Model-Based Design of Stimulus Trains to Increase Selectivity in CNS Microstimulation

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Abstract

The goal of this project was to design stimulus trains that would enhance selectivity between microstimulation of cells and axons in the central nervous system (CNS). Detailed computer-based models of CNS cells and axons were developed that accurately reproduced the dynamic firing properties of mammalian neurons. The results demonstrate that alterations in the stimulus frequency, based on differences in the post-action-potential recovery cycles of cells and axons, enabled differential activation of cells or axons equidistant from the electrode. This provides a useful tool for selective stimulation of the CNS and provides a basis for understand frequency-dependent outputs during CNS stimulation.

Introduction

Microstimulation in the central nervous system (CNS) can activate populations of neurons with greater specificity than is possible with larger electrodes on the surface of the spinal cord or brain [1]. The potential thus arises for electrical activation of intact neuronal circuitry, and in turn, generation of distributed and controlled motor outputs for application in neural prostheses [2]. In many regions of the CNS, cells and axons are intermingled and selective activation of targeted populations is required for device efficacy. The goal of this project was to develop techniques that would enable improved selectivity between activation of local cells and axons of passage.

The thresholds of cells and fibers in close proximity to the electrode are similar with conventional stimuli [3]. We have previously developed asymmetrical biphasic charge-balanced stimuli that increased the selectivity between local cells and axons [4], however this analysis was limited to single stimuli. Neural prostheses use trains of stimuli with frequencies of tens of Hz. Therefore, we developed computer-based models of local cells and axons that could reproduce the dynamic firing properties of mammalian CNS neurons. We then used these models to study the influence of stimulus frequency on selectivity between cells and axons of passage. The results demonstrate that the appropriate choice of stimulus frequency, based on the changes in excitability that occur following an action potential, provides another method to improve selectivity between neural elements in the CNS.

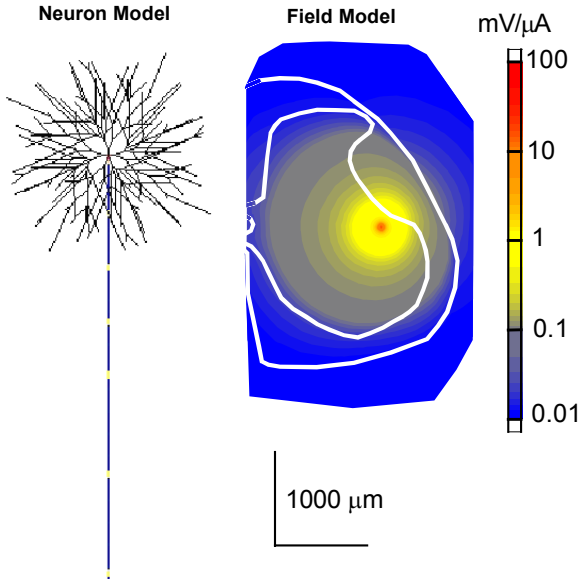

Figure 1: Integrated field-neuron model. The neural models developed in this study had a 3-dimensional architecture derived from experimental staining studies on mammalian motoneurons. The model included 610 individual compartments representing the dendrites, soma, initial segment, and myelinated axon. The potentials resulting from microstimulation were determined using a 3-dimensional finite element volume conductor model of the spinal cord. The potentials were then coupled to the model neurons to study excitation patterns.

Methods

This project used an integrated field-neuron model to study neural activation by stimulation with microelectrodes within the spinal cord (Fig.1). Three-dimensional (3-D) multi-compartment cable models of spinal motoneurons were generated with branching dendritic trees, multicompartment cell bodies and myelinated axons including explicit representation of the myelin sheath. The geometry and membrane properties of the neural models were based upon experimental results from mammalian motoneurons. A 3-D finite

element model of the spinal cord was used to calculate the potential distribution generated in the spinal cord by intraspinal electrodes. These potentials were then applied to the neuron models to predict excitation using equivalent intracellularly injected currents [4,5].

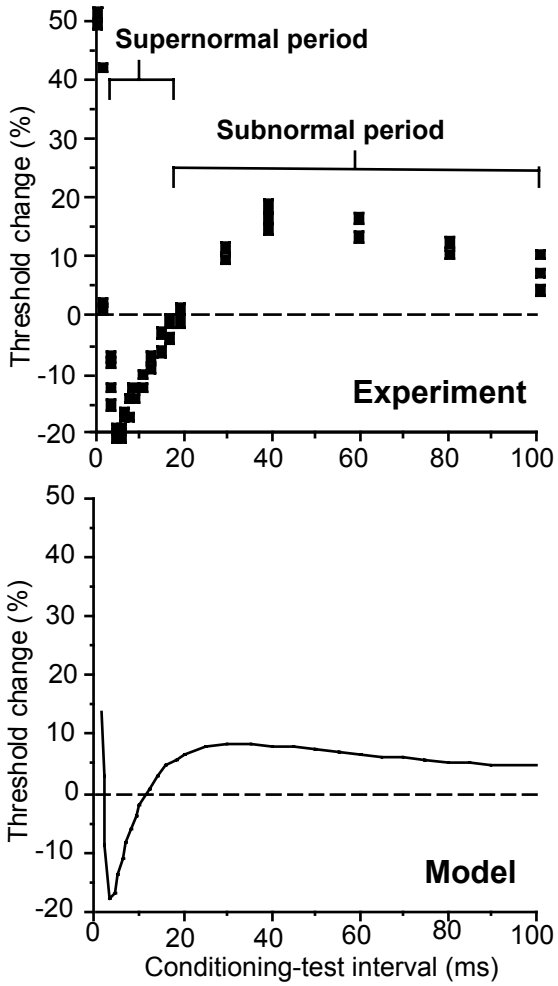

Figure 2: Recovery cycle of human myelinated axons measured experimentally [Kiernan et al., 1996] and generated by the model. The model accurately reproduced the changes in excitability that occur following an action potential.

Results

The neuron models were able to replicate a wide range of experimental data from mammalian motoneurons. Most importantly for dynamic firing properties, the models reproduced accurately the shape of the after-potentials in both the cell body and the axon. In mammalian neurons there are both depolarizing afterpotentials (DAP) and hyperpolarizing afterpotentials (AHP). In the cell body the DAP is 1-5 mV in amplitude and lasts for 3-7 ms. This is followed by an AHP 3-7 mV in amplitude and 30-60 ms in duration. Similarly, in the myelinated axon there is a DAP of 2-6 mV in amplitude and 14-18 ms in duration, followed by an AHP of 1-3 mV and 60-80 ms in duration. These afterpotentials effect the threshold for generation of subsequent impulses, and this change in excitability is commonly referred to as the recovery cycle (fig. 2). Our models were able to reproduce accurately the recovery cycle measured experimentally in both the cell body and axon. The models were also able to reproduce other dynamic firing properties including spike frequency adaptation and the firing frequency as a function of the amplitude of a long-duration constant current stimulus.

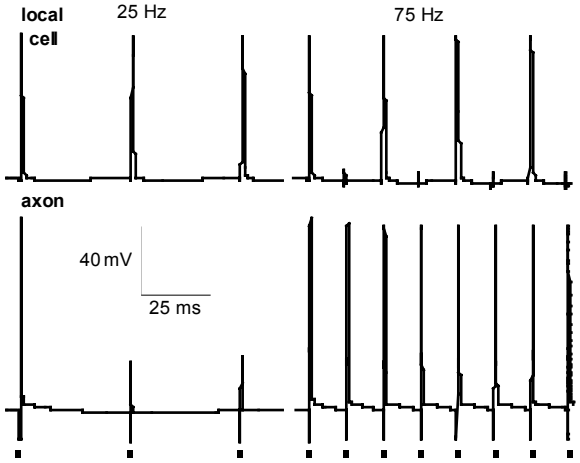

Figure 3: Frequency modulation enhances selectivity between local neurons. These example plots show the transmembrane potential as a function of time for the soma of one neuron near the electrode and an axon node of another neuron (fiber) passing by the electrode. Both of the neurons are activated by the initial stimulus, however changes in the stimulus frequency can alter the ratio of impulses transmitted to the end organ for both the target and non-target neuron.

The neuron models were used to predict excitation using charge-balanced trains of stimuli applied to the spinal cord model. We hypothesized that due to differences between the post-action potential recovery cycles of cells and axons, that selectivity could be enhanced by an appropriate choice of stimulus frequency. In fig. 3 is shown the response of the model cell and axon to a 25 Hz stimulus train and a 75 Hz stimulus train. Both the cell and the axon fire in response to the first stimulus pulse in both trains. The subsequent stimuli in the 25 Hz train fall within the subnormal period of the axon (fig. 2) and no further action potentials are generated in the axon, while the cell fires on every stimulus. Conversely, the axon fires on every stimulus in the 75 Hz train, while the cell fires on

only every other stimulus pulse. These results demonstrate that modulation of the stimulus train, in accordance with the recovery cycle of the targeted neural elements, can enhance selectivity between activation of cells and axons within the CNS.

Discussion/Conclusions

The goal of this study was to design stimulus trains that would enhance selectivity between microstimulation of cells and axons in the central nervous system. The results demonstrate that alterations in the stimulus frequency, based on differences in the recovery cycles of cells and axons, enabled differential activation of cells or axons equidistant from the electrode.

In our previous work we developed charge-balanced stimulus waveforms that were effective in activating targeted neuronal populations, however only single stimuli were considered. This study represents an extension of that work, examining the effects of trains of stimuli. Studying the effects of stimulus frequency on excitation patterns required models that were able to reproduce accurately the dynamic firing properties of the neurons being stimulated. The development of the neuron models used in this study allowed for the first time, an accurate response to stimulation frequencies greater than 10 Hz. The results demonstrate that manipulation of the non-linear conductances of the neural membrane can enable selective activation of targeted neuronal populations, and this manipulation can be accomplished by the stimulus waveform as well as the stimulus frequency.

The results also provide insight into the effect of stimulus frequency on arrest of tremor by high-frequency stimulation of the thalamus (deep brain stimulation). It has been observed that low frequency stimulation of the thalamus drives rather than suppresses tremor. At higher frequencies (> 80 Hz) tremor is arrested, with a nadir in the stimulus amplitude-frequency tuning curve at ~ 125 Hz [7]. The present results demonstrate that local neurons will be activated preferentially at low frequencies, thus exacerbating the tremor, while high frequency stimulation will preferentially activate axons. There are large numbers of pre-synaptic GABAergic axons in the thalamus, and preferential activation of these axons by high frequency stimulus trains may inhibit tremor activity in thalamocortical cells.

References

[1] Ranck (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* 98:417-440.

[2] Barbeau et al. (1999). Tapping into spinal circuits to restore motor function. *Brain Res. Rev.* 30:27-51.

[3] Gustafusson and Jankowska (1976). Direct and indirect activation of nerve cells by pulses applied extracellularly. *J. Physiol. (Lond.)* 258:33-61.

[4] McIntyre and Grill (2000). Selective micro-stimulation of central nervous system neurons. *Ann. Biomed. Eng.* 28:219-233.

[5] Warman et al. (1992). Modeling the effects of electric fields on nerve fibers: determination of excitation thresholds. *IEEE Trans. Biomed. Eng.* 39:1244-1254.

[6] Kiernan et al. (1996) Differences in excitability in sensory and motor axons of human median nerve. Brain 119:1099-1105.

[7] Benabid et al. (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337:403-406.

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