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Analysis of NMDA-dependent voltage bistability in thin dendritic compartments

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Abstract

We analyze the parameter ranges under which the voltage in a dendritic cable model exhibits bistability. We find (1) the magnitude of NMDA and GABA conductances limit the maximum cable diameter for which the system is bistable. For the investigated parameter ranges, the maximum diameter scales linearly with conductance. (2) NMDA current in the absence of GABA inhibition is not capable of generating bistability. (3) For small cable diameters (~0.1 μm), the bistable equilibra of membrane potential occur at −33.3 and −79.2 mV, independent of the NMDA and GABA conductance.

Keywords: Bistability; Hippocampus; CA1; Gating; NMDA

1. Introduction

Recent experimental and theoretical evidence suggests that dendrites may serve as active computational devices [14,15]. Supporting this idea is evidence for dendritic spikes [19–23], non-linear computations [15], backpropagating action potentials [26] and active Na^+, Ca^{2+}, K^+ and synaptic channels including NMDARs in dendrites [5,8]. Moreover, evidence has been reported for bistability of dendritic membrane potentials induced by NMDAR activation [19,24,25]. Schiller et al. [18,19] have recently shown that not only can Na^+ or Ca^{2+} spikes can be generated in dendrites, but NMDAR-induced spikes occur as well. Coactivation of clustered neighboring basal inputs into cortical pyramidal neurons initiated local dendritic spikes. In contrast to sodium or calcium spikes, they were mediated mostly by NMDARs. Depending upon the amount of NMDARs, three qualitatively different behavioral regimes are observed: 'boosting', 'bistable' and 'self-triggering' [19]. The conditions under which such bistability can occur have not been analyzed, to our knowledge, other than a charge transfer effectiveness study in bistable dendrites [9].

As is well-known, the current–voltage curve for NMDA receptors is non-linear with a negative slope conductance region caused by a voltage-dependent magnesium block [12]. It is this negative slope conductance that enables NMDARs to induce bistability in the membrane voltage. We investigated bistability regimes using a simple cable model. To make the bifurcation analysis tractable, the dynamics of the postsynaptic potential and the magnesium block were simplified by removing the time dependency. This allows the model to be cast as a dynamical system of the form $dV/dt = F(V, \alpha)$, where the function F is time independent and depends upon V and a multidimensional parameter, α. Formulation of the problem in this manner allows us to apply bifurcation analysis [6,10]. Removal of the time dependency can be justified, to first order, by the relatively long-time constants of NMDA and $GABA_B$ activation. The $GABA_B$ component in our simulation represents feedforward inhibition.

We model the Schaffer collateral afferents to pyramidal cells in the hippocampal CA1 area, which are known to

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contain NMDARs in abundance [16]. These synapses are localized at apical dendrites in stratum radiatum layer.

2. Construction of the model

The model consists of a cable divided into $N = 19$ compartments (numbered 1–19). The total length of the cable $L = 1000\,\mu\text{m}$. The diameter of $d\,\mu\text{m}$ is constant across all compartments and is a free parameter of the simulation. Passive membrane parameters are set to values used for CA1 pyramidal cell models [3]: specific axial resistance $R_A = 100\,\Omega\,\text{cm}$, specific capacitance of $C_M = 1\,\mu\text{F/cm}^2$. The leakage current has a reversal potential set at $E_L = -65\,\text{mV}$ and a specific conductance of $R_M = 33\,\text{k}\Omega\,\text{cm}^2$. Only the middle compartment (number 10) is endowed with NMDA and GABA synapses, all other compartments are passive. The NMDA current is modeled after Jahr and Stevens [7] with the double exponential time envelope removed. The NMDA current has an instantaneous magnesium block modeled by a sigmoid function of voltage. The reversal potential is set to $E_{NMDA} = 0\,\text{mV}$. The steady-state conductance G_{NMDA} (in pS) is a free parameter of the simulation. The upper limit of number of NMDARs in a 50 μm length of dendrite was calculated by assuming 2 receptors per spine [13] and 1.19 spines per 1 μm [17], which gives 119 receptors. Single channel recordings report an NMDA conductance of 60 pS [4]. We therefore vary G_{NMDA} in the range 600–6000 pS. The GABA current has a reversal potential of $E_{GABA} = -100\,\text{mV}$ [11] and a steady-state conductance G_{GABA} in pS that is a free parameter of the simulation. Bifurcation analysis is performed in CL_MATCONT [2] implemented in MatLab (Mathworks, Inc.) to determine parameter regimes for the three variables (d, G_{NMDA}, G_{GABA}) under which bistability would be observed.

We characterized the dynamics of the membrane voltage in all 19 compartments by the following system of differential equations:

$$C_m \mathrm{d}V_1(t)/\mathrm{d}t = -G_l(V_1(t) - E_L) + (V_2(t) - V_1(t))/R_a,$$

$$C_m \mathrm{d}V_{19}(t)/\mathrm{d}t = -G_l(V_{19}(t) - E_L) + (V_{18}(t) - V_{19}(t))/R_a,$$

$$C_m \mathrm{d}V_i(t)/\mathrm{d}t = -G_l(V_i(t) - E_L) + (V_{i+1}(t) + V_{i-1}(t) - 2V_i(t))/R_a \quad \text{for } i = 2, \ldots, 9, 11, \ldots, 18,$$

$$C_m \mathrm{d}V_{10}(t)/\mathrm{d}t = -G_l(V_{10}(t) - E_L) + (V_{11}(t) + V_9(t) - 2V_{10}(t))/R_a - I_{NMDA} - I_{GABA},$$

$$I_{NMDA} = G_{NMDA} V_{10}(t)/(1 + 0.336\,\exp(-0.06 V_{10}(t))),$$

$$I_{GABA} = G_{GABA}(V_{10}(t) - E_{GABA}),$$

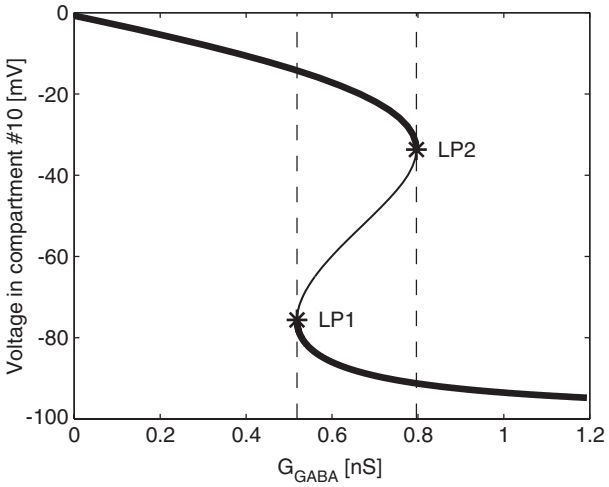

Fig. 1. Equilibrium manifold of the system for $G_{NMDA} = 6000\,\text{pS}$ and $d = 0.1\,\mu\text{m}$. Points LP_1 and LP_2 (asterisks) are limit points where the system has a fold bifurcation. Thick lines denote stable equilibria and the thin line unstable equilibria.

$$C_m = 10^{-2}\pi \mathrm{d} L C_M/N, \quad G_l = 10^{-2}\pi \mathrm{d} L/R_M,$$
$$R_a = 10^{-5} 4 R_A L/(N\pi \mathrm{d}^2),$$

where $V_i(t)$ is the membrane potential of the compartment i, with initial condition $V_i(0) = V_{init}$ for $i = 1, \ldots, 19$.

3. Results

We analyze how bistability depends upon the three parameters d, G_{NMDA}, and G_{GABA}, and will examine these parameters in turn. We begin by setting the NMDA conductance in compartment number 10–6000 pS and the cable diameter d to 0.1 μm. Then, for a given value of G_{GABA} the system will converge from any initial condition V_{init} to some equilibrium value, called a steady state of the membrane voltage. As shown in Fig. 1, when the parameter G_{GABA} is in the range (0, 0.51852) or $(0.796587, +\infty)$ pS, the system has one global equilibrium (thick line). But when $0.5185 < G_{GABA} < 0.796587$, the system has three equilibria: two stable (thick lines) and one unstable (thin line). Depending upon the initial condition V_{init} the system will approach either the upper equilibrium or the lower equilibrium.[1] The stable equilibria decrease with the parameter G_{GABA}. The transition points where stable and unstable branch merge, labeled on the Fig. 1 by LP_1 and LP_2, are *limit points*, and are of most interest as the system exhibits bistability behavior for parameter G_{GABA} in the range between these limit points. At these points the system has a co-dimension 1 fold bifurcation. The locations of these points depend upon the choice of G_{NMDA} and d.

Let us now keep d fixed but allow G_{NMDA} to be a free parameter. The set of the limit points has a "V" shape (Fig. 2, the thin lines). The region inside this area is the set

[1] Theoretically the system can stay at the unstable equilibrium when initiated there, but it is biologically implausible.