Modeling Motoneurons after Spinal Cord Injury: Persistent Inward Currents and Plateau Potentials

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Keywords:

Hysteresis, Rat, Self-sustained firing, Calcium current, Spasticity

Acknowledgment:

This work was partially supported by funds from The Biodesign Institute.

Abstract

A single-compartment conductance-based computational model to mimic the behavior of rat tail motoneurons after acute and chronic spinal cord injury (SCI) was developed. The model includes a calcium-dependent potassium current, $I_{K(Ca)}$, that contributes to afterhyperpolarizations. In the chronic SCI model, the presence of sodium and calcium persistent inward currents (PICs) causes plateau potentials resulting in prolonged self-sustained firing. The interaction between the calcium PIC and $I_{K(Ca)}$ affects the magnitude and duration of plateau potentials as well as the hysteresis seen during injected current ramps. The model responses mimic experimental observations and may explain the spasticity observed after chronic SCI.

1. Introduction

Spasticity is a major complaint of people with chronic spinal cord injury (SCI) as well as an impediment to the recovery of functional locomotion after SCI [7,8,14], but the mechanisms underlying spasticity are poorly understood. Recent studies with a rat sacral spinal cord transection model suggest that after chronic SCI, changes in the membrane properties of spinal motoneurons lead to plateau potentials that may play a large role in spasticity [1,2,3]. Although normal motoneurons may use plateau potentials to amplify synaptic input and have been shown to develop plateau potentials in response to the application of certain neurotransmitters [9,11], after acute SCI, rat motoneurons lose the endogenous ability to generate plateaus [3]. After chronic SCI in rats, plateau potentials appear in almost all motoneurons and have been found to be caused by voltage-dependent calcium and sodium persistent inward currents (PICs) [2,3,13]. In the presence of these PICs brief stimuli can trigger prolonged self-sustained firing [13], much as spasticity increases following sensory stimuli in human SCI patients [7]. Recent evidence indicates that plateau potentials are also present in human motoneurons [5].

Here, we have developed a computational model to mimic the behavior of rat motoneurons after acute SCI as seen in Ref. [3]. We utilize this model to examine the effects of calcium and sodium PICs in altering the behavior of the motoneurons after chronic SCI.

2. The Model

A single-compartment conductance-based model is developed to mimic the behavior of rat motoneurons after acute SCI by modifying a previous vertebrate motoneuron model [4]. The current balance equation for this “acute model” is given by:

$$C_m \frac{dV}{dt} = -I_{Na} - I_{K-dr} - I_{Ca} - I_{K(Ca)} - I_L + I_{app} \quad (1)$$

where C_m is the membrane capacitance and V is the membrane voltage. I_{Na} and $I_{K\text{-}dr}$ are Hodgkin-Huxley-like sodium and potassium delayed rectifier currents that produce action potentials. I_{Ca} and $I_{K(Ca)}$ are calcium and calcium-dependent potassium currents, respectively, that have been found to contribute to afterhyperpolarizing potentials (AHPs) in rat motoneurons [6,15]. I_L is a leak current and I_{app} is an applied (injected) current that takes the form of slow (0.5 nA/s) ramps or pulses. The currents are modeled as:

$$I_{Na} = g_{Na} m_{\infty(Na)}^3(V) h_{Na}(V - E_{Na}) \quad (2)$$

$$I_{K-dr} = g_{K-dr} n^4 (V - E_K) \quad (3)$$

$$I_{Ca} = g_{Ca} m_{Ca}^2 h_{Ca}(V - E_{Ca}) \quad (4)$$

$$I_{K(Ca)} = g_{K(Ca)} \frac{[Ca]}{[Ca] + S_{Ca}} (V - E_K) \quad (5)$$

$$I_L = g_L (V - E_L) \quad (6)$$

where g_x is the maximum ionic conductance, m_x, h_x, and n_x describe the gating kinetics, E_x is the reversal potential, $[Ca]$ is the intracellular calcium concentration, and S_{Ca} is the half-saturation concentration of calcium. The sodium current is modeled as having an instantaneous activation. The intracellular calcium concentration is modeled as:

$$\frac{d[Ca]}{dt} = f(-\alpha I_{Ca} - r_{Ca}[Ca]) \quad (7)$$

where f is the ratio of free to bound calcium, α is a conversion factor that changes the calcium current into a calcium concentration, and r_{Ca} represents the calcium removal rate. The parameter α implicitly involves cell membrane surface area and cell volume, though these values are not explicitly calculated.

The acute model is then modified to a “chronic model” in order to mimic the behavior of rat motoneurons after chronic SCI. This is accomplished solely by including

calcium and sodium PICs based on Ref. [13] and changing the calcium concentration equation, Eq. (7), to include the calcium PIC. The additions to the chronic model are described by:

$$I_{Ca-P} = g_{Ca-P} m_{Ca-P} (V - E_{Ca}) \quad (8)$$

$$I_{Na-P} = g_{Na-P} m_{Na-P} (V - E_{Na}) \quad (9)$$

$$\frac{d[Ca]}{dt} = f\{-\alpha_1 I_{Ca} - \alpha_2 I_{Ca-P} - r_{Ca}[Ca]\} \quad (10)$$

where $I_{Ca\text{-}P}$ is the persistent calcium current, $I_{Na\text{-}P}$ is the persistent sodium current, and all other symbols are the same as above. Separate conversion factors, α_1 and α_2, for the two calcium currents are included because in motoneurons of other species, persistent calcium currents have been localized to dendrites, thus making it reasonable to assume that the two calcium currents affect the calcium concentration in the soma differently (i.e. the calcium PIC, $I_{Ca\text{-}P}$, contributes less to intracellular calcium concentration) [10,12]. The parameters of the persistent currents, as well as the value of α_2 are determined such that the behavior of the chronic model approximates the behavior of rat motoneurons after chronic SCI, as reported in Ref. [3].

We examine the responses of these models to injected ramp currents and injected pulse currents and investigate the role of the calcium PIC, the calcium-dependent potassium current, and the conversion factor α_2 in the development of plateau potentials.

3. Results

3.1 Response to Current Injection

The behavior of the acute and chronic models during current injections is reasonably similar to behavior seen experimentally in acute and chronic SCI rat motoneurons (compare Fig. 1 here with Figs. 2 and 3 in Ref. [3]). On injection of

increasing and decreasing ramp currents in the acute model the membrane voltage depolarizes as a ramp, resulting in spiking that begins and ends at approximately the same applied current (Fig. 1A). The frequency vs. current curve (Fig. 1B) is linear to slightly clockwise, with recruitment and derecruitment frequencies approximately the same. During a current pulse, the acute model demonstrates a constant frequency response (Fig. 1C). No plateau potentials are observed in either case. In the chronic model, during increasing and decreasing ramp currents, spiking ends at a lower current value than when it started (Fig. 1D). The frequency vs. current curve is counter-clockwise, with derecruitment generally occurring at a lower frequency than recruitment (Fig. 1E). During a current pulse (Fig. 1F), the chronic model displays spiking that increases in frequency during the pulse, with prolonged self-sustained spiking that decreases in frequency after the pulse ends. The differences between the acute and chronic model are due to the fact that the PICs in the chronic model cause a plateau potential to develop. The plateau potential can be seen clearly when spiking is eliminated (Fig. 2).

3.2 Calcium PIC and Calcium-Dependent Potassium Current Affect Plateaus

In order to examine the contribution of the calcium PIC to the plateau potentials, spiking in the model was eliminated by setting the sodium conductances to zero. This is equivalent to applying the sodium channel blocker tetrodotoxin (TTX) experimentally (compare Fig. 2 here with Fig. 2B in Ref. [13]). The magnitude and duration of the plateau potential in the chronic model depends on an interaction between the depolarizing calcium current and the repolarizing calcium-dependent potassium current. The conversion factor α_2 determines the amount of the calcium PIC available to induce the

calcium-dependent potassium current. As such, decreasing the value of α_2 leads to plateau potentials of greater magnitude and duration (Fig. 2). With sodium conductances active, this would equate to a higher initial spiking frequency and a more prolonged self-sustained firing. Decreasing the magnitude of the calcium PIC by decreasing its conductance ($g_{Ca\text{-}P}$) results in exactly the opposite effect: plateau potentials with lower magnitudes and shorter durations. In Fig. 2, an α_2 value of 0.00125 was found to produce behavior most similar to experiments [13] and was set as the default value. Note that this is much lower than the value for α_1 (0.009), thereby simulating the dendritic origin of the calcium PIC.

3.3 Calcium PIC Affects Hysteresis During Injected Current Ramps

Hysteresis in the frequency vs. current curves during injected ramp currents is also affected by the magnitude of the calcium PIC in the chronic model. At low values of $g_{Ca\text{-}P}$, and thus low magnitudes of $I_{Ca\text{-}P}$, the hysteretic effect is less obvious. As the magnitude of $g_{Ca\text{-}P}$ increases, however, the degree of hysteresis increases dramatically (Fig. 3). This is due to a positive feedback cycle: the depolarizing calcium PIC increases spiking frequency, which increases the average cell membrane potential, which increases the magnitude of the calcium PIC. This cycle is interrupted when the intracellular calcium concentration rises high enough to fully activate the repolarizing calcium dependent potassium current. In Fig. 3, a $g_{Ca\text{-}P}$ value of 0.05 was found to produce behavior most similar to experiments [13] and was set as the default value.

4. Conclusions

The goal of this modeling effort was to reproduce experimental behavior from the motoneurons of rats with acute and chronic spinal cord injuries. The behavior of acute

SCI rat motoneurons was reasonably modeled with a small number of currents, including a calcium-dependent potassium current to reproduce AHPs. To reproduce the behavior of chronic SCI rat motoneurons it was only necessary to add the recently discovered calcium and sodium PICs. The calcium PIC and the calcium-dependent potassium current influence the magnitude and duration of plateau potentials as well as the hysteresis in the frequency vs. current relationship during injected current. Plateau potentials result in prolonged self-sustained firing. Such firing in response to brief stimuli is likely to be responsible for the spasticity developed after SCI. The computational models developed here could, in later studies, be included in simple networks in order to examine spinal reflexes and explore the role of intrinsic motoneuron properties in altering supraspinal-spinal sensorimotor integration after spinal cord injury.

5. References

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6. Figure Legends

Figure 1: Acute and chronic model behavior during injected current. Acute Model: (A) Response to ramp current with interspike frequency illustrated above spiking; (B) Frequency vs. ramp current shows lack of hysteresis; (C) Response to pulse current shows constant interspike frequency. Chronic Model: (D) Response to ramp current with interspike frequency illustrated above spiking shows prolonged spiking; (E) Frequency vs. ramp current shows pronounced hysteresis; (F) Response to pulse current shows altered frequency profile due to plateau potential.

Figure 2: Effect of calcium concentration conversion factor (α_2) on plateau potential with sodium conductances inactive in chronic model. Decreasing α_2 results in plateau potentials with higher magnitudes and longer durations.

Figure 3: Effect of calcium PIC conductance ($g_{Ca\text{-}P}$) on hysteresis in frequency vs. ramp current relationship in the chronic model. Increasing $g_{Ca\text{-}P}$ results in increased hysteresis.

7. Biosketches

 Joe Graham, a National Merit Scholar, received his BSe in bioengineering from Arizona State University in 2001. He is currently working on his PhD as a NSF IGERT Fellow in the Harrington Department of Bioengineering at Arizona State University. He is also a member of the Center for Rehabilitation Neuroscience and Rehabilitation Engineering, a branch of The Biodesign Institute at Arizona State University. His research interests include electrophysiology and computational neuroscience.

 Victoria Booth received her PhD in applied mathematics from Northwestern University. She has held positions at the mathematical research branch at NIH, the Department of Mathematical Sciences at the New Jersey Institute of Technology, and is currently at the University of Michigan in the Mathematics Department and the Anesthesiology Department. Her research interests are in biophysical modeling of neuronal networks.

 Ranu Jung is Associate Professor of Bioengineering and Co-Director of the Center for Rehabilitation Neuroscience and Rehabilitation Engineering, The Biodesign Institute at Arizona Sate University, Tempe, AZ, USA. She received her doctorate in Biomedical Engineering from Case Western Reserve University and has been an American Heart Association Research Fellow and a NIH Individual National Research Service Award Fellow. Her research interests are in Neural Engineering, Neurotrauma, Sensorimotor Integration, Computational Neuroscience, and Nonlinear Signal Processing. She is a Senior Member of the Society of Women Engineers and a member of AAAS, IEEE, the Biomedical Engineering Society, the Society for Neuroscience, and the National Neurotrauma Society. She serves on the Board of the Rocky Mountain Bioengineering Organization and the Computational Neuroscience Organization.

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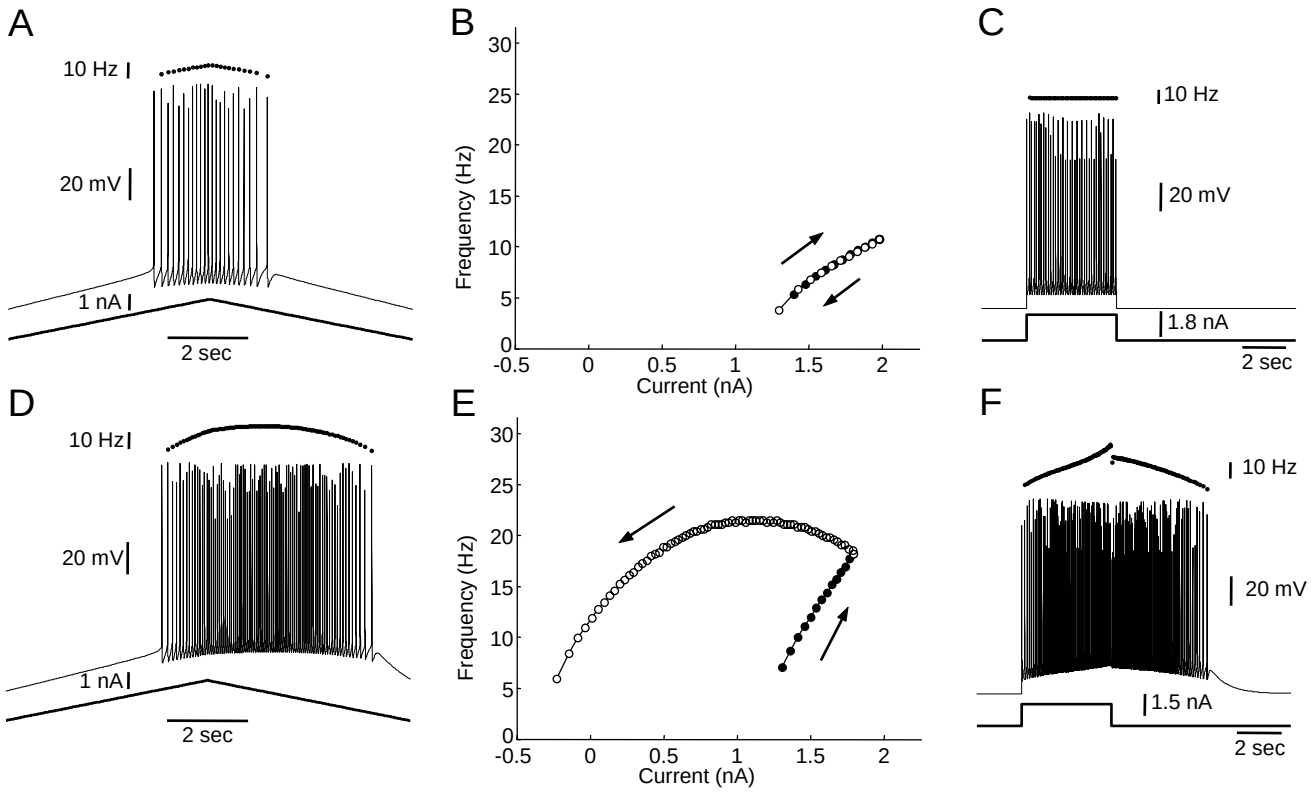

Fig. 1
(Graham et al.)

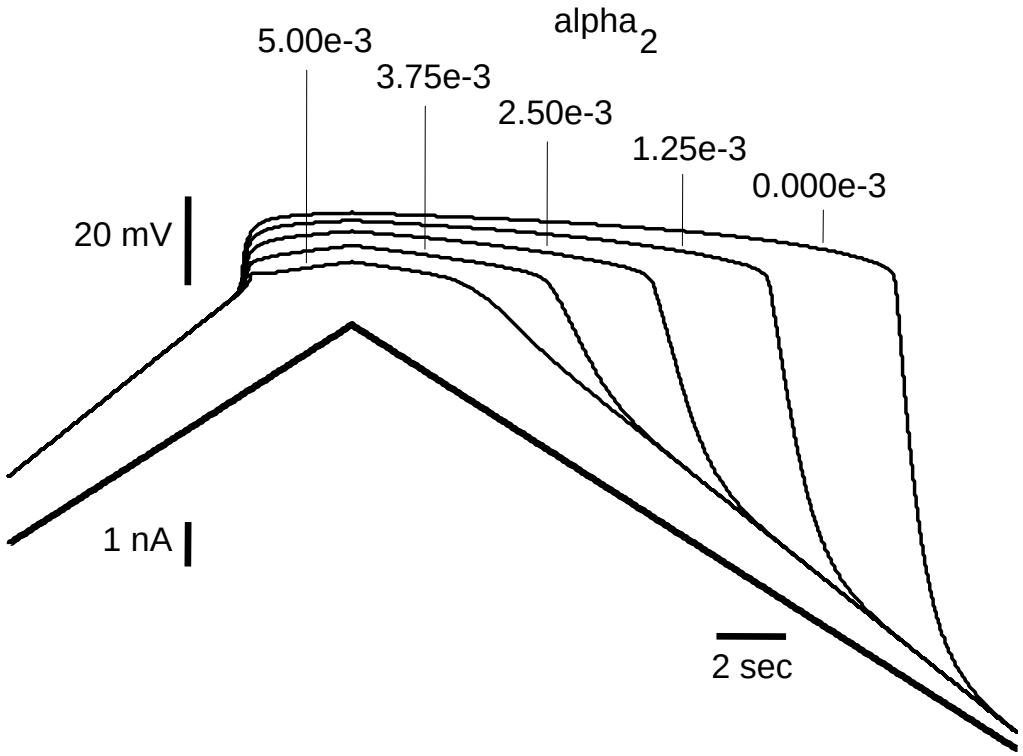

Fig. 2
(Graham et al.)

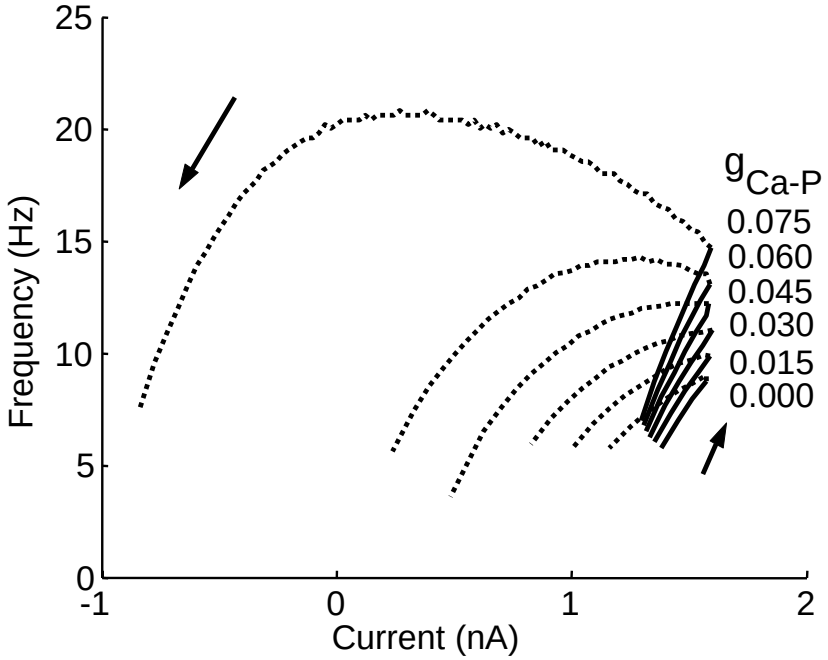

Fig. 3
(Graham et al.)