

Bistability in Hodgkin-Huxley-type equations

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Abstract—We study how initial conditions of the Hodgkin-Huxley model affect the dynamics of simulated neurons. We systematically vary the amplitudes of depolarization currents in order to bring neuron dynamics to stable equilibrium. Our results demonstrate that simulated neurons can have spontaneous spiking or a silent state, depending on the initial conditions. We propose the methodology to study the circumstances under which Purkinje cells transit between hyperpolarized quiescent state (down state) and a depolarized spiking state (up state). We show that results derived using the Hodgkin-Huxley methodology should be carefully analyzed before suggesting a direct relevance to neuroprosthetic implants.

BACKGROUND

Soon after publication of Shannon’s seminal paper “A Mathematical Theory of Communication” [23], several research groups developed theoretical foundations of the application of information theory in neuroscience [2], [17], [20]. The framework included the use of neural information constraints [2], limits on information capacity in neurons [17], and the concept of neurons as relay elements in an information processing system [20]. Neurons encode sensory information in the spike train transmitted from one neuron to another. Models of spike train generation include integrate-and-fire neurons, Hodgkin-Huxley neurons, and others.

The Hodgkin-Huxley model, originally modeling action potential generation in the giant squid axon [12], is widely used in computational neuroscience [3], [8], [9], [15], [22], [29] and to study responses of neurons to electrical stimulation in medical bionics applications [1], [18]. Hodgkin and Huxley’s paper proposed a relatively simple mathematical theory to fit a model of differential equations to experimental data, and was quickly recognized as ground breaking work that led to the Nobel Prize in 1963. The theory accounts for the shape and time propagation of the action potential based on voltage-clamp *in vitro* data by modeling time- and voltage-dependence of ion conductances and gating parameters. The original form of the Hodgkin-Huxley model described three ion channels: sodium, potassium, and the leak. The model can be easily adapted to include other types of ion channels, such as mixed cation, persistent, and low-voltage activated currents [25], [26], [27].

Mathematical aspects of Hodgkin-Huxley-type equations have been widely studied [3], [4], [5], [24]. The existence of chaotic solutions in the Hodgkin-Huxley model with

its original parameters was investigated by Guckenheimer and Oliva [10]. They showed that there is a degree of unpredictability in the system’s response to current injection. The nonlinear nature of action potentials leads to an inherent lack of predictability to determine how much stimulation current is required for the system to cross the threshold for firing.

The Hodgkin-Huxley model with high intracellular potassium was studied by Jahangiri and Durand [14]. They showed that elevation of the potassium equilibrium potential leads to oscillations in the membrane potential and gating parameters for sodium and potassium currents. In addition, the authors predict the exact amplitude, duration, and timing of a single anodic pulse injection to stop spontaneous activity in the Hodgkin-Huxley model [14].

Bistable dynamics in the Hodgkin-Huxley model was investigated by several research groups [6], [7], [11]. Durand and Jahangiri [6] extended results from Jahangiri and Durand [14] and predicted exact stimulus parameters and timing that suppresses spontaneous spikes in hippocampal slices with high extracellular potassium.

Fukai and coauthors [7] investigated the bifurcation structure in $I_{\text{ext}} - V_K - V_{\text{Na}}$ space, where I_{ext} is an applied stimulus, and V_K and V_{Na} are reversal potentials for potassium and sodium currents, respectively. Hang and Durand [11] showed that a stable limit cycle and a stable fixed point coexist in the Hodgkin-Huxley model and investigated the effect of perturbations on the high-potassium model activity. The effect of initial conditions on the model dynamics was not investigated in these papers.

In this work, we study how initial conditions of the Hodgkin-Huxley model affect the dynamics of simulated neurons. In addition, we systematically vary the amplitudes of depolarization and hyperpolarization currents in order to bring simulated neurons to stable equilibrium. We show that, depending on the initial conditions, simulated neurons can have spontaneous spiking or a silent state.

We propose that our investigation has relevance to the electrophysiology of Purkinje cells. Purkinje cells have two resting membrane potential states: a hyperpolarized quiescent state (down state, no spiking) and a depolarized spiking state (up state). Up states in Purkinje cells are not sustained by synaptic activity; the persistence of two states is maintained by the intrinsic electrophysiological properties of the cell membrane [16]. This bistability has been observed from *in vitro* and *in vivo* recordings, in anesthetized animals, and in slices [16], [19], [21]. It has been proposed that bistability in Purkinje cells plays a key role in the short-term processing and storage of sensory-motor information.

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To simulate Purkinje cells, we use the Hodgkin-Huxley-type formalism. The same methodology can be extended to model other cell types.

Hodgkin-Huxley formalism is often used to study the response on neurons to electrical stimulation. Such methodology is often used in computational neuroscience and biomedical engineering in application to neuroprosthetics. Our work shows that due to the sensitivity of the equation dynamics to the initial conditions, results obtained using Hodgkin-Huxley methodology should be carefully considered before implying direct relevance to neuroprosthetic implants.

METHODS

We used computer simulations in NEURON [13] to investigate bistability of the neuronal resting state. We simulated single compartment neurons and used the Hodgkin-Huxley-type formalism to study how initial conditions affect neuronal response. We systematically applied intracellular current pulse stimulation to set the membrane potential to different levels and observed the neuronal dynamics after the stimulation was released. We summed leak, sodium, slow activating, A-type, calcium-activated potassium, and hyperpolarization-activated currents using Kirchoff's law. Sodium and three types of potassium currents are often present in spiking neurons; also, it was shown that hyperpolarization-activated current is present in rat cerebellar Purkinje neurons [28].

The membrane equation was

$$C_m \frac{dV}{dt} = \bar{g}_L(V - V_L) + \bar{g}_{Na} m^3 h (V - V_{Na}) \\ + \bar{g}_{Ca} c^3 (V - V_{Ca}) \\ + (\bar{g}_K n^4 + \bar{g}_{K,A} p^3 q + \bar{g}_{K(Ca)}) (V - V_K) \\ + \bar{g}_h l (V - V_h) + I_{stim},$$

where V is the time-dependent membrane potential, C_m is the specific capacitance of the membrane, and \bar{g} is the maximum conductance of an ionic current defined by its subscript. Leak, sodium, calcium, delayed rectifier potassium, A-type, and Ca-activated potassium currents had dynamics as in [8]. The hyperpolarization-activated current was modelled as in [27]. These currents were included to illustrate bistability in Purkinje cells. I_{stim} is an intracellular stimulation current. We did not include synaptic currents in the model. The only reversal potential that was allowed to vary with time was V_{Ca} [8],

$$V_{Ca}(t) = \frac{RT}{2F} \ln \left(\frac{[Ca^{2+}]_e}{[Ca^{2+}]_i(t)} \right),$$

where $F = 9.684 \cdot 10^4$ C/M is the Faraday constant, $R = 8.314$ J/(M·K) is the gas constant, and T is temperature in Kelvin. The extracellular calcium ion concentration is constant: $[Ca^{2+}]_e = 1.8$ mM. The dynamics of the intracellular calcium ion concentration was described as:

$$\frac{d[Ca^{2+}]_i(t)}{dt} = \frac{-3I_{Ca}(t)}{2Fr} - \frac{[Ca^{2+}]_i(t) - [Ca^{2+}]_{res}}{\tau_{Ca}},$$

where $r = 0.1$ μ m and $\tau_{Ca} = 1.5$ ms is the time constant for the calcium current.

Gating variables m, h, c, n, p, q, l of the voltage-gated ionic currents were described as:

$$\frac{dx}{dt} = -(\alpha_x + \beta_x)x + \alpha_x,$$

where x is a gating variable. The expressions for the voltage-dependent rate constants α_x and β_x are in Table 2 in [15].

The numerical values for the parameters used in simulations are given in Table 1. Initialization values for gating parameters and membrane potential are given in Table 2. Parameters were chosen to produce spontaneous activity in the simulated neurons.

Table 1. Simulation parameters.

$T = 22^0$ C	$C_m = 1 \mu$ F/cm ²
$V_{Na} = 35$ mV	$\bar{g}_{Na} = 0.212084$ S/cm ²
V_{Ca} is variable	$\bar{g}_{Ca} = 0.01024$ S/cm ² S/cm ²
$V_K = -70$ mV	$\bar{g}_K = 0.01024$ S/cm ²
	$\bar{g}_{K,A} = 0.036$ S/cm ²
	$\bar{g}_{K(Ca)} = 0.00005$ S/cm ²
$V_L = -60$ mV	$\bar{g}_L = 0.00005$ S/cm ²
$V_h = 0$ mV	$\bar{g}_h = 6.58436e - 9$ S/cm ²

Table 2. Initialization values.

A depolarized spiking state	$V = -65$ mV
A hyperpolarized quiescent state	$V = -55$ mV
Initial value for gating parameters for both states	
	$m = 0.948968$
	$h = 0.00654266$
	$n = 0.786369$
	$p = 0.989877$
	$q = 0.00214715$
	$c = 0.801969$
	$l = 4.5022e-5$

The model employed a single compartment consisting of one segment, taken as a cylinder with diameter and length both 25 μ m. The standard Euler numerical integration method with time step 0.025 ms was used in the simulations. Responses of neurons to depolarization and hyperpolarization current injection were explored.

RESULTS

Results show that different initial conditions lead to different neuronal dynamics even when all other parameters in the Hodgkin-Huxley-type model are set the same. Figure 1 shows simulated neuron dynamics for different initial conditions. Subplots (a) and (b) illustrate membrane potential dynamics; subplots (c) and (d) show phase plots, i.e., the derivative of membrane potential plotted as a function of the potential. Subplots (a) and (c) illustrate up state dynamics, while subplots (b) and (d) show down state dynamics. Refer to the figure caption for more details.

Figure 1 illustrates the response of the system to depolarization current injections. Results show that depolarization current injection can transition the system from up-state into down-state, as illustrated by the black traces in Figure 1(b) and in Figure 2(c)-(e). Results show that the neural

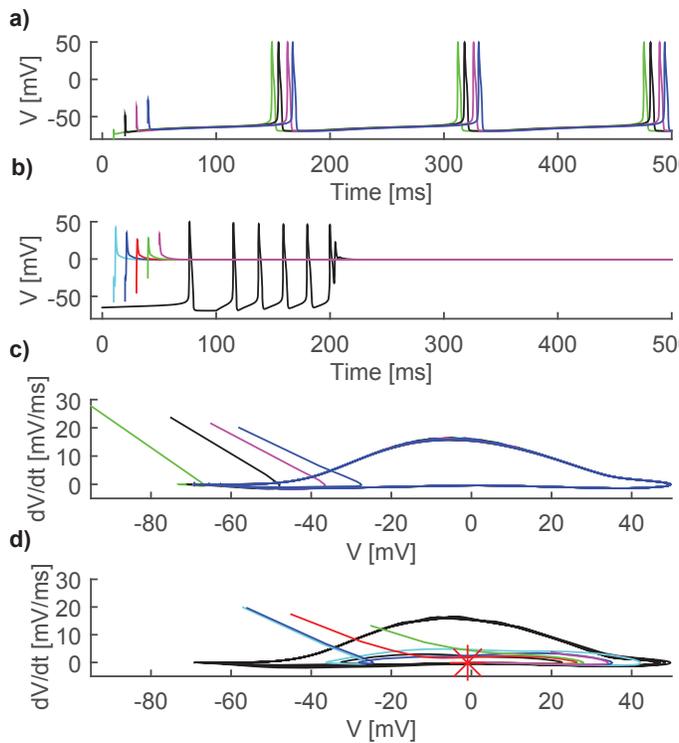


Fig. 1. Membrane potential dynamics (subplots a,b) and phase plot (subplots c,d) for different initial conditions. a) and c) Dynamics when initialized at up state. Initialization at -95 mV, -75 mV, -65 mV, -58 mV. b) and d) Dynamics when initialized at down state. Initialization at -57 mV, -56 mV, -45 mV, -25 mV, 20 mV and at -65 mV (up state) with a depolarization current 0.02 nA applied at 100 ms and released at 200 ms (black trace). In subplots a) and b) the traces are shifted by 10 ms for better visualization. The red star represents a stable point.

response after the end of pulse stimulation depends on the amplitude of the applied current. For some stimulation levels, the cells return to the level of the activity prior to stimulation (refer to Figure 2(b)), while for other levels, the neuronal dynamics are different to prior activity levels for a long duration post stimulation (Figure 2(c)-(e)). A large amplitude hyperpolarization current can bring the system back into the spiking state, as illustrated in Figure 2(e).

Dynamics of gating variables in response to pulse stimulation are shown in Figure 3. Results show that during down state, the activation variables for sodium, calcium, slow-activating, and A-type potassium currents are in open state (80% of channels are open), while inactivation variables for sodium and A-type potassium and the activation variable for hyperpolarization-activated are in closed state.

CONCLUSION AND DISCUSSION

This work demonstrates a potential method to explore the mechanisms underlying bistability in Purkinje cells. In particular, the proposed methodology allows the exploration of the circumstances under which Purkinje cells transit from the down state to the up state and return.

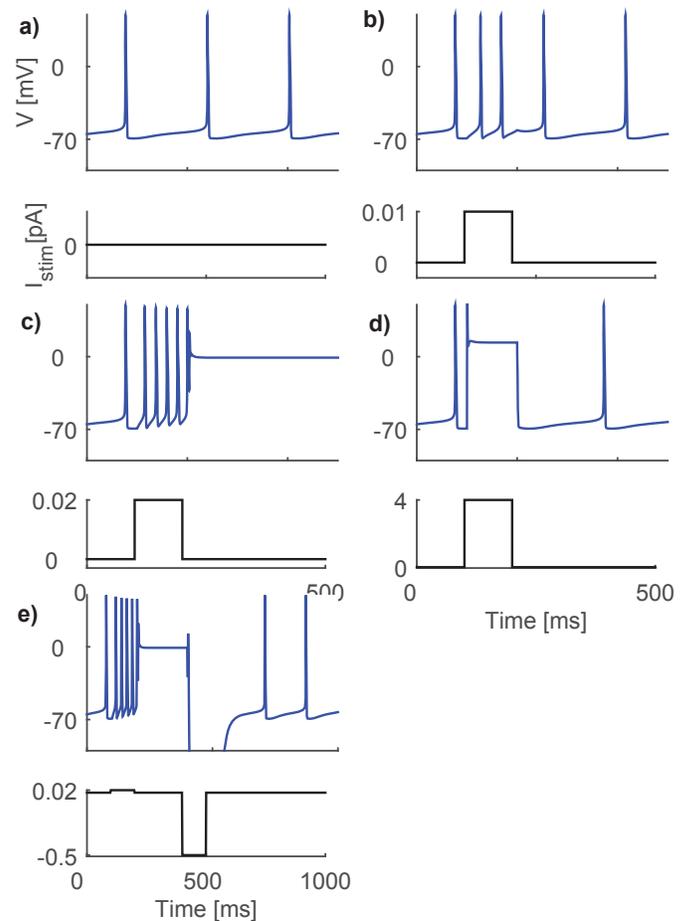


Fig. 2. Membrane potential dynamics in response to current stimulation of different amplitudes. a) 0 nA; b) 0.01 nA; c) 0.02 nA; d) 4 nA; e) 0.02 nA followed by -0.5 nA.

It has been shown that calcium current plays an important role in the state of the membrane potential and contributes to the complex spike waveform in Purkinje cells [21]. We did not investigate complex spike waveforms here. Williams and colleagues [28] proposed that hyperpolarization-activated current contributes to bistability in Purkinje cells. The effect of individual ionic currents on the transition from up state to down state was not investigated here and is left for future work.

Palmer and colleagues [19] showed that both complex and simple spikes are generated in the proximal axon in Purkinje cells. Our model includes a single compartment only; however, incorporating realistic cell morphology will not affect our qualitative results.

The framework proposed here can be used to investigate bistability in other types of neurons and in abnormal neuronal networks, i.e., bistability of neuronal systems observed with high-extracellular potassium in epilepsy patients.

Hodgkin-Huxley equations are often used to predict neu-

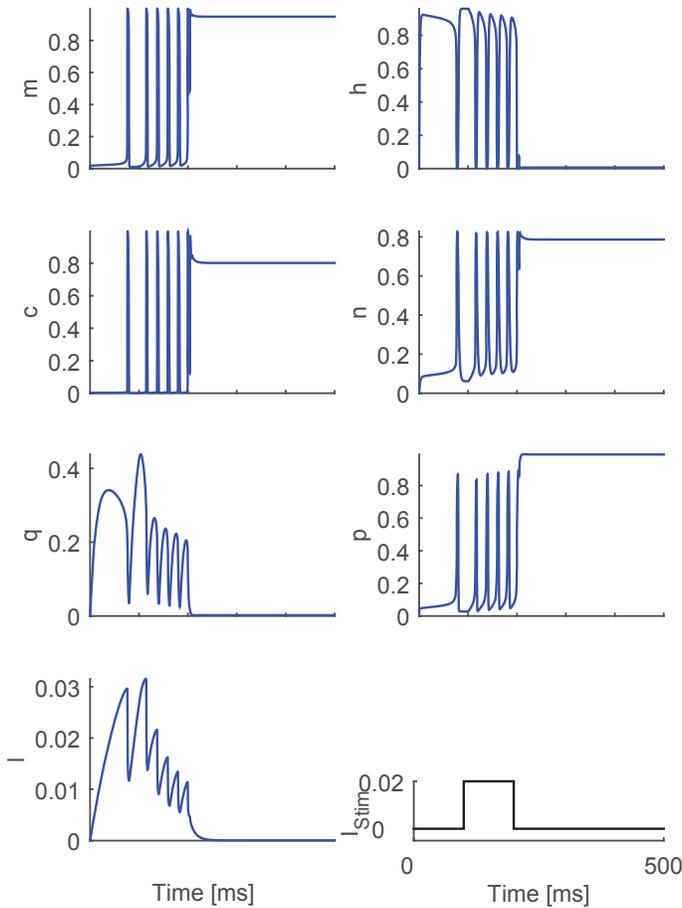


Fig. 3. Dynamics of gating variables m, h, c, n, p, q, l of the voltage-gated ionic currents in response to current stimulation of 100 ms, 0.02 nA amplitude.

ronal response to electrical stimulation in neuroprosthetics. Our work demonstrates that results obtained using the Hodgkin-Huxley formalism should be carefully considered since the choice of initial conditions may significantly affect the final outcome.

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