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Non-linear Recovery of Neuronal Excitability in the Inter-pulse-intervals of High-frequency Stimulation-A Modeling Study

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***Abstract*—High-frequency stimulation (HFS) of pulses has been used in deep brain stimulation (DBS) to treat neurological diseases. The inter-pulse-interval (IPI) of HFS is one of the critical parameters to dominate the stimulation efficacy, not only because IPIs determine pulse rates but also because the IPIs are commonly too short to allow neuronal state to recover completely during sustained HFS. Therefore, varying IPI can generate various neuronal reactions. However, the recovery of neuronal excitability along with the time of IPI is not clear. In this study, we investigated the recovery progress by utilizing a computational model of a myelinated neuron. The results show a non-linear recovery of the neuron to obtain re-firing ability during sustained HFS, which is dominated by the non-linear dynamics of sodium channels in the axonal membrane.**

I. Introduction

DBS has been successfully used for treating movement disorders by utilizing HFS with a pulse rate around 100 Hz. To improve DBS therapy and to extend its applications, new stimulation paradigms with varying IPI have been tried in clinic [1]. However, the underlying mechanisms of varying IPI have been inconclusive. We hypothesized that non-linear recovery dynamics of neuronal membranes under the stimulation could determine the neuronal responses to varying IPIs. Here, we verified the hypothesis by a neuron model with a mechanism of potassium accumulation during HFS [2].

II. Method and Materials

The neuron model was created in the NEURON 7.5, including a soma, dendrites and a myelinated axon with 21 nodes. The electrical field of biphasic-pulses applied by a bipolar electrode was simulated by COMSOL Multiphysics 5.3. The neuron is located below the stimulation electrode in a certain distance, for instance, with its center node ($Node_{10}$) ~104 μm from the bottom center of the electrode (Fig. 1A). Details of the model have been reported previously [2]. To test the re-firing ability of the neuron immediately after sustained 100 Hz HFS (10 s, 0.3 mA), a test pulse was delivered in different timings of 5 - 13 ms, termed as interval (Fig. 1B).

III. Result and Discussion

During the initial period of 10-s 100 Hz HFS, the neuron is able to respond to every pulse by firing an action potential (AP). Later, it can only fire one AP every two pulses (Fig. 1B) due to a slowed recovery of membrane depolarization by a potassium accumulation in the peri-axonal spaces [2]. Depolarization can cause inactivation of sodium (Na^+) channels described by the variable h (termed h_Na) in the famous HH model. The change of h_Na dominated the recovery of neuronal excitability, as showed by the h_Na curve after the final AP following the last pulse of HFS (Fig. 1C). A longer interval facilitated the recovery of membrane excitability and caused a greater depolarization potential (ΔV_m) following the test pulse. Only when the test pulse was applied after an interval longer than 12.5 ms was it able to induce a sufficient large depolarization potential in the axon, which successfully conducted along the axon and induced an AP in the soma (Fig. 1C & D & E).

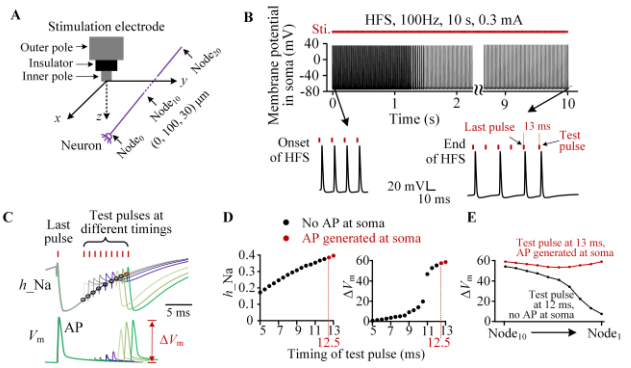

Figure 1. Simulation study of non-linear recovery of excitability of a neuron after sustained HFS. (A) Schematic diagram of the locations of a stimulation electrode and a neuron. The center of the neuronal axon ($Node_{10}$) is located 30 μm below and 100 μm beside the center of the electrode bottom. (B) An example of membrane potentials in soma induced by each pulse of a 10-s 100 Hz HFS and by a test pulse delivered after HFS with an interval of 13 ms. (C) Superimposed curves of the variable h of Na^+ channels (h_Na) and the membrane potentials (V_m) at $Node_{10}$ induced by the last pulse of HFS and by test pulses delivered at a timing at 5, 6, 7, 8, 9, 10, 11, 12 or 13 ms after HFS. (D) The h_Na values at the delivery timings of test pulses with a temporal resolution of 0.5 ms (left) and the changes of membrane potentials ΔV_m at $Node_{10}$ induced by the test pulses (right). (E) The different outcomes of ΔV_m conductions for test pulses delivered at 12 and 13 ms.

The abrupt change of ΔV_m with an increase of interval and the bifurcation of ΔV_m along the axon nodes (Fig. 1E) suggest a nonlinear recovery in the IPI of HFS that provides clues for developing new stimulation paradigms.

References

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