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ANALYSIS OF TIME-COURSE OF THE RECOVERY FROM INACTIVATION OF IONIC CURRENTS IN CEREBELLAR PURKINJE CELL

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Abstract- In this study, time-course of the recovery from the inactivation of ionic currents which have inactivation in cerebellar Purkinje cell is examined. Kinetics of the ionic currents are expressed with Hodgkin-Huxley equations. Peak value function of the recovering conductance is given explicitly, and the curve of recovery and its approximation are obtained. It's shown that recovering conductance of ionic currents which are studied is asymptotically exponential.

Keywords- Recovery, inactivation, ionic current, purkinje cell, peak value function.

1. INTRODUCTION

Purkinje cell is one output neuron of cerebellar cortex[1]. Dendritic tree of rat cerebellar Purkinje cell receives around 175.000 excitatory inputs from granule cells and 1500 $GABA_A$ inputs from local neurones[2]. Spike activity of Purkinje cell is determined using interaction between ionic currents and the inputs. The large amount of inputs indicate complexity of the interaction.

Determining of kinetics of ionic currents and understanding of dynamical behaviour of them are of great importance. There are several experimental procedures for determining of kinetics of ionic currents[3]. Reconstruction of recovery process is one of them and used for estimating the inactivation time-constant[4]. It's shown that recovering conductance of voltage-gated ionic channels of Purkinje cell which have inactivation examined in this study using that procedure is asymptotically exponential.

2. THE HODGKIN-HUXLEY-TYPE MATHEMATICAL MODEL OF AN IONIC CURRENT

An ionic current channel is assumed to have gates which are in one of two states(open or closed) in Hodgkin-Huxley mathematical formalism[5]. It's assumed that an ionic channel have a number of physical gates which regulate flow of ionic current through corresponding ionic channel[6]. Conductance of an ionic channel is given by

$$G_X(v,t) = g_X m^p(v,t) h^q(v,t) \tag{1}$$

where m and h respectively show fraction of activation and inactivation gates in open state, g_X is maximal conductance of ionic channel, p is the number of activation gates and q is the number of inactivation gates.

Transitions between open and closed states are modelled with first order differential equations as follow:

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m = \frac{m_\infty(v) - m}{\tau_m(v)} \tag{2}$$

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h = \frac{h_\infty(v) - h}{\tau_m(v)} \tag{3}$$

where $\alpha(v)$ and $\beta(v)$ are voltage-dependent rate functions which determine speed of transitions from one state to the other within the ion gates, and given by

$$\alpha(v) = \frac{a + bv}{c + e^{(d+v)/f}} \tag{4}$$

where a, b, c, d, f are constants.

$m_\infty(v)$ and $h_\infty(v)$ are steady-state activation and inactivation respectively; $\tau_m(v)$ and $\tau_h(v)$ are voltage-dependent activation and inactivation time constants which are the times taken to reach a steady-state value respectively; and may be written as

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)} \tag{5}$$

$$\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)} \tag{6}$$

$h_\infty(v)$ and $\tau_h(v)$ have similar forms. When the voltage is held constant, solution of Eqn(2) is given by

$$m(t) = m_\infty(v) - (m_\infty(v) - m_0)e^{-t/\tau_m} \tag{7}$$

where m_0 is initial value of m. Similarly, under the same condition, solution of Eqn(3) is given by

$$h(t) = h_\infty(v) - (h_\infty(v) - h_0)e^{-t/\tau_h} \tag{8}$$

where h_0 is initial value of h.

3. INACTIVATED VOLTAGE-GATED IONIC CURRENTS IN PURKINJE CELL

A large number of studies are reported in literature on which ionic currents take part in Purkinje cell and how is their kinetics[7-14]. Fast sodium (NaF), P-type calcium(CaP), T-type calcium(CaT), A-type potassium(KA), delayed rectifier(Kdr) ionic currents are inactivated voltage-gated ionic currents present in cerebellar Purkinje cell[15,16]. Kinetics of the ionic currents used in this study is based on the model of the cerebellar Purkinje cell constructed by De Schutter and Bower[16]. Constants of the rate functions are also taken from the model by De Schutter and Bower[16].

3.1 Fast Sodium Current

Conductance of fast sodium current(NaF) is given by

$$G_{NaF}(v,t) = g_{NaF} m^3(v,t) h(v,t) \tag{9}$$

Voltage-dependent rate functions are as follows:

$$\alpha_m(v) = \frac{35000}{e^{(v+0.005)/(-0.01)}} \; ; \; \beta_m(v) = \frac{7000}{e^{(v+0.065)/(0.02)}} \tag{10}$$

$$\alpha_h(v) = \frac{225}{1+e^{(v+0.08)/(0.01)}} \; ; \; \beta_h(v) = \frac{7500}{e^{(v-0.003)/(-0.018)}} \tag{11}$$

3.2 P-type Calcium Current

Conductance of P-type calcium current(CaP) is given by

$$G_{CaP}(v,t) = g_{CaP} m(v,t) h(v,t) \tag{12}$$

Voltage-dependent rate functions are as follows:

$$\alpha_m(v) = \frac{8500}{1+e^{(v-0.008)/(-0.0125)}} \; ; \; \beta_m(v) = \frac{35000}{1+e^{(v+0.074)/(0.0145)}} \tag{13}$$

$$\alpha_h(v) = \frac{1.5}{1+e^{(v+0.029)/(0.008)}} \; ; \; \beta_h(v) = \frac{5.5}{1+e^{(v+0.023)/(-0.008)}} \tag{14}$$

3.3. T-type Calcium Current

Conductance of T-type calcium current(CaT) is given by

$$G_{CaT}(v,t) = g_{CaT}m(v,t)h(v,t) \tag{15}$$

Voltage-dependent rate functions are as follows:

$$\alpha_m(v) = \frac{2600}{1+e^{(v+0.021)/(-0.008)}} \; ; \; \beta_m(v) = \frac{180}{1+e^{(v+0.04)/(0.004)}} \tag{16}$$

$$\alpha_h(v) = \frac{2.5}{1+e^{(v+0.04)/(0.004)}} \; ; \; \beta_h(v) = \frac{190}{1+e^{(v+0.05)/(-0.01)}} \tag{17}$$

3.4. A-type Potassium Current

Conductance of A-type potassium current(KA) is given by

$$G_{KA}(v,t) = g_{KA}m^4(v,t)h(v,t) \tag{18}$$

Voltage-dependent rate functions are as follows:

$$\alpha_m(v) = \frac{1400}{1+e^{(v+0.027)/(-0.012)}} \; ; \; \beta_m(v) = \frac{490}{1+e^{(v+0.03)/(0.004)}} \tag{19}$$

$$\alpha_h(v) = \frac{17.5}{1+e^{(v+0.05)/(0.008)}} \; ; \; \beta_h(v) = \frac{1300}{1+e^{(v+0.013)/(-0.01)}} \tag{20}$$

3.5. Delayed Rectifier Current

Conductance of delayed rectifier current(Kdr) is given by

$$G_{Kdr}(v,t) = g_{Kdr}m^2(v,t)h(v,t) \tag{21}$$

Activation time-constant is given by

$$\tau_m = \frac{1}{a_1 + b_1} \tag{22}$$

where

$$a_1 = \frac{-23500(v+0.012)}{e^{(v+0.012)/(-0.012)}-1} \tag{23}$$

$$b_1 = 5000e^{-(v+0.147)/(0.03)} \tag{24}$$

Inactivation time-constant is as follows:

$$\tau_h = \begin{cases} 1.2\ s & ; v < -0.025\ Volt \\ 0.01\ s & ; v > -0.025\ Volt \end{cases} \tag{25}$$

4. RECOVERING PROCEDURE

Detailed experimental procedure of recovering is given by Toth and Crunelli[4]. Toth and Crunelli also derived mathematical equivalent of the experimental procedure, and gave the peak value function of recovering conductance. But the peak value function of recovering conductance which they gave is not explicit in terms of C (in their Eqn(9,10)), and doesn't include the number of inactivation gates, q. We obtain the peak value function of recovering conductance in the same manner by Toth and Crunelli[4] with the same symbols including the number of inactivation gates, q.

In the first step, membrane is depolarized for sufficiently long time, so complete inactivation of the current is provided. Therefore it can be assumed m_0=1, and h_0=0 at V_0 depolarized potential. Then a voltage step from V_0 to V_1 is applied for variable time duration (t_1) so that complete removal of inactivation is provided, $m_{1\infty}$=0 and $h_{1\infty}$=1. This voltage step hyperpolarizes the membrane. In the hyperpolarized condition, activation and inactivation variables after time t_1 are obtained respectively from Eqn(7) and Eqn(8) using values given above:

$$m_1(t_1) = e^{-t_1/\tau_{m1}(V_1)} \tag{26}$$

$$h_1(t_1) = 1 - e^{-t_1/\tau_{h1}(V_1)} \tag{27}$$

In the second step, membrane is depolarized to V_0 potential at $t=t_1$. In the depolarized condition, activation and inactivation variables for $t>t_1$ are obtained respectively from Eqn(7) and Eqn(8) using initials values given in Eqn(26) and Eqn(27):

$$m_2(t;t_1) = 1 - (1 - m_1(t_1))e^{-(t-t_1)/\tau_{m0}(V_0)} \tag{28}$$

$$h_2(t;t_1) = h_1(t_1)e^{-(t-t_1)/\tau_{h0}(V_0)} \tag{29}$$

Conductance response to depolarization step is obtained substituting Eqn(28) and Eqn(29) into Eqn(1):

$$G_{X,2}(t;t_1) = g_X m_2^p(t;t_1) h_2^q(t;t_1) \tag{30}$$

The peak value function of recovering conductance in terms of t_l is obtained by differentiating Eqn(30) according to t as:

$$G_{X,2,peak}(t_1) = C \frac{h_1^q(t_1)}{(1-m_1(t_1))^{\frac{q\tau_{m0}}{\tau_{h0}}}} \tag{31}$$

where

$$C = f(p,q,\tau_{m0},\tau_{h0}) = g_X \left[1 - \frac{1}{(1+\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p \frac{1}{(1+\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})^{\frac{q\tau_{m0}}{\tau_{h0}}}} \tag{32}$$

The details of the derivation of Eqn(31) are given in Appendix A.

If kinetics of $m_l(t_l)$ is much faster than kinetics of $h_l(t_l)$, the peak value function of recovery conductance becomes asymptotically exponential as follows:

$$G_{X,2,peak}(t_1) \approx C\, h_1^q(t_1) \tag{33}$$

5. SIMULATION RESULTS

In the simulations, V_0 voltage was selected so that complete inactivation of the current was provided, i.e. $m_0=1$, $h_0=0$. V_l voltage was selected so that complete removal of inactivation was provided, i.e. $m_{l\infty}=0$ and $h_{l\infty}=1$. Five simulations were carried out.

In the first simulation, V_0 voltage was taken as 50 mV for fast sodium current(NaF). Activation and inactivation time constants were calculated from Eqn(6,10,11) as τ_{m0}=1.167646e-7 s, τ_{h0}=9.793718e-6 s at the voltage. V_l voltage is taken as -180 mV. Activation and inactivation time constants were calculated from Eqn(6,10,11) as τ_{ml}=4.54683e-7 s, τ_{hl}=4.43896e-3 s at the voltage. g_{NaF} was taken as 75000 S/m^2 . C value was calculated from Eqn(32) as 69382.5679 S/m^2. The curves of recovery and its approximation by Eqn(33) are shown in Figure 1a. The curve of recovery reached to its C value at t_l=0.1176 s.

In the second simulation, V_0 voltage was taken as 70 mV for P-type calcium current(CaP). Activation and inactivation time constants were calculated from

Eqn(6,13,14) as τ_{m0}=1.184482e-4 s, τ_{h0}=0.181820 s at the voltage. V_1 voltage was taken as -100 mV. Activation and inactivation time constants were calculated from Eqn(6,13,14) as τ_{m1}=3.332527e-5 s, τ_{h1}=0.666598 s at the voltage. g_{CaP} was taken as 45 S/m^2 . C value was calculated from Eqn(32) as 44.7562 S/m^2. The curves of recovery and its approximation by Eqn(33) are shown in Figure 1b. The curve of recovery reached to its C value at t_l=8.9998 s.

In the thirth simulation, V_0 voltage was taken as 50 mV for T-type calcium current(CaT). Activation and inactivation time constants were calculated from Eqn(6, 16,17) as τ_{m0}=3.846692e-4 s, τ_{h0}=5.263396e-3 s at the voltage. V_1 voltage was taken as -150 mV. Activation and inactivation time constants were calculated from Eqn(6,16,17) as τ_{m1}=5.555548e-3 s, τ_{h1}=0.398625 s at the voltage. g_{CaT} was taken as 5 S/m^2 . C value was calculated from Eqn(32) as 3.8287 S/m^2. The curves of recovery and its approximation by Eqn(33) are shown in Figure 1c. The curve of recovery reached to its C value at t_l=4.2592 s.

In the fourth simulation, V_0 voltage was taken as 50 mV for A current(KA). Activation and inactivation time constants were calculated from Eqn(6,19,20) as τ_{m0}=7.154529e-4 s, τ_{h0}=7.706433e-4 s at the voltage. V_1 voltage was taken as -140 mV. Activation and inactivation time constants were calculated from Eqn(6,19,20) as τ_{m1}=2.040342e-3 s, τ_{h1}=0.057131 s at the voltage. g_{KA} was taken as 150 S/m^2 . C value was calculated from Eqn(32) as 13.8183 S/m^2. The curves of recovery and its approximation by Eqn(33) are shown in Figure 1d. The curve of recovery reached to its C value at t_l=0.7174 s.

In the fifth simulation, V_0 voltage was taken as 80 mV for delayed rectifier current(Kdr). Activation and inactivation time constants were calculated from Eqn(22-25) as τ_{m0}=4.617658e-4 s, τ_{h0}=0.01 s at the voltage. V_1 voltage was taken as -100 mV. Activation and inactivation time constants were calculated from Eqn(22-25) as τ_{m1}=9.568909e-4 s, τ_{h1}=1.2 s at the voltage. g_{Kdr} was taken as 6000 S/m^2 . C value was calculated from Eqn(32) as 4811.6525 S/m^2. The curves of recovery and its approximation by Eqn(33) are shown in Figure 1e. The curve of recovery reached to its C value at t_l=21.5098 s.

6.CONCLUSIONS

In this paper, time-course of the recovery from the inactivation of the ionic currents present in cerebellar Purkinje cell is examined. The peak value function of recovering conductance is obtained in general form includes the number of inactivation gates, and given explicitly. It's seen from the curves of recovery and its approximation in Figure 1 that there is no deviation between recovery curves and and its exponential curves, and both of the curves coincide. Therefore the recovering conductance of the ionic currents studied is asymptotically exponential.

APPENDIX A. DETAILS OF THE PEAK VALUE FUNCTION OF THE RECOVERING CONDUCTANCE

Differentiating Eqn. (30) and setting the derivative to zero gives

$$\frac{\partial G_{X,2}(t;t_1)}{\partial t} = g_X p\left[1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]^{p-1}\left[\frac{1}{\tau_{m0}}(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]\left[h_1(t_1)e^{-(t-t_1)/\tau_{h0}}\right]^q$$

$$+ g_X q\left[1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]^p\left[h_1(t_1)e^{-(t-t_1)/\tau_{h0}}\right]^{q-1}\left(-\frac{1}{\tau_{h0}}\right)h_1(t_1)e^{-(t-t_1)/\tau_{h0}} = 0$$

$$g_X p\left[1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]^{p-1}\left[\frac{1}{\tau_{m0}}(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]\left[h_1(t_1)e^{-(t-t_1)/\tau_{h0}}\right]^q =$$

$$g_X q\frac{1}{\tau_{h0}}\left[1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]^p\left[h_1(t_1)e^{-(t-t_1)/\tau_{h0}}\right]^q$$

$$p\left[1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right]^{-1}\left[\frac{1}{\tau_{m0}}(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}\right] = \frac{q}{\tau_{h0}}$$

$$\frac{\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}}(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}}{1-(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}}} = 1 \Rightarrow \left(\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}}+1\right)(1-m_1(t_1))e^{-(t-t_1)/\tau_{m0}} = 1$$

$$e^{-t/\tau_{m0}} = \frac{e^{-t_1/\tau_{m0}}}{(1-m_1(t_1))\left(1+\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}}\right)} \Rightarrow e^{-t} = \left[\frac{e^{-t_1/\tau_{m0}}}{(1-m_1(t_1))\left(1+\frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}}\right)}\right]^{\tau_{m0}} \quad \text{(A1)}$$

Rearranging Eqn (30) with (A1) gives

$$G_{X,2,peak}(t_1) = g_X \left[1 - (1 - m_1(t_1)) e^{t_1/\tau_{m0}} \frac{e^{-t_1/\tau_{m0}}}{(1 - m_1(t_1))(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p$$

$$x \left[h_1(t_1) e^{t_1/\tau_{h0}} \left[\frac{e^{-t_1/\tau_{m0}}}{(1 - m_1(t_1))(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^{\frac{\tau_{m0}}{\tau_{h0}}} \right]^q$$

$$G_{X,2,peak}(t_1) = g_X \left[1 - \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p \left[h_1(t_1) \frac{1}{(1 - m_1(t_1))^{\tau_{m0}/\tau_{h0}} (1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})^{\tau_{m0}/\tau_{h0}}} \right]^q$$

$$G_{X,2,peak}(t_1) = g_X \left[1 - \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p \frac{h_1^q(t_1)}{(1 - m_1(t_1))^{\frac{q\tau_{m0}}{\tau_{h0}}} (1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})^{\frac{q\tau_{m0}}{\tau_{h0}}}} \tag{A2}$$

$$= g_X \left[1 - \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})^{\frac{q\tau_{m0}}{\tau_{h0}}}} \frac{h_1^q(t_1)}{(1 - m_1(t_1))^{\frac{q\tau_{m0}}{\tau_{h0}}}} = C \frac{h_1^q(t_1)}{(1 - m_1(t_1))^{\frac{q\tau_{m0}}{\tau_{h0}}}}$$

$$C = g_X \left[1 - \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})} \right]^p \frac{1}{(1 + \frac{p}{q}\frac{\tau_{h0}}{\tau_{m0}})^{\frac{q\tau_{m0}}{\tau_{h0}}}} \tag{A3}$$

REFERENCES

1. S. C. Nam and P. E. Hockberger, Analysis of spontaneous electrical activity in cerebellar Purkinje cells acutely isolated from postnatal rats, *J.Neurobiol.* **33**, 18-32, 1997.
2. R. M. A. Napper and R. J. Harvey, Number of parallel fiber synapses on an individual Purkinje cell in the cerebellum of the rat, *J.Comp.Neurol.* **274**, 168-177, 1988b.
3. R. W. Allan, J. B. Deborah, M. H. W. Ronald and G. John, An Improved Parameter Estimation Method for Hodgkin-Huxley Models, *Journal of Computational Neuroscience* **6**, 145-168, 1999.
4. T. I. Toth and V. Crunelli, The Theoretical Basis for Non-Exponential Time-Course of Recovery from Inactivation of Hodgkin-Huxley-type Ionic Currents, *Neuroscience* **71(2)**, 367-369, 1996.
5. A. L. Hodgkin and A. F. Huxley, The Dual Effect of Membrane Potential on Sodium Conductance in the Giant Axon of Loligo, *Journal of Physiology* **116**, 497-506, 1952a.
6. D. J. Aidley and P. R. Stanfield, *Ion Channels*, Cambridge University Press, 1996.
7. D. L. Gruol and C. R. Deal, Expression of calcium conductances in Purkinje neurons in culture, *Abstr. Soc.Neuroscience* **16**, 677, 1990.
8. M. Kaneda, M. Wakamori, M. Ito and N. Akaike, Low-threshold calcium current in isolated Purkinje cell bodies of rat cerebellum, *J.Neurophysiol.* **63**, 1046-1051, 1990.
9. L. J. Regan, Voltage-dependent calcium currents in Purkinje cells from rat cerebellar vermis, *J.Neuroscience* **11**, 2259-2269, 1991.
10. J. Eilers, G. J. Augustine and A. Konnerth, Subthreshold synaptic Ca^{2+} signaling in fine dendrites and spines of cerebellar Purkinje neurons, *Nature* **373**, 155-158, 1995.
11. F. Crepel and J. Penit-Soria, Inward rectification and low threshold calcium conductance in rat cerebellar Purkinje cells. An in vitro study, *J. Physiol. (London)* **372**, 1-23, 1986.
12. B. H. Gähwiler and I. Llano, sodium and potassium conductances in somatic membranes of rat Purkinje cells from organotypic cerebellar cultures, *J.Physiol. (London)* **417**, 105-122, 1989.
13. J. L. Bossu, J. L. Dupont and A. Feltz, Calcium currents in rat cerebellar Purkinje cells maintained in culture, *Neuroscience* **30**, 605-617, 1989a.
14. T. Hirano and S. Hagiwara, Kinetics and distribution of voltage-gated Ca, Na and K channels on the somata of rat cerebellar Purkinje cells, *Pflügers Arch.* **413**, 463-469, 1989.
15. M. Tsugumichi, T. Hiroshi, S. Hideo, W. Shigeo, I. Masashi, K. Yoshihisa and M. Hiroyoshi, Low-threshold Potassium Channels and a low-threshold Calcium Channel regulate Ca^{2+} spike firing in the dendrites of cerebellar Purkinje neurones: a modelling study, *Brain Research* **891**, 106-115, 2001.
16. E. De Schutter and J. M. Bower, An Active Membrane Model of the cerebellar Purkinje cell: I.Simulation of current clamps in slice ., *J. Neurophysiol.* **71**, 375-400, 1994a.

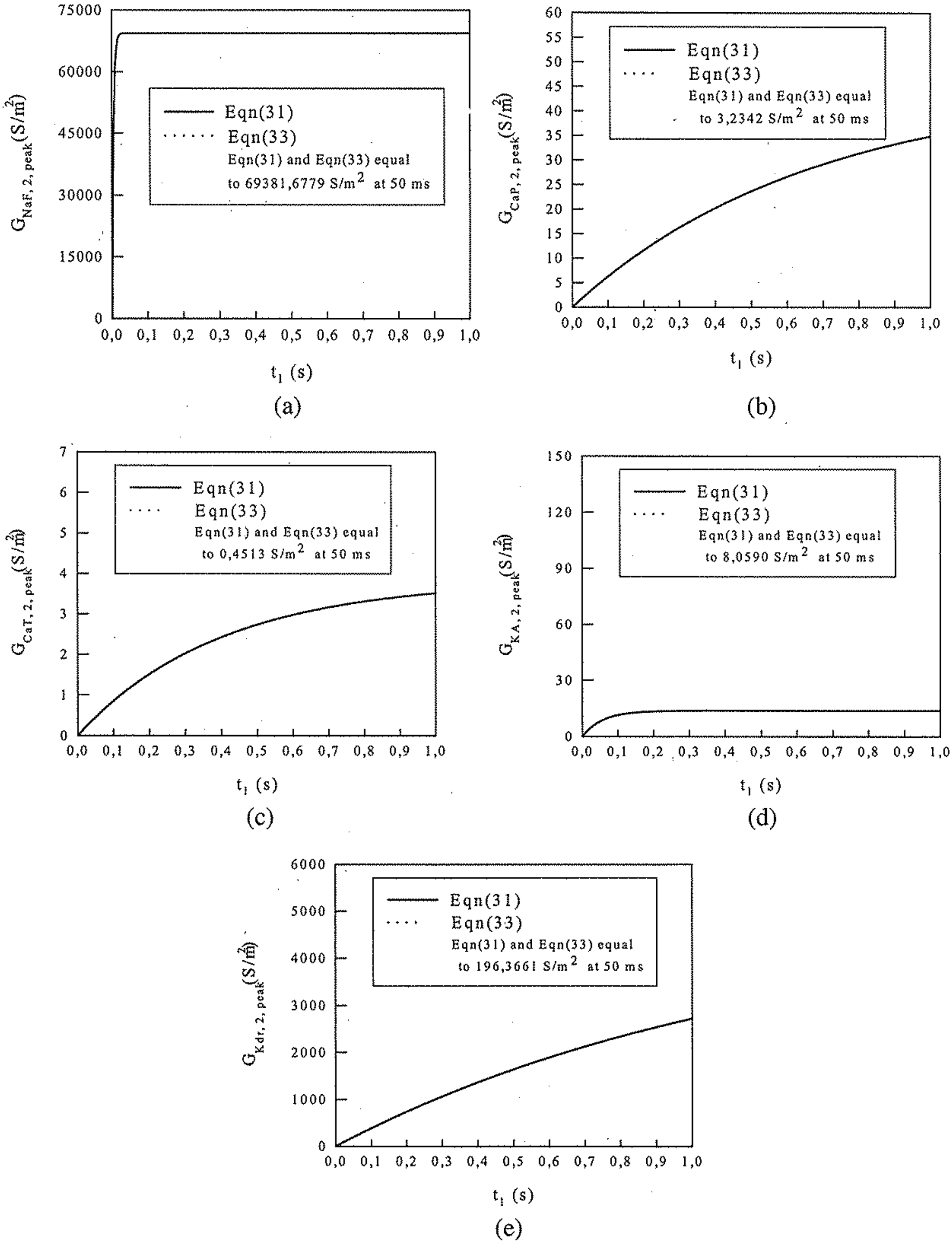

Figure 1. The curve of recovery and its approximation for (a) NaF, (b) CaP, (c) CaT, (d) KA, (e) Kdr currents.