by sodium channels continuous (second order) phase change as the potential increases and as the small outgoing total ionic current starts to decrease. In the present theory the inception polarization currents taper off at approximately the maximum rate of rise of the action potential at about 60 mV when the fraction of open sodium channels is about 0.2. Polarization capacitive and membrane currents start large at the inception canceling each other resulting in a small polarization ionic current. The membrane current advances the leading edge of the action potential through Ohm’s law pushing positive charges down the potential gradient. Since the membrane current provides the bulk of the capacitive current, the value of the ionic current is small. The ionic polarization current starts outgoing and promptly turns incoming increasing the potential across the membrane, which in turn proceeds to increase the mAvrani incoming sodium’s activation current.

According to Eq. (9) the ionic current \(J_I(V)\) crosses the zero current axis twice when the membrane current \(J_m(V)\) is equal to the capacitive current \(C_m\Phi(V)\) which happens when:

\[
\frac{d\Phi(V)}{dV} = k \tag{11a}
\]

The first crossing occurs when \(\Phi(V)\) starts decreasing from the initial linear growth with potential (the initial exponential growth in time) and immediately after the inception of the action potential (See Fig. 7) and the second crossing occurs shortly after the peak of the action potential (See Fig. 9).

The first crossing for Sweep 170 happens at

\[
\frac{d\Phi(V)}{dV} \bigg|_{V=38mV} \approx 4.12 \tag{11b}
\]

and for Sweep 425 it happens at

\[
\frac{d\Phi(V)}{dV} \bigg|_{V=35.6mV} \approx 7.81 \tag{11c}
\]

Using axon’s parameters, the Eq. (5) gives \(k = 4.1 \) 1/mSec and \(k = 7.86 \) 1/mSec which are the values we have inputted into the cable equation for Sweeps 170 and 425 respectively.

3. The inception of the action potential occurs, just prior the crossing of the zero current axis by the total ionic current, with the incoming sodium mAvrani current \(J_m\) Eq. (17d) and the corresponding mAvrani capacitive and membrane currents starting from zero (See Fig. 7 and SM Fig. 21).

The quasilinear region straddling the first voltage point at which the ionic current crosses the zero current axis is very short and it is displayed in Fig. 7 for Sweep 425. The trend line of the capacitive current portion intercepts the zero axis current at a negative potential \(V = -3mV\) and the trend lines of the corresponding ionic and membrane currents intercept at a positive current above \(V = 3mV\). Trend lines are not shown in the SM Fig. 21. Similar situation involving the intercepts of the three trend lines will be shown to occur at the second quasilinear region straddling the potential at which total ionic current crosses the zero current axis (See Fig. 9 and SM Fig. 22).

All three mAvrani activation currents exhibit a quasilinear behavior near the AP peak according to the cable equation Eq. (6):

\[
C_m\Phi_M(V) = -C_m\mu_M(V-V_M) \tag{12a}
\]

\[
J_m = C_m\mu_M(V-V_M) \tag{12b}
\]

\[
J_M = g_M(V-V_M) \tag{12c}
\]

where

\[
g_M = C_m\mu_M\left(\frac{\mu_M}{k} + 1\right) \tag{12d}
\]

is the maximum conductance and \(\mu_M\) is the time rate of the sodium M-channel. The large mAvrani membrane and small capacitive currents add up resulting in a large incoming ionic current.

Note that the capacitive polarization current in the proximity of the action potential peak covers
a much smaller region than the polarization ionic and membrane currents. These two currents at first negative add to a very small capacitive current are positive in the immediate proximity of the peak adding to a negative capacitive polarization current (See Fig. [7] and SM Fig. [21]). The situation is very clear at the peak itself where the total capacitive current is null and \( J_f(V_p) = J_m(V_p) \) (See Fig. [9]). The incoming (negative) mAvrani \( J_M \) current (Eq. 17f) is driven by the reversal potential \( V_M \) and its absolute value at the peak where all the \( M \)-channels are open \( |J_M(V_p)| = |g_M(V_p - V_M)| \) is much larger than the absolute value of the total ionic current \( |J_I(V_p)| \) implying a decrease in conductance. The decrease of conductance is taken into account by HH with the variable \( h \) that is independent of activation. In 1997 Patlak [40] proposed a sodium channel structure of four voltage dependent units which is consistent with the fact that inactivation is not independent from activation. In either model inactivation is caused by a gate blocking the channel from inside the axoplasm. The expected gating current has yet to be detected. The blocking of sodium channels at the mouth of the channel can’t explain by itself the reversal of incoming sodium current to outgoing to be shown in what follows.

In the present theory, having established the experimental existence of two outgoing current in the recovery region, inactivation follows activation and the already small polarization capacitive current straddling the AP peak flips from from negative to positive as the polarization ionic and polarization membrane currents flip from positive to negative (See figures [9] and [8]). The flipping of the polarization currents is associated with the continuous phase change from sodium M-channel symmetry to H-channel symmetry.

The total ionic current \( J_I \) and the membrane current \( J_m \) are negative before and after the peak and they tend to cancel each other resulting in a small capacitive current. This fact begs the question: Does the membrane current drive the ionic current or vice versa? The answer is that all three currents participate and affect each other: sodium’s current is driven by sodium’s concentration gradient across the membrane (i.e its reversal potential) and by the detailed physical and electric potential gradient configuration and polarization currents within the channel and near the channel’s mouth where the membrane current accumulates positive charges. Approaching the AP peak the charging of the membrane slows down and all three currents become suddenly smaller. The overall result is the decrease of sodium’s effective reversal potential and the accompanying decrease in sodium’s current conductance as the action potential traverses its peak and starts its descent into recovery (See Fig. [14]).

The ion intracellular current (ionic inactivation current) (Eq. 17f with \( i = 3,4 \)) starts as incoming and turns outgoing in the very proximity of the AP peak. This outgoing polarization current, opposing the mAvrani activation current and thus decreasing total incoming ionic current is caused by the driving force of the electrostatic gradient opposing the driving force of the sodium concentration gradient and selectively pushing sodium ions out through the available open sodium channels. The net result is inactivation manifested by a decrease of the overall sodium’s current conductance, the decrease of the overall effective reversal potential from \( V_M \) of the mAvrani \( J_M \) activation current down to reversal potential \( V_H \) as the inactivation is completed after the AP peak accompanied by the mAvrani deactivation current \( J_H \) (See Figures [14] and [9]). This process is equivalent to a structural blocking of sodium channels from the inside of the axoplasm if the role of the Ohm’s current is ignored and the outward sodium current is taken as not existing because it has not been detected by the voltage clamp experiments.

After the AP peak everything slows down. Recovery is much longer in extension and it takes much longer in time than the rising edge and in consequence the membrane current’s Ohm’s factor makes it small and slowly varying assuring that the membrane mainly discharges via outward ionic current and not via motion of charges in the axoplasm. If no outward current were available the membrane would discharge by ptering out via axoplasmic current and the propagation would stop.

4. The continuous phase transition from sodium M-channel symmetry to sodium H-channel symmetry at the peak of the action potential (See Fig. [9] and SM Fig. [22]) is straddled by polarization currents. The total capacitive current is zero at the AP peak and the ionic current is equal to the membrane current \( J_I(V_p) = J_m(V_p) \). Their value at the peak is given by the cable Eq. (13a)

\[
J_I(V_p) = \lim_{V \to V_p} C_m \Phi(V) \frac{1}{k} \frac{d\Phi(V)}{dV} = J_I(t)|_{t=0} \quad (13a)
\]

and

\[
J_I(t)|_{t=0} = \frac{R}{2v^2R_i} \frac{d^2V(t)}{dt^2} |_{t=0} \quad (13b)
\]

For Sweep170 \( J_I(t)|_{t=0} \approx -64 \text{ mA/cm}^2 \) (See Eq. [A2d]).

The three mAvrani activation currents and the three polarization currents are discontinuous at the AP peak while the total currents are continuous. At the peak, the capacitive current is null,
$C_m\Phi(V_p) = J_m(V_p) - J_I(V_p) = 0$, and the membrane current is equal to the ionic current. The negative membrane current straddling the peak of the action potential tends to cancel the incoming ionic current straddling the peak resulting in a small capacitive current changing from positive to negative as it crosses the peak from the rising edge to the recovery region of the action potential.

5. According to Eq. (6) the ionic current crosses the zero current axis when the tangent $\frac{d\Phi(V)}{dV}$ is equal to the propagation constant $k$ (See Fig. 3). The second crossing of zero current axis by the ionic current for Sweep 170 happens at

$$\frac{d\Phi(V)}{dV}|_{V=105.5mV} \approx 4.1 \quad (14a)$$

and for Sweep 425 at

$$\frac{d\Phi(V)}{dV}|_{V=102mV} \approx 7.89 \quad (14b)$$

AP recovery region starts with: a) the capacitive current crossing the zero current axis from positive to negative and slowly decreasing the potential across the membrane.; b) Ohm’s law and its derivative start to decrease the absolute value of the negative membrane current, first sharply and then slowly eventually crossing the capacitive current at the potential where the ionic current $J_I$ turns outward; c) Fig. 7 and SM Fig. 22 show that the extrapolations of the three mAvrami activation currents intercept zero current axis at the sodium reversal potential $V_M$. The extrapolation of the mAvrami deactivation (recovery) capacitive current $C_m\Phi_H(V)$ also intercepts the zero current axis at the sodium reversal potential $V_M$ while the corresponding membrane current $J_{mH}(V)$ and the ionic current $J_H(V)$ intercept each other below the zero current axis at the potential $V_M$, $J_{mH}(V_M) = J_H(V_M)$. These facts strongly suggest that the ionic current $J_H$, first incoming and then outward, is a sodium current and that local polarizations that do not affect sodium reversal potential are responsible for the relative strengths of the membrane and ionic currents. This interpretation recalls the 1990 paper "Outward sodium current in beating heart cells" by Wells, DeFelice and Mazanti [50]. Authors detected outward sodium current with patch clamp experiments and speculated: "It is possible, however, that the reversal potential of the Na action current reflects a local build-up of Na near the inner mouth of the Na channel..." and added "Our results imply that beating elevates internal Na, at least during some phases of the cycle." Actually, Fig. 2 and Fig. 4 demonstrate that, as the slope of the action potential turns negative the axoplasmic positive (negative) charges descend (climb) the potential resulting in the accumulation and excess of undifferentiated positive (mostly potassium) charges near mouths of sodium channels increasing the electrostatic gradient across the membrane. Eventually the electrostatic gradient overwhelms sodium’s concentration gradient and sodium ions are selectively pushed outward through already open sodium H-channels. We conclude, that the deactivation current $J_H$, first incoming and then outward, is a sodium current. In fact, this result was already anticipated long time ago. Edward Carmeliet in his 1992 Masterclass paper [10] "A fuzzy subsarcolemmal space for intracellular Na\(^+\) in cardiac cells?", without questioning the existence of the outward sodium current, addresses the question "Should the reversal potential for Na\(^+\) change?" by saying "The answer is not straightforward..." but the following remarks can be made." His remarks can be summarized as follows: "(1) The reversal potential may differ substantially from the equilibrium potential of an ion. (2) The reversal potential is not affected by the concentration in the space where surface charges establish an electrostatic potential. " and (a) "...eventually affect the conductance of the channel, and (b) alter the potential gradient across the channel and as such modify the kinetics of the channel." and "It is less generally realised that these shifts in kinetics are not accompanied by any shift in the reversal potential."

6. Outgoing sodium mAvrami deactivation current $J_H$ with 1st order phase transition going from open to closed sodium H-channels is driven by the sodium density gradient and by the competing charge density gradient across the membrane. The modulated Ohm’s current causes an accumulation of positive charges in the axoplasm increasing the electrostatic driving force that eventually overcomes the sodium density gradient driving force. The deactivation current has a smaller maximum conductance $g_H$ than $g_M$, a result of sodium channel’s symmetry change at the AP peak. It also has the effective reversal potential $V_H$ that is lower than sodium equilibrium potential $V_M$. There is no simple relation between $g_H$, $\mu_H$ and $k$ as the ones for the activation currents, a signature that the outward sodium current $J_H$ is the result of two competing driving forces. However there are several significant relations (See SM Fig. 22):

$$\frac{d\Phi_H(V)}{dV}|_{V=V_p} = \mu_H \approx -\frac{C_m\Phi_H(V_H)}{(V_M - V_H)} \quad (15a)$$

$$\frac{d\Phi_H(V)}{dV}|_{V=V_H} = k \quad (15b)$$

$$J_H(V_H) = J_{mH}(V_H) - C_m\phi_H(V_H) = 0 \quad (15c)$$
\[
J_{mH}(V_M) = J_H(V_M)
\]
(15d)

\[
\frac{dJ_H(V)}{dV} |_{V=V_k} = -g_H \approx - \frac{J_H(V_M)}{(V_M - V_H)}
\]
(15e)

Opening potassium N-channels overlap with closing sodium H-channels (See Fig. 8) and potassium activation currents exhibit quasilinear behavior near potassium’s reversal potential \(V_N\) according to Eq. 9:

\[
C_m\Phi_N(V) = -C_m\mu_N(V - V_N)
\]
(16a)

\[
J_{mN} = C_m\mu_N^2(V - V_N)
\]
(16b)

\[
J_N = C_m\mu_N\left(\frac{\mu_N}{k} + 1\right)(V - V_N) = g_N(V - V_N)
\]
(16c)

where

\[
g_N = C_m\mu_N\left(\frac{\mu_N}{k} + 1\right)
\]
(16d)

is the maximum conductance of the potassium N-channel.

7. Slow climb from potassium reversal potential \(V_N\) to the resting potential of the action potential mediated by sodium-potassium pump.

In sum, sodium M-channel region covers the region from the H-M polarization flip at the inception of the action potential to the M-H polarization flip at the AP peak, while the sodium H-channel region covers the region from the M-H polarization flip the AP peak to the H-M polarization flip at the inception of the action potential.

### III. ANALYSIS - PART 2

The Phase Space cable equation Eq. 6 yields time rates, maximum conductance and reversal potentials for various currents. The complete description of currents includes the fractions of open channels \(Xo/X\):

\[
C_m\Phi_K(V) = \mu_K(V - V_K)f(Ko/K)
\]
(17a)

\[
J_K(V) = g_K(V - V_K)(Ko/K)
\]
(17b)

\[
C_m\Phi_M(V) = \mu_M(V - V_M)(Mo/M)^{1/3}
\]
(17c)

\[
J_M(V) = g_M(V - V_M)(Mo/M)
\]
(17d)

\[
J_{mM}(V) = J_M(V) + C_m\Phi_M(V)
\]
(17e)

\[
J_{MP}(V) = J_I(V) - J_M(V) \approx \Sigma_i g_{Pi}(V - V_{Pi})(Pio/Pi)
\]
(17f)

\[
i = 1, 2 \quad g_1 = g_2 = g_{12} \quad V_{Pi} = V_{P12}
\]

\[
i = 3, 4 \quad g_3 = g_4 = g_{34} \quad V_{P3} = V_{P4} = V_{P34}
\]

\[
J_{HP}(V) = J_I(V) - J_H(V) \approx \Sigma_i g_{Pi}(V - V_{Pi})(Pio/Pi)
\]
(17g)

\[
i = 5, 6 \quad g_5 = g_6 = g_{56} \quad V_{P5} = V_{P6} = V_{P56}
\]

\[
J_H(V) = -g_H(V - V_H)(Ho/H)
\]
(17h)

\[
J_N(V) = g_N(V - V_N)(No/N)
\]
(17i)

Hodgkin and Huxley fitted the fraction of open potassium channels with an S curve in time and potential elevated to 4th power and the sodium S curve elevated to the 3rd power with dimensionless constants. These constants were interpreted as the number of structural sequential concurrent steps necessary to open the ionic channel. We assume instead that the fraction of open channels for all activation currents \(J_X\) during the steady action potential propagation in the lab is given by the Avrami S curve equation:

\[
\frac{Xo(t)}{X} = 1 - e^{-A_X(t-tox)^{\theta_X}}
\]
(18)

where \(toX\) is the inception time, the time when the ionic channels start opening, and \(A_X\) is the Avrami parameter and \(\theta_X\) is the Avrami exponent. The Avrami equation is best known for describing isothermal phase changing in solids and crystallization processes. The particular value of the exponent \(\theta = 3\) comes from from three dimensions of growth and one representing a constant nucleation rate. Avrami parameter \(A_X\) is typically very temperature dependent. In particular, for incoming sodium’s current \(A_M\) varies exponentially from about 60 at 1°C to 15000 at 25°C.

Our preliminary fittings of activation currents \(J_X\) revealed a strong experimental correlation between the highly temperature dependent Avrami parameter \(A_X\) and the temperature dependent ionic time rate \(\mu_X\) characteristic of capacitive currents (See Fig. 5):

\[
A_X = \alpha_X(\mu_X)^{\theta_X}
\]
(19)

where \(\alpha_X\) are dimensionless and temperature independent constants. The preliminary fits of three pertinent parameters \(\alpha_M, \alpha_H\) and \(\alpha_N\) showed that they are close in value to the fine-structure constant \(\alpha\). There is a very small number of such constants in physics and in all final fittings presented in this version of the manuscript we have seeded all \(\alpha_X\) with the value of the fine-structure constant \(\alpha \approx 0.007297...\) (See what Richard Feynman said about the FSC [13]).

We posit that the modified Avrami (mAvrami) equation:

\[
\frac{Xo(t)}{X} = 1 - e^{-[\mu_X(t-tox)]^{\theta_X}}
\]
(20)
is the mathematical synthesis of functional and structural homologies for all ionic channels created by Nature to conduct action potentials. The fine-structure constant $\alpha$ and the Avrami exponent $\theta_X$ inform about the structure of the ionic channel $X$. See Fig. 6.

The inclusion of channel’s time rate $\mu_X$ into Avrami equation gives physical meaning to the elusive Avrami constant $A_X$. This is a novel result in the extensive field of Avrami equation’s applications. It is remarkable that the correlation Eq. [19] includes simultaneously the novel understanding of an Avrami application and the novel role of the fine-structure constant in the passage of ions through ionic channels. Here to now there was no example or proof of the role of the fine-structure constant in either of the two involved classical realms of physics. This remarkable fact implies that the ions traversing the ionic channel interact with a two-dimensional array of atoms defining the ionic pore. The physics of a two-dimensional array of atoms is different from the solid state physics.

Fits of experimental data show that the time rates are related to the total time that channels are open during the propagation of the action potential (See Fig. 27). We parse the experimental ionic current $J_i$ in the rising edge from Eq. [1], or equivalently from Eq. [6], into the mainly undifferentiated AP foot current $J_K$ and in the M-channel symmetry region into sodium mAvrami activation current $J_M$ and mAvrami polarization currents $\Sigma_i J_{MPi}$ (i=1,4) (See Fig. 7) SM Figures 21 and 22.

Similarly, we parse the total ionic current in the recovery region into sodium current $J_H$, potassium current $J_N$, and mAvrami polarization currents $\Sigma_i J_{HPi}$ (i=5,6) (See Figures 8 and 9). The currents $J_{MPi}$ are present in two separate segments: the first one, $J_{MP1,2}$, starts at the inception of excitation and ends at the maximum of the capacitive current $C_m \Phi(V)|_{max}$, and the second segment, $J_{MP3,4}$, covers the negative resistance region of the rising edge. The currents $J_{HP5,6}$ occur right after the peak of the action potential. We did not attempt to fit the polarization currents associated with the mAvrami activation current $J_N$. The ionic currents $J_K$, $J_M$, $J_H$, $J_N$ and ionic polarization currents $J_{MPi}$ and $J_{HPi}$ are taken to have the familiar structure, displayed by Eq. [17] as the product of maximum conductance $g_X$, driving force $(V - V_X)$, and fraction of open channels $Xo/X$ for ionic currents or fractions of open channels $Pie/Pi$ for polarization currents. Our fittings reveal that: a) polarization currents are very small compared to the mAvrami current $J_M$ except in the immediate vicinity of the inception point where the reverse is true; b) the Avrami exponents $\theta_{P1,2,3,4} = 3.78$ are equal to $\theta_M$; c) the reversal potential $V_{P12}$ is close to the inception potential, very different from the $V_M$ reversal potential; d) the equilibrium potential $V_{P34}$ is very close to recovery sodium’s equilibrium potential $V_H$ and to the AP peak $V_p$, but different from
rising edge sodium’s reversal potential $V_M$; e) both polarization segments include incoming and outgoing currents; f) the maximum conductance $g_{p12}$ is almost the same value as the potassium maximum conductance $g_N$; g) the conductance $g_{p34}$ is comparable to $g_M$ if one ignores the narrow polarization flip segment (See Fig. 14); h) the time rates $\mu_{p,i}$ (i=1,2,3,4), are approximate multiples of sodium time rate $\mu_M$ (See Fig. 15); i) the conductance $g_{p56}$ is comparable to $g_M$ (See Fig. 14); j) the time rate $\mu_{p5}$ is very large and the rate $\mu_{p6}$ is an approximate multiple of sodium time rate $\mu_H$ (See Fig. 15).

We modified the Avrami equation Eq. (18) by incorporating into it the temperature dependent ionic time rates $\mu_X$ and we fitted the fractions of open channels $Mo(t)/M$, $Ho(t)/H$ and $No(t)/N$ with the so modified Avrami equation (mAvrami Eq. (20)) equations seeded with the value of the FSC. We also fitted the fractions of open channels in Phase Space as functions of the potential $X_0(V)/X$. Fittings of polarization currents fractions $Pio(t)/Pi$ with mAvrami equations reveals the polarization flip from H-channel symmetry to M-channel symmetry and the polarization flip from M-channel symmetry to H-channel symmetry (See Figures 15 and 16 and SM Figures 25 and 26).

Plots of ionic time rates as Boltzmann’s kinetic rates yield ionic activation and inactivation energies of the same order as the average of 0.65 eV rate-limiting metabolic biochemical reactions (See Fig. 13). The propagation constant and sodium maximum conductance of incoming sodium have similar temperature dependence allowing the evaluation of a realistic optimum density of sodium ions (See Fig. 12 and Appendix B Optimum channel density).

Also listed are the capacitive current $C_m \Phi_K$ corresponding to ionic current $J_K$ at the foot of the action potential, sodium and potassium capacitative currents $C_m \Phi_M$ and $C_m \Phi_N$ that are structured as a product of the time rate, the driving force and some function of the fraction of open channels. In particular for the M-channels this function is approximately the fraction of open channels exponentiated to $1/3$, $(Mo/M)^{1/3}$. The exponent $1/3$ is an ad hoc parameter that yields almost the same mAvrami or Phase Space parameters for the fraction $Mo/M$ in Eq. 17c and Eq. 17d. Note that the region of fitting covers the potential from the inflection of the action potential to the start of the negative resistance of the action potential, allowing for a small inaccuracy of the capacitive activation current due to the ad hoc choice of the parameter (1/3).

The resting potential $V_K = 0$ is determined by sodium, potassium and chloride permeabilities and their concentrations inside and outside of the axon with potassium contributing most to determine the resting potential. Potassium’s Nernst potential is slightly on the negative side of the resting potential. Chloride’s reversal potential is around the resting potential. Sodium’s reversal potential is much higher on the positive side. As a result, the total ionic current at the foot of the action potential is a complex superposition of ionic and diffusion potential, potassium, chloride, some sodium and ionic polarization
current. The slope of the capacitive current \(C_m \Phi_K\) at the action potential foot is the rate \(\mu_K\) and the slope of \(J_K\) is the conductance \(g_K\). The corresponding fraction of completed process \(K_0/K\) is included in Eq. 17a and Eq. 17d to account for the negative slope segment of \(J_K\) current where the excitation inception occurs. We have not attempted to fit this factor. In the traditional HH picture, the negative slope of the total ionic current at the foot of the action potential is reached when the incoming sodium current overtakes the outgoing potassium current. The HH model also requires a leak current. In our interpretation of experimental data the current \(J_K\) includes unresolved parsing of ionic and polarization currents up to the inception potential. The total ionic current is continuous passing through the inception point. The post inception region starts with the three discontinuous polarization currents and the inception of \(J_M, C_m \Phi_M\) and \(J_{NM}\) activation currents. The ionic polarization current segment starts as an outgoing decreasing current, equal to the total ionic current at the inception potential, switching to incoming after crossing its reversal potential and thus depolarizing the axon and promoting the mAvrami incoming sodium current \(J_M\) (See Fig. 7 and SM Figures 21 and 23). The ionic polarization current extends approximately up to the inflection point of the AP.

The quasilinear segments of capacitive currents \(C_m \Phi_K, C_m \Phi_M\) and \(C_m \Phi_N\) are closely related to corresponding quasilinear segments of \(J_K, J_M\) and \(J_N\), as already described, using the phase space cable equation Eq. 6 and originally obtained for linear currents by other authors, see Eq. 21. No such simple relationship exists between \(C_m \Phi_H\) and \(J_H\) because \(C_m \Phi_H\) and \(J_H\) intercept the zero current axis at different potentials (See Fig. 9).

However, for the deactivation current \(J_H\) we have one point of information: the current \(J_H\) crosses the zero current axis at the point where \(d\Phi(V)/dV = k\).

Fig. 7 displays the capacitive current \(C_m \Phi = C_m d\Phi/dt\), the ionic current \(J_I\) and the membrane current \(J_m = C_m \Phi + J_I\) as functions of the potential \(V\) at 12.5 °C for the rising edge region of the action potential. Fig. 8 displays the capacitive current \(C_m \Phi = C_m d\Phi/dt\), the ionic current \(J_I\) and the membrane current \(J_m = C_m \Phi + J_I\) as functions of the potential \(V\) at 4.5 °C for the recovery region of the action potential. Also displayed are the mAvrami and Phase Space fits for \(J_M, J_H\) and \(J_N\), respectively incoming sodium M-channel current, incoming and outgoing sodium H-channel current, and outgoing potassium N-channel current. In the recovery region, the currents \(J_N\) and \(J_H\) overlap adding to the total outgoing current. Fig. 7 also displays the three polarization currents \(C_m \Phi_M = C_m \Phi - C_m \Phi_M, J_{MP} = J_I - J_M\) and the membrane polarization current \(J_{MP} = J_{MP} + C_m \Phi_{MP}\). Similarly SM Figures 21 and 23 display the currents at 4.5 °C, 14.6 °C and 19.8 °C.

The sudden polarization flip from H-channel symmetry to M-channel symmetry at the inception of \(J_M, C_m \Phi_M\) currents and the corresponding polarization currents keep the total ionic, capacitive and membrane currents continuous. However, the corresponding polarization currents are discontinuous at the inception point.

The maximum conductance for each current \(J_K, J_M\) and \(J_N\) is a function of its rate and the propagation constant \(k\) as given by Eq. 21. Several segments of Eq. 17f for \(J_{MP}\), the rising edge ionic polarization current, are displayed in Figures 7 and SM Figures 21 22 23 24. The first term \(J_{P1}\) starts at the inception of the action potential and the fourth term \(J_{P4}\) finishes at the action potential peak polarization flip. Eq. 17f accounts for at least two consecutive, \(J_{MP1}\) and \(J_{MP2}\), polarization current segments associated with the inception polarization flip and for at most two, \(J_{MP3}\) and \(J_{MP4}\), associated with the AP peak flip (See Fig. 16 for a typical Sweep 425).

The post inception ionic polarization current covers the region from the inception to the inflection of the AP. It starts outgoing and decreasing as it crosses the zero current axis and then turns incoming furthering the depolarization of the membrane and thus furthering the opening of sodium M-channels. The post inception ionic polarization current has a small maximum conductance \(g_{p1} = gp2\). The reversal potential \(V_{p1} = V_{p2}\) decreases from about 40 mV to about 30 mV as temperature increases and is much closer to the resting potential \(V = 0\) than to sodium reversal potentials \(J_H < J_M\).

The pre AP peak ionic polarization current covers the negative resistance region of the AP and has a reversal potential close and below the AP peak polarization flip. Its conductance, excluding the polarization flip region, is of the same order of sodium M-channels maximum conductance. Also, the polarization rate \(\mu_{p4} = 20.6e^{0.065T}\) has the same exponential temperature dependance as the sodium M-channel time rate \(\mu_M = 10.4e^{0.063T}\) indicating the same thermodynamic origin. And, the polarization Avrami exponent \(\theta_{p3,4}\) is equal to \(\theta_{M}\). The \(P4\) channel activation energy \(\epsilon_{p4} = 0.46\) eV is slightly larger than the M channel activation energy \(\epsilon_M = 0.44\). The main difference between sodium M-channels and the AP peak ionic polarization channels is that M-channels start opening at the inception potential while the AP peak ionic polarization starts at the beginning of the negative resistance region with a reversal potential \(V_{p3,4}\) close to the peak of the AP. We conclude that the AP peak ionic polarization current (inactivation current) is a sodium current.

Note that Eq. 17f is only approximately valid because the first and the fourth segments of \(Pio/Pi\) include the polarization flips at the inception point and at the peak of the action potential \(V_r\) respectively (See Fig. 10 and SM Fig. 23). Similarly for Eq. 17f which includes the polarization flip at the peak of the action potential.

Immediately after the peak of the action potential, the total ionic current is parsed into the quasilinear portion of the mAvrami current \(J_H\) and the polarization current \(J_{HP}\). Fig. 9 and Fig. 22 display a detail
FIG. 7. The rising edge of the action potential covers the region from the resting potential to the peak of the action potential. Capacitive, membrane and ionic currents, and their parsing into charge conserving mAvrami fits portions and the corresponding charge conserving polarization portions are displayed. Note that $\mu M$ and $g_M$ are related by equation Eq. (21b). The Phase Space fits, also displayed, have been constrained requiring $V_o M$ to correspond to the value $to_M$. At the inception point the three mAvrami fits $C_m \Phi_M$, $J_m|_M$ and $J_M$ are zero and the corresponding polarization currents $C_m \Phi_M|_P$, $J_m|_P$ and $J_1|_P$ are discontinuous. At the peak of the action potential all six currents, mAvragi fits and polarizations, are discontinuous. At the inception, the small ionic polarization current $J_1|_P$ is outgoing before turning incoming whereas the sodium current $J_M$ starts flowing inward from zero as the potential increases. The first segment of the capacitive polarization current (gating current) $C_m \Phi_P$ and $J_m|_P$ start large at the inception and vanish at the inflection point of the AP. The total capacitive polarization charge (gating charge) of about $10 \times 10^{-9}$ Coulomb/cm$^2$ has moved inside across the membrane by the time the fraction of open sodium channels $M_o/M$ is about 0.2. The second segment of the capacitive polarization current near the AP peak moves a much smaller charge in opposite direction. Note that the inception’s continuous phase change precedes the crossing of the zero current axis by the ionic current, when $C_m \frac{d \Phi(V)}{dV} = k$, by about 3 millivolts.
FIG. 8. Following currents are shown: total experimental ionic and capacitive currents from Eq. (6) with their 6th order polynomial fits that avoid the polarization segments, sodium's $J_H$ and potassium's $J_N$ ionic mAvrami fits with their quasi linear segments matching the polynomial fits. Membrane current is shown as $J_m(V) = (1/k)C_m \Phi(V)d\Phi(V)/dV$ of the 6th order polynomial fit of $\Phi(V)$ plus a small experimental part close to the AP peak. Recovery polarization currents are not shown. The ionic polarization current, within few mV of the action potential peak, is displayed in Fig. 9. The linear slope of the $J_H(V)$ ionic current and the linear slope of the corresponding capacitive current $C_m \Phi_H(V)$ intercept the zero current axis at different points while the membrane doesn’t intercept the zero current axis in the vicinity of the AP peak. All three potassium’s activation currents intercept the zero current approximately at the same value as read from the graph. The two linear segments of the capacitive current correspond to rate constants of sodium H-channel $\mu_H$ and potassium N-channel $\mu_N$. The slope of $J_H$ linear segment is $-g_H$ where $g_H$ is the maximum conductance of the sodium H-channel. The slope of the ionic current $J_N$ is the maximum conductance $g_N$. Note: When fitting the PhS currents we did not require that $V_{o_N}$ and $V_{o_H}$ correspond to $t_{o_N}$ and $t_{o_H}$ respectively as we did for the rising edge $V_{o_M}$. 

Recovery region currents [$\mu A/cm^2$] vs. $V$ [mV]
Sweep 170 - Temp. 4.5 °C

$J_N = 5.31(V + 6.70)$

$J_H = -4.49(V - 104.9)$

$C_m \Phi(V) = -2.42(V + 7.14)$

$C_m \Phi(V) = 4.29(V - 111.2)$
FIG. 9. Currents detail around the peak of the action potential. Arrows → indicate time direction. The activation mAvrami sodium current at the peak of the action potential $V_p$ with all channels open is $J_M = g_M(V_p - V_M)$ where $g_M$ is the maximum conductance for the sodium M-channels. Similarly, the corresponding capacitive current is $C_m\Phi_M(V) = C_m dV/dt|_M = -\mu_M(V_p - V_M)$ where $\mu_M$ is the time rate constant. The polynomial trend lines for the mAvrami rising edge currents intercept the zero-current axis at sodium’s reversal potential $V = V_M$. The polynomial trend line of the deactivation mAvrami recovery ionic current $J_H$ intercepts the zero-current axis at $V = V_H$ that is about 6.5 mV lower than $V_M$. The polynomial trend line segment of the membrane current below the zero current axis at $V = V_M$. However, the recovery capacitive current polynomial trend line segment $C_m\Phi_H(V) = C_m dV/dt|_H$ intercepts the zero current axis at $V \approx V_M$. Fig. 10 shows that this behavior is present at all temperatures. While outgoing sodium current has not been observed in voltage clamp experiments, these facts support the conclusion that the recovery ionic current, $J_H$, is in fact sodium current. The continuous phase change of sodium M-channel symmetry into sodium channel H-channel symmetry keeps almost all the mAvrami channels open (see Fig. 15). The polynomial trend lines for the rising edge currents are fits from 72 to 95 mV. The fits for the recovery region cover 107 to 92 mV. Note that $\frac{d\Phi(V)}{dt}|_{V=V_H} \approx 4.1 \approx k$. 
FIG. 10. Recovery Capacitive Current Reversal potential vs. Temperature [°C]. As given by mAvrami fits, the recovery capacitive current reversal potentials and rising edge sodium current reversal potentials $V_M$ are closely matched across all temperatures. The polarization flip from M-channel symmetry to H-channel symmetry structure pushes the recovery ionic current reversal potential $V_H$ below the action potential peak value $V_p$. The results displayed in this graph support the conclusion that the recovery ionic current, $J_H$, is in fact sodium current and that the polarization flip from M-channel symmetry to H-channel symmetry structure is real.

around the peak of the action potential for Sweep 170 and Sweep 425 at 4.5 °C and 12.5 °C respectively. It is clear from the graphs that the recovery currents display two different behaviors near the AP peak, one clearly quasilinear slowly varying with potential (and time) over ≈ 20 mV, and the other dramatically varying over a few mV straddling the AP peak. We fit both behaviors with modified Avrami equations with different time rates (See Fig. 13).

The extension of the polynomial trend line of the quasilinear portion of the recovery capacitive current $C_m \Phi \approx C_m \Phi_H$ intercepts the zero current axis at $V \approx V_M$ (See Fig. 9 and Fig. 22). As we later apply the parsing of the rising edge ionic current into the activation mAvrami sodium current $J_M$ and the corresponding ionic polarization currents our fits find that the reversal potential of the incoming activation current is $V_M$. The fact that reversal potentials of $J_M$, $J_mM$, $C_m \Phi_M$ and $C_m \Phi_H$ are the same supports the fact that the outgoing current $J_H$ is in fact sodium current. This result is also independent of any other assumption and it is solely determined by the charge conserving cable equation.

However, the current $J_H$ intercepts the zero current axis at $V = V_H$ that is significantly lower than the reversal potential $V_M$, and its polynomial trend line extension intercepts the slope of the recovery linear segment of the membrane current $J_{m,H}$ at the potential $V_M$ but below the zero current axis. Fig. 10 displays the same behavior at all temperatures. These facts support the conclusion that $J_H$ is in fact sodium current with its reversal potential modified from $V_M$ to $V_H$ by the inactivation currents and the continuous phase change of the sodium M-channel symmetry into the sodium H-channel symme-
try while keeping almost all the mAvrami channels open (see Fig. 15).

Linear segments of \( J_K \) and \( J_N \) and \( J_H \), apparent at once in Figures 7, 9 and SM Figures 21 and 23 correspond to fractions of open channels equal to one; i.e. all channels open. The slopes of the capacitive linear segments correspond to time rate parameters \( \mu_K, \mu_M, \mu_H, \mu_N \), and the slopes of the ionic current linear segments correspond to maximum conductance \( g_K, g_M, g_H \) and \( g_N \). Maximum conductance and time rates vs. Temperature are plotted in Fig. 12.

Fig. 11 displays the rising edge currents and the percentage of open sodium M-channels plotted against time for Sweep170. The three mAvrami fitted currents \( C_m \Phi_M, J_{mM}, J_M \), and the \( Mo(t)/M \) curve begin and intersect the zero-current axis at the inception point \( t = t_0M \), the start time of the first order phase change, i.e. the start of sodium M-channels opening. Capacitive and membrane polarization currents, \( C_m \Phi_{MP} \) and \( J_{mMP} \) start with large abrupt jumps at \( t = t_0M \) and then decay mostly canceling each other according to the cable equation, while the corresponding small ionic polarization current starts outgoing and promptly turns incoming (See also SM Fig. 24 for Sweep525 and Sweep695). The surface under the first segment of capacitive polarization curve \( C_m \Phi_{MP} \) is equal to the polarization charge \( Q_p \approx 10^9 \) Coulomb/cm² moved across the membrane (a.k.a. gating charge). The flip from H-channel symmetry to M-channel symmetry symmetry and the transfer of charges across but within the membrane in conjunction with the ionic polarization current coincides with the inception of sodium M-channel current \( J_M \). In the present theory the motion of gating charges tapers off at approximately the maximum rate of the action potential at about 60 mV when the percentage of open sodium channels is about 20%. The value of the charge \( Q_p \) remains approximately the same at all temperatures. By comparison, the total gating charge deduced from Fig. 8 of frequency domain analysis of gating currents is \( \approx 8.5 \times 10^{-9} \) Coulomb/cm² although the distributions and the two potential ranges differ. Note that, while the inception of six currents is simultaneous, the capacitive polarization current (‘gating current’) membrane polarization current initially dwarfs the total incoming ionic current. In other words, a sizable ‘gating’ charge moves before a detectable sodium current is developed (See also Fig. 12 of [8] with data for potassium channel gating current). Towards the peak of the action potential, preceding the flip from M-channel symmetry to H-channel symmetry at the peak, there is an opposite charge transfer across and also within the membrane amounting to \( q_P \approx 2.6 \times 10^{-9} \) Coulomb/cm². On the recovery side of the AP peak the, not shown, polarization currents and the charge transfer change sign.

Linear segments of ionic currents \( J_K \), \( J_M \) and \( J_N \) intersect the zero current axis at the same point as the corresponding linear segments of capacitive and membrane currents. The cable Eq. 6 yields for these linear segments the relationships between maximum conductance and corresponding time rate. See also the reference [44]:

\[
g_K = \mu_K \left[ \frac{\mu_K}{k} - 1 \right] C_m \tag{21a}
\]

\[
g_M = \mu_M \left[ \frac{\mu_M}{k} + 1 \right] C_m \tag{21b}
\]

\[
g_N = \mu_N \left[ \frac{\mu_N}{k} + 1 \right] C_m \tag{21c}
\]

where \( k \) is the so called propagation constant

\[
k = \frac{2C_mR_sV^2}{R} \tag{21d}
\]

Fig. 12(a) and Fig. 13(a) show that up to 20 °C sodium channels time rate \( \mu_M \), propagation constant \( k \) rate and polarization channels rate \( \mu_P \) have essentially the same exponential temperature dependence, indicating a common underlying thermodynamic cause. (Polarization channels time rates are displayed in Fig. 16(a), SM Fig. 25(a) and SM Fig. 26(a)). The maximum conductance \( g_M \) also has the same dependence, as it should according to Eq. (21b). This fact allows to estimate the optimum density of channels in the axon (See Appendix: Optimum channel density).

Time rates \( \mu_X \) can be expressed as Boltzmann kinetic rates as given by the Arrhenius equation. See for example the reference [11]:

\[
\mu_X = \kappa X e^{-\epsilon_X/\kappa_B T} \tag{22a}
\]

\[
\ln(\mu_X) = \ln(\kappa_X) - \epsilon_X/\kappa_B T \tag{22b}
\]

where \( T \) is the temperature in Kelvin degrees, \( \kappa_B \) is the Boltzmann constant. \( \epsilon_X \) and \( \kappa_X \) are respectively the so called activation energy and the Boltzmann time rate. See Fig. 13 for graphs of Eqs. 23 for the ions traversing sodium and potassium channels and for the propagation constant \( k \). All fits are linear for up to about 20°C.
FIG. 11. The rising edge capacitive, membrane, ionic and corresponding polarizations, and mAvrami fitted currents are plotted against time. The three mAvrami fitted currents $C_m \Phi_M$, $J_m M$, $J_M$, and the $M(t)/M$ curve begin and intersect the zero-current axis at the inception point $t = t_{oM}$, the time at which M-sodium channels start to open. Capacitive and membrane polarization currents $C_m \Phi_{MP}$ and $J_{mMP}$, start with the polarization flip at $t = t_{oM}$ and then decay. The surface under the first segment of capacitive polarization curve $C_m \Phi_{MP}$ is equal to the polarization charge $Q_P \approx 10^{10^{-9}}$ Coulomb/cm$^2$ moved across the membrane (a.k.a. gating charge). The flip from H-channel symmetry to M-channel symmetry symmetry and the transfer of charges across but within the membrane in conjunction with the ionic polarization current precedes the opening of sodium channels. In the present theory the motion of gating charges tapers off at approximately the maximum rate of rise of the action potential at about 60 mV when the fraction of open sodium channels is about 20%. The value of the charge $Q_P$ remains approximately the same at all temperatures. Towards the peak of the action potential, preceding the flip from M-channel symmetry to H-channel symmetry at the peak, there is an opposite charge transfer across and also within the membrane amounting to $q_P \approx -2.6 \times 10^{-9}$ Coulomb/cm$^2$. 

\[ C_m \frac{dV}{dt} \]  
Experimental capacitive current

\[ J_m = (R/2v^2R) \frac{d^2V}{dt^2} \]  
Experimental membrane current

\[ J_I = (R/2v^2R) \frac{d^2V}{dt^2} - C_m \frac{dV}{dt} \]  
Experimental ionic current

\[ J_{mMP} = C_m \frac{dV}{dt} \mid_{t=M} + J_M \]  
Membrane current mAvrami fit

\[ J_M = g_m(V-V_M)(1-\text{EXP}(-\alpha [\mu_M(t-t_{oM})^{\mu_M}])) \]  
Sodium current, mAvrami fit

\[ C_m \frac{dV}{dt} \mid_{t=M} = -C_m \mu_M(V-V_M)(1-\text{EXP}(-\alpha [\mu_M(t-t_{oM})^{\mu_M}]))^{1/3} \]  
Capacitive current, mAvrami fit

\[ J_{mMP} = J_I - J_M \]  
Ionic polarization current

\[ J_M \mid_{P} = J_M - J_{mMP} \]  
Membrane polarization current

\[ C_m \frac{dV}{dt} \mid_{P} = C_m \frac{dV}{dt} - C_m \frac{dV}{dt} \mid_{M} \]  
Capacitive polarization current

\[ Q_P \sim 10^{10^{-9}} \text{Coulomb/cm}^2 \]

\[ q_P \sim -2.6 \times 10^{-9} \text{Coulomb/cm}^2 \]
The values of activation energies $\epsilon_X$ from Eqs. (23) and Fig. 13 are consistent with the average activation energy $\epsilon$ of 0.65 eV from research predicting a joint universal mass and temperature scaling law for rate-limiting biochemical metabolic reactions [15]. Mass $^{-1/4} e^{-\epsilon/k_B T}$. We conclude that the passage of ions through axon’s membrane is mediated by rate-limiting biochemical reactions.

We have fitted the fraction of open channels with two different versions of $X_0/X$, the first one directly in the laboratory frame with Avrami equation [4–6]. In particular, the Avrami equation for the fraction of open M-channels is:

$$\frac{Mo(t)}{M} = 1 - e^{-\alpha_M(t-t_{oM})^\theta_M}$$  \hspace{1cm} (24)

where $t_{oM}$ is the inception time, the time when sodium channels start opening, and $\alpha_M$ and $\theta_M$ are Avrami parameters. The Avrami equation is best known for describing isothermal phase changing in solids and crystalization processes. The particular value of the exponent $\theta = 4$ is said to have contributions from three dimensions of growth and one representing a constant nucleation rate. Avrami parameter $A_X$ is typically very temperature dependent. In particular, for incoming sodium current $A_M$ varies exponentially from about 60 at 1°C to 15000 at 25°C (See SM Fig. 20 for the table of parameters.)

The modified Avrami equations are more meaningful for the propagated action potential:

$$\frac{Mo(t)}{M} = 1 - e^{-\alpha_M[\mu_M(t-t_{oM})]^\theta_M}$$  \hspace{1cm} (25a)

$$\frac{Ho(t)}{H} = 1 - e^{-\alpha_H[\mu_H(t-t_{oH})]^\theta_H}$$  \hspace{1cm} (25b)

$$\frac{No(t)}{N} = 1 - e^{-\alpha_N[\mu_N(t-t_{oN})]^\theta_N}$$  \hspace{1cm} (25c)

$$\frac{Pio(t)}{P_i} \approx 1 - e^{-\alpha_{P_i}[\mu_{P_i}(t-t_{oP_i})]^\theta_{P_i}}, \ i = 1, 3, 4$$  \hspace{1cm} (25d)
FIG. 13. Logarithm of Boltzmann rates vs. $1/k_B T$. (a), (b). Plots of logarithmic fits of Boltzmann kinetic rate for $\mu_M$, $\mu_K$, $\mu_H$, $\mu_N$ yielding the activation energy and Boltzmann rate for the respective ions. These activation energies are of the same order as those of the rate-limiting biochemical metabolic reactions.

$$\frac{P2o(t)}{P2} = 1 - e^{-\alpha_P [\mu_P(t_{CP2} - t)]^{\alpha_P}}$$  \hspace{1cm} (25e)$$

where $t_{OM}$ and $t_{ON}$ are the temperature dependent times when sodium M and potassium N channels start to open, $t_{CH}$ is the time when sodium H channels close, $t_{OP1,3,4}$ are the times when polarization segments $P1, 3, 4$ channels open and $t_{CP2}$ is the time when the segment $P2$ channels close. We did not attempt the detailed fitting of Ko/K. The very small ionic current at the foot of action potential is a dynamical equilibrium of potassium, chloride and sodium currents.

The incorporation of temperature dependent time rate parameters $\mu_X$ into Avrami equations yields temperature independent dimensionless constants $\alpha_X$ for each ion channel. Allowing all parameters to vary, the average values of the mAvrami parameters over a range of temperatures, $\alpha_{M,N,H}$ are close to the value of the fine-structure constant $\alpha \approx 0.0073$. In what follows, all the mAvrami parameters $\alpha_{OM}$, $\alpha_{HN}$, $\alpha_{OP1}$, are seeded with the value of the FSC $\alpha = 0.0072973$. Similarly, we have seeded the values of $\theta_H$ and $\theta_P$, with the value 3.78. The average values of Avrami exponents in the recovery region are: $\theta_H = 3.01$ and $\theta_N = 3.02$ for 7 sweeps from 4.5 °C and 19.8 °C.

Approximate time rate parameters $\mu_K$, $\mu_M$ and $\mu_N$ and maximum conductance $g_K$, $g_M$ and $g_N$ can be read from Fig. [21], Fig. [8] and Fig. [9] or, the maximum conductance can be determined by Eqs. (21a), (21b) and (21c) respectively if the corresponding time rate is known (or vice versa). There is no such relation for sodium H-channel currents. Both, the rate $\mu_H$ and maximum conductance $g_H$ are to be read separately from Fig. [9] $\mu_H \approx J_{mH}(V_H)/(V_M - V_H)$

$$g_H \approx J_H(V_M)/(V_M - V_H) - J_{mH}(V_M)/(V_M - V_H).$$  \hspace{1cm} (26b)$$

Quasilinear segments in phase space are segments of all corresponding ion channels open and as such are amenable to fittings by the usual expressions for ionic currents Eq. [17d], Eq. [17g] and Eq. [17h] where the fractions of open channels are fitted by corresponding mAvrami equations which describe a completion process by the S curve in time. Fittings, by mAvrami equations Eq. [25a], Eq. [25b] and Eq. [25c] are very sensitive to values of time parameters $t_{OM}$, $t_{ON}$, $t_{OP1}$ and the corresponding time rates $\mu_X$, and less so to values of $\alpha$ and $\theta_X$.

Similarly, the fraction of completed polarization processes, as approximated by the mAvrami Eq. [25d] are also fitted by seeding the values of $\alpha_P$, with the value of the fine-structure constant. In what follows, for lack of known constraints, $\mu_{P1}$ are independent parameters in
our fitting. In fact, the fitting reveals that polarization time rates $\mu_{Pi}$, with some exceptions, are close multiples of sodium’s M-channel time rate $\mu_M$.

Incidentally, there is a linear relationship between $1/\mu_M$, $1/\mu_{P4}$ and $t_{oP4}$ respectively, see SM Fig. 27. Knowing the time rate $\mu_M$ (or conductance $g_M$), the relationship predicts the total time $|t_{oM}|$ to open all M-channels or vice versa.

There is experimental evidence [46] for the existence of a first-order phase transition (involving volume and temperature changes) in nerve cells, fibers and synapses. While the role of quantum effects in first order transitions is not ruled out, there are no known examples [16]. The modified Avrami (mAvrami) Eqs. 20 for open-close ion channels are possibly the first example of first order phase transition involving quantum effects.

The current $J_M(V)$ is about three times larger at 19.8 °C than at 4.5 °C since $g_M$ is about three times larger at 19.8 °C than at 4.5 °C and the factor $[M_{o}(V)/M] (V - V_M)$ is moderately temperature dependent. And, M channels open completely in a time interval about three times shorter at 19.8 °C than at 4.5 °C. Therefore, the total number of incoming sodium ions, at 4.5 °C and up to 19.8 °C, is about the same at all temperatures.

Fig. 16 and SM Figures 25, 26 display, as functions of time, the mAvrami fits for $Mo/M$ and $Pi/o/Pi$ for $i = 1, 3, 4$ and $P2/o/P2$, the fraction of open sodium M-channels and fractions of completed polarization processes at 12.5 °C, 4.5 °C and 14.6 °C respectively. These figures also display the plots of $\ln[-\ln(1-Mo/M)]$ vs. $\ln[\mu_M(t-t_{oM})]$ and $\ln[-\ln(1-Pi/o/Pi)]$ vs. $\ln[\mu_{Pi}(t-t_{oPi})]$ for $i = 1, 3, 4$ and $\ln[-\ln(1-P2/o/P2)]$ vs. $\ln[\mu_{P2}(t_{cP2} - t)]$. Note that the fraction of open channels $Mo/M$ at a particular time or corresponding potential is the same as the fraction of time that a single ionic sodium M-channel is open.

The ionic polarization current has two stages in the post inception polarization segment, both with same maximum conductance $gK << gP1 << gM$ and with same reversal potential $V_{P1} = V_{P2} << V_M$. The polarization segment with the time rate $\mu_{P1}$ starts with the channel symmetry polarization flip from H-symmetry to M-symmetry. The second segment with the time rate $\mu_{P2}$ follows shutting down the inception ionic polarization current. Among 11 sweeps at different temperatures,
only Sweep170 appears to close the inception ionic polarization current via two different time rates. We have fitted only the first one (See SM Fig. 25) For a typical sweep see Fig. 16.

in the negative resistance segment, polarization channels also act via two consecutive stages, both with the same maximum conductance \( g_{P3} = g_{P4} > g_M \), and with the same reversal potential \( V_{P3} = V_{P4} < V_p \). Note that \( g_M \approx g_{P4} \) if one exclude the polarization flip. The time rate \( \mu_{P4} \) leads to the AP peak polarization flip and has the same temperature dependence as the time rate \( \mu_M \). The two time rates are: \( \mu_{P3} \approx \mu_M \) and \( \mu_{P4} \approx 2\mu_M \). The exceptions are Sweep170 and Sweep525. For Sweep170, the lower time rate \( \mu_{P4} \approx \mu_M \) precedes the polarization flip while \( \mu_{P3} \approx 2\mu_M \). For Sweep525, there is only one polarization segment, with time rate \( \mu_{P4} \approx 1.36\mu_M \) leading to the flip (See SM Fig. 26).

Fits for \( Mo(t)/M \), \( Ho(t)/H \), \( No(t)/N \) and \( Pio(t)/P_i \), follow mAvrami S curves that involve quantum effects. Both polarization flips, the HM flip and the MH flip, are displayed in Figures 14, 16, and SM Figures 25, 26.

Fig. 17 displays mAvrami fits for sodium and potassium currents in the recovery region for 4.5 °C and 14.6 °C. We have also fitted the experimental data for the fraction of open channels in the phase space. Fig. 18 displays phase space open channels fractions fits of Equations (27), for Sweep170 at 4.5 °C.

\[
\frac{M_o(V)}{M} = \frac{\left(V - V_{OM}\right)^{4M}}{\left(V_p - V_{OM}\right)} \tag{27a}
\]

\[
\frac{H_o(V)}{H} = \frac{\left(V - V_{CH}\right)^{4H}}{\left(V_p - V_{CH}\right)} \tag{27b}
\]

\[
\frac{N_o(V)}{N} = \frac{\left(V_oN - V\right)^{4N}}{\left(V_oN - V_N\right)} \tag{27c}
\]

\[
\frac{Pio(V)}{P_i} = \frac{\left(V - V_{OP}\right)^{4P_i}}{\left(V_p - V_{OP}\right)} \tag{27d}
\]
FIG. 16. Rising edge mAvtami fits of fraction of open Mo/M sodium M-channels and fits of polarization channels fractions $P_o/P_i$. Inception and AP peak polarization flips are displayed. Parameters $\alpha_M$ and $\alpha_P$ from Eq. (20) are seeded with the value of the fine-structure constant $\alpha = 0.007297352$ and parameters $\theta_M, \theta_P$ are seeded with the value 3.78. **Note:** $g_{P_1} = g_{P_2}$, $V_{P_1} = V_{P_2}$, $g_{P_3} = g_{P_4}$ and $V_{P_3} = V_{P_4}$. (a) Both, the inception and AP peak polarization segments consist of two concatenated portions with different time rates. Inception polarization flip interpolation: + . **Note,** that polarization time rates $\mu_{P_2, P_4}$ are close multiples of sodium’s M-channel time rate $\mu_M$. See SM Fig. 25 where all four $\mu_P$ are close multiples of $\mu_M$. (b), (c), (d) **Note:** $\ln \alpha = \ln(0.007297352...) = -4.920243...$.
FIG. 17. Recovery mAtrami fits of fraction of open sodium H-channels $H_o/H$ and potassium N-channels $N_o/N$. Parameters $\alpha_H$ and $\alpha_N$ from Eq.(20) are seeded with the value of the fine-structure constant $\alpha = 0.007297352$ and parameters $\theta_H$, $\theta_N$ are adjusted by fitting. (a), (c) Plots of experimental fractions $H_o(t)/H$ and $N_o(t)/N$ vs. time[mSec] are fitted with mAtrami Eq.(25b) and Eq.(25c) respectively. (b), (d) Plots of experimental $\ln[-\ln(1 - H_o(t)/H)]$ vs. $\ln[\mu_H(to_H - t)]$ and $\ln[-\ln(1 - N_o(t)/N)]$ vs. $\ln[\mu_N(t - to_N)]$ are fitted with linear functions. Note: $\ln \alpha = \ln(0.007297352...) = -4.920243...$
where \( V_p \) is the value of the potential at the peak of the action potential, \( V_{OM} \) and \( V_{ON} \) are the respective potentials at which sodium M-channels and potassium N-channels start to open. \( V_{CM} \) is the potential at which sodium H-channels close, and \( V_{OP3.4} \) is the potential at which the polarization \( P3 \) channel start opening. Fits for fractions \( Mo(V)/M \) are seeded with the value \( V_{OM} \) corresponding to \( t_{OM} \). The average value of the \( \delta_M \) exponent for ten sweeps from 1°C to 25.2°C is \( \delta_M = 3.07 \). Fits for fractions \( Ho(V)/H \) and \( No(V)/N \) have been done with values \( V_{oH} \) and \( V_{oN} \) as free parameters. Note that the fractions of open channels \( Mo(V)/M \), \( Ho(V)/H \) and \( No(V)/N \) at any given time can be interpreted as the fraction of time that the corresponding single M-channel, H-channel or N-channel is stochastically open. The corresponding phase space ionic currents fits for Sweep 170 are plotted in Fig. 21 and Fig. 8. AP peak polarization segments, with steep tangents in the proximity of the peak and with more than one time rate, are less amenable to phase space fitting.

**IV. DISCUSSION AND CONCLUSION**

Nature has designed the giant squid axon to propagate a steady action potential along its length. The axon exists to provide communication between the external stimulus and squid’s physiological response. In general, Nature provides various ways to initiate all or nothing pulse. At the synapse, the release of acetylcholine by the action potential at the end of the nerve initiates the signal at the connecting nerve. In the lab, injecting current into the axon will generate an all or nothing action potential depending on the magnitude of the stimulus. Hodgkin and Huxley used detailed and separate voltage clamp experimental data for sodium and potassium currents in conjunction with the cable equation to describe the initiation and propagation of the action potential caused by a sufficient injection of charge into the axon. This approach, while providing an empirical description for the generation of the action potential did not provide deeper physical insight into it.

The excitation process involves time and electrical potential evolution of the non-linear all or nothing event. However, once initiated and propagating, the action potential has no memory of how it was generated. Steady
state propagation is a simpler physical phenomenon to analyze than the all or nothing particular way of excitation leading to propagation.

In the present work we have analyzed the simplest giant squid axon experimental data that measures the steadily propagating action potential at two separate points at a given temperature. The time elapsed between signals at the two points provides the values of the velocity of propagation. All other results stem from values of axoplasm’s resistivity $R_i$, axon’s capacitance $C_m$, axon’s radius $R$ and the shape of the action potential in space along the axon and from the time evolution of the action potential when observed at a fixed point along the axon in conjunction with the charge conserving cable equation. The steady propagation allowed us to write the simplified cable equation directly in the phase space providing insights into the complex relationship between its three currents. Capacitive current charges and discharges the membrane capacitor. Ionic current flows trough open ionic channels driven by corresponding specific ionic density gradients and undifferentiated charge density gradients. The so-called membrane current, the product of Ohm’s current and its derivative in the axoplasm, has the most varied and complex role through modulation of charge density in the axoplasm. At the advancing foot of the action potential, it provides the accumulation of positive charges necessary to carry forward the excitation of the axon. As sodium deactivation current and the sodium current crosses the zero current axis and the sodium’s outward current caused by its buildup of positive charges near the mouths of sodium channels in the axoplasm. While the incoming sodium ions are driven by the concentration gradient of sodium ions, they are opposed by the electrical gradient across the membrane built by all positive charges accumulating in the axoplasm. The net result is sodium’s conductance decrease and the decrease of the effective sodium’s reversal potential. The two competing forces oppose each other down from the AP peak to the potential where $\frac{d\phi(V)}{dV}|_{V=v_H} = k$ and the sodium current crosses the zero current axis and becomes outward flowing (see Fig. 3).

A clear and a definitive answer is presented by the display of currents in the APF Fig. 4. In the APF the three current problem is reduced to a two current problem: the total ionic current multiplied by the derivative of the action potential. The total axial current has two components: the Ohm’s component and the motion of capacitive charges with $v$, the velocity of AP propagation. When the derivative of the total axial current is zero the total ionic current is zero crossing the zero current axis and the capacitive current is equal to the membrane current. If Ohm’s current is turned off (made null) during the recovery the recovery outward ionic current is null as well. Ohm’s current determines that the ionic current during the descent of the total axial current from its peak must be outward. At first, the charge conservation forces the bulk of positive charges excess to be carried outwards by sodium ions through the available open sodium channels. As sodium deactivation current decreases, potassium outward current increases.

As the action potential decreases and potassium current reaches the zero current axis, the membrane current is the result of the cancellation of potassium and capacitive currents and it determines the extent of the action potential. Furthermore, without any further assumption it tells us that the derivative of the total axial current is zero when the capacitive current is equal to the membrane current, or more precisely when: $d\phi(V)/dV = k$.

Steady state propagating action potential allows the display of all three currents from the cable equation - capacitive, ionic and membrane current - in phase space as functions of temperature and electrical potential. These displays exhibit two currents with distinct quasilinear segment in the recovery region and the corresponding capacitive currents with quasilinear segments: sodium’s current $J_H$ at the beginning of the recovery, potassium’s current $J_N$ ending in the undershoot of the action potential, $C_m\phi_K$ at the foot of the action potential and potassium’s $C_m\phi_N$.

We have parsed the rising edge ionic current as the sum of currents $J_K$, the mAvrami sodium current $J_M$ and the polarization currents $\Sigma J_{P}$. The current $J_M$ exhibits its own quasi linear segment and the polarization currents $J_{P12}$ and $J_{P34}$ follow the inception polarization flip and lead to AP peak polarization flip respectively. The recovery region currents are parsed into mAvrami currents $J_H$, $J_N$ and the polarization current $J_{HP}$. We did not extract the $J_{NP}$ current. The current $J_{HP} = J_{P6}$ is much smaller in value and extension than its counterparts $J_{P34}$. The cable equation separately conserves charge for the three mAvrami components and the corresponding three polarization currents for sodium M-channels and H-channels.

Our phenomenological fittings reproduce the experimental data for the propagating action potential accurately and yield a number of novel conclusions, differing from the HH empirical model:

1. **Phase Space cable equation.** We have derived the Phase Space cable equation for the propagating action potential and showed that its three currents and Ohm’s current in the axoplasm are proportional to $\phi(V) = dV/dt$. We have also shown that the total ionic
current crosses the zero current axis at two points when \( \phi(V)/dV = k \) without any other assumption. Plots of the three currents exhibit the functional complexity of the membrane current in perpetuating the propagation and keeping the shape of the action potential. In particular, the plot of currents in the action potential frame exhibits the role of the Ohm’s current in accumulating positive charges near the mouths of sodium channels increasing the electrostatic gradient that overwhelms sodium’s concentration gradient resulting in outward flow of sodium ions through open sodium channels during recovery.

2. **Currents at the foot of the action potential.** While the present work deals only with the steady propagation of the action potential, the phase space cable equation provides without any additional assumption an insight into the excitation itself. The propagation of the advancing action potential foot is generated by the membrane current in perpetuating the propagation and keeping the shape of the action potential. In particular, the plot of currents in the action potential frame exhibits the role of the Ohm’s current in accumulating positive charges near the mouths of sodium channels increasing the electrostatic gradient that overwhelms sodium’s concentration gradient resulting in outward flow of sodium ions through open sodium channels during recovery.

3. **Currents straddling the AP peak, inactivation and deactivation sodium current \( J_H \).** Detailed plots of currents straddling the AP peak reveal a small fast changing region immediately surrounding the peak followed by a larger and slower changing portion in the recovery region with the ionic current crossing the zero current axis from incoming to outgoing at a potential, predicted by the phase space cable equation, that is below the AP peak value. The corresponding capacitive current’s trend line crosses the zero current axis at the reversal potential of the sodium’s incoming activation current. The \( J_H \) current starts with all channels open at the AP peak and we conclude that this current is sodium’s deactivation current.

Furthermore, as capacitive current crosses the zero current axis from positive to negative at the AP peak, the membrane and ionic current intercept while remaining negative and incoming respectively. The ionic conductance decreases through the AP peak and the ionic current eventually crosses the zero current axis at the point below the AP peak. This behavior is consistent with membrane current accumulating positive charges (including sodium) in the axoplasm and thus reducing the effective sodium’s reversal potential and eventually reversing the sodium current \( J_H \) into outgoing by electrostatic gradient overwhelming sodium’s concentration gradient. If there is no outward sodium current the inlet activation is consistent with the closing of sodium channels by gates localized on the axoplasmic side of sodium channels. However, the outward sodium current cannot be achieved by closing the channels. We conclude that inactivation is caused by electrostatic suppression of incoming flux of sodium ions followed by the outward flux of sodium ions through open sodium channels caused by the excess of positive charges near the mouth of the sodium channel. This conclusion recalls the 1990 paper “Outward sodium current in beating heart cells” [50]. The authors detected outward sodium current with patch clamp experiments and, without mentioning the role of the membrane current, speculated: "It is possible, however, that the reversal potential of the Na action current reflects a local build-up of Na near the inner mouth of the Na channel." and added "Our results imply that beating elevates internal Na, at least during some phases of the cycle." In his 1992 Masterclass paper "A fuzzy subsarcolemmal space for intracellular Na\(^+\) in cardiac cells?" Edward Carmeliet, without challenging the existence of the outward sodium current, addressed the question "Should the reversal potential for Na\(^+\) change?" by concluding: "The answer is not straightforward but the following remarks can be made."

His remarks can be summarized as follows: "(1) The reversal potential may differ substantially from the equilibrium potential of an ion. (2) The reversal potential is not affected by the concentration in the space where surface charges establish an electrostatic potential.” and (a) ”...eventually affect the conductance of the channel, and (b) alter the potential gradient across the channel and as such modify the kinetics of the channel,” and "It is less generally realised that these shifts in kinetics are not accompanied by any shift in the reversal potential.” Our conclusion regarding the origin of the outward sodium current is consistent with Carmeliet’s remarks.

4. **Fine-structure constant \( \alpha \), the elusive Avrami parameter \( A_X \) and the modified Avrami equation mAvRami.** There are many applications of the Avrami equation in the literature featuring the opaque temperature dependent parameter \( A_X \) with dimensions depending on the value of the dimensionless Avrami exponent \( \theta_X \). Our preliminary fittings of the squid data unexpectedly revealed a strong correlation between \( A_X \) and the ionic time rates \( \mu_X \) for the sodium and potassium channels mediated by the dimensionless and temperature independent constants \( \alpha_X \), all three close in value of the fine-structure constant \( \alpha \) associated with quantum electrodynamics (See Fig. 5).

Inclusion of channel’s time rate \( \mu_X \) into Avrami equation gives physical meaning to the elusive Avrami constant \( A_X \). This is a novel result in the extensive field of Avrami equation’s applications. It is remarkable that the correlation Eq. [19] includes simultaneously the novel understanding of an Avrami application and the novel role of the fine-structure constant from two hereto unrelated fields of physics.

It has been shown unexpectedly that the opacity of
suspended graphene, a two-dimdimensional carbon sur-
face [38], is defined solely by the FSC, with authors say-
ing: "It is remarkable that the fine-structure constant
can so directly be assessed practically by the naked eye." In
our theory, unexpectedly, we were able to fit the frac-
tions of open channels by seeding the value of the fine-
structure constant $\alpha$ for the constants $\alpha_M, \alpha_H, \alpha_N$, and
the Avrami exponent $\theta_M$, with the value 3.78. The inverse of $\alpha$,
while optimizing the parameters $t_{0M}, t_{0H}, t_{0N}, \mu_M, \mu_H, \mu_N,
\theta_H$ and $\theta_N$. The initial approximate values of $\mu_M, \mu_H
and \mu_N$ can be read from graphs of currents. Our modi-
ied Avrami equation ties together a novel interpretation
of the Avrami parameter and the novel role of the fine-
structure constant in the passage of ions through pores
that are essentially two-dimensional surfaces interacting
with passing ions at microscopic distance.

We have also fitted the fractions $P_{Io}/P_{I1}$ by seeding the
value of the fine-structure constant $\alpha$ for the con-
stants $\alpha_{P1}$ and the Avrami exponents $\theta_{P1}$ with the value 3.78, while optimizing the corresponding parameters $\mu_{P1}$, and $t_{0P1}$.

Our only and initial assumption when fitting ionic activation (and deactivation) currents is that fractions of open channels in the lab are given by mAvrami equations. This assumption led to the parsing of total currents into activation currents and corresponding polarization cur-
rents also fitted with mAvrami equations that include the
fine-structure constant. These facts point to the uni-
versal role of the fine-structure constant in the flow of
ions through channels. Bertil Hille wrote [18]. „Ion channels are found in the membranes of all cells...”. It follows
that ionic channels are essential for life. We conclude that
finestructure constant is essential for life as we know it
and that it plays an exciting role in the rate-limiting bio-
chemical reactions mediating the passage of ions through
channel ions. Furthermore, "were FSC to change by 4 %,
stellar fusion would not produce carbon, so that carbon-
based life would be impossible" [7].

mAvrami equations including the fine-structure con-
stant are the universal mathematical synthesis of ionic
cannel's structural and functional homologies.

5. The continuous phase change at the AP in-
ception and at AP peak. Both, the outgoing potas-
sium and incoming sodium currents are present at the
foot of the AP in HH models. As the potential increases,
sodium current overcomes potassium current, and the
derivative of the total current becomes negative. Any
perturbation in this region triggers the further opening
of sodium channels.

In model the perturbation that starts the inception
of incoming ionic sodium current $J_M$ is a continuous
phase change with a polarization flip and the inception of the mAvrami activation current $J_M$ and a small po-
alization current which depolarizes the membrane after
crossing the zero current axis furthering the opening of sodium M-channels and thus increasing the $J_M$
incoming sodium current. We have fitted the ionic pola-
larization current leading to the AP peak with some of
sodium current $J_M$ signature properties: same Avrami exponent 3.78, time rates that are multiples of sodium
current time rate $\mu_M$, conductance $g_{P3} = g_{P4} \approx g_M$ if one excludes the narrow region of the polarization flip, the activation energy $\epsilon_M$ slightly smaller than $\epsilon_{P4}$, the reversal potential $V_P = V_{P4} < V_p$ but somewhat close to $V_M$. The AP peak continuous phase change takes the sodium M-channel symmetry into sodium H-channel
symmetry. It follows that the inception AP polarization
flip must take sodium H-channel symmetry into sodium
M-channel symmetry triggering the action potential. The
fitted fraction of open incoming ionic polarization chan-
els has: same Avrami exponent 3.78 of M-channel frac-
tion of open channels $M o(t)/M$, and time rates rates $\mu_{P1}$ and $\mu_{P2}$ at most temperatures are approximate multiples
of sodium's current time rate $\mu_M$. However, the con-
ductance $g_{P1,2}$ is much smaller than $g_M$. The effective
reversal potential $V_P = V_{P2}$ is slightly higher than the
inception potential of about 40 mV at 4.5°C, increasing
as the temperature increases. Also, note, that this pola-
larization current changes from outward to incoming as
the membrane polarization current crosses the capacitive
polarization current. The chloride reversal potential in
the axon at rest is reported to be about 15 mV. One
should also probably expect a small contribution from
polarization channels below the inception potential while
in dynamical equilibrium with other players in the AP
foot: potassium and sodium permeability, chloride chan-
els current and sodium-potassium pump. However, the
present analysis doesn’t provide further insight into the
details of the $J_K$ current components.

The present work posits that sodium’s channels lattice/dominains act as ferroelectric sensors triggering the
continuous phase change at the inception of the action
potential in response of any number of electro-chemical-
mechanical stimuli. As all channel open at the peak of the
action potential a continuous phase change is triggered
reverting the open sodium’s channels to the resting state
symmetry.

6. Gating currents and gating charge. Hodgkin
and Huxley foresaw the existence of moving gating
charges inside the membrane as the signature of sodium
channels opening. Gating currents were detected [2], [3],
[31] and total gating charge $Q_g \approx 9 \times 10^{-9}$ Coulomb/cm$^2$
was measured. However, no direct correlation between
the gating current and the sodium current had been es-

tablished as one would expect from HH proposed classical
mechanism that posited each channel with its own charge
moving gate.

Our theory, by parsing the total experimental cur-
rrents into mAvrami fits of activation currents plus the
 corresponding polarization currents, yields discontinu-
ous polarization currents at the AP inception and at the
AP peak. The capacitive polarization current, in other
words charges moving inside the membrane or simply 'the
gating current' that starts discontinuously and large at
the inception point and then vanishes at the inflection
point of the rising edge of AP. So does the membrane
polarization current. Their difference is the small in-ception ionic polarization current, that starts as out-going and decreasing and then turns to incoming. Meanwhile, the mAvrami sodium current $J_M$ starts from zero and promptly overtakes the incoming polarization current. The surface under the capacitive polarization current in Lab yields the value of ‘the gating charge’, as $Q_g \approx 10 \times 10^{-9}$ Coulomb/cm$^2$ at all temperatures (See Fig. 11). The capacitive polarization current (‘gating current’) precedes in size the incoming sodium current $J_M$. In other words, a sizable ‘gating’ charge moves before a detectable ionic current is developed as seen in Fig. 11 and SM Fig. 24 (See also Figures 8 and 12 of [8]).

The discontinuity of polarization currents at the inception point presumes the existence of polarization currents of opposite sign approaching the inception potential position. The discontinuity of polarization currents at the inception point presumes the existence of polarization currents of opposite sign approaching the inception potential possibly smoothing out the experimental capacitive polarization (gating) current.

7. Inactivation. In the HH model inactivation is a process, independent from activation, described by the variable $h$ that blocks sodium channels during depolarization and it overlaps with activation described by the variable $m^3$. In the present model inactivation is not independent from activation. Inactivation follows and overlaps with activation when the increasing depolarization triggers the polarization currents straddling the AP peak (See Fig. 14). This is consistent with the 1977 work of Bezanilla and Armstrong [9] whose experiments were first to demonstrate that activation precedes inactivation. They concluded that the inactivation gating current was small and difficult to detect. The modeling of inactivation as caused by blocking of sodium channel from inside the axoplasm expects to detect the corresponding gating current.

Total ionic current $J_I$ and the membrane current $J_m$ are negative before and after the peak and they tend to cancel each other resulting in a small capacitive current switching from charging the membrane to discharging it, i.e from positive to negative. This fact begs the question: Does the membrane current drive the ionic current or vice versa? The answer is all the three currents participate, however their relative strengths change at the AP peak. Before the peak $|J_m(V)| < |J_I(V)|$ and after the peak $|J_m(V)| > |J_I(V)|$ and the capacitive current changes from positive to negative. The incoming ionic current is the immediate source of sodium ions at the mouth of the channel and the membrane current modulates the concentration of positive charges while enforcing current conservation thus diminishing sodium’s effective reversal potential and the accompanying decrease in sodium’s current conductance (See Fig. 14). As long as there is no outward sodium current this process is equivalent to blocking of sodium channels from the inside of the axoplasm. However, as ionic current changes from incoming to outgoing at the potential $V_H$ there is no blocking of sodium channels.

Our model predicts that the charge transferred up to the AP peak is $q_g \approx 2.6 \times 10^{-9}$ Coulomb/cm$^2$, about one fourth of the activation gating charge at all temperatures (See Fig. 11 and SM Fig. 24). Immediately after the AP peak there is another small capacitive charge transferred in opposite direction making the overall charge transfer even smaller. It is difficult to discern the role of both opposite charge motions relating to the motion of gates closing the axoplasm end of sodium channel. Rather, it is the signature of polarization flipping associated with the continuous phase transition. The motion of capacitive charges in this region is associated with the continuous phase change at the AP peak and symmetry change from M-channel symmetry to H-channel symmetry. Furthermore, as the modulated Ohm’s current accumulates positive charges in the axoplasm the electrostatic gradient overwhelm sodium’s concentration gradient and the ionic current crosses the zero current axis as predicted by the phase space cable equation. This interpretation is supported by the experimental 1990 observation of an outward sodium current in beating heart cells [50].

8. The recovery region. The recovery region of the HH action potential is not quite right when compared with the experiment. In addition, the HH model features a significant cancellation of opposing sodium and potassium currents straddling the peak of the action potential. This feature of the HH equations results in a decrease of velocity of propagation and waste of energy [13, 15]. Increasing the delay of potassium conductance onset and delaying sodium channel inactivation reduces the discrepancy between Hodgkin and Huxley’s predicted and observed velocity of propagation [13].

Present model fits the action potential experimental data everywhere and doesn’t exhibit cancellation of opposing sodium and potassium currents anywhere. The phase space plot of total ionic current in the recovery region clearly displays the overlap of two non-cancelling currents bracing the recovery region with quasilinear segments. The later linear segment intercepts the zero current axis at the potassium reversal potential, while the first segment intercepts the zero current axis in the vicinity of the rising edge sodium reversal potential and at a value lower than the value of the potential at the peak. Even though no outgoing sodium current has been observed experimentally in the squid axon, it is difficult to come up with an alternate ion carrying the outgoing current with a reversal potential close to sodium’s reversal potential. In fact, the fitting of recovery capacitive current $C_m \Phi(V)$ with a 3rd order polynomial, excluding the capacitive polarization region of the H-channel, intercepts the zero axis at the M-channel sodium’s reversal potential $V_M$ supporting the argument that $J_H$ is indeed a sodium current. The mAvrami ionic and membrane currents intercept each other at the same potential but below the zero current axis (See Fig. 21 and SM Fig. 22). We conclude that we are dealing with a continuous phase polarization flip from all sodium M-channel open to almost all H-channels open at the peak of the action potential and with a briefly incoming and then outgoing mAvrami sodium current $J_H$. The continuous phase po-
larization flip changes the M-channel symmetry into H-channel symmetry, with H-channel polarization currents decreasing the effective reversal potential of the sodium current from $V_M$ to $V_H$. The H-channel polarization currents are the measure of the flux of sodium ions driven by the electrostatic gradient opposing the flux of incoming sodium ions driven by their concentration gradient.

The continuous phase change at the peak, in addition of changing the time rate and the maximum conductance also changes the Avrami exponent from 3.78 to $\approx 3$ indicating that steps involved in closing the sodium channel are different from steps when opening the channel.

9. Sodium channels optimum density. While various approaches to estimate the optimum density of sodium channels using the HH equations have failed, the propagation constant and sodium maximum conductance of incoming sodium have similar temperature dependence allowing the evaluation of a realistic optimum density of sodium ions (See Fig. 12 and Appendix B Optimum channel density). Our model arrives closely at the density observed in nature (See Appendix B).

10. Temperature and thermodynamics. The HH model doesn’t say anything directly about temperature dependence. This limitation precludes applying thermodynamics to the study of the action potential and by extension it has nothing to say about possible phase changes involved. It is questionable if voltage clamp experiments can detect continuous phase change, even if present in a normally functioning axon.

Rozenthal-Bezanilla [42] data covers a range of temperatures from 1°C to 25°C yielding the exponential temperature dependence for parameters of interest in our phenomenological theory. Passage of ions through a membrane channel involves interactions with the surface of the pore at microscopic distances. Plots of ionic time rates as Boltzmann’s kinetic rates yield temperature independent Arrhenius activation energies for the passage of ions through the membrane. These energies are of the same order as the average of 0.65 eV rate-limiting metabolic biochemical reactions [15]. The fine-structure constant plays a role of universal scaling parameter across sodium, potassium and polarization channels. (See Fig. 13). We conclude that the passage of ions through ionic channels is mediated by metabolic biochemical reactions.

11. Ferroelectric phenomena. The opening of polarization channels and the accompanying polarization current proceeding in the negative resistance region, are manifested by the decrease of conductance for the total ionic current $\sigma_{\text{exp}} = J_I/(V - V_M)$, the change in the effective ionic equilibrium potential and possibly by the presence of optic phenomena [48]. At the peak of the action potential the sodium’s M-channel maximum conductance changes abruptly from $g_M$ to $g_H$ with $g_H$ about one order of magnitude smaller than $g_M$ and the effective equilibrium potential change is completed by an abrupt but continuous decrease from $V_M$ to $V_H$ while keeping the ionic current continuous. The abrupt decrease in sodium’s maximum conductance is caused by the polarization flip put in evidence by the polarization current discontinuity. The sodium’s M-channel and H-channel have different symmetry and different structure. The transition from M-channel symmetry to H-channel symmetry is a continuous phase transition interpreted as a ferroelectric polarization flip mediated by polarization currents straddling the peak of the action potential. This process, involving a region with many channels, is consistent with the view that in ferroelectric phenomena "The mechanism of switching is understood to take place on scales longer than the unit-cell scale [51]."

Similarly, at the inception of the action potential there is a continuous phase transition from sodium H-channel symmetry to M-Lattice symmetry. In addition to properties of individual channels, nerve excitability also involves ferroelectric phenomena pertaining to domains/lattices of ion channels [48], [51].

12. Single channel behavior. The fractions of open channels $Mo(V)/M$, $Ho(V)/H$ and $No(V)/N$ at any given time can be interpreted as the fraction of time that any corresponding single M-channel, H-channel or N-channel is stochastically open.

13. Memory storing and retrieval. The role of the ferroelectric lattice behavior defined by continuous phase transitions associated with morphological changes in sodium channels lattice described in the present work has implications for encoding of memories. Encoding of memories across invertebrates, insects and mammals are also associated with steplike morphological changes in neuron’s cytoskeleton.

It has been suggested that evolution has conserved across species the underlying molecular mechanism involved in encoding of memories. It is accepted that invertebrates and mammalians share many of the same memory encoding properties [17], [32]. There is an extensive accumulation of research and experimental data on the associative memory storage and retrieval by Drosophila. There is a general agreement as expressed by [37]: "...that there is a cytoskeletal pathway underlying the very first steps towards associative olfactory memory encoding in Drosophila". Also, "... larvae learned in a switch-like (all-or-none two-state quantized) manner. The learning process was better described as a sudden transition between states... [34]". Also, "The learning curves for individual subjects show an abrupt, often step-like increase from the untrained level of responding to the level seen in the well trained subject [14]".

At the same time, there is experimental evidence that "Sodium channels in axons are distributed in a periodic pattern coordinated with the underlying actin-spectrin–based cytoskeleton" [51], implying the existence of sodium channels lattice in general. Also, according to [48]: "presence of optical changes during nerve excitation are consistent with the view that the process of excitation is accompanied by conformational changes in macromolecules of the nerve". Polarization flips (continuous phase transitions - CPTs) at the inception and at
the peak of the giant squid axon action potential modify the structure of sodium channels lattice in a step like manner.

Although the duration of the M-channel symmetry structure in squid axon is ephemeral lasting only during the rising edge of the action potential while cytoskeleton modifications involving memory encodings with definitive lifetimes, minutes/hours short lived or permanent, we posit that memory encodings are also initiated by neuron’s cytoskeletal continuous phase transitions. Note that while domains involved in CPTs are too large in principle to involve quantum effects, the different M and H configurations of sodium’s channels cytoskeletal lattice correspond respectively to different M and H sodium channels time rates, and Avrami exponents.

We posit that these steplike changes of the cytoskeleton structure are initiated by a continuous phase change. The hysteresis loop with two different symmetry states of sodium channels lattice implies the possibility of additional neuronal stable states besides the resting state. Additional neuronal stable states are the physical basis for long term memory formation and retrieval. [22].

14. What is next? Our analysis of the propagation action potential of the fully functioning giant squid’s axon presents several shifting and new paradigms:

1. The phase space display of the charge conserving cable equation giant squid’s propagating currents exhibits in the recovery region a second outgoing current in addition to the potassium current. We have presented arguments that the hereto not observed second current is in fact sodium current. This prediction should be confirmed experimentally.

Other nonlinear propagating phenomena like solitons should also lend themselves to be analyzed in the phase space eliminating the explicit time dependence.

2. Our coherent and self-consistent description of the propagating action potential by parsing the currents into the mAvrami and the corresponding polarization currents traversing ion channels predicts the existence of two structural configurations of the sodium channel lattice: the resting state H configuration and the excited state M configuration related through the continuous phase changes. These two states and the predicted phase changes should be observable and measurable through mechanical, optical, and thermodynamic /ferroelectric properties.

In particular, the computational tools and programs, such as AlphaFold, Rosetta and others, could be used to find the distinct sodium channel configurations and could possibly detect another stable configuration with implication for memory storage and retrieval.

3. The ions traverse ionic pores interacting with the surface of the pore at microscopic distances. Our fittings of the fraction of open channels with mAvrami equations yield the phenomenological role of the fine-structure constant and the Arrhenius activation energies of the same order as the activation energies of metabolic biochemical reactions. It is known that the fine-structure constant has an explicit role in photons interacting with graphene’s two-dimensional carbon surface. These facts point to the possibility of an explicit quantum theory justifying the empirical mAvrami equation.

Presented results will provide a framework for further experimental analysis of excitability role by sodium channels lattice and its thermodynamic phase changing behavior, the role of quantum mechanics in biochemical reactions mediating the flow of ions across ion channels and the plasticity of neuronal stable states essential for memory storage and retrieval mediated by continuous phase changes.

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[1] R. H. Adrian. Conduction velocity and gating current in the squid giant axon. Proc. R. Soc. Lond. B, 189:81–86, 1975.
[2] C. M. Armstrong and F. Bezanilla. Currents related to movement of the gating particles of the sodium channels. Nature, Lond., 242:459–461, 1973.
[3] C. M. Armstrong and F. Bezanilla. Charge movement associated with the opening and closing of the activation gates of the na channels. J. Gen. Physiol., 63:533–552, 1974.
[4] M. Avrami. Kinetics of phase change. i. general theory. Journal of Chemical Physics, 7(12):1103–1112, 1939.
[5] M. Avrami. Kinetics of phase change. ii. transformation-time relations for random distribution of nuclei. Journal of Chemical Physics, 8(2):212–224, 1940.
[6] M. Avrami. Kinetics of phase change. iii. granulation, phase change, and microstructure. Journal of Chemical Physics, 9(2):177–184, 1941.
[7] John D. Barrow. Cosmology, life, and the anthropic principle. Annals of the New York Academy of Sciences.
associated proteins form a periodic cytoskeletal structure in axons. Science, 339:452–456, 2013.

Appendix A: Action potential hysteresis loop

The observation of a propagating AP in the lab starts with the increasing potential and the increasing outgoing small potassium current. At the AP inception there is a polarization flip from H-channel symmetry to M-channel symmetry and incoming sodium current $J_M$ with $V_M$ reversal potential is initiated. For the purpose if this Appendix we are neglecting the effects of the ionic polarization current following the inception. At the AP peak, while the potassium channels are closed, the effective sodium reversal potential has an abrupt decrease from $V_M$ to $V_H$ correlated with the polarization flip. As the sodium H-channels with $V_H$ reversal potential are closing, the potassium channels with $V_N$ reversal potential are opening. Potassium current turns incoming after $V_N$ is crossed and the effective potassium reversal potential has a very slow increase from $V_N$ to $V_K$ mediated by the potassium-sodium transport mechanism while sodium channels are closed. Eventually the equilibrium between potassium and chloride permeabilities and sodium-potassium pump determines the resting potential and the effective reversal potential hysteresis loop is closed. Fig. 19(a) shows the linear correlation between $(V_M - V_H)$ and $(V_K - V_N)$ over a range of temperatures. Fig. 19(c) shows that linear fits for $(V_N - V_K)$ and $(V_M - V_H)$ vs. temperature have similar slopes. The average ratio $(V_M - V_H)/(V_K - V_N)$ for six sweeps is approximately 0.9. Figs. 19(b) and 19(d) show the hysteresis loops for sweeps at 4.5 °C and 19.8 °C. The surface of the hysteresis loop at 19.8 °C is about twice as large as the surface at 4.5 °C, indicating that the heat generated by the AP is twice as large at 19.8 °C than at 4.5 °C.

Fig. 9 for Sweep 170 at 4.5 °C shows that both, the rising edge polarization current and the recovery polarization current have quasi-linear segments, before reaching the action potential peak and after the action potential peak respectively. Therefore, they can be represented approximately as follows:

$$J_{PM}(V) \approx g_{PM}[Po(V)/P]_M(V - V_{PM})$$  \hspace{1cm} (A1a)

$$J_{PH}(V) \approx g_{PH}[Po(V)/P]_H(V - V_{PH})$$  \hspace{1cm} (A1b)

The mAvrami fit fails as the potential nears the peak of the action potential since the derivative of the polarization current, a component of the total ionic current, tends to infinity. As $V$ tends to $V_p$, the derivatives of $g_{PM}(V)[P4o(V)/P4]$ tend to infinity and the total ionic current tends to a finite value.

The rising edge portion of the polarization current $J_{PM}(V)$ displays two distinct segments. The outgoing current’s quasi-linear part intercepts the current axis with the slope $g_{PM} \approx 56 \, \text{mS/cm}^2$ and the value of the intercept is $V_{PM} \approx 106.6 \, \text{mV}$. Note however that the tangent of the polarization current tends to infinity as the voltage tends to the peak of the action potential, so the quasilinear behavior is only present away from the peak of the action potential. The polarization current at first increases the incoming total sodium current and then it decreases it. This implies first an increase and then a steep decrease of sodium’s M-channel effective equilibrium potential (Meep). Thus, up to a fraction of a milli-volt from the peak of the action potential, the M-channel total ionic current $J_M(V)$ and Meep(V) can be written as follows:

$$J_I(V)_{\text{Experiment}} = J_M(V) + J_{PM}(V) = g_M[Mo(V)/M][V - \text{Meep}(V)]$$  \hspace{1cm} (A2a)

or

$$\text{Meep}(V) = V - \frac{J_I(V)_{\text{Experiment}}}{g_M[Mo(V)/M]}$$  \hspace{1cm} (A2b)

In the close proximity of the action potential peak $V_p$ we have:

$$\text{Meep}(V) \approx V - \frac{J_I(V)_{\text{Experiment}}}{G_M(V)}$$  \hspace{1cm} (A2c)

where $G_M(V)$ goes from $g_M$ to infinity (See Fig. 9) as $V$ approaches $V_p$. Since, respectively, at 4.5 °C and 19.8 °C

$$J_M(V_p) = \frac{R}{20^2 R_i} \frac{d^2V}{dt^2} |_{V = V_p} \approx -64 \mu A/cm^2 \implies \text{Meep}(V_p) = V_p$$  \hspace{1cm} (A2d)

$$J_M(V_p) = \frac{R}{20^2 R_i} \frac{d^2V}{dt^2} |_{V = V_p} \approx -442 \mu A/cm^2 \implies \text{Meep}(V_p) = V_p$$  \hspace{1cm} (A2e)

The recovery polarization current is much smaller and it covers a smaller region than its counterpart leading
FIG. 19. Schematic ferroelectric hysteresis. (a) $(V_M - V_H)$ [mV] vs. $(V_K - V_N)$ [mV]. (b), Schematic ferroelectric hysteresis loop at 4.5 °C, Polarization = $(V_M - V_H)$[mV]. (c), $(V_K - V_N)$ and $(V_M - V_H)$[mV] vs. Temp.[°C]. (d), Schematic ferroelectric hysteresis loop at 19.8 °C, Polarization = $(V_M - V_H)$[mV] vs. Electric field [mV]. Time direction is given by the arrow $\rightarrow$.

to the AP peak. Neglecting the outgoing portion, we have plotted (See Fig. 19) only its incoming part covering about 1.5 mV below the peak of the action potential and where all the H channels are open, $H_0/H = 1$. Here, away from close proximity of the action potential peak the equivalent of Eq. A2b is:

$$J_I(V)|_{Experiment} = J_H(V) + J_{PH}(V) = g_H[H_0(V)/H][V - Heep(V)]$$  \hspace{1cm} (A3a)

or

$$Heep(V) = V + \frac{J_I(V)|_{Experiment}}{g_H[H_0(V)/H]}$$  \hspace{1cm} (A3b)
In the close proximity of the action potential peak \( V_p \) we have:

\[
Heep(V) \approx V - \frac{J_H(V)|_{\text{Experiment}}}{G_H(V)}
\]

(A3c)

where \( G_H(V) \) goes from \( g_H \) to infinity (See Fig. 9) as \( V \) approaches \( V_p \). Since, respectively, at 4.5 °C and 19.8 °C

\[
J_{1H}(V_p) = \frac{R}{2v^2R_i} \frac{d^2V}{dt^2} |_{v=V_p} \approx -64 \mu A/cm^2 \implies Heep(V_p) = V_p
\]

(A3d)

\[
J_{1H}(V_p) = \frac{R}{2v^2R_i} \frac{d^2V}{dt^2} |_{v=V_p} \approx -442 \mu A/cm^2 \implies Heep(V_p) = V_p
\]

(A3e)

As the potential traverses the peak, total ionic current and sodium’s effective equilibrium potential are continuous and the polarization current is discontinuous.

Hippel [49] and Leuchtag [35] have suggested that ferroelectricity plays a role in biological excitability. A hypothesis that a single sodium channel exhibits ferroelectric behavior has been advanced [36] based on measurements by Palti [39] of axon’s capacitance in the temperature region with membrane excitability.

A ferroelectric hysteresis loop is a graph of polarization vs. electrical field. Fig. 19(b) and Fig. 19(d) display the phase space trajectory of the schematic hysteresis loop traversed by the action potential in terms of sodium and potassium effective equilibrium potentials at 4.5 °C and 19.8 °C. Deviation from chemical equilibrium potentials is caused by the polarization that is function of electrical field which in turn is proportional to the potential across the membrane. Note that \( V_H \) decreases by 13 mV as temperature increases from 4.5 °C to 19.8°C while \( V_M \) decreases by less than 6 mV.

The inception polarization flip closes the potassium channels and changes \( g_H \) to \( g_M \) and \( \mu_H \) to \( \mu_M \), and starts to open the M-sodium channels. The polarization flip at the peak of the action potential changes \( g_M \) to \( g_H \) and \( \mu_M \) to \( \mu_H \) while sodium channels are open as observed in Fig. 9 and changes \( g_K \) to \( g_N \) while potassium channels are closed. The sodium-potassium pump changes \( g_K \) to \( g_K \) while potassium channels are open. Fig. 19(a) shows the linear correlation between \( (V_M - V_H) \) and \( (V_K - V_N) \) over a range of temperatures. Fig. 19(c) shows that linear fits for \( (V_N - V_K) \) and \( (V_M - V_H) \) vs. temperature have similar slopes. The average ratio \( (V_M - V_H)/(V_K - V_N) \) for six sweeps is \( \approx 0.9 \). Sodium’s M-channel maximum conductance \( g_M \) and H-channel maximum conductance \( g_H \) are different and so are the respective time rates \( \mu_M \) and \( \mu_H \). Sodium’s M-channel lattice and H-channel lattice have different symmetry. These facts are a signature of a continuous (second order) phase transition [33 p. 445].

The surface enclosed by the hysteresis loop is proportional to energy spent, i.e. it is proportional to heat released. The surface enclosed at 19.8 °C is approximately twice the surface enclosed at 4.5 °C and so is the corresponding heat released. There are many experimental instances reporting heat production associated with electrical excitability; see the review article by I. Tasaki [47].

**Appendix B: Optimum channel density**

Hodgkin [19] hypothesized that there is an optimum sodium channel density to achieve the maximum velocity of propagation and that the maximum sodium conductance \( g_{Na} \), i.e. \( g_M \), is expected to be proportional to the surface density of sodium channels \( M \). His calculation arrives at the optimum density of about 1000 sodium channels per \( \mu m^2 \), which is about twice the number measured by Keynes and Rojas [31]. Adrian [11] calculated the maximum velocity of propagation by means of modified Hodgkin-Huxley equations allowing for a sodium gating current, which reduces the velocity of propagation significantly below the observed one.

Assuming as Hodgkin that the maximum sodium conductance is proportional to sodium channel density we have:

\[
g_M = g_{Na} M
\]

(B1)

where \( g_{Na} \) is the single channel conductance at a particular temperature. Increasing \( M \) increases the velocity of propagation, but at the same time it increases the fraction of the membrane capacitance due to the channels. In the linear region, where all the channels are open, sodium maximum conductance is given by Eq. (21b):

\[
g_M = \mu_M (\frac{\mu_M}{k} + 1) C_m
\]

(B2)

See Fig. 12(a) and note that for up to about 20 °C the temperature rates are approximately the same for \( g_M, k \) and \( \mu_M \). The rates \( \mu_M \) and \( k \) exhibit a constant ratio:

\[
\frac{\mu_M}{k} \approx 3.2
\]

(B3)

for up to about 20 °C. It is reasonable to assume that the rate constant \( \mu_M \) has the same dependency on \( R_i \),
$R$, $v$ and $C_n$ up to 20 °C as the propagation constant $k$. Using Eq. (B3) and the expression Eq. (214) for $k$, Eq. (B2) is written as:

$$g_M \approx 13.54kC_m = 27.1v^2C_m^2 \frac{R_i}{R} \quad \text{(B4)}$$

or

$$v^2 \approx \frac{g_{Na}^2R}{27.8R_i(C_0 + MC_{Na}^2)} \quad \text{(B5)}$$

where $C_{Na}^*$ is the capacitance of a single channel and $C_0$ is the capacitance of the membrane without channels. If $C_0$ remains fairly constant as $M$ varies, the velocity of propagation has a maximum at the observed velocity $v$ when:

$$M \approx \frac{C_m}{2C_{Na}^*} \quad \text{(B6)}$$

or specifically $M \approx 625/\mu m^2$ when $C_{Na}^* = 8 \times 10^{-18}$ F and $C_m = 1 \mu F/cm^2$. Keynes and Rojas [31] estimated sodium channel density $M$ to be $M \approx 500/\mu m^2$ when $g_{Na} = 2.5 \ pS$ and $C_{Na}^* = 8 \times 10^{-18}$ F.

**Appendix C: Fitting Procedure**

Rosenthal-Bezanilla data provides the action potential $V$ at two points along the axon at different temperatures. The action potential data was analyzed at the point furthest away from the stimulus. Rosenthal measured the resistivity at 18.5°C and determined that his measurement was consistent with the generally used expression for resistivity, also used in this work:

$$R_i = 51.05 \times 1.35^{-\left[\frac{x-4.3F}{m}\right]} \left[\text{Ohm} \times \text{cm}\right]. \quad \text{(C1)}$$

Rosenthal-Bezanilla experimental data of the action potential at different temperatures are discrete values taken at fixed time intervals. The amount of noise in the data depends on its rate of change and on the temperature. To improve fitting we have used Gauss sigma smoothing while trying to minimize the loss of accuracy. At lower temperatures there is more noise and there are many more data points than at high temperature. Larger Gauss sigma smoothing values are required at low temperature than what is required at higher temperatures. The recovery region, being noiser, required more smoothing than the rising edge at a given temperature.

Approximate time rate parameters $\mu_K$, $\mu_M$ and $\mu_N$ and maximum conductance $g_K$, $g_M$ and $g_N$ can be read from Fig. 21, Fig. 8 and Fig. 3 or, the maximum conductance can be determined by Equations (21a), (21b) and (21c) respectively when the corresponding time rate is known (or vice versa). There is no such relation for H-channel currents. Both, the rate $\mu_H$ and maximum conductance $g_H$ are to be read separately from Fig. 21. Quasilinear segments in phase space are segments of all corresponding ion channels open and as such are amenable to fittings by the usual expressions for ionic currents Eq. [17d], Eq. [17g] and Eq. [17h] where the fractions of open channels are fitted by corresponding mAvrami equations describe a completion of a crystallization process from zero to one by the S curve in time. Fittings, by mAvrami equations Eq(25a), Eq (25b) and Eq (25c) are very sensitive to values of time parameters $t_{0M}$, $t_{0N}$, $t_{0H}$ and the corresponding time rates $\mu_X$ and less so to values of $\alpha_X$ and $\theta_X$. As a result, we have seeded all $\alpha_X$ with the value of the fine-structure constant: $\alpha = 0.007297352$. Also, all three Avrami exponents were seeded, $\theta_X = 3.78$. While the linear segment of recovery sodium current presents itself clearly and intersects the zero current axis below but close to AP peak, the rising edge total incoming sodium doesn’t present a clear quasilinear segment. Inclusion of points beyond the start of negative resistance region in the fit for fraction of open channels results in a quickly diverging Avrami exponent $\theta_{Pi}$ indicating that incoming sodium current consist of an additional superimposed polarization process in the negative resistance region and up to just before the action potential peak. The fitting region was chosen to be between the inflection point of the action potential (the maximum value of the capacitive current) and the beginning of the negative resistance region. These choices result in the values for sodium’s reversal potential $V_M$, time rate $\mu_M$ (and $g_M$ according to Eq. (21b)) and the time $t_{0M}$ for Eq. (17d) and (25a). The difference between the experimental current $J_I$ and thus obtained sodium current $J_M$ yields the polarization current $J_P = \Sigma J_{Pi} = J_I - J_M$.

Similarly, the fraction of completed polarization process, as approximated by the mAvrami Eq. (25d) was also fitted by seeding the values of $\alpha_{Pi}$ with the value of the fine-structure constant and Avrami exponents $\theta_{Pi}$ were seeded with the value 3.78. For lack of known constraints, $\mu_{Pi}$ are independent parameters in our fitting. In fact, fitting revealed that polarization time rates $\mu_{Pi}$, with some exceptions, are close multiples of sodium’s M-channel time rate $\mu_M$. While all parameters present smooth curves when plotted against temperature, the values of $g_{Pi}$ vary up and down greatly from one sweep to another because they include polarization flips. However, prior to a polarization flip, the polarization conductance $g_{Pi}$ is $g_M$ at all temperatures.

Capacitive current fitting of Eq. [17c] and ionic current fitting of Eq. [17d] would be equivalent except for the exponent 1/3 in the capacitive current factor $(M_0/M)^{1/3}$. Both currents have the same reversal potential $V_M$ and the time rate $\mu_M$ and maximum conductance $g_M$ are related by Eq. (21b). The exponent 1/3 gives a good fit for the capacitive current $C_m \Phi_M$. We did not try to determine if the factor $(X_0/X)^{1/3}$ also holds for recovery capacitive currents.

The fittings of the recovery region were done by approximating total ionic experimental data $J_I$, already smoothed by Gauss sigma method, with a sixth order polynomial $J_I|_{6th}$ covering the region from the potas-
sium reversal potential $V_N$ to close to reversal potential $V_H$ avoiding the small region of the polarization flip. The recovery region presents itself as an evident superposition of two currents. We separated them by first extracting the potassium current $J_N$ which presents a clear reversal potential at the end of the quasi-linear segment which renders the maximum conductance $g_N$ and time rate $\mu_N$. Next, the fraction $N_0/N$ is fitted and recovery potassium current $J_N$ is obtained. The sodium current $J_H$ is obtained by subtracting the potassium current $J_N$ from the sixth order polynomial fit $J_1|_{6th}$. The 6th order polynomial fit curve intercepts the zero current axis at the effective reversal potential $V_H$ where a fraction of sodium channels is already closed as the potential has decreased from its peak. The maximum conductance $g_H$ is determined at the AP peak with $g_H = \frac{dJ_H(V)}{dV}|_{V=V_p}$ and the time rate is $\mu_H = \left. \frac{d\Phi_H(V)}{dV} \right|_{V=V_p}$. The fit is completed by optimizing the time rate $\mu_H$ and $t_{cH}$.

We have also fitted the fractions of open ion channels, $M_0(V)/M$ for all sweeps with Eq. 27a, and $H_0(V)/H$ and $N_0(V)/N$ for Sweep170 with Eq. 27b and Eq. 27c with three parameters. For $M_0(V)/M$, the parameter $V_p$ is known, and $V_{OM}$ was fixed to correspond to $t_{OM}$ previously obtained fitting $M_0(t)/M$. The resulting exponent $\delta_M$ is $\approx 3$ at all temperatures.

All fittings were done using Gauss sigma smoothing and Excel’s Solver software. All fittings are sensitive to number of points included, the sensitivity increasing with temperature since fewer and fewer points were recorded. In addition, $J_H$, the outgoing sodium current displays more granularity for sweeps at lower temperatures. In particular there is a prominent bump just above 55 mV (See Fig. 8 and Fig. 23b). Although each fit individually may present some uncertainty and latitude, the cumulative picture gathered over several temperatures presents a precise, exacting, coherent and self-consistent scenario.

The exception is Sweep 525 with parameters $V_M$, and $\mu_P^4$ that are outliers while the behavior of others such as $g_M$, $\mu_M$, $t_{0M}$, $\delta_M$ and $Q_g$ is consistent with parameters at other temperatures.

Appendix D: Supplemental Material - Additional Graphs
### M-Sodium channel

| Sweep | Temp [°C] | ν [m/Sec] | k [1/mSec] | dV/dt|max [V/Sec] | Vp [mV] | gM [mS/cm²] | VM [mV] | μM [1/mSec] | μM^3.78 | A_M = αμM^3.78 | t_M [mSec] | V_M [mV] | δ_M [number] |
|-------|-----------|-----------|------------|--------|-------------|--------|-------------|--------|-------------|-----------|----------------|-------------|--------|---------------|
| 181   | 1         | 8.2       | 3.23       | 198    | 109.2       | 47.5   | 111.9       | 10.9   | 8295        | 61        | -0.597         | 43.0        | 3.00   |
| 170   | 4.5       | 9.5       | 4.10       | 246    | 108.3       | 56.0   | 111.1       | 13.2   | 17441       | 127       | -0.467         | 39.4        | 3.06   |
| 225   | 7.5       | 11.3      | 5.17       | 323    | 108.5       | 71.1   | 111.2       | 16.8   | 42448       | 310       | -0.363         | 37.0        | 3.00   |
| 327   | 10        | 13.3      | 6.76       | 402    | 107.3       | 79.3   | 111.4       | 20.0   | 83168       | 607       | -0.292         | 34.3        | 3.09   |
| 425   | 13        | 14.8      | 7.86       | 464    | 106.1       | 90.8   | 109.9       | 23.1   | 142084      | 1037      | -0.250         | 32.7        | 3.03   |
| 525   | 15        | 16.2      | 8.74       | 530    | 105.5       | 113.7  | 108.6       | 27.5   | 273990      | 1999      | -0.215         | 34.2        | 3.02   |
| 630   | 17        | 17.5      | 9.72       | 625    | 103.8       | 132.5  | 107.8       | 31.4   | 453084      | 3306      | -0.178         | 31.2        | 3.11   |
| 695   | 20        | 19.1      | 10.5       | 711    | 102.0       | 174.4  | 105.3       | 37.8   | 916745      | 6688      | -0.150         | 33.0        | 3.07   |
| 754   | 25        | 21.4      | 11.19      | 815    | 96.0        | 245.6  | 99.2        | 47.1   | 2113680     | 15424     | -0.116         | 32.6        | 3.28   |

### H-Sodium channel

| Sweep | Temp [°C] | g_H [mS/cm²] | μ_H [1/mSec] | μ_H^θH | A_H = αμ_H^θH | V_H [mV] | θ_H [number] | g_N [mS/cm²] | μ_N | μ_N^θN | A_N = αμ_N^θN | V_N [mV] | θ_N [number] |
|-------|-----------|--------------|-------------|--------|---------------|--------|-------------|--------------|-----|--------|---------------|--------|--------------|
| 170   | 4.5       | 4.61         | 4.9         | 113    | 0.83          | 104.9  | 2.99        | 5.5          | 3.1 | 33     | 3             | -6.7   | 3.08         |
| 220   | 7.5       | 7.09         | 5.9         | 193    | 1.41          | 104.3  | 2.97        | 10.9         | 5.4 | 169    | 1.2           | -8.2   | 3.05         |
| 327   | 10        | 10.12        | 8.8         | 523    | 3.82          | 102.3  | 2.87        | 18.1         | 8.2 | 524    | 3.8           | -9.6   | 2.98         |
| 425   | 13        | 11.91        | 10.4        | 1063   | 7.76          | 100.7  | 2.98        | 25.6         | 10.8 | 1142   | 8.3           | -10.9  | 2.96         |
| 525   | 15        | 17.99        | 11.2        | 1665   | 12.15         | 99.6   | 3.08        | 28.7         | 12.1 | 1902   | 13.9          | -12.1  | 3.03         |
| 630   | 17        | 24.81        | 15.8        | 6718   | 49.02         | 96.2   | 3.19        | 44.7         | 16.4 | 4506   | 32.9          | -13.0  | 3.01         |
| 695   | 19.8      | 31.23        | 19.1        | 6763   | 49.35         | 92.5   | 2.99        | 56.3         | 19.6 | 8233   | 60.1          | -14.1  | 3.03         |

FIG. 20. Table MHN (a) M-Sodium channel parameters. θ_M = 3.78 and α = 0.007297..., dimensionless and temperature independent parameters are seeded and inform about sodium M-channel structure. Avrami parameter A_M is determined by the fine-structure constant and sodium’s time rate parameter. (b) H-Sodium channel parameters. The correlation A_H = α(μ_H)^θ_H also holds for the deactivation current J_H. H-Sodium channel time rate and conductance are different from M-Sodium channel’s parameters as result of the continuous phase change from M channel structure to the H structure. α and θ_H ≈ 3 are dimensionless and inform about sodium H-channel structure. Avrami parameter A_H is determined by the fine-structure constant and H channel’s time rate parameter μ_H. (a) N-Potassium channel parameters. α and θ_H ≈ 3 are dimensionless and inform about sodium H-channel structure. Avrami parameter A_N is determined by the fine-structure constant and potassium’s time rate parameter μ_N.
FIG. 21. The rising edge of the action potential covers the region from the resting potential to the peak of the action potential. Capacitive, membrane and ionic currents, and their parsing into mAvrami fits of the activation currents and the polarization portions are displayed. Note that $\mu_M$ and $g_M$ are related by equation Eq. (21b). Fig. 15 displays detailed mAvrami fits of fractions of open channels for activation and polarization currents. The Phase Space fits, also displayed, have been constrained requiring $V_{OM}$ to correspond to the value $t_{OM}$. At the inception point the three activation fits of $C_m\Phi_M$, $J_{mM}$ and $J_M$ are zero and the corresponding polarization currents $C_m\Phi_P$, $J_{mP}$ and $J_P$ are discontinuous. At 4 °C the inception potential appears to coincide with the potential at which the ionic current crosses the zero current axis. At higher temperatures, the inception precedes by an increasing number of millivolts. At the peak of the action potential all currents are discontinuous. See SM Figures 7 and 23 for sweeps at higher temperatures. Arrows → indicate the direction of time.
FIG. 22. Currents detail around the peak of the action potential. Arrows $\rightarrow$ indicate time direction. mAvrami sodium current at the peak of the action potential $V_p$ is $J_M = g_M(V_p - V_M)$ where $g_M$ is the maximum conductance for the sodium M-channels. Similarly, the corresponding capacitive current is $C_M\Phi(M(V)) = C_MdV/dt|_M = -\mu_M(V_p - V_M)$ where $\mu_M$ is the time rate constant. The polynomial trend lines for the rising edge currents intercept the zero-current axis at sodium’s reversal potential $V = V_M$. The polynomial trend line of the recovery ionic current $J_H$ intercepts the zero-current axis at $V = V_H$ that is about 6.5 mV lower than $V_M$ and it intercepts the polynomial trend line segment of the membrane current below the zero current axis at $V = V_M$. However, the recovery capacitive current polynomial trend line segment $C_M\Phi_H(V) = C_MdV/dt|_H$ intercepts the zero current axis at $V \approx V_M$. While outgoing sodium current has not been observed in voltage clamp experiments, these facts support the conclusion that the recovery ionic current, $J_H$, is in fact sodium current. The continuous phase change of sodium M-channel symmetry into sodium channel H-channel symmetry keeps almost all the mAvrami channels open (see Fig. 15). The polynomial trend lines for the rising edge currents are fits from 72 to 95 mV. The fits for the recovery region cover 107 to 92 mV. Note that $\frac{d\Phi(V)}{dV}|_{V=V_H} \approx 7.89 \approx k$. 

The polynomial fits for $J_m(V)$, $J_m(V)$, and $J_m(V)$ are:

1. $J_m(V) = C_m\Phi(M(V)) = C_m\Phi(V)$
2. $J_m(V) = J_m(V) = g_m(V-M(V))(1-\exp(-\alpha(M(V)-M(V))|^\theta_M))$ Na mAvrami fit
3. $J_m(V) = g_m(V-M(V))(1-\exp(-\alpha(M(V)-M(V))|^{(1/3)})$
4. $J_m(V) = C_m\Phi(M(V)) + J_m(V)$ mAvrami membrane current fit

$\Phi(V) = \Phi(V)|_M$
FIG. 23. Currents and linear segments. Note that all currents look almost the same (scale) at the three temperatures (including Fig. 21 and Fig. 8) except the currents $J_K$ and $J_H$ which increase and decrease relatively as compared with other currents. (a), (c), Capacitive, membrane and ionic currents are displayed with their parsing into mAvrami fits and corresponding polarization currents. The linear slope of the current $J_K$ and the corresponding slope of the capacitive current linear segments are the time rate constant $\mu_K$ and maximum conductance $g_K$. The slope of the linear segment of the ionic current $J_M$ is the maximum conductance $g_M$ for the sodium M-channel. The corresponding capacitive current linear slope is $-\mu_M$ where $\mu_M$ is the time rate constant of the M-channel. The polarization currents are discontinuous at the inception of the mAvrami fits of activation currents. (b), (d), The linear slopes of sodium’s and potassium’s capacitive currents are $\mu_H$ and $-\mu_N$ corresponding to rate constants $\mu_H$ and $\mu_N$. The linear slopes of $J_H$ and $J_N$ are $-g_H$ and $g_N$ where $g_H$ and $g_N$ are the maximum conductance of the sodium H-channel and potassium N-channel respectively. While slopes of $J_H$ and capacitive current $C_m\Phi_H$ intercept the potential axis at different points, $C_m\Phi_H$ intercepts the axis at $V \approx V_M$. 
FIG. 24. The rising edge mAvrami fits of capacitive and ionic currents and the corresponding polarizations currents are plotted against time. The three mAvrami fitted currents $C_m \Phi_M$, $J_{MM}$, $J_M$, and the $M(t)/M$ curve begin and intersect the zero-current axis at the inception point $t = t_{oM}$, the time at which sodium M-channels start to open ($J_{MM}$ is not displayed, $J_{MM} = C_m \Phi_M + J_M$). Capacitive and membrane polarization currents $C_m \Phi_{MP}$ and $J_{MP}$, start with the polarization flip at $t = t_{oM}$ and then decay. The surface under the first segment of capacitive polarization curve $C_m \Phi_{MP}$ is equal to the polarization charge $Q_P \approx 10 \times 10^{-9}$ Coulomb/cm$^2$ moved across the membrane (a.k.a. gating charge). The flip from H-channel symmetry to M-channel symmetry and the transfer of charges across but within the membrane in conjunction with the ionic polarization current precedes the opening of sodium channels. In the present theory the motion of gating charges tapers off at approximately the maximum rate of rise of the action potential at about 60 mV when the fraction of open sodium channels is about 20%. The value of the charge $Q_P$ remains approximately the same at all temperatures. Towards the peak of the action potential, preceding the flip from M-channel symmetry to H-channel symmetry at the peak, there is an opposite charge transfer across and also within the membrane amounting to $q_P \approx -2.6 \times 10^{-9}$ Coulomb/cm$^2$. 
with the value of the fine-structure constant $\alpha = 0.007297352$ and parameters $\theta_M$ and $\theta_P_i$ from Eq. (20) are seeded with the value 3.78. Note: $g_{P1} = g_{P2}, V_{P1} = V_{P2}, g_{P3} = g_{P4}$ and $V_{P3} = V_{P4}$. (a) The inception polarization segment consists, only for Sweep170, of three concatenated portions with different time rates. We did not fit the third one. The AP peak polarization segment consists of two concatenated portions. However, only for Sweep170, the order of pertinent time rates is reversed. For this sweep the portion with $\mu_{P3} \approx \mu_M$ precedes the polarization flip instead of the portion with $\approx 2\mu_M$. Note, that polarization time rates $\mu_{P1,2,3,4}$ are close multiples of sodium’s M-channel time rate $\mu_M$. (b), (c), (d) Note: $\ln \alpha = \ln(0.007297352...) = -4.920243...$
FIG. 26. Rising edge mAvrami fits of fractions of open Mo/M sodium M-channels and fractions of completed Pi/o/Pi M-channels morphing. Inception and AP peak polarization flips are displayed. Parameters $\alpha_M$ and $\alpha_{Pi}$ from Eq. (20) are seeded with the value of the fine-structure constant $\alpha = 0.007297352$ and parameters $\theta_M, \theta_{Pi}$ are seeded with the value 3.78. Note: $g_{P1} = g_{P2}, V_{P1} = V_{P2}$, and that there is no segment $P3$. (a) The inception polarization segment consists of two concatenated portions with different time rates. The AP peak polarization segment $P4$ is a single one. Note that polarization time rates $\mu_{P1}$ and $\mu_{P2}$ are close multiples of sodium’s $M$-channel time rate $\mu_M$, but $\mu_{P4}$ is not. (b), (c), (d) Note: $\ln \alpha = \ln(0.007297352...)$ = $-4.920243...$.
FIG. 27.