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A Method to Model Neuron Activity

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***Abstract*— This paper presents a model to simulate the activity of excitable membrane displaying Hodgkin and Huxley (H-H)-type kinetics implemented using the general-purpose circuit analysis program PSPICE. The H-H equations are represented by electrical equivalent circuit elements and the model is validated by comparison with published theoretical and measured data. The model is very easy to use and can be inserted as a sub-circuit into PSPICE simulations of more complex neural systems.**

I. Introduction

Non invasive multisite recording of electrical activity of neurons cultured *in vitro* is increasingly attracting interest as a cheaper, longer-term alternative to more conventional methods using e.g., patch clamping. Among the techniques that seem to be the most appropriate [1-3] electrical recording by means of flat arrays of microtransducers (e.g. microelectrodes, Ion-Sensitive Field Effect transistors (ISFETs) [2], [3] appears to be the most suitable method for long-term (i.e., several days) recording and stimulation. In such systems microtransducers are connected directly to neurons by a neur-electronic junction, and the neuronal electrical activity can be analyzed by monitoring the extracellular voltage drop along the narrow cleft between the membrane and the microtransducer itself. However, since in this approach the microelectrode has no direct access to the interior of the cell, the transmembrane potential can not be measured directly. Therefore a critical aspect of this technique, and a key point for a better understanding of the recorded signal, is the electrical characterization of the membrane activity itself and of the neuron-to-microtransducer coupling [4].

This paper focuses on the simulation of the electrical activity of excitable membrane using an electrical equivalent circuit approach implemented using PSPICE. PSPICE modeling has already proven effective in simulating excitable axons with simple geometries [4], [5]. The circuit configuration presented here describes the membrane activity using simple functional blocks and is thus easy to use. It can be treated as a subsystem and very conveniently inserted into PSPICE files to facilitate the simulation of more complex neural systems. It will be shown that, given a suitable choice of parameters, a wide range of different responses can be obtained using this approach, which match published data very accurately [6].

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II. Cell activity and model formulation

The electrophysiological behavior of a neuron can be modeled using the well-known Hodgkin and Huxley (H-H) equations [6]. These equations describe the total current through an excitable membrane during an action potential as the sum of a capacitive current and three ionic currents, carried by sodium, potassium, and other ions. The formulation of this model leads to the electrical equivalent circuit of Fig. 1 [6].

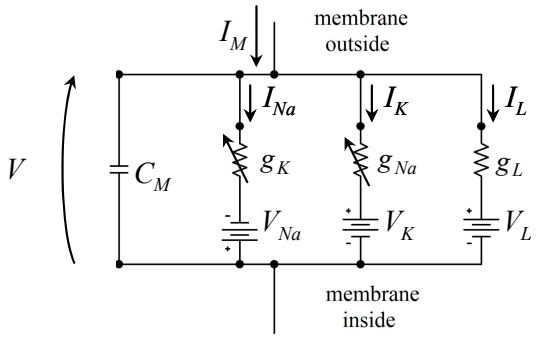

Fig. 1. Electrical equivalent circuit representation of a neuron following H-H formulation.

A key feature of the H-H description is that the sodium and potassium currents flow through conductances that are time- and voltage- dependent, while the third (leakage) conductance is constant. This dependence is made explicit by a biophysical interpretation of the sodium and potassium conductances as contributions of many single units (channels) whose open fractions are governed by equilibrium constants which in turn depend exponentially on the membrane potential [6].

In the H-H formulation the total current I_M flowing through the membrane is given by:

$$I_M = C_M \frac{dV}{dt} + I_K + I_{Na} + I_L$$
$$= C_M \frac{dV}{dt} + \bar{g}_{Na} m^3 h(V - V_{Na}) + \quad (1)$$
$$+ \bar{g}_K n^4 (V - V_K) + \bar{g}_L (V - V_L)$$

where V is the membrane potential and C_M is the membrane capacitance; I_K and I_{Na} are the currents generated by the flow of the sodium and potassium ions through the channels and I_L is a 'leakage' current with V_{Na}, V_K and V_L the corresponding equilibrium potentials. $\bar{g}_{Na}$, $\bar{g}_K$, $\bar{g}_L$ are the sodium, potassium and leakage maximum conductances through the membrane, respectively. m and h are the activation and inactivation parameters of the sodium channels, respectively, and n is the activation parameter of the potassium channel; m, h, n correspond to the fractions of open/closed channels:

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (2)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \quad (3)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \quad (4)$$

where α_m, β_m, α_h, β_h, α_n and β_n are the exponentially V-dependent rate constants described by the remaining pair of H-H equations [6]. α_m, α_h and α_n determine the rate of ion transfer from outside to inside while β_m, β_h and β_n determine the transfer in the opposite direction [6]. The values for the maximum ionic conductances, for the leakage conductance and the corresponding equilibrium (reversal) potentials, are those used in literature [6] and are summarized in Table 1.

TABLE I
MEMBRANE CHARACTERISTIC PARAMETERS

Symbol	Value
$\bar{g}_{Na}$	$120 m.mho/cm^2$
$\bar{g}_K$	$36 m.mho/cm^2$
$\bar{g}_L$	$0.3 m.mho/cm^2$
V_{Na}	$-115 mV$
V_K	$12 mV$
V_L	$-10.6 mV$

III. PSPICE IMPLEMENTATION

The approach followed by the authors to implement the H-H equation in PSPICE exploits the suggestion by Chua [7], [8] that the H-H equations for the sodium and potassium currents can be represented by sub-circuits made up of linear capacitors and non-linear time-invariant resistive elements only, thus eliminating the problem of time-varying conductances. Chua's theory relies on the equivalence between the operation performed by the available standard circuit elements and the formal mathematical operations described in (1)-(4). Specifically, capacitors are used to

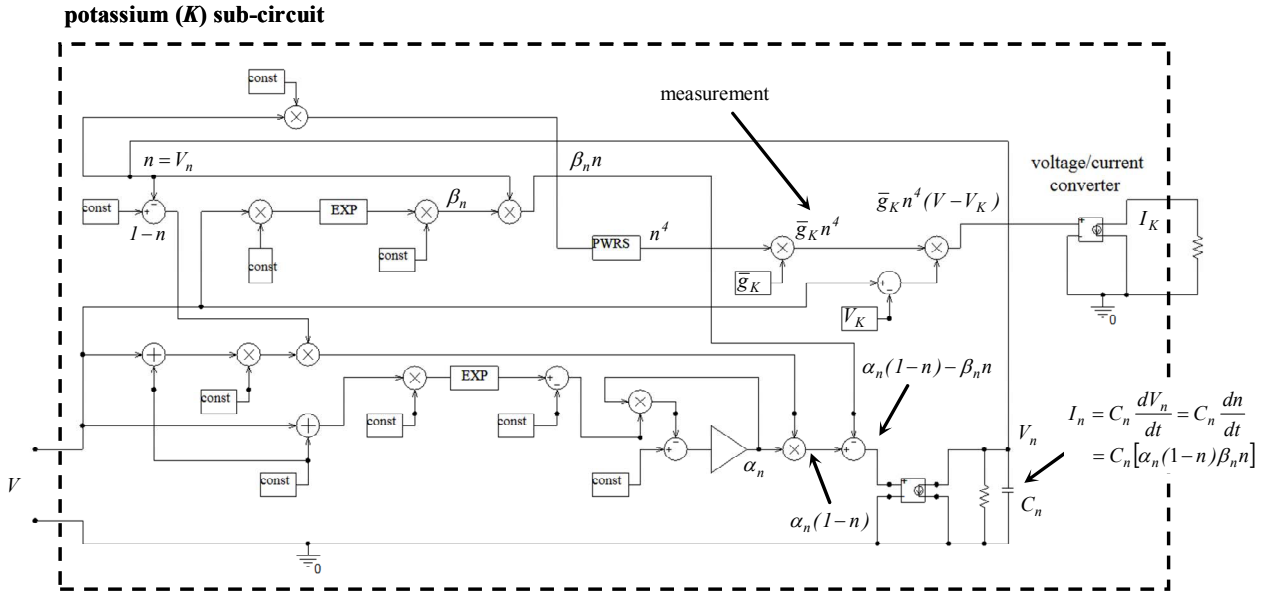

Fig. 2. Details of the PSPICE circuit used to produce the potassium current I_K. The node where the conductance $\bar{g}_K n^4$ is measured is also indicated.

perform differentiation. The dimensionless activation parameters can be thought of as proportional to the voltages across linear capacitors: the currents flowing through the capacitors are proportional to the time-derivatives of the capacitor voltages. This approach was first adopted by Storace et al. [5] but no circuit details were presented.

The sub-circuit to generate the potassium current (I_K) is shown in Fig. 2 (the sub-circuit for the sodium current can be obtained in a completely analogous way). In this specific case the activation parameter n is taken as the voltage V_n across the linear capacitor C_n (n=V_n), with the current I_n flowing through C_n being proportional to the time-derivative of the capacitor voltage, Fig. 2:

$$I_n = C_n \frac{dV_n}{dt} = C_n \frac{dn}{dt} \tag{5}$$

Unlike the method described in [5] no additional proportional factors are needed to evaluate n and only C_n acts as fitting parameter. Given the membrane voltage V, Fig. 2, the first step is to calculate the value of the rate constants α_n and β_n. Then, an iterative loop is used to self-consistently calculate the voltage- and time-dependent properties of the potassium conductance.

The dynamics of the loop can be described by the equation obtained by substituting equation (4) in equation (5), resulting in equation (6):

$$I_n = C_n \left[\alpha_n (1-n) - \beta_n n\right] \tag{6}$$

Once I_n is known, then both dn/dt and n can be evaluated from the voltage across C_n through the relation expressed in equation (5). Therefore both terms in the equivalence of equation (4) can be calculated, and the equation can be solved. The nodes in the sub-circuit where the various terms are calculated are indicated in Fig. 2.

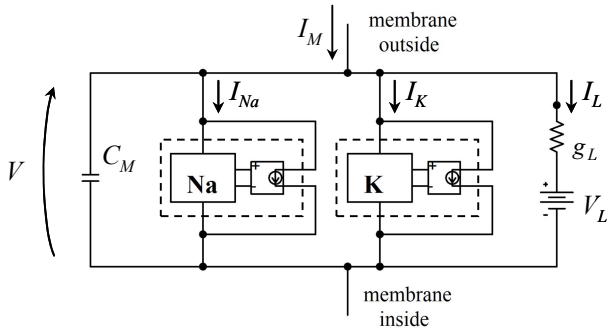

Fig. 3. Sub-circuit (block) representation of the neuron electrical equivalent circuit of Fig. 1.

Finally, a voltage-to-current converter is used to calculate the potassium current I_K. For consistency with [6] n is normalized so that n = 1 for V = 110mV.

The potassium (K) sub-circuit of Fig. 2 replaces the I_K shunt arms in the H-H membrane equivalent circuit of Fig. 1 [6] (similarly for the sodium (Na) sub-circuit). The resulting circuit is shown in Fig. 3, where the K-block depicted in dashed box corresponds to the circuit in the dashed box of Fig. 2.

To verify the validity of the model, we examine, as H-H did in their original paper, the behavior of a nerve that is voltage-clamped. The resting potential is taken to be zero and depolarization is positive. The membrane area is assumed to be 1cm^2, with specific membrane capacitance of 1μF/cm^2.

Fig. 4 and Fig. 5 show simulated voltage-clamp data, which are very similar to those obtained by H-H in their studies [6]. For consistency with the data presented in [6] for these simulations the potassium and sodium maximum conductances are chosen to be respectively $\bar{g}_K = 24 m.mho/cm^2$ and $\bar{g}_{Na} = 70 m.mho/cm^2$.

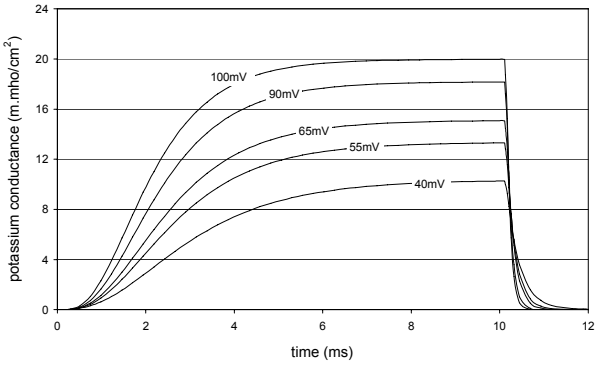

Fig. 4. Simulated voltage-clamp data illustrating rise and fall of the potassium conductance associated with different depolarizations lasting 10ms. The number on each curve indicates the polarization in mV.

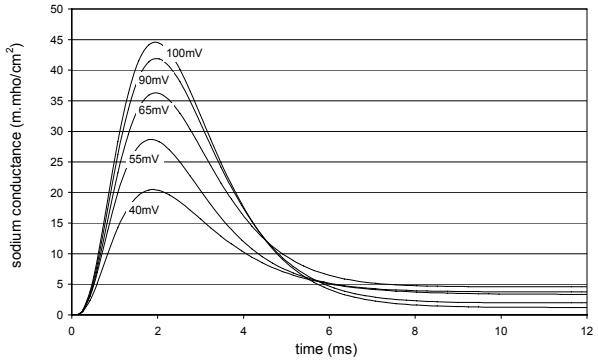

Fig. 5. Simulated voltage-clamp data illustrating activation and inactivation properties of the sodium conductance associated with different voltage steps. The number on each curve indicates the polarization in mV.

The figures show the time course of the change in potassium and sodium conductance, $\bar{g}_K n^4$, $\bar{g}_{Na} m^3 h$ respectively, associated with varying levels of depolarization, between $40mV$ and $100mV$. Figure 4 also shows the fall of potassium conductance associated with repolarization to the resting potential. Two, typical, qualitative effects are apparent in all the data. Firstly the steady-state conductance level increases with increasing membrane depolarization. Secondly the onset of conductance change becomes faster with increasing depolarization.

Fig. 6 shows the simulation of the membrane current resulting from a voltage-clamp depolarization of 65mV. The figure also shows the resulting action potential (AP) modeled by passing the membrane current through a parallel *RC* circuit simulating the characteristics of the membrane at resting potential. The values used for the simulations are those in Table 1. At constant voltage the coefficients α and β are constant and the solution to equation (1) depends directly on *n, m* and *h* only. The net membrane current is zero except during the stimulus [6].

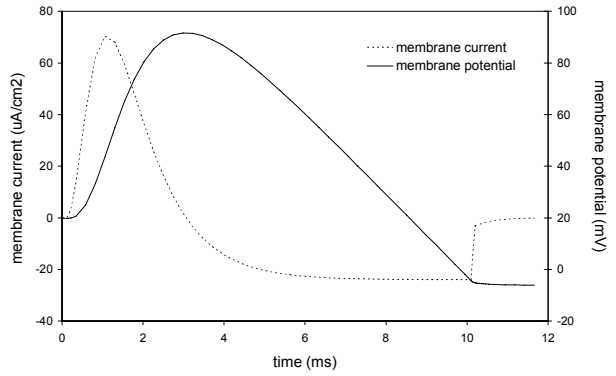

Fig. 6. Membrane current resulting from a $65mV$ depolarization lasting $10ms$. The corresponding modeled action potential is also shown.

IV. CONCLUSIONS

An electrical equivalent circuit model is presented that simulates the response of excitable membrane displaying the kinetics described by the Hodgkin-Huxley (H-H) equations. The four H-H non-linear partial differential equations [6] are implemented using the general circuit analysis program PSPICE. The model is validated by comparison with the theoretical and measured voltage-clamp data published by H-H. Other signal shapes reported in the literature can be readily reproduced and interpreted.

Although in this paper the model was realized in PSPICE, the same methods enable the H-H equation to be implemented using other circuit CAD packages.

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