Analyzing Ion Dynamics in Muscle Contraction: Expanding on Electrophysiology in the 1981 Morris-Lecar Model

UNC COLLEGE OF ARTS AND SCIENCES Mathematics

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Background

- Concentration of ions and changes in electrochemical gradients cause muscle contraction.
- Calcium, potassium, and sodium are the ions of interest.
- Na^+ influx starts the process.
- There are two sources of cytosolic Ca^{++}, intracellular storage in the sarcoplasmic reticulum (SR) and extracellular environment.
- Ca^{++} is essential for binding myosin and subsequent muscle contraction.
- K^+ activity repolarizes the cell, restoring homeostasis

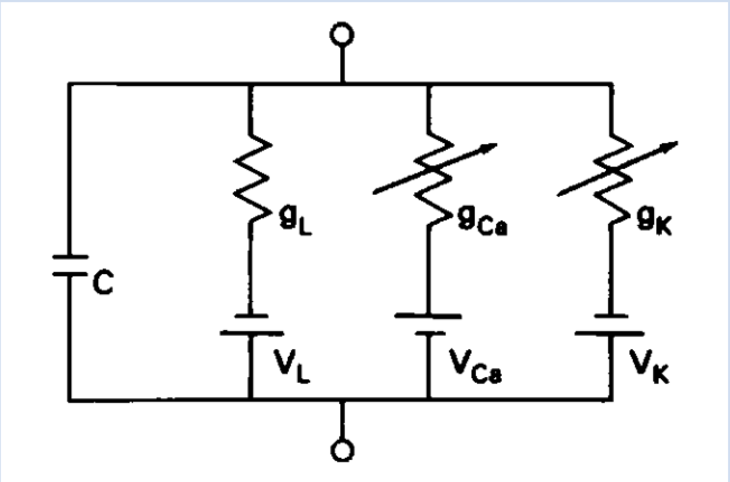

Figure 1. Morris-Lecar model for noninactivating conductances, analogous to an electrical circuit

Original Model

$$\frac{dV}{dt} = C^{-1}[I - g_L V_L + g_{Ca} M V(V - V_{Ca}) + g_K N V(V - V_K)] \quad (1)$$

$$\frac{dM}{dt} = \lambda_M(V)[M_\infty(V) - M] \quad (2)$$

$$\frac{dN}{dt} = \lambda_N(V)[N_\infty(V) - N] \quad (3)$$

For the potassium-only (ion specific) model, we drop the calcium term $g_{Ca}MV(V - V_{Ca})$ from (1), and do not use the ODE modeling Ca^{2+} (2).

$$\frac{dV}{dt} = C^{-1}[I - g_L V_L + g_K \mu V(V - V_K)] \quad (4)$$

$$\frac{d\mu}{dt} = \lambda_\mu(V)[\mu_\infty(V) - \mu] \quad (5)$$

Expanded Model

$$\frac{d[Ca^{2+}]_{SR}}{dt} = \frac{V_{max}[Ca^{2+}]_{cyt}}{[Ca^{2+}]_{cyt} + K_m} - P_{max}(1 - \exp[\frac{-t}{\tau_{on}}])\ \exp[\frac{-t}{\tau_{off}}]([Ca^{2+}]_{SR} - [Ca^{2+}]_{cyt})$$

$$\frac{d[Ca^{2+}]_{cyt}}{dt} = K[(CF)^{-1} g_{Ca} M_\infty(V) R] - \frac{V_{max}[Ca^{2+}]_{cyt}}{[Ca^{2+}]_{cyt} + K_m} + P_{max}(1 - \exp[\frac{-t}{\tau_{on}}])\ \exp[\frac{-t}{\tau_{off}}]([Ca^{2+}]_{SR} - [Ca^{2+}]_{cyt})$$

$$\boldsymbol{\frac{dV}{dt} = C^{-1}[I - g_L(V - V_L) + g_{Ca} M_\infty(V) R]}$$

$$electrodiffusion\ term\ (R): \frac{V(1 - \frac{[Ca^{2+}]_{cyt}}{[Ca^{2+}]_{ext}} \exp\left[\frac{V}{12.5}\right])}{1 - \exp\left[\frac{V}{12.5}\right]} \qquad reuptake: \frac{V_{max}[Ca^{2+}]_{cyt}}{[Ca^{2+}]_{cyt} + K_m}$$

$$release: P_{max}(1 - \exp[\frac{-t}{\tau_{on}}])\ \exp[\frac{-t}{\tau_{off}}]([Ca^{2+}]_{SR} - [Ca^{2+}]_{cyt})$$

Results

Simulations of Expanded Model

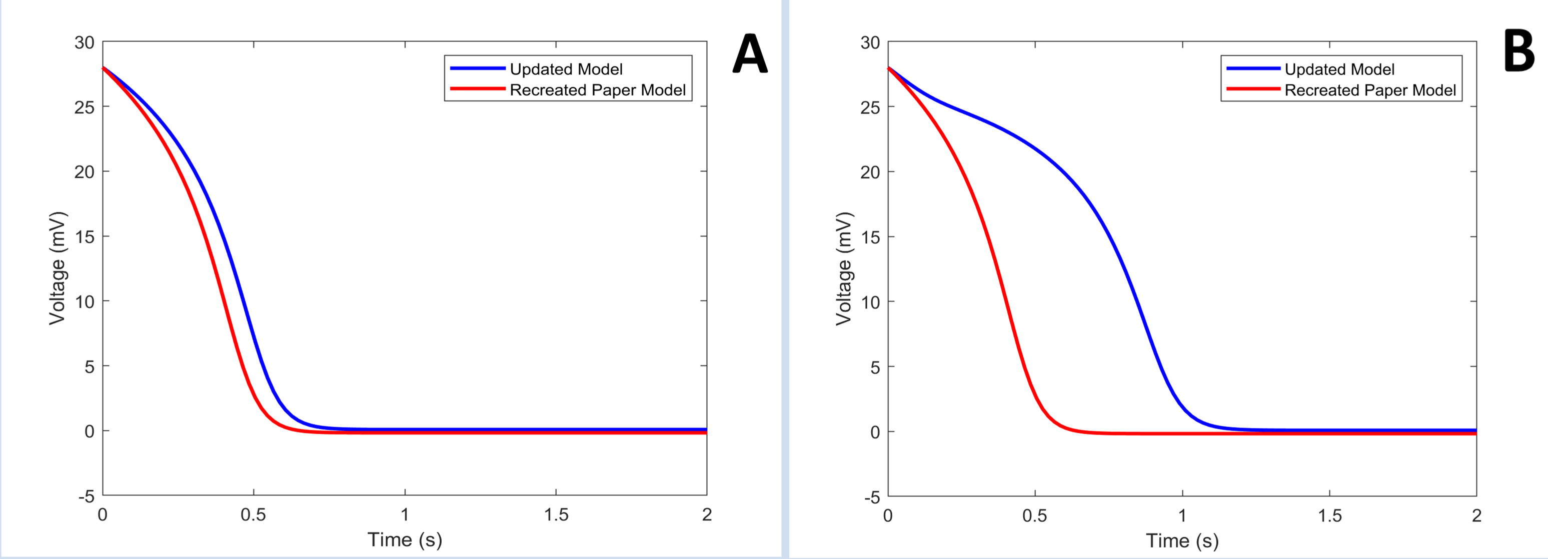

Figure 2: Model Comparison. MATLAB computed plot. Numerical solution for voltage in the 3-ODE expanded system. The parameters were as follows: Pmax = 60, Vmax = 4, τon = 1, τoff = 5, KM = 0.5, gCa = 40, gL = 2, K = −10−4, VL = −35 Initial conditions for voltage, calcium, and cytosolic calcium were 28, and 0.001 respectively. **A) Ignoring storage.** SR concentration set to 0**. B) Separated cytosolic and SR system.** Initial storage set to 20.

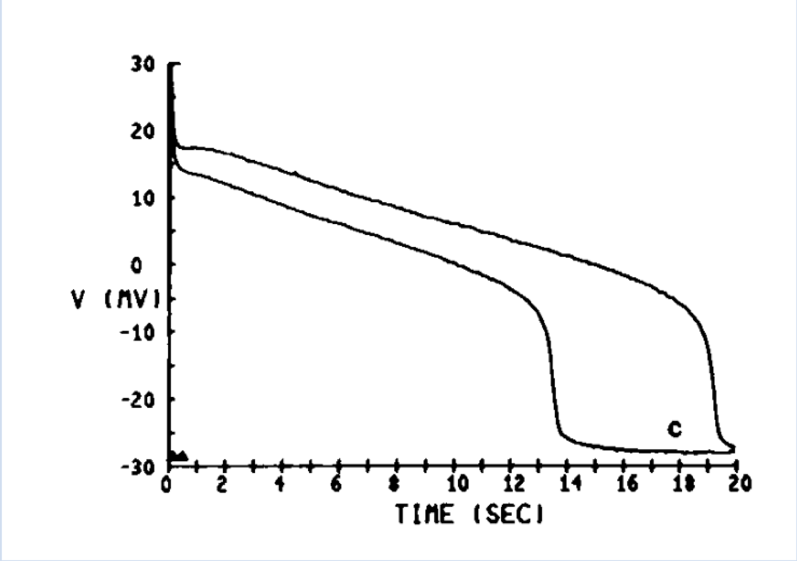

Figure 4: Original experimental Morris-Lecar data for Ca++. only voltage dynamics. Description from Morris-Lecar: Responses of a fiber to two subsequent current stimuli (360 µA) 1 min apart (upper trace first). Durationof the stimulus is 100ms.

Stability Analysis of Original Model

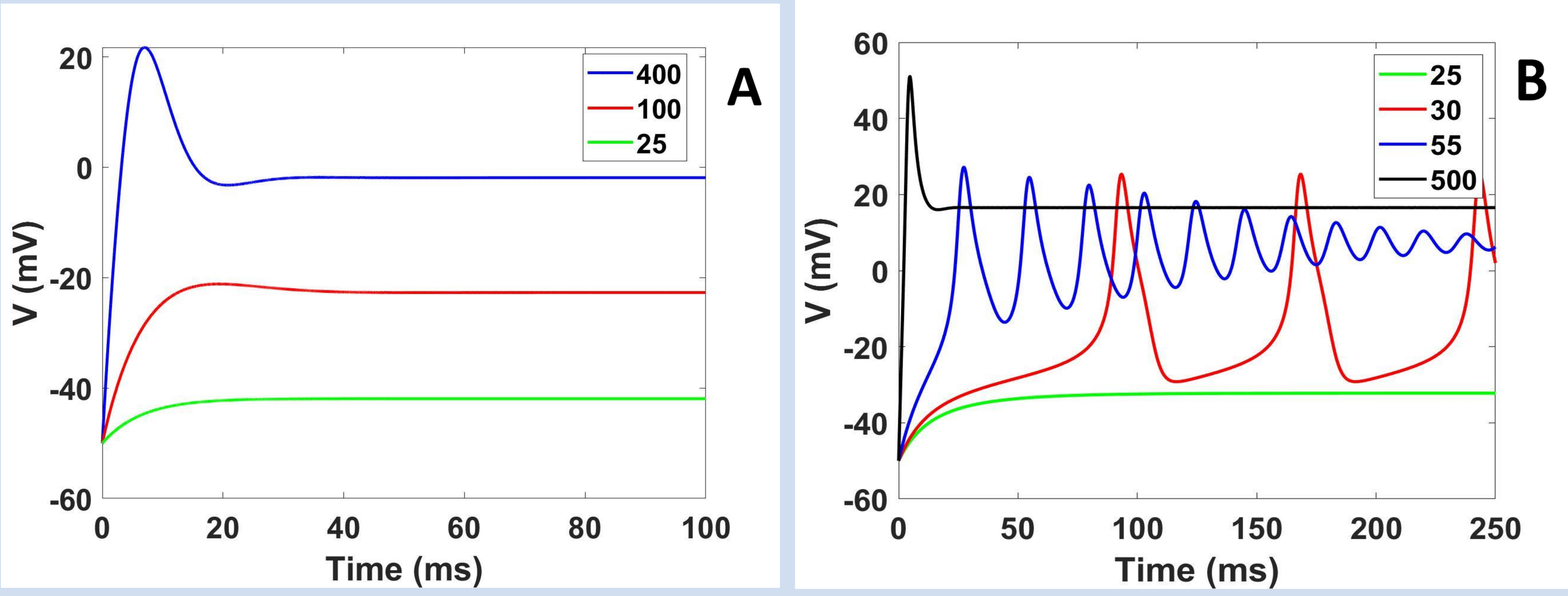

Figure 4. Plateau Potentials and Oscillations. MATLAB computed model for voltage response to increasing applied current with initial conditions: V(0) = -50, N(0) = Ninf (-50), and M(0) = Minf (-50). **A) K+ Only System.** The plot represents numerical solutions to the reduced 2-ODE model (Eqns. 4 & 5) for I = 25, 100, and 400 µA. The other parameters used for the system were as follows: gK = 8, gL = 3, V3 = -1, V4 = 14.5, λN = 1/15, VL = -50, and VK = -70. **B) Joint K+ and Ca++ system.** The plots represent numerical solutions to the 3-ODE system (Eqns. 1-3) for I = 25, 30, 55, and 4500 µA with values for the parameters as follows: gK = 12, gCa = 6, gL = 2, V1 = 0, V2 = 15, V3 = 10, V4 = 10, λN = 0.1, λM = 1, VL = -50, VK = -70, VCa = 100.

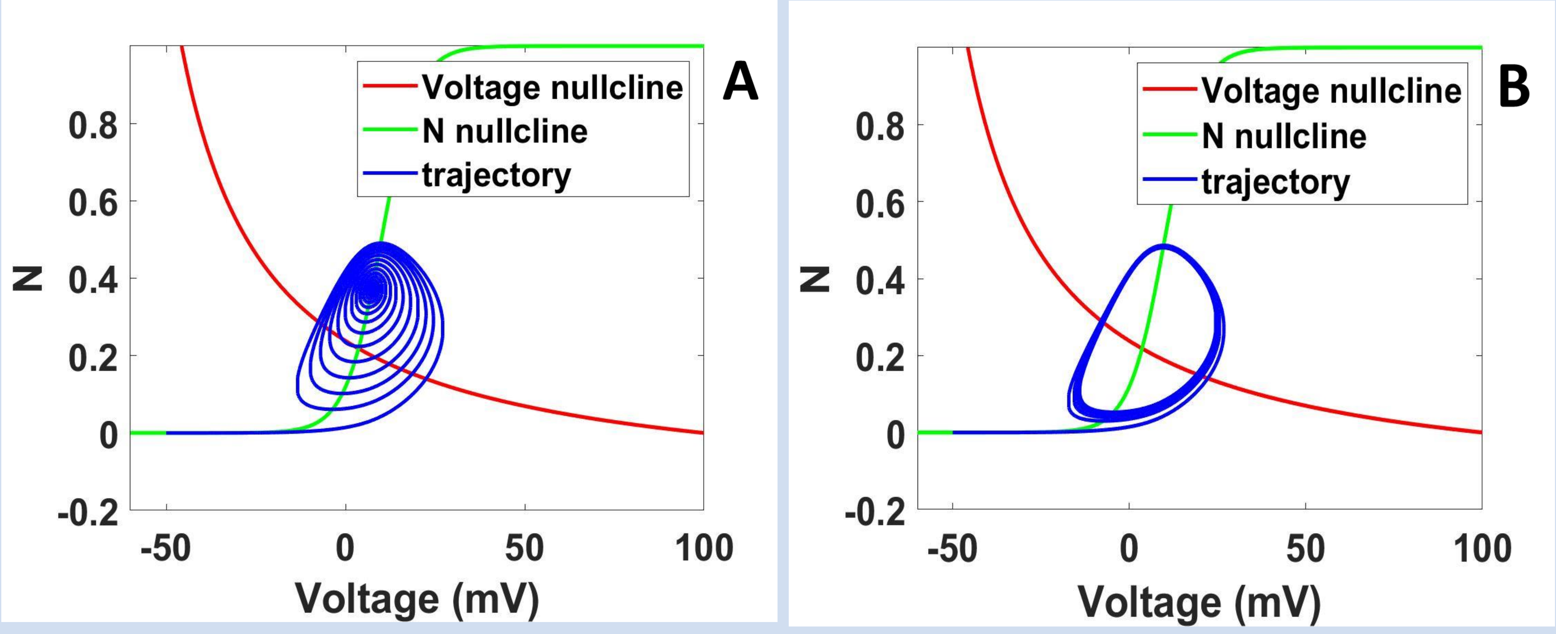

Figure 5. Example Trajectories Computed for the Joint K+ and Ca++ System. MATLAB computed model for voltage response to various applied currents with nullclines for the ODE system also plotted. The plots represent numerical solutions to the full V, M, N ODE system (Eqns. 1-3) with values for the parameters as follows: gK = 12, gCa = 6, gL = 2, V1 = 0, V2 = 15, V3 = 10, V4 = 10, λN = 0.1, λM = 1, C = 20, VL = -50, VK = -70, VCa = 100. And the initial conditions used for the system were V(0) = -50, N(0) = Ninf (-50), and M(0) = Minf (-50). **A) Limit Cycle Oscillation**. ODE system with parameters listed above and applied current of 30 µA. **B) Damped Oscillation.** ODE system with parameters listed above and applied current of 55 µA.

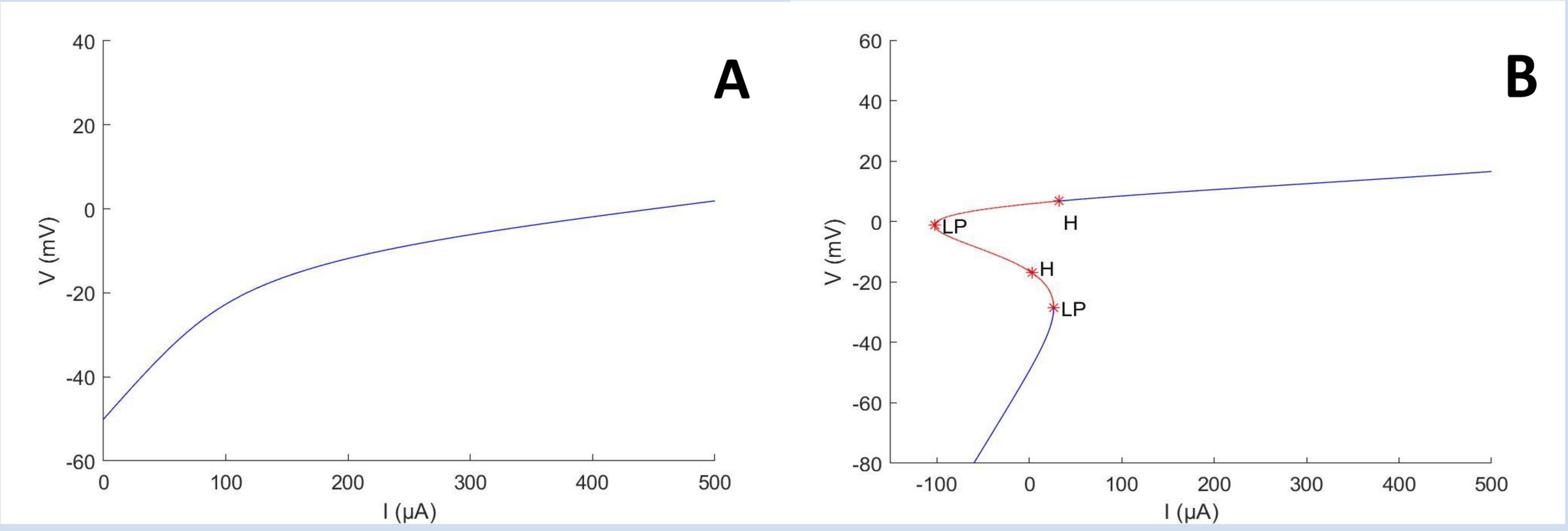

Figure 6. Bifurcation Diagrams for Ion Systems. Matcont computed bifurcation plot model for voltage response to parameter (I) applied current. Stable steady-states with a blue trace and unstable points in the system with a red trace and limit points are labeled LP and Hopf bifurcation points are labeled H. Initial conditions: V(0) = -50, N(0) = Ninf (-50), and M(0) = Minf (-50). **A) Bifurcation diagram for the K+ system.** The bifurcation plot uses solutions from Eqns. 15 and 16 for parameters as follows: gK = 8, gL = 3, V3 = -1, V4 = 14.5, λN = 1/15, C = 20, VL = -50, and VK = -70. **B) Bifurcation diagram for the joint K+ and Ca++ system.** Uses solutions from Eqns. 12, 13, and 14 for parameters as follows: gK = 12, gCa = 6, gL = 2, V1 = 0, V2 = 15, V3 = 10, V4 = 10, λN = 0.1, λM = 1, C = 20, VL = -50, VK = -70, VCa = 100.

Future Directions:

- Capturing more complex oscillatory behaviors not observed with the current model, such as: oscillations that grow over time, bistable oscillation patterns, and amplitude modulated oscillations
  - The perfect space clamp approach of the Morris-Lecar model might oversimplify the intricate dynamics
- Investigating ion accumulation and additional conductances not accounted for in the current model

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