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PHASE-PLANE ANALYSIS FOR A SIMPLIFIED MODEL OF PURKINJE CELL DENDRITE

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Abstract- In this study, phase-plane analysis is carried out for a simplified model of Purkinje cell dendrite in terms of voltage-gated ionic channels involved. State variables, nullclines and equilibrium points of the model are determined, and effects of ionic channel conductance and injected current on the shape of nullclines and the equilibrium points are investigated.

Keywords- Purkinje cell dendrite, phase-plane, nullcline, equilibrium point, stability.

1. INTRODUCTION

Purkinje cell is one output neurone of cerebellar cortex. Dendritic tree of rat cerebellar Purkinje cell receives around 175000 excitatory inputs from granule cells and 1500 $GABA_A$ inputs from local neurones[1]. Many different types of voltage-gated ionic currents are found in Purkinje cell dendrite[2]. Voltage-gated ionic currents are of great importance in integrating the information received by the neurones[3].

The analysis of realistic neuronal models is very complex due to too many variables in the models. So the analysis of the neurone with a simplified model captured the complex behaviour of a realistic model provides valuable insight into the information processing capabilities of the nervous system[4]. In this context, Yuen et al. used a single-compartmental model of the dendrite with high threshold calcium and delayed rectifier potassium conductances to investigate bistability in cerebellar Purkinje cell dendrites using phase-plane analysis[5]. Pinsky and Rinzel[6] used a simplified model of Traub et al.[7] with just two compartments. Mainem and Sejnowski[8] used another simple model similar to that of Pinsky and Rinzel[6] for neocortical neurones.

2. DENDRITIC CELL MODEL

Many different types of voltage-dependent calcium and voltage- and calcium-concentration dependent potassium channels are present in Purkinje cell dendrite. In this study, we use a simplified model described by Yuen et al.[5]. So the model has only one compartment and consists of high threshold calcium and delayed rectifier potassium channels. Voltage-gated ionic current used in the model obey Hodgkin-Huxley mathematical formalism[9]. Ionic channel parameters are based on a recent study[10]. The model can be described by the following equations:

$$C\frac{dV}{dt} = -\sum I_{ion(i)}(V,n) + I_{inj} = -[I_{Ca}(V) + I_{Kdr}(V,n) + I_{leak}(V)] + I_{inj} \tag{1}$$

$$I_{Ca}(V) = g_{ca} m_\infty(V)(V - V_{Ca}) \tag{2}$$

$$m_\infty(V) = \frac{1}{1 + e^{-(V+19)/7.16}} \tag{3}$$

$$I_{Kdr}(V,n) = g_{Kdr} n^4 (V - V_{Kdr}) \tag{4}$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \tag{5}$$

$$n_\infty(V) = \frac{1}{1 + e^{-(V+20)/10}} \tag{6}$$

$$\tau_n(V) = \frac{1.85}{1 + e^{(V+27)/15}} + 0.37 \tag{7}$$

$$I_{leak}(V) = g_{leak}(V - V_{Leak}) \tag{8}$$

where C =1 μF/cm^2, g_{Ca}=0.47 mS/ cm^2, g_{Kdr}=12 mS/cm^2, g_{leak}=0.03 mS/ cm^2, V_{Ca}=120 mV, V_{Kdr}=-90 mV, V_{Leak}=-70 mV. The interaction between I_{leak} and resting I_{Kdr} gave rise to a resting dendritic membrane potential of –65.76 mV in contrast to the study given in [10] due to calcium-activated potassium currents involved in that study.

Current equation (1) indicates that change in dendritic membrane potential is proportional to sum of ionic and injected currents. V_{Ca} ,V_{Kdr}, and V_{Leak} are Nernst equilibrium potential for calcium, potassium and leakage currents respectively. m and n are voltage-dependent probability of being open state for activation gates for calcium and potassium channel respectively. Gating variables (m, n) take values between 0 and 1. m_∞ and n_∞ are steady-state activation and inactivation for calcium and potassium channel respectively. $\tau_n(v)$ shows voltage-dependent potassium activation time constant which is the time taken to reach a steady-state value for a given potential.

3. PHASE-PLANE ANALYSIS

Phase-plane analysis allows us to view the response of multiple variables and their relation with physiological functions at the same time, and can be used to analyze the complex dynamics of the neurones during simulations[11]. The dendritic model given above is described by two differential equations, so it has just two state variables: dendritic membrane potential (V) and delayed rectifier potassium channel gating variable (n). In the first step, system nullclines are estimated. Nullclines are derived by setting time derivative of the state variables to zero:

$$\frac{dV}{dt}=0 \Rightarrow I_{inj}=\left[g_{ca}m_{\infty}(V)(V-V_{Ca})+g_{Kdr}n^{4}(V-V_{Kdr})+g_{leak}(V-V_{leak})\right]$$

$$n=\left[\frac{I_{inj}-\left[g_{ca}m_{\infty}(V)(V-V_{Ca})+g_{leak}(V-V_{leak})\right]}{g_{Kdr}(V-V_{Kdr})}\right]^{4} \qquad (9)$$

Equation (9) shows the voltage nullcline. Delayed rectifier potassium gating variable(n) nullcline is obtained as:

$$\frac{dn}{dt}=0 \Rightarrow n=n_{\infty}(V)=\frac{1}{1+e^{-(V+20)/10}} \qquad (10)$$

System nullclines are shown in Figure 1.

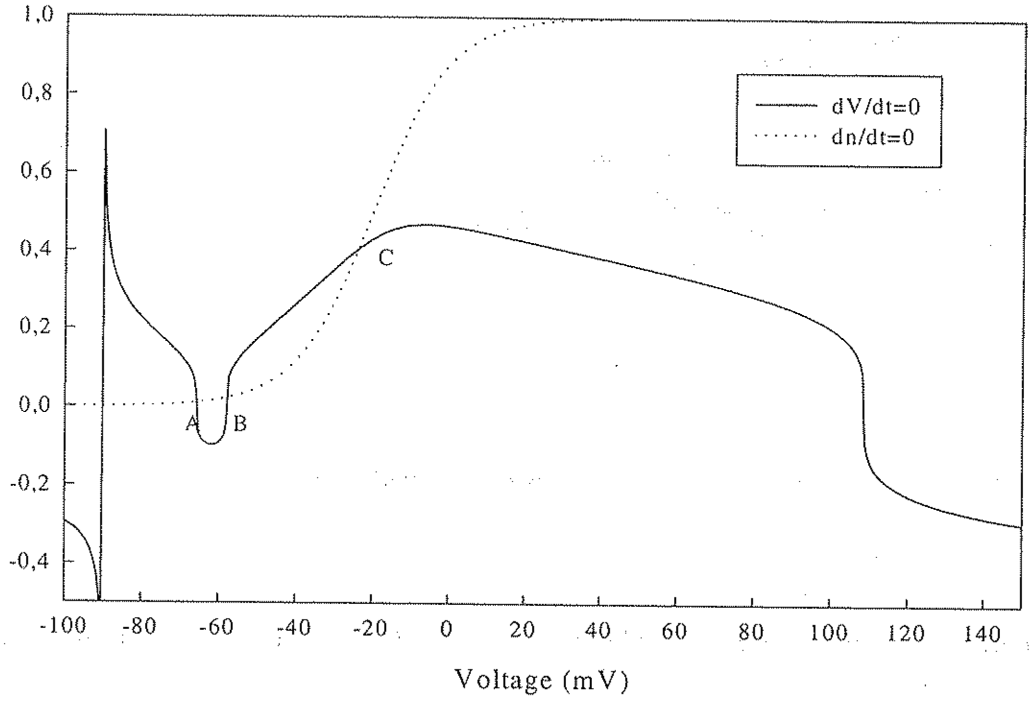

Figure 1. System nullclines and equilibrium points

The intersections of the nullclines are defined as equilibrium points where both of the time derivative of the state variables are equal to zero. Therefore the system state isn't changing . There are three equilibrium points (V, n) for our system as seen in Figure 1: A(-65.76,0.01), B(-57.94, 0.022) and C(-23.837,0.4052). Phase trajectories converge toward the equilibrium points. Negative values on n-axis indicate unrealizable imaginary values. The shape of the voltage nullcline includes a dip between about –65 and –58 mV, and a hump between about –58 and 110 mV.

In the second step, local stability procedure is applied for three equilibrium points. The procedure is given by Rinzel and Ermentrout explicitly[11]. It aims to determine if small disturbances from an equilibrium point are converging toward it. Therefore the procedure linearizes differential equations of the system, and evaluates the partial derivatives at the equilibrium points(Jacobian matrix). Linearized equations describing small disturbances from an equilibrium point(V_0 , n_0) assuming $V \approx V_0+x$; $n \approx n_0+y$ as follow:

$$\frac{dx}{dt} = Ax + By \quad ; \quad \frac{dy}{dt} = Cx + Dy \tag{11}$$

where

$$A = -\frac{\partial I_{ion}(V_0, n_0)}{\partial V} = -\left[g_{Ca} m_\infty(V_0) + g_{Ca} \frac{dm_\infty(V_0)}{dV}(V_0 - V_{Ca}) + g_{Kdr} n_0^4 + g_{leak} \right] \tag{12}$$

$$B = -\frac{\partial I_{ion}(V_0, n_0)}{\partial n} = -\left[4 g_{Kdr} n_0^3 (V_0 - V_{Kdr}) \right] \tag{13}$$

$$C = \frac{1}{\tau_n(V_0)} \frac{dn_\infty(V_0)}{dV} = \frac{1}{\tau_n(V_0)} \left(\frac{\frac{1}{10} e^{-(V_0+20)/10}}{\left(1 + e^{-(V_0+20)/10}\right)^2} \right) \tag{14}$$

$$D = -\frac{1}{\tau_n(V_0)} \tag{15}$$

Eigenvalues of the Jacobian matrix are roots of the quadratic form as:

$$\lambda^2 - (A + D)\lambda + (AD - BC) = 0 \tag{16}$$

Calculated values of coefficients and eigenvalues for A, B and C equilibrium points are given in Table 1.

Table 1. Calculated values of coefficients and roots for Equation (16)

	A	B	C	D	λ_1	λ_2
(-65.76,0.01)	-0.01295	-1.1635e-3	4.82601e-4	-0.47842	-0.4784	-0.013
(-57.94, 0.022)	0.01828	-0.01638	1.07020e-3	-0.49717	-0.4971	0.0183
(-23.837,0.4052)	1.59837	-211.28308	0.02012	-0.83484	0.3818+i1.6647	0.3818-i1.6647

If all exponential solutions of the forms $e^{\lambda_1 t}$ and $e^{\lambda_2 t}$ have growing modes, then equilibrium point is unstable. If all exponential solutions have decaying modes, then equilibrium point is stable. So A equilibrium point is stable and B equilibrium point is unstable. C equilibrium point has complex conjugate eigenvalues. It is hopf bifurcation point, and gives rise to a limit cycle. As it is unstable, bifurcation is subcritical[10].

In the third step, effects of the ionic conductance and injected current on the shape of nullclines and equilibrium points are investigated. The shape of the voltage nullcline is a result of calcium, delayed rectifier potassium and leakage conductance while the shape of delayed rectifier potassium gating variable nullcline is a result of just dendritic membrane potential.

The effect of specific conductance for calcium channel on voltage nullcline is shown in Figure 2. The hump in the voltage nullcline attenuates and narrows on the voltage axis, also the dip widens when the calcium conductance is decreased as seen in Figure2. Sufficient decreased calcium conductance moves the lowest equilibrium point(A) leftward. It also moves the hump below the potassium gating variable nullcline. Therefore it eliminates the other two equilibrium points.

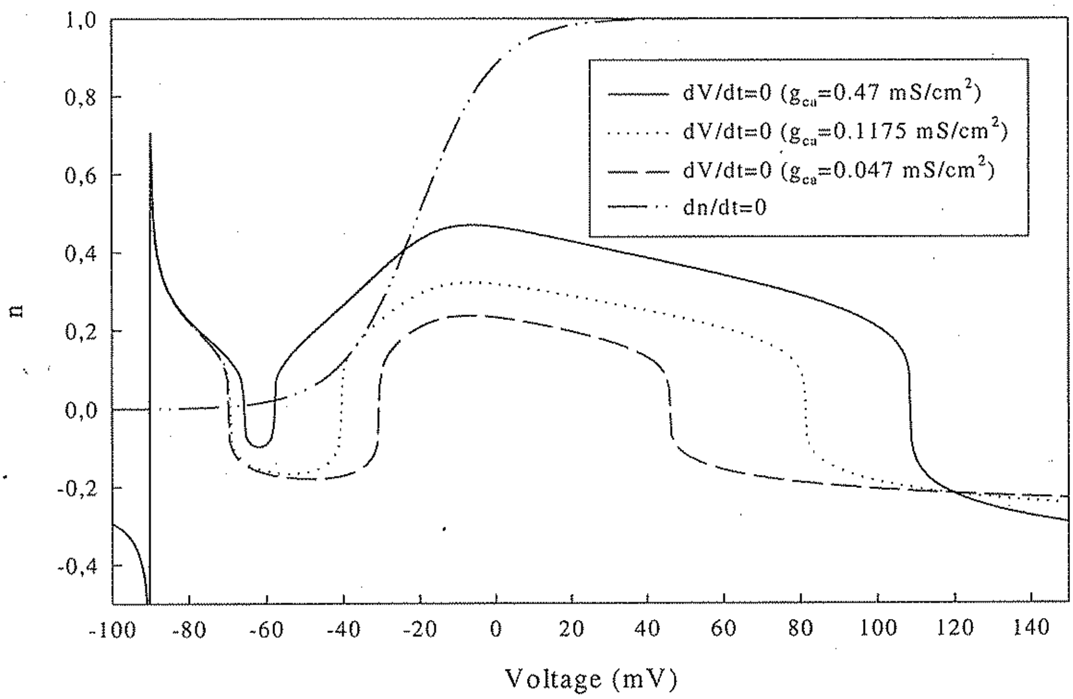

Figure 2. Effect of calcium conductance on voltage nullcline and equilibrium points

The effect of specific conductance for delayed rectifier potassium channel on voltage nullcline is shown in Figure 3. The voltage nullcline shifts upward when the potassium conductance is decreased as seen in Figure 3. So the highest equilibrium point moves upward. But the other lower equilibrium points and voltage range which corresponds to the hump don't change. This also shows that the shape of the hump is dependent on calcium current.

The effect of steady depolarizing current on the voltage nullcline is shown in Figure 4. Steady depolarizing current attenuates the dip and shifts voltage nullcline upward as seen in Figure 4. This results in elimination of the lower equilibrium points and remaining the highest equilibrium point elevated slightly.

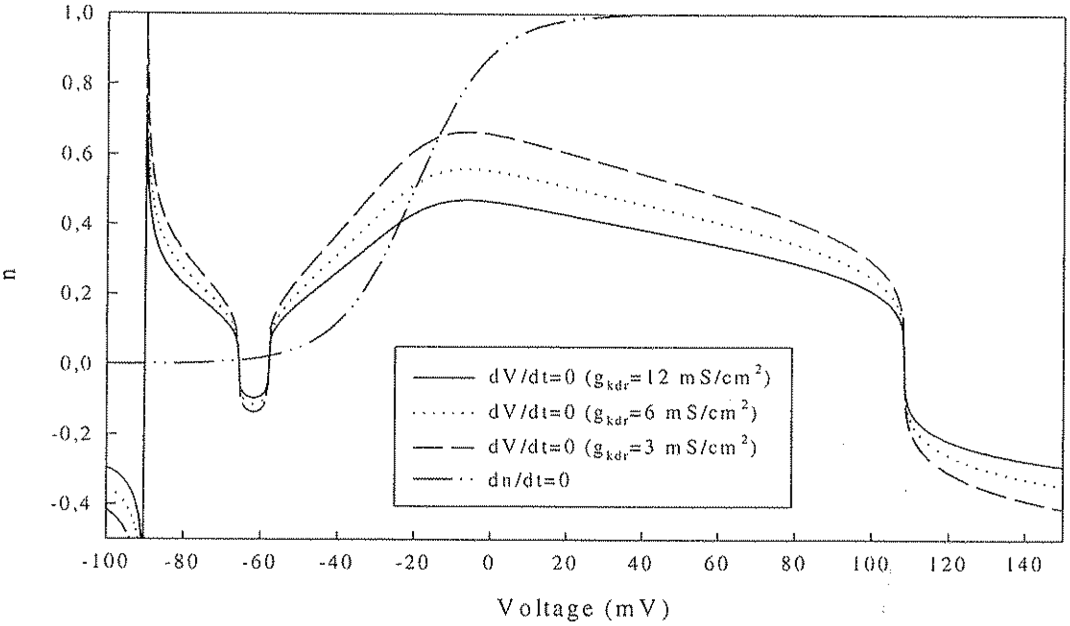

Figure 3. Effect of potassium conductance on voltage nullcline and equilibrium points

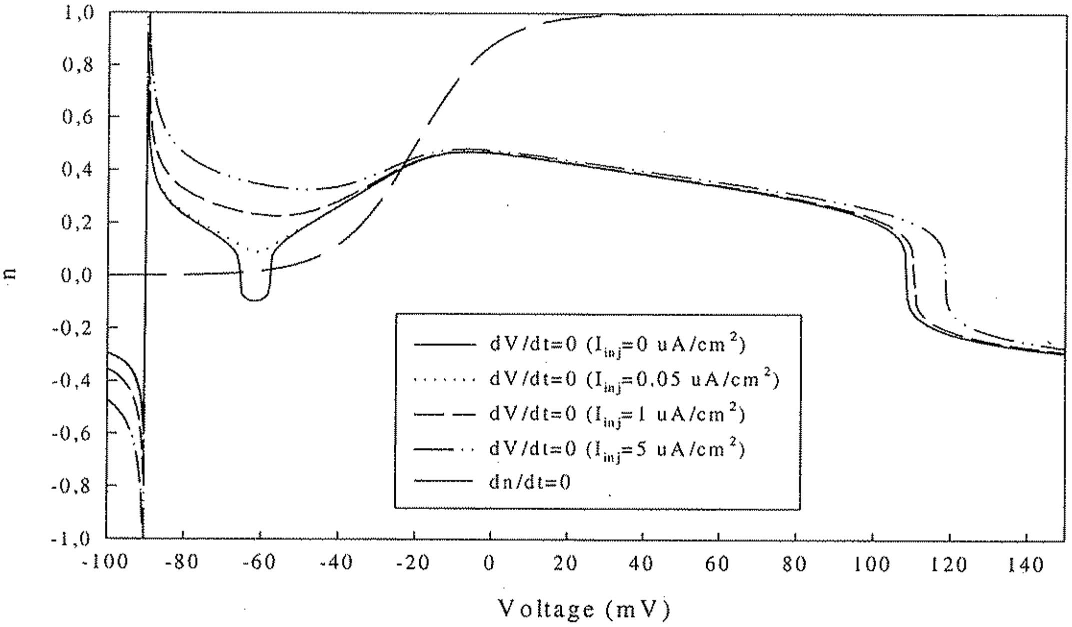

Figure 4. Effect of steady depolarizing current on voltage nullcline and equilibrium points

The effect of steady hyperpolarizing current on voltage nullcline is shown in Figure 5. Steady hyperpolarizing current accentuates the dip in the voltage nullcline. And it also shifts the voltage nullcline downward. This result in elimination of the upper equilibrium points.

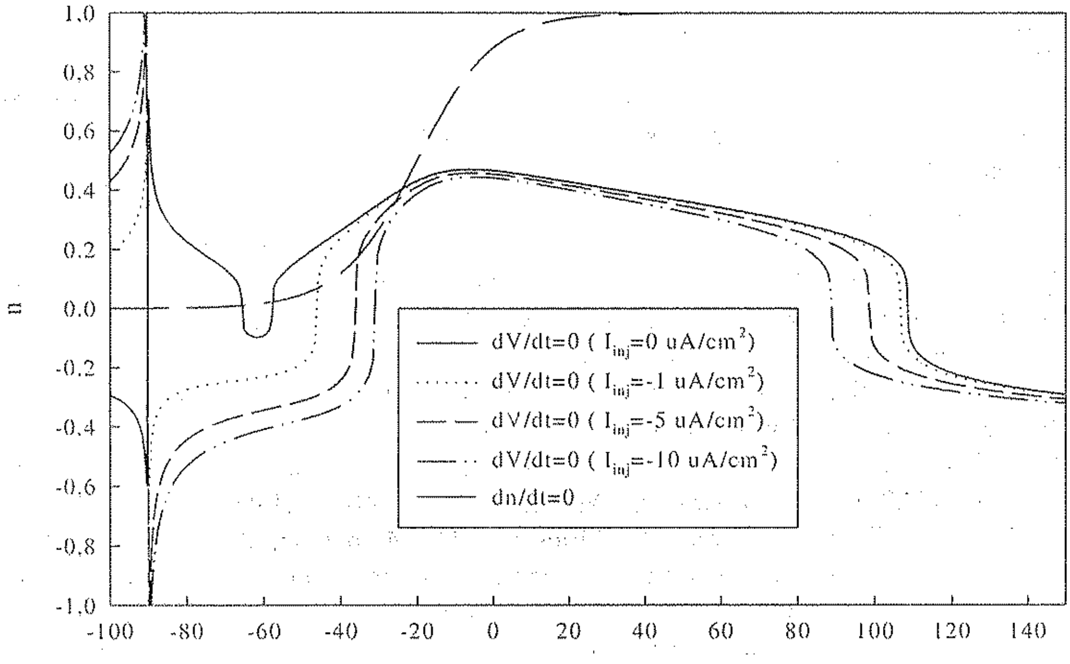

Figure 5. Effect of steady hyperpolarizing current on voltage nullcline and equilibrium points

4. CONCLUSION

In this study, phase plane analysis is carried out for Purkinje cell dendrite using a simplified model reported in literature. Nullclines are determined, and three equilibrium points of the model are obtained. Then stability of the equilibrium points is studied. Stability analysis indicates that the model has one stable, one unstable and one bifurcation points. Then effects of the ionic channel conductances involved in the model and steady depolarizing and hyperpolarizing currents on equilibrium points are investigated. Results show that the lowest equilibrium point moves leftward and the other two equilibrium point is eliminated when calcium conductance is decreased, the highest equilibrium point moves upward and the other lower equilibrium points don't change when potassium conductance is decreased, increasing steady depolarizing current eliminates the lower equilibrium points and elevates the highest equilibrium point slightly, and increasing steady hyperpolarizing current eliminates the upper equilibrium points.

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