



# PERFORMANCE ANALYSIS OF FITTED CURVES FOR STEADY-STATE (IN)ACTIVATION OF IONIC CURRENTS PRESENT IN PURKINJE CELL SOMATA ON SOMATIC MEMBRANE POTENTIAL

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## ABSTRACT

In this study sigmoid-shaped curves are fitted for steady-state activation and inactivation data of ionic currents which are defined in literature to be present in Purkinje cell somata. Marquardt-Levenberg nonlinear least-square parameter estimation algorithm is used for curve fitting. Then a somatic compartmental model of Purkinje cell is constructed, and somatic membrane potentials are calculated for several different current injection cases. It's shown that means and standard deviations of differences between somatic membrane potentials which are calculated with fitted curves and original equations separately are so small.

**Key Words :** Purkinje cell, Soma, Membrane, Activation, Inactivation

## PURKINJE HÜCRESİ SOMASINDA BULUNAN İYONİK AKIMLARIN SÜREKLİ-HAL (İN)AKTİVASYONU İÇİN UYDURULAN EĞRİLERİN SOMA MEMBRAN GERİLİMİ ÜZERİNDE PERFORMANS ANALİZİ

## ÖZET

Bu çalışmada Purkinje hücre somasında bulunan iyonik akımların sürekli-hal aktivasyon ve inaktivasyon datası için sigmoid-şekilli eğriler uydurulmaktadır. Eğri uydurmada Marquardt-Levenberg nonlineer enküçük-kareler parametre kestirim algoritması kullanılmaktadır. Daha sonra Purkinje hücrenin soma bölgesi modeli oluşturulmakta, ve birkaç farklı akım enjeksiyonu durumu için soma membran potansiyeli hesaplanmaktadır. Uydurulan eğriler ve orijinal denklemlerle ayrı ayrı hesaplanan soma membran potansiyelleri arasındaki farkın ortalama ve standart sapmalarının oldukça küçük olduğu gösterilmiştir.

**Anahtar Kelimeler :** Purkinje hücresi, Soma, Membran, Aktivasyon, İnaktivasyon

## 1. INTRODUCTION

Purkinje cell is one output neurone of cerebellar cortex (Nam and Hockberger, 1997). Dendritic tree of rat cerebellar Purkinje cell receives around 175.000 excitatory inputs from granule cells and 1500 GABA<sub>A</sub> inputs from local neurons (Napper and Harvey, 1988). Such a large amount of inputs

indicate that somatic spike activity of Purkinje cell is so complex.

It's reported in literature a number of modeling studies for Purkinje cells. Llinas and Nicholson (1976), Shelton (1985), and Rapp et al. (1992) constructed the model using just passive electrical properties of the cell. These models didn't include

voltage-dependent conductances reported recently to be present in Purkinje cells. The most comprehensive and detailed model of Purkinje cell was constructed by De Schutter and Bower (1994). The model consisted of 1600 compartments and included ten different-type voltage- and concentration-dependent ionic currents. In a recent study, it's shown that class-E  $Ca^{2+}$  channels and D-type  $K^+$  channels are present and functioning in the Purkinje cell dendrites, and used in the constructed model in addition ten ionic channels (Tsugumichi et al., 2001).

In this study, investigation consists of two step. In the first step, sigmoid-shaped curves are fitted for steady-state activation and inactivation data of ionic currents present in Purkinje cell somata. In the second step, a compartmental model of Purkinje cell somata is constructed, and somatic membrane potentials are calculated for several different current injection cases. Then means and standard deviations of differences between somatic membrane potentials obtained using fitted curves and original values separately are calculated.

## 2. MATHEMATICAL MODEL OF AN IONIC CURRENT

Ionic currents present in Purkinje cell obey Hodgkin-Huxley mathematical formalism. In that formalism an ionic current channel is assumed to have gates which are in one of two states, i.e. open or closed state (Aidley and Stanfield, 1996). Conductance of an ionic channel is defined with Hodgkin-Huxley (Hodgkin and Huxley, 1952) as follows :

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

where  $m$  and  $h$  show voltage-dependent probability of being open state for activation and inactivation gates respectively,  $g_X$  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 follows:

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

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

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

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

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

$m_\infty(v)$  and  $h_\infty(v)$  are steady-state activation(i.e. steady-state open gate fraction for activation) and inactivation (i.e. steady-state open gate fraction for 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 values respectively; and may be written as

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)} ; h_\infty(v) = \frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)} \quad (5)$$

$$\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)} ; \tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)} \quad (6)$$

## 3. SOMATIC IONIC CHANNELS

It's reported that fast sodium channel (NaF), persistent sodium channel (NaP), T-type calcium channel (CaT), A-type potassium channel (KA), persistent potassium channel (KM), anomalous rectifier channel (Kh), and delayed rectifier channel (Kdr) are present in the somata of Purkinje cell (Hirano and Hagiwara, 1989; Gahwiler and Llano, 1989; Kaneda et al., 1990; Reagan, 1991; De Schutter and Bower, 1994; Tsugumichi et al., 2001). Kinetics of ionic currents used in this study is based on the model of the cerebellar Purkinje cell by De Schutter and Bower (1994). Constants of rate functions are given in Table 1.

## 4. CURVE FITTING

Steady-state activation and inactivation curves of the ionic currents have sigmoid-shaped, and are either rising from zero to one or falling from one to zero. Therefore sigmoid-shaped curves are fitted for steady-state activation and inactivation data obtained

using Eqn(4-5) based on the parameters given by De Schutter and Bower (1994). Marquardt-Levenberg nonlinear least-square parameter estimation algorithm is used for curve fitting. Fitted curves have a general form as follows:

$$a_{\infty} = \frac{1}{1 + e^{-(v-v_a)/s}} \quad (7)$$

where  $v_a$  is half-activation or half-inactivation voltage, and  $s$  is slope parameter of curve. The slope of the curve at  $v_a$  is proportional to  $1/s$ . If  $s$  is negative then curve falls from one to zero, and

positive then curve rises from zero to one. The magnitude of  $s$  determines the steepness of the curve. If absolute value of  $s$  is small then there is a steep transition region, while if it is large then curve rises or falls slowly (Willms et al., 1999).

#### 4. 1. Curve Fitting Results

In this section, curve fitting results are given. Estimated parameter values for steady-state activation and inactivation curves are given in Table 2.

Table 1. Constants of the Rate Functions

Ionic Channel	Factor	Rate Function	a	b	c	d	F
NaF	m(=3)	$\alpha$	35000	0	0	0.005	-0.01
		$\beta$	7000	0	0	0.065	0.02
	h(=1)	$\alpha$	225	0	1	0.08	0.01
		$\beta$	7500	0	0	-0.003	-0.018
NaP	m(=3)	$\alpha$	200000	0	1	-0.018	-0.016
		$\beta$	25000	0	1	0.058	0.008
CaT	m(=1)	$\alpha$	2600	0	1	0.021	-0.008
		$\beta$	180	0	1	0.04	0.004
	h(=1)	$\alpha$	2.5	0	1	0.04	0.008
		$\beta$	190	0	1	0.05	-0.01
KA	m(=4)	$\alpha$	1400	0	1	0.027	-0.012
		$\beta$	490	0	1	0.03	0.004
	h(=1)	$\alpha$	17.5	0	1	0.05	0.008
		$\beta$	1300	0	1	0.013	-0.01
Kdr	m(=2)		Equations by De Schutter and Bower (1994)				
	h(=1)						
Kh	m(=1)						
KM	m(=1)						

Table 2. Estimated Parameter Values For Steady-State Activation and Inactivation Curves

Ion channel	Factor	$v_a$ (mV)	$s$ (mV)
NaF	m	-35.73 ± 3.7e-18	6.67 ± 3.22e-18
NaF	h	-77.33 ± 1.098e-3	-9.251 ± 9.51e-3
NaP	m	-44.89 ± 7.48e-4	6.254 ± 6.5e-4
CaT	m	-45.23 ± 9.38e-4	5.499 ± 8.17e-4
CaT	h	-93.09 ± 2.44e-4	-10.22 ± 2.01e-4
Kh	m	-82 ± 3.41e-18	-7 ± 2.94e-18
Kdr	m	-11.61 ± 9.74e-4	11.78 ± 8.14e-4
Kdr	h	-25 ± 0.00	-4 ± 0.00
KM	m	-35 ± 0.00	10 ± 0.00
KA	m	-39.71 ± 3.09e-3	9.479 ± 2.66e-3
KA	h	-59.56 ± 1.19e-3	-7.619 ± 1.009e-3

### 5. COMPARTMENTAL MODEL OF PURKINJE CELL SOMATO

Purkinje cell somata model is constructed using compartmental modeling approach. Compartmental modeling in which a neuron is divided into small parts called as a compartment is derived from linear cable theory (De Schutter, 1989). Equivalent electrical circuit for the constructed compartment is

shown in Figure 1. Maximal conductances and reversal potentials of ionic channels are given in Table 3. Soma compartment is modeled spherically, and radius of sphere is taken 29.8  $\mu\text{m}$ . Specific membrane capacitance, CM is taken as 0.0164 F/m<sup>2</sup>, specific membrane resistance, RM as 1  $\Omega\text{m}^2$ , resting potential as -68 mV, and reversal potential of leak current as -80 mV.

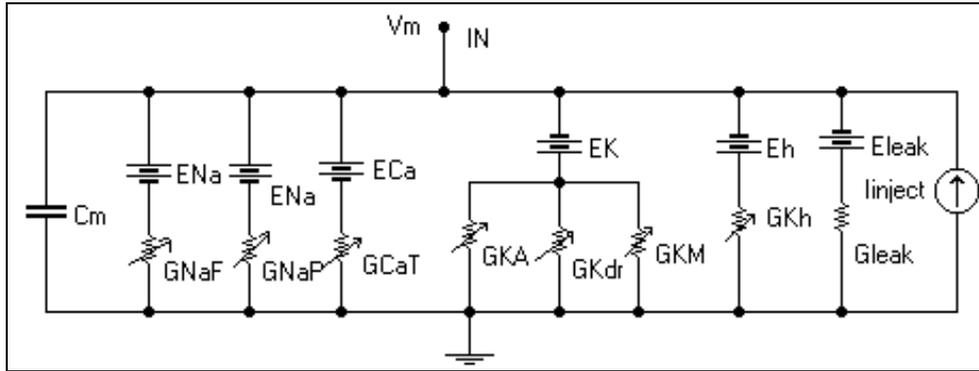


Figure 1. Equivalent electrical circuit for the constructed compartment

Table 3. Ionic Channel Parameters

Ionic channels	Maximal Conductance (S/m <sup>2</sup> )	Reversal Potential (mV)
NaF	75000	45
NaP	10	45
CaT	5	135
Kh	3	-30
Kdr	6000	-85
KM	0.4	-85
KA	150	-85

In Figure 1, current equation is obtained as,

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{inject} \quad (8)$$

where  $C_m$ ,  $V_m$ ,  $I_{ion}$ ,  $I_{inject}$  represent membrane capacitance, membrane potential, sum of ionic currents, and injected current respectively. Sum of the ionic currents is given by

$$I_{ion} = \sum G_k (V_m - E_k) \quad (9)$$

$$= I_{NaF} + I_{NaP} + I_{CaT} + I_{KA} + I_{Kdr} + I_{Kh} + I_{KM} + I_{leak}$$

So the change in membrane potential is expressed as follows :

$$\frac{dV_m}{dt} = \frac{1}{C_m} [I_{inject} - I_{ion}] = \frac{I}{C_m} \quad (10)$$

## 6. INTEGRATION METHOD

It's necessary to compute  $m$  and  $h$  values at each time step before calculating of membrane potential. Eq. (2) and Eq. (3) have a general form as,

$$\frac{dy}{dt} = A - By \quad (11)$$

where  $A = \alpha$ ,  $B = \alpha + \beta$ . We use Exponential Euler method to obtain the values of  $m$  and  $h$  for each time step. Solution of Eq. (11) for time increment  $\Delta t$  is given as follows (Bower and Beeman, 1998):

$$y(t + \Delta t) = y(t)e^{-B\Delta t} + \frac{A}{B}(1 - e^{-B\Delta t}) \quad (12)$$

Substituting  $A = \alpha$ ,  $B = \alpha + \beta$  into Eq. (12) gives

$$y(t + \Delta t) = y(t)e^{-(\alpha+\beta)\Delta t} + \frac{\alpha}{\alpha+\beta}(1 - e^{-(\alpha+\beta)\Delta t})$$

$$= y(t)e^{-\Delta t/\tau} + y_{\infty}(1 - e^{-\Delta t/\tau}) \quad (13)$$

$$= y_{\infty} + (y(t) - y_{\infty})e^{-\Delta t/\tau}$$

where  $y_{\infty}$  represents steady-state activation or inactivation value at present step voltage;  $y(t)$  represents activation or inactivation value calculated at the last step according to Eq. (13).  $\tau$  represents time constant of activation or inactivation at present step voltage.

After calculating of  $m$  and  $h$  values, it's easy to calculate an ionic current with Eq. (1) and Eq. (9).

Next step at the integration is to calculate the membrane potential according to Eq. (10). The expression on the right side of Eq. (10) was calculated, so have a constant value. Therefore the integration of membrane potential is done with Forward Euler method (Bower and Beeman, 1998):

$$V_m(t + \Delta t) = V_m(t) + \Delta t \frac{I}{C_m} \quad (14)$$

## 7. SIMULATION RESULTS

Initial control simulations were run with different time increments to determine which time increment produced numerically accurate results. Then fixed time increment of 10 μs was selected. Different

magnitude currents are injected into the soma, and somatic membrane potentials are calculated. Calculations are carried out at two separate steps. In the first step, voltage-dependent rate functions, α and β, are calculated, and then steady-state values of activation and inactivation values are estimated using Eq. (5). Finally this calculated values are used in Eq. (13) to obtain values of m and h at each simulation step. In the second step, steady-state values of activation and inactivation are directly calculated from the fitted curves given in Eq. (7) and Table 2, and the calculated values are used in Eq. (13). Means and standard deviations of differences between somatic membrane potentials which are calculated using original equations and the fitted curves separately are shown in Table 3.

Table 3. Means and Standard Deviations of Differences Between Somatic Membrane Potentials

Injected Current (nA)	$\bar{X}$	$\sigma_x$
0.5	-1.941479e-5	0.031403
1	6.734906e-5	0.029361
1.5	-2.654986e-3	0.029552
2	-3.414407e-3	0.033403
3	-2.683327e-3	0.031046

## 8. CONCLUSIONS

In this paper, sigmoid-shaped curves are fitted for steady-state activation and inactivation data of ionic channels present in Purkinje cell somata, and somatic membrane potentials are calculated for both original equations and fitted curves separately. Simulation results show that means and standard deviations of differences between somatic membrane potentials calculated with both original equations and fitted curves separately are so small. The results indicate validity of fitted curves. Therefore the fitted curves can be used directly in the model instead of calculating them from rate functions. This will also reduce simulation time considerably in models include a large number of compartments.

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