jz-2023-02562y.R1

Name: Peer Review Information for "Iontronic Nanopore Model for Artificial Neurons: the Requisites of Spiking"

First Round of Reviewer Comments

Reviewer: 1

Comments to the Author

The paper by J. Bisquert proposes a new model for artificial neurons based on conical nanofluidic diodes. The autor demonstrates that it is posible to obtain a neuron-like system with the minimal configuration of a single nanopore. The topic is timely and appropriate for the Journal of Physical Chemistry Letters, and the results provide new insights to the field. Overall I would recommend publication provided that the autor addresses the following minor issues:

1) The author should explain the reason why the paper starts with an equivalent circuit model while the transport equations are presented later.

2) The results shown in Fig. 4 occur assuming certain values for the parameters involved in the model. Could the autor give some experimental support for the values of these parameter?

Taking into accout the above points I find the above paper of great interest for a Journal of Physical Chemistry Letters reader.

Reviewer: 2

Comments to the Author

The author proposes a physical model for the simple configuration of an iontropic neuron, based on diode devices. The model somewhat simplifies the famous Hodgkin-Huxley electrical model of biological neurons, explaining, through impedance analysis, the transition from capacitive to inductive properties and then to a region of negative resistance correlated to spiking activity of neurons via Hopf bifurcations. The results will be immediately significant for moving forward using spiking systems for practical applications. I suggest the paper be published after minor revisions, as stated below.

The author shows that the model explains complex systems dynamics, observed commonly in experimental scenarios, from frequency domain. Is the same true for the relaxation processes corresponding to time domain (i.e., exponential decay (spectra A), negative transient spikes (spectra B) and oscillatory behavior (spectra C correlated to Figure 4))? This point should be explained with appropriate references to this transition of electrical behavior in the time domain.

It is not clear the relationship between Eqs. 4-6 and 14-16. I understand that the first ones are general expressions estimated from nonlinear equations and the last ones are that corresponding to specific steady-state situations (e.g., in impedance measurements). This should be clarified in any case.

In experimental measurements, biological neurons are considered current-controlled systems. Nevertheless, the author, throughout the paper, considers potentiostatic experiments. How can this critical point affect to the mathematical approach in this work?

I suggest adding units to the formula or the variables to allow the reader to follow equations easily and, in addition, correct the typographical errors found in the paper (e.g., Fig. 3. uH1= 0.0.05060).

Author's Response to Peer Review Comments:

Journal: The Journal of Physical Chemistry Letters
Manuscript ID: jz-2023-02562y

Reply to reviewers

Reviewer: 1

Recommendation: This paper is publishable subject to minor revisions noted. Further review is not needed.

Comments:
The paper by J. Bisquert proposes a new model for artificial neurons based on conical nanofluidic diodes. The autor demonstrates that it is posible to obtain a neuron-like system with the minimal configuration of a single nanopore. The topic is timely and appropriate for the Journal of Physical Chemistry Letters, and the results provide new insights to the field.

Thank you for the positive comment and suggestions.

Overall I would recommend publication provided that the autor addresses the following minor issues:

1) The author should explain the reason why the paper starts with an equivalent circuit model while the transport equations are presented later.

We have modified the presentation introducing the transport model and the impedance is discussed later on.

2) The results shown in Fig. 4 occur assuming certain values for the parameters involved in the model. Could the autor give some experimental support for the values of these parameter?

The analysis of experimental values has been made based on the available published data:

Finally we analyze the practical values that can be obtained with the proposed neuron system. The frequency of oscillation in Eq. (25) can be expressed

$$\omega_o = \left[\frac{1}{L_a C_m}\left(1+\frac{R_a}{R_b}\right)\right]^{1/2} \qquad (1)$$

Since $R_b \approx R_a$ the frequency is mainly determined by that of the typical LC circuit, namely

$$\omega_o \approx \left[\frac{1}{L_a C_m}\right]^{1/2} \qquad (2)$$

The capacitance of single nanopores depends on the geometry, the electrolyte, and the dielectric constants of the material. Different values provided in the literature[1] are in the range 1-100 pF. There are some reports of negative capacitance and inductive behaviour

concentration (0.001-1 M). Then by Eq. (19) the value of the pore inductor can

of molecules confined in nanopores.[2] The measured characteristic frequency is in the range 0.1-1 Hz.[3] The conductivity of the electrolyte[4] is 1-100 nS depending on electrolyte

be oscillations

estimated 10^7-10^9 H. Therefore Eq. (28) indicates that the frequency of obtained may be in

the interval 3-300 Hz.

This range coincides with the frequencies of natural neurons in the brain.[5]

Taking into accout the above points I find the above paper of great interest for a Journal of Physical Chemistry Letters reader.

Reviewer: 2

Recommendation: This paper is publishable subject to minor revisions noted. Further review is not needed.

Comments:

The author proposes a physical model for the simple configuration of an iontropic neuron, based on diode devices. The model somewhat simplifies the famous HodgkinHuxley electrical model of biological neurons, explaining, through impedance analysis, the transition from capacitive to inductive properties and then to a region of negative resistance correlated to spiking activity of neurons via Hopf bifurcations. The results will be immediately significant for moving forward using spiking systems for practical applications. I suggest the paper be published after minor revisions, as stated below.

Thank you for the positive comment and suggestions.

The author shows that the model explains complex systems dynamics, observed commonly in experimental scenarios, from frequency domain. Is the same true for the relaxation processes corresponding to time domain (i.e., exponential decay (spectra A), negative transient spikes (spectra B) and oscillatory behavior (spectra C correlated to Figure 4))? This point should be explained with appropriate references to this transition of electrical behavior in the time domain.

This interesting point has been explained:

Furthermore we remark that the different types of spectra shown in Fig. 2b indicate the arc produces type of time domain response to a step of the current. The RC A an exponential decays. The chemical inductor response gives damped oscillation and negative spikes. And the spectra with negative resistance results in oscillatory behaviour as shown in Fig. 4b. Examples of the various transients are shown in Refs. [6-10].

It is not clear the relationship between Eqs. 4-6 and 14-16. I understand that the first ones are general expressions estimated from nonlinear equations and the last ones are that corresponding to specific steady-state situations (e.g., in impedance measurements). This should be clarified in any case.

We have clarified the GENERAL impedance expressions and the specific equivalent circuit elements of the model:

We emphasize that Eqs. (10-13) are fairly general results valid for all neurons with a single state variable of the class of Eqs. (1-2).

We calculate the equivalent circuit elements in Eqs. (11-13) for the specific model of Eqs. (3, 6) with the results

In experimental measurements, biological neurons are considered current-controlled systems. Nevertheless, the author, throughout the paper, considers potentiostatic experiments. How can this critical point affect to the mathematical approach in this work?

We have clarified this point:

The application to neuron models has been reviewed recently.[7,11,12] Here we focus on the galvanostatic (constant current) operation that is frequently applied in the analysis of neurons. Since the current of Fig. 2a is not multivalued we can characterize each point by the applied voltage as well. We examine the evolution of the impedance spectra as we increase the voltage from 0 to 0.08 (A-C) to pass across the Hopf bifurcation in Fig. 2d.

I suggest adding units to the formula or the variables to allow the reader to follow equations easily and, in addition, correct the typographical errors found in the paper (e.g., Fig. 3. uH1= 0.0.05060).

The analysis of experimental values has been made based on the available published data: The Finally we analyze the practical values that can be obtained with the proposed neuron system. The frequency of oscillation in Eq. (25) can be expressed

$$\omega_o = \left[\frac{1}{L_a C_m}\left(1+\frac{R_a}{R_b}\right)\right]^{1/2} \qquad (3)$$

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The capacitance of single nanopores depends on the geometry, the electrolyte, and the dielectric constants of the material. Different values provided in the literature[1] are in the range 1-100 pF. There are some reports of negative capacitance and inductive behaviour

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This range coincides with the frequencies of natural neurons in the brain.[5]

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