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Isn't there an inductance factor in the plasma membrane of nerves?

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It is established knowledge that the action potential event of nerves is formed by the combination of a phasic inward Na^+ current and a following outward K^+ current which increases gradually. These changes in current are commonly referred to as conductance changes of channels for Na^+ and K^+ with time. On the other hand, electric requirements for action potential generation in phenomena such as anode break excitation, hyperpolarizing break stimulation and accommodation, strongly suggest an existence of an inductance factor in the plasma membrane of nerves. In this study, the possibility that the Na^+ channel could be simulated by a circuit composed serially of resistance (R), inductance (L), and capacitance (C) was examined using a computer simulation. Electric responses of the RLC circuit ($R^2/4L^2 \geq 1/LC$) to step voltages are as followings: (1) A transient potential is produced on the inductor, (2) the circuit current simulates well the Na^+ current manner, and (3) time course of the capacitor potential resembles the K^+ current change.

Key words: action potential, anode break excitation, voltage clamp, Na^+ current, RLC circuit

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The action potential event of nerves is discussed supposing that the plasma membrane has micro pores selectively permeable to ion species, which are called (ion) channels represented by the registers. It is well known that depolarization of the inside of nerve above a certain voltage, so called the threshold, activates Na^+ channels, leading to the generation of an action potential. When a nerve fiber is stimulated by a battery or other electric devices using paired electrodes placed on the axon, at switch-on (onset) an action potential is generated at the place corresponding to the negative pole (cathode) of the battery. On the other hand, at the switch-off (break), it is generated at the place corresponding to the positive pole (anode). The former is called a cathode circuit-closed excitation (CE), and the latter, an anode break excitation (AE) [1,2]. The action potential generation in CE is understandable as the depolarization occurs (or outward current flows) at the electrode, but AE is a strange phenomenon as the action potential is produced even though the membrane potential does not reach its threshold voltage level. The AE phenomenon is interpreted commonly as follows. During a rectangular pulse stimulation, the inside of the axon at the positive electrode is under hyperpolarization which decreases the degree of inactivation of Na^+ channels, and activation of Na^+ channels occurs when the hyperpolarization returns to the resting level by the break of the stimulus [3,4].

◀ ***Significance*** ▶

The mechanism of action potential generation of nerves has been explained based on the conductance change of Na^+ (and K^+) channel in the membrane with time. However, the substantial source of the change isn't necessarily obvious. It is estimated that the change in the state of molecular particles at its gate would cause the conductance change, but it could be also explained from a view that the Na^+ channel for action potential generation is represented by the series circuit of resistance (R), inductance (L), and capacitance (C). The current pattern of the RLC circuit as a model of the Na^+ channel simulates well the conductance change in the voltage clump examination of nerves.

A phenomenon similar to the AE is observed when a hyperpolarizing rectangular pulse voltage is applied directly to the inside of nerve, in which the action potential is generated at the return of the stimulus to the resting potential [5,6]. Here, the question arises "Doesn't the nerve membrane possess inductance factor?" If a nerve membrane possesses an inductance factor, another discussion about the AE and hyperpolarizing break stimulation becomes possible.

An essential property of an inductor is generation of a terminal voltage (V_L) to prevent the "change" of current. It is proportional to its rate, $V_L=-L\cdot di/dt$: L is inductance measured in henrys (H) if the voltage is in volts (V) and the current change is in amperes per second (A/sec). The inductor produces a transient terminal voltage at the onset of a voltage pulse, and that of opposite polar voltage at its break as the current changes abruptly at both edges of the pulse. In a serial circuit of a resister (R) and an inductor (L) (Fig. 1A), the voltage of the inductor in relation to time (t) in the rectangular pulse of V_E volts is expressed as $+V_E\cdot e^{-Rt/L}$ for the onset and as $-V_E\cdot e^{-Rt/L}$, for the break (Fig. 1B). In the pulse stimulation of nerve with paired electrodes, the inside positive and negative transient voltages are generated at the place for the cathode electrode to the onset and to the break, respectively, if the membrane has an inductance factor. We understand in the stimulation that an action potential is generated at the place for the cathode electrode only in the onset. The opposite potential events occur at the place for the anode electrode, and the action potential should be originated at the break of the stimulus (Fig. 1C). The same could be said for the hyperpolarizing break stimulation of the cell inside.

There is another noticeable phenomenon for action potential generation. A slow-rising stimulating current applied across the membrane fails to trigger the action potential nevertheless it depolarizes the membrane to its usual threshold membrane potential, which is called accommodation [3,7,8]. This phenomenon is interpreted as follows. During the slow approach to the threshold membrane voltage, inactivation of the Na^+ channel and activation of the K^+ channel advance before the voltage reached to the threshold [3]. Based on the idea that the membrane possesses an inductance factor responsible for action potential generation, the following interpretation is also possible: As the potential produced on the inductor is proportional to the rate of change of the current, the slow increment of the current cannot produce enough voltage for triggering the action potential generation. In the circuit shown in Figure 1A, the resister also originates the potential that is linear to the current, so it is rational to think that the potential produced on the inductance plays a main role in triggering the action potential generation, which must become obvious especially in the pulse stimulation.

Phenomena such as the AE, hyperpolarizing break stimulation, and accommodation demonstrate that so called the threshold for action potential generation doesn't mean an absolute depolarizing level of the membrane potential, but

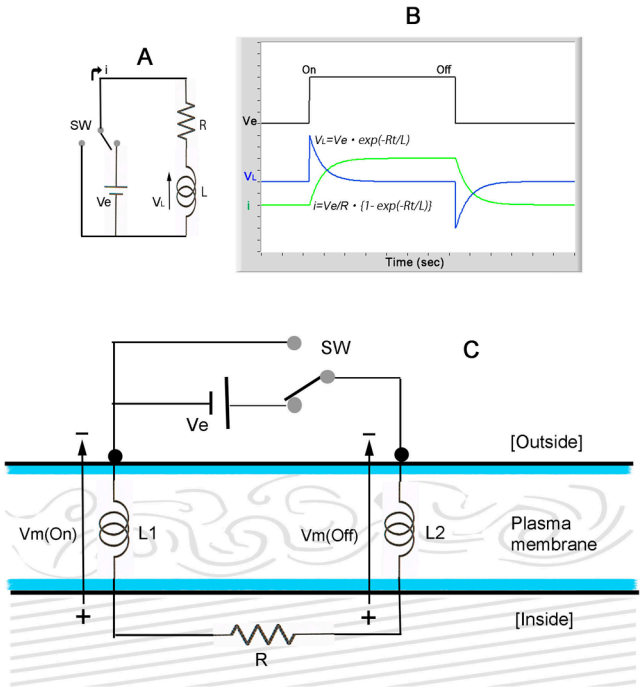

Figure 1 Responses of RL circuit and the application on a nerve membrane. (A) Circuit composed of a series of a resistor (R) and an inductor (L) with a switch (SW) and a voltage supply (Ve). Arrow for V_L is the positive voltage direction. (B) Potential response of the inductor (V_L) and circuit current (i) to switch–On, and switch-Off. Formations of V_L and i for switch-On are indicated on the curves. (C) Potentials originated across the membrane of nerve at a pair of electrodes to switch–On, and switch-Off, supposing that the membrane possesses inductance element (L1, L2). Arrows for Vm (On), and Vm (Off) mean the positive voltage direction in switch-On and switch-Off, respectively.

certain amount of positive change from its preceding (or holding) potential. This feature of the threshold seems to be well explained by supposing that the membrane of nerve has an inductance factor, potential produced on which leads to action potential generation. It is understandable that the plasma membrane has both factors of resistance and capacitance, but there is no discernible structure resembling a coil anywhere in the plasma membrane. It is, however, known that electric components such as resistors, capacitors, and connecting wire possess their own intrinsic inductance. Circuits where these electric elements are not discriminated obviously are called "distributed constant circuits", and every material is considered to have more or less all factors of resistance, capacitance, and inductance. It also seems to be conceivable that the plasma membrane of nerves possesses an inductance factor. In this study, the possibility that the Na^+ channel would contain inductance factor involving to the conductance (or current) change in action potential generation was examined by way of computer simulation.

Methods

As an inductor is merely a wire to a DC signal and shorts

sooner or later the potential difference such as a resting potential, it is difficult to think that the Na^+ channel would be represented by only an inductance (plus resistance) element. In this study, the examination was performed supposing that the Na^+ channel would be represented by a circuit composed serially of resistance (R [Ω]), inductance (L [Henry]), and capacitance (C [Farad]). The electric property of the circuit was studied using a personal computer system. The circuit current and voltages produced in the inductor and the capacitor of the serial RLC circuit in supplying variable magnitudes of rectangular pulse signal were analyzed by solving a basic formation obtained by applying the Kirchhoff's law on the circuit. The patterns of the current and voltages with time were drawn with the software, LabVIEW-ver.8.5 (National Instruments Corporation). The values of R, L, and C were varied properly referring to the results reported mainly by Hodgkin & Huxley [3].

Results and Discussion

Hodgkin & Huxley's hypothesis

In the investigation of the mechanism of action potential generation, a technique, called the voltage clamp, has been frequently used, where ionic currents across the membrane in fixing cell inside with a step voltage of various levels are measured. It was first introduced by Cole (1949) [9] and Marmont (1949) [10] and was subsequently developed by Hodgkin & Huxley (1952) [3] and Hodgkin, Huxley & Katz (1952) [11] using the squid giant axon. The method revealed that phasic inward current of Na^+ ions occurs immediately after the effective depolarizing clamp, and outward K^+ current follows with a short delay, which increases gradually towards the steady level. Graphs of Supplementary Figure S1B, C presented first by Hodgkin [12] and redrawn by Kuffler *et al.* [13] illustrate these current manners which were also ensured pharmacologically by Hill [14]. As the potential across the membrane is fixed in the test, the change of the Na^+ and K^+ currents could be understood as the changes of conductance for the corresponding ionic current. (It is conventional, in electric studies of neurons, to use the term "conductance" instead of resistance as its reverse, so we also use "conductance" henceforth.)

Supposing that ions flow through the exclusive channels for each ion, Hodgkin and Huxley described the membrane potential (V_m) and time (t) dependences of conductances for Na^+ channel (g_{Na}) and K^+ channel (g_K) using the following equations, respectively [3].

$$g_{Na}(V_m,t) = G_{Na} \cdot m(V_m,t)^3 \cdot h(V_m,t),$$
$$g_K(V_m,t) = G_K \cdot n(V_m,t)^4,$$

where G_{Na} and G_K represent the maximum Na^+ and maximum K^+ conductance, respectively; m and n, activation parameters for Na^+ and K^+ conductance, respectively, which vary from 0 to 1 as a function of Vm and t; and h, an inactivation parameter for Na^+ conductance that also varies from 0 to 1 as a function of Vm and t. The time dependence of m^3h and n^4 to step voltages match well to the curves estimated from Na^+ current and K^+ current in voltage clamp tests, respectively, when m, n, and h are given by $m=1-exp(-t/\tau_m)$, $n=1-exp(-t/\tau_n)$, and $h=exp(-t/\tau_h)$: τ_m, τ_n, and τ_h are time constants for their exponential curves which are decided from transfer rates in two states, for instance, activation and inactivation, which can be calculated on the base of voltage clamp data [3,15]. Supplementary Figure S1D, E are samples of the conductance changes reported by Hodgkin and Huxley, showing that experimental estimates for Na^+ and K^+ conductance changes match well to their theoretical curves. As for the powers of m, h, and n, they explained as follows: the gates of ion channels are considered to be controlled by the shift of charged particles, where the gate of Na^+ channel would be composed of the three activation particles, m^3, and one inactivation particle, h, and the gate of K^+ channel, by the four activation particles, n^4.

Serial RLC circuit model as Na^+ channel for action potential generation

Apart from the Hodgkin & Huxley hypothesis, let us, here, examine the electric property of a circuit composed serially of resistance (R), inductance (L), and capacitance (C) as an electric model of Na^+ channel per unit area. Figure 2A shows this RLC circuit model, where a battery formed by its equilibrium potential is omitted as it is not essential in examining the circuit property. (A notice is that the capacitor element in this RLC circuit model is different from the capacitor composed by a lipid bilayer of the membrane, which doesn't involve directly in action potential generation.) In supplying step voltage (V_e) to this RLC circuit, the following formation is formed for time (t) from the Kirchhoff's law supposing that the capacitor is initially charged with V_0 volts and circuit current (i) flows clockwise.

$$Ve = i \cdot R + L \cdot di/dt + (V_0 + 1/C \cdot \int i dt)$$

Differentiating this by t and rearranging the terms, we get,

$$L \cdot d^2i/dt^2 + R \cdot di/dt + 1/C \cdot i = 0$$

This is known as a second order linear differential equation for describing oscillatory movements with a resistance factor [16]. Its solution is established, so we shall take, in this article, only its result.

The solution separates two cases, $R^2/4L^2 \geq 1/LC$ and $R^2/4L^2 < 1/LC$. In the former case, the circuit current doesn't exhibit the oscillation and converges to zero with simple time course, whereas in the latter case, the circuit current oscillates, amplitude of which decreases exponentially with time [17]. In this study, we shall restrict our examination to the former case, because oscillation isn't observed in the Na^+ current in voltage clamp test. The established solution of the former case is,

$$i = A_1 \cdot e^{(-\alpha+\beta)t} + A_2 \cdot e^{(-\alpha-\beta)t}$$

(A_1, A_2: integration constants, $\alpha = R/2L$, $\beta = \sqrt{R^2/4L^2 - 1/LC}$)

A_1 and A_2 can be obtained from the circuit conditions, $i=0$ in $t=0$, and V_C (capacitor voltage) = Ve in $t=\infty$. The final form of i becomes the following.

$$i = \frac{Ve - V_0}{2\sqrt{\frac{R^2}{4} - \frac{L}{C}}} \{e^{(-\alpha+\beta)t} - e^{(-\alpha-\beta)t}\}$$

$$= \frac{Ve - V_0}{\sqrt{\frac{R^2}{4} - \frac{L}{C}}} e^{-\alpha t} \sinh\beta t$$

We get also voltages produced in the inductor (V_L) and the capacitor (V_c). As the resolution processes are complicated, only the results are presented.

$$V_L = L \cdot di/dt = L \frac{Ve - V_0}{\sqrt{\frac{R^2}{4} - \frac{L}{C}}} e^{-\alpha t} \ (-\alpha \sinh\beta t + \beta \cosh\beta t)$$

$$Vc = V_0 + 1/C \cdot \int i dt = V_0 + \frac{Ve - V_0}{C\sqrt{R^2 - \frac{4L}{C}}} \left\{\frac{1}{\alpha-\beta}(1 - e^{(-\alpha+\beta)t}) - \frac{1}{\alpha+\beta}(1 - e^{(-\alpha-\beta)t})\right\}$$

Although there are many combinations of R, L, and C values, time courses of the circuit current, inductor potential, and capacitor potential are similar for whatever values we chose if they satisfy the condition, $R^2/4L^2 \geq 1/LC$. As a sample, we shall briefly examine them in a case of R=20 [Ω]), L=1500 [μH]), and C=50 [μF]); the resistance of 20 Ω is adopted referring to the peak current in 76~100 mV reported in voltage clamp test (Supplementary Fig. S1D), and the values of inductance and capacitance are selected to fit approximately to the manner of Na^+ current (Supplementary Fig. S1C). Figure 2B, C, and D show the graphs respectively of the circuit current (i), inductor potential (V_L), and capacitor potential (V_C) in supplying step voltages of –15, 0, 15, 30, 45, and 60 mV, in no initial charges of the capacitor (V_0=0). (Although the initial charge has be set to 0 mV, it is also possible to set it to a resting potential, for instance, –65 mV, where 65 mV will substitutes for V_0 and the value will be added to each of the supplying voltages.)

A possibility that nerve membrane has an inductance factor, inside positive potential produced mainly on which leads to the action potential generation has mentioned above. Potential response of the inductor in this RLC circuit is similar to that in serial RL circuit (Fig. 1B), but biphasic (Fig. 2C). Deflection of the early transient potential is larger than the following opposite polar potential which approaches gradually to the base, 0 mV. (The return to 0 mV is independent on initial charges of the capacitor as the inductor cannot hold the potential to DC signal.) The polar becomes negative-positive when the supplying voltage is negative (Fig. 2C, –15 mV). Negative supplying voltage produces anticlockwise current which means, in nerves, an outward current, and the negative potential of the early phase, depolarization.

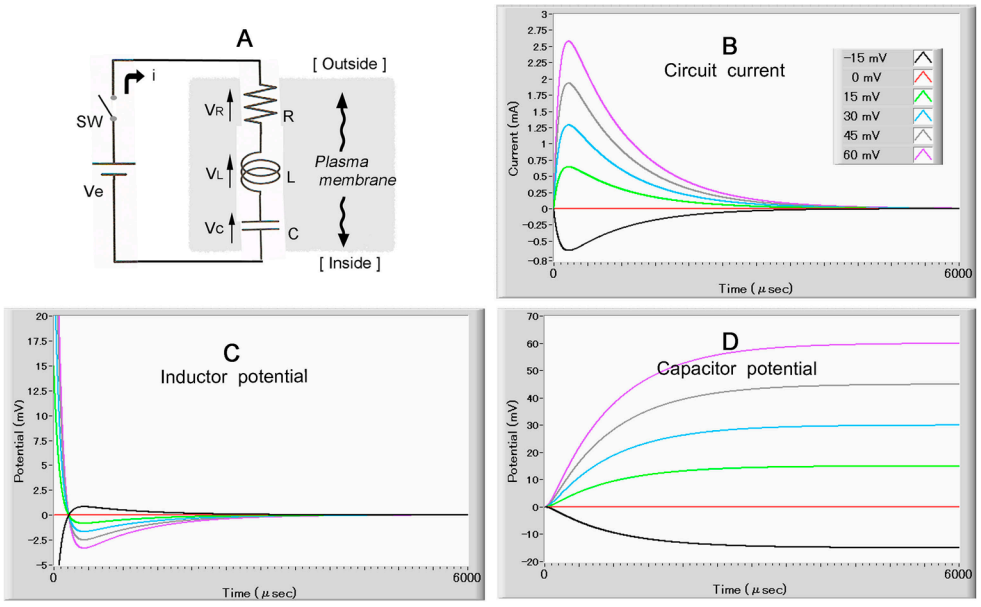

Figure 2 Serial RLC circuit and the response properties. (A) R(resistance)-L(inductance)-C(capacitance) circuit as a model of Na+ channel for action potential generation. Arrows for the resister potential (V_R), inductor potential (V_L), capacitor potential (V_C), and circuit current (i) indicate the positive direction. (B to D) Electric responses during 6 msec for the indications in setting supplying step voltages (Ve) to the values indicated in B.

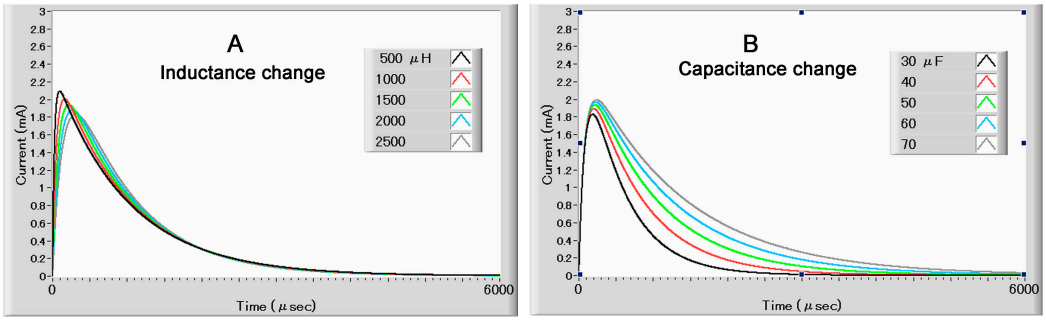

Figure 3 Current patterns in changes of inductance and capacitance in RLC circuit. Changes of current pattern with indicted values of inductance (A) and capacitance (B) of serial RLC circuit in supplying 45 mV step voltage. In A, resistance is 20 Ω, and capacitance, 50 μF. In B, resistance is 20 Ω, and inductance, 1500 μH.

Supposing that only the positive potential produced on the membrane inductor would link to generate action potential, the early negative potential produced on the inductor of the RLC circuit must be responsible for the action potential generation.

Then, we shall examine the circuit current of the RLC circuit. In clamp test, membrane potential (V_m) of nerve is fixed, in regular, positive (depolarization) to activate the Na^+ channel with various values. Na^+ ions are thought to move according to the formation, $I_{Na}=g_{Na}(V_m-E_{Na})$ where E_{Na} and g_{Na} are respectively Na^+ equilibrium potential and Na^+ conductance [3]. Na^+ current is known to flow inward in early phase when V_m is lower than E_{Na}, and it changes, in regular, to the outward current around at the condition, $V_m=E_{Na}$. Supplying voltage of *Ve* and positive currents in the RLC circuit correspond respectively to V_m-E_{Na} and to the inward current in clamp test. In supplying the positive voltages, circuit current exhibits an early positive peak decreasing gradually to zero (15, 30, 45, and 60 mV in Fig. 2B). As *Ve* is constant during the supply, the current pattern for each supplying voltage expresses simultaneously the change of conductance in time. Although it depends on combination of R, L, and C values, current patterns of the RLC circuit to step voltages simulate well the manner of Na^+ conductance changes estimated from voltage clamp test (Supplementary Fig. S1D). The change of Na^+ conductance was reported to depend on the membrane potential; its peak becomes faster with the magnitude of depolarizing clamps, and the peak value saturates at high depolarizations. Simulating these features is possible in RLC circuit by changing R, L, and (or) C values with *Ve* magnitudes using any function. Figure 3 shows samples of the circuit currents in changing simply values of the inductance (A) and capacitance (B) in 45 mV step voltages, where we can observe shift of the peak and change of the time course.

About K^+ channel activity

From the voltage clamp test, Na^+ inward current is followed by K^+ outward current that increases gradually towards the constant level (Supplementary Fig. S1B). The capacitor in the RLC circuit is charged gradually toward the supplying voltages (Fig. 2D). We notice that its time course is similar to the K^+ current in voltage clamp test. Then an idea arises that the voltage produced in the capacitor of the RLC circuit model would link to the activation of K^+ channel through any intermediating mechanism. In short, a Na^+ channel for action potential generation can be represented by a serial RLC circuit, where the inductance element would be responsible for controlling the Na^+ channel activity and the capacitance element would link remotely to the K^+ channel activity.

Additional considerations in RLC circuit model

Up to here the argument mainly has focused on the electric responses of RLC circuit as Na^+ channel for action potential generation to step signals. The current property of serial RLC circuit to alternating signals is also known. Its essence is a change of circuit impedance with signal frequencies. It is established knowledge that a serial RLC circuit exhibits the lowest impedance at a certain frequency, in which the circuit current becomes maximum. The frequency for the maximum current is called the resonance frequency (f_0), value of which is calculated from the equation, $f_0=1/(2\pi\sqrt{LC})$. The action potential once originated propagates along the nerve fiber, mechanism of which is explained as following: Currents formed around the action potential, so called the local currents, stimulate neighboring portion by flowing across the membrane from the inside to outside, generating a new action potential if the current makes the inside depolarize enough [18,19]. From the view of the resonance, an additional idea that the preceding action potential stimulates neighboring Na^+ channels with the resonation current might be possible. It doesn't contradict the local current theory as the neighboring Na^+ channel simply stimulated stronger by the resonance current. Incidentally, the resonance frequency of the circuit in L=1500 μH and C=50 μF is 581Hz which seems not to be an inadequate value, considering that the electric event of almost action potentials completes within a few msec. Examining the optimum frequency for eliciting the action potential will add an evidence on this RLC circuit model.

In this article, electric responses of serial RLC circuits

have been studied restricted to the condition exhibiting no oscillations. As mentioned, the circuit current oscillates with decreasing amplitude in condition, $R^2/4L^2 < 1/LC$. There are many kinds of neuron in the nervous system, most of which originate, in a regular physiological state, a train of impulses in response to effective synaptic (or receptor) potentials. It may be a consideration that the RLC circuit as the Na^+ channel at a place initiating the action potential, for instance at the axon hillock or the initial segment of the axon [20,21], would satisfy the oscillating condition, and the impulse trains of nerves would be any reflection of the oscillation of the circuit. It is a consideration that the action potential could be elicited successively till the positive potential on the corresponding inductor in the oscillation becomes lower than the threshold level, where the frequency of the impulse train is decided by the L and C values. This seems to be another interesting subject for the RLC circuit model as a representation of the Na^+ channel.

Conclusion

The action potential event could be also explained from the view point that the Na^+ channel is composed of resistance, inductance, and capacitance elements, where the inductance element would function in controlling the Na^+ channel activity, and the capacitance element, the K^+ channel activity remotely.

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Conflict of interest

The author declares no potential conflicts of interest.

Author Contributions

The author wrote all part of the manuscript.

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