

From Neuronal Ionic Channels to Muscle Control: A Web-based Simulator and Its Application to Teaching

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Abstract—A Web-based simulator was developed as a tool to improve the understanding of the spinal cord neurophysiology and how it controls muscle activation. Besides researchers, instructors should also benefit from such a tool because it will allow the student to grasp phenomena and mechanisms at different levels, from the neuronal membrane to muscle behavior. The illustrations presented are focused towards teaching fundamental concepts that cover firing threshold, the effect of a slow potassium channel on neuron behavior, the train of action potentials generated by a neuron in response to an increasing injected current, the behavior of a motoneuron pool for an injected ramp current and the resulting force and EMG waveforms, and finally, the generation of the H reflex.

Index Terms—Computational neuroscience, mathematical modeling, neurons, simulation.

I. INTRODUCTION

The integration of knowledge from several levels of complexity is a continuous challenge in the teaching of biology and biomedicine. In neuroscience much is known about ionic channels but their integrated actions on neuronal behavior are less well understood. Synaptic dynamics have also been well studied, but how they affect the collective behavior of a population of interconnected neurons is difficult to grasp. Muscle force is controlled in complex ways by the recruitment of motor units and their firing patterns. The EMG and spinal reflexes arise from the multiple activity of motor units in response either to voluntary drive or external stimulation to a nerve. Therefore, there are important neuromuscular phenomena and mechanisms that are generated at different levels and need to be well understood if an overall picture is to emerge.

A Web-based simulator is proposed here as a useful tool for teaching some of the complexities listed above. The simulator is appropriate for neuroscience, biomedical engineering or systems biology courses and may be used from any browser by entering the site <http://remoto.leb.usp.br>. Neuron models permit the investigation of how the dynamics of certain neuronal channels affects the firing patterns of the neuron. The effect of one neuron on another may be studied because the

parameters of the synaptic dynamics may be changed in the simulator and the membrane potential of the postsynaptic cell may be visualized. The network structure adopted is that of the mammalian spinal cord because it forms the basis for understanding how muscle control is achieved in humans. The simulator can be used to compare the network behavior with or without a certain type of interneuronal feedback, with a smaller or larger number of motoneurons, and with different synaptic features. Finally, the motoneuron pool output drives muscle fibers that produce simulated electromyogram and force, which can, therefore, also be analyzed. The basic philosophy of the simulator is presented in what follows, as well as a few illustrative examples of its use for teaching purposes.

II. THE SIMULATOR

The simulator represents mathematically the motoneuron pools that activate the following leg muscles: soleus, gastrocnemius medialis, gastrocnemius lateralis and tibialis anterior. Each motoneuron pool receives synaptic contacts from: descending tracts, afferents from the periphery and from interneurons. Each motoneuron drives a motor unit which generates electrical activity (a motor unit potential) and force twitch. Fig 1 shows a block diagram of one motoneuron pool and its inputs and outputs.

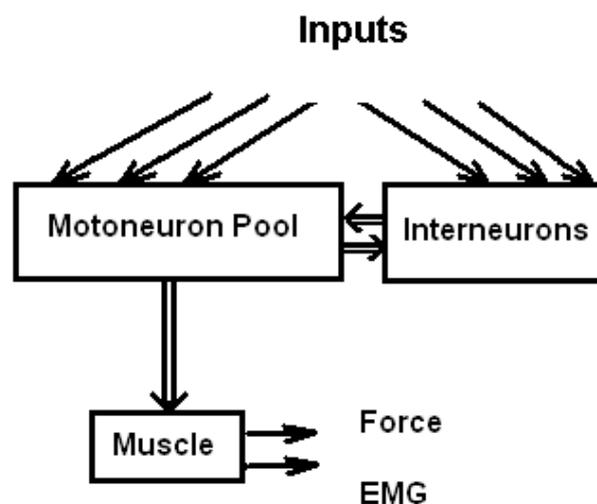


Fig 1 – Interrelationship between the main blocks that define the control of a given muscle in the simulator. The inputs which are available in the simulator are: injected current,

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electrical stimulation to sensory and motor axons, spike trains from descending tracts representing brain activation. Each motoneuron is modeled as a two-compartment system, with active channels in the somatic compartment and passive channels in the dendritic compartment (Fig 2). The somatic compartment has fast sodium and potassium channels and a slow potassium channel besides a leakage channel. The slow potassium channel is responsible for the characteristic

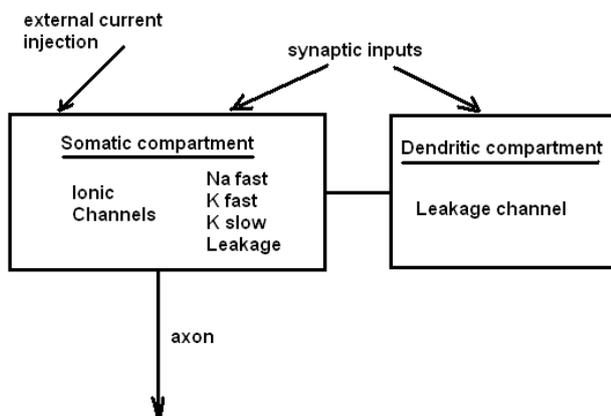


Fig 2 – Block diagram of motoneuron model composed of two compartments.

afterhyperpolarization (AHP) found in mammalian motoneurons. The neuron may be excited by current injection in the soma. Synaptic inputs may be applied to the somatic and dendritic compartments. Interneurons are modeled using a single compartment having ionic channels similar to that of the motoneuronal soma. The dynamics of this compartment follow a very fast implementation that approximates the Hodgkin-Huxley formulation [1]. The neuronal parameters were estimated from the cat literature and are probably well suited to humans too [2]. The synapses may either have a standard behavior or they may have depression when activated repeatedly. The dynamics of depression follows a basic first order kinetic model [3] and cause a decrease in the amplitudes of excitatory postsynaptic potentials that occur in sequence. After a motoneuron has fired an action potential in the simulator, there is a delay until it reaches the muscle end plate. There it causes action potential firing which is represented in the simulator by an extracellular muscle fiber action potential recorded by surface electrodes (MUAP). The MUAP is modeled by Hermite-Rodriguez functions [4], which are then bandpass filtered in the simulator to represent what happens in a real electromyography machine.

Every time a motor unit fires an action potential (MUAP) there is a corresponding muscle fiber twitch (force pulse), which is represented in the simulator as the output of a critically damped second order system [5]. The muscle EMG is the sum of all MUAPs and the muscle force is the sum of all motor unit twitches.

Finally, the motoneuron pool may be driven by descending tracts from the brain (Fig 1), by the activity of afferent fibers or also by current injection in the soma. These last two modes are used to mimic what happens during experiments or clinical tests. In cat experiments, for example, current injection in the soma is employed to study the dynamic behavior of the motoneuron. In clinical neurophysiology,

nerve stimulation that activates the afferent and efferent fibers is used to elicit H reflexes and M waves [6].

More details about the mathematical modeling may be found in a paper by the same authors, which is under revision (Simulation system of spinal cord motor nuclei and associated nerves and muscles, in a web-based architecture, submitted to Journal of Computational Neuroscience). Information about the detailed structure of the network and further simulation examples may be found in the main page of the simulator and in the tutorials.

III. EXAMPLES

The first didactic example is to show the existence of a *firing threshold*, i.e., below a certain level of injected current the neuron does not fire and above it, it does. Fig 3a shows the membrane potential for a subthreshold injected current pulse, with duration 1 ms and 6.5 nA amplitude. The voltage threshold is near 8 mV and the membrane potential did not reach that value. The membrane potential waveform is that of a capacitor charging and discharging. Fig 3b shows the case for a suprathreshold stimulus, with 6.6 nA (duration 1 ms), which was able to discharge an action potential. Notice the different ordinates in the two Figs.

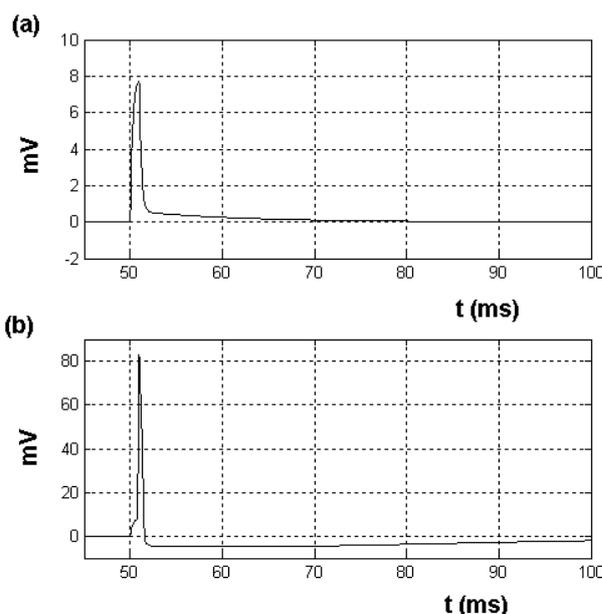


Fig 3 - Membrane voltage of a neuron in response to a subthreshold (a) and suprathreshold pulse of injected current.

The next example illustrates the effect of changing a parameter of an ionic channel that sets the duration of the AHP. Fig 4 shows the discharges of a motoneuron having the default parameter values for the slow potassium conductance (peak value of beta for slow K conductance= 0.025 ms⁻¹, in window “V-d conductances” in the simulator site).

This should be compared with Fig. 5 where a faster recovery of the slow potassium conductance was used (value 0.05 ms⁻¹ used for peak value of beta for slow K conductance, in window “V-d conductances”). Comparing Figs 4 and 5 it can be seen that the after-hyperpolarization (AHP) is slower in Fig. 4, which is the reason for the slower neuronal discharge rate. The faster recovery of the AHP in Fig 5 led to a faster discharge rate.

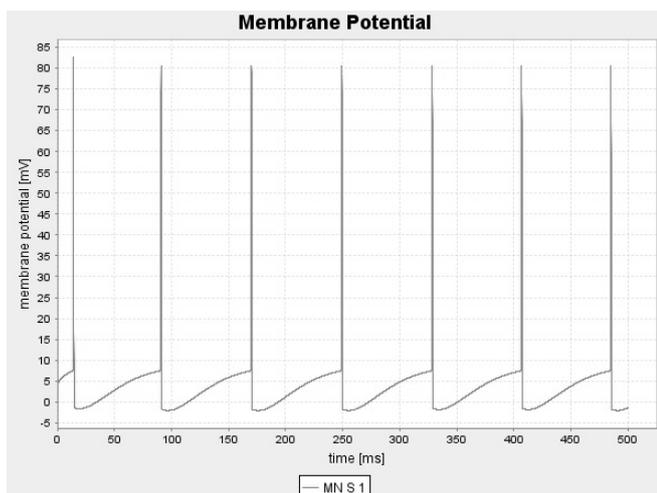


Fig. 4 Membrane potential of a neuron showing periodic discharges around 10 spikes/s and with

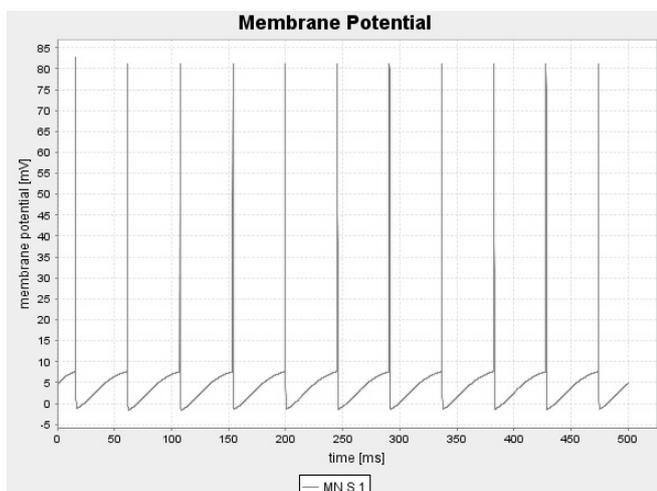


Fig. 5 The same neuron of Fig 4 with a faster recovery of the slow potassium conductance leads to a faster discharge rate (around 20 spikes/s).

The next property shown using the simulator is the increase in firing rate when a linearly increasing current is injected in the soma, as can be seen in Fig 6. It may be mentioned at this point that sensory neurons usually increase their firing rate when the stimulus intensity increases, the basis of this property being similar to that indicated in this example.

When the same current injection is applied to each motoneuron of a pool composed of 100 motoneurons, one can obtain the muscle force, which increases gradually (Fig 7 upper panel), and the firing times of each motoneuron of the pool, called the raster plot (Fig. 7 medium panel). This indicates that the motoneurons are recruited in their size order (Henneman's principle) and each increases its firing rate with time. The force reaches a steady state because all the motoneurons of the pool have been recruited. The bottom panel in Fig 7 shows the resulting EMG that would be recorded by surface electrodes attached to the muscle.

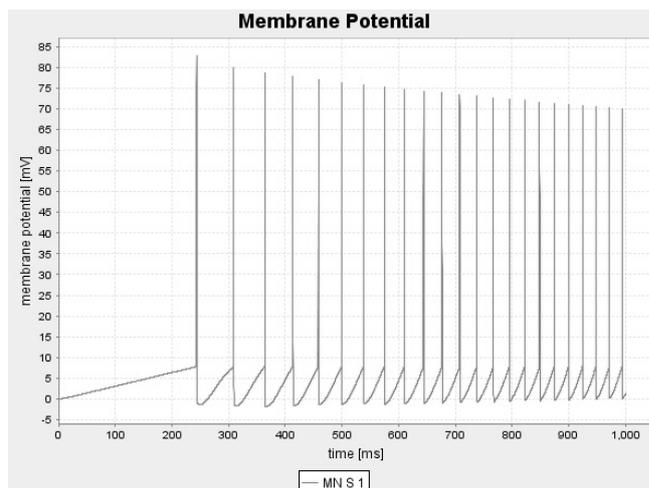


Fig 6 A motoneuron increases its firing rate when the amplitude of an injected current increases linearly from 0 to 15 nA during the interval from 0 to 1000 ms.

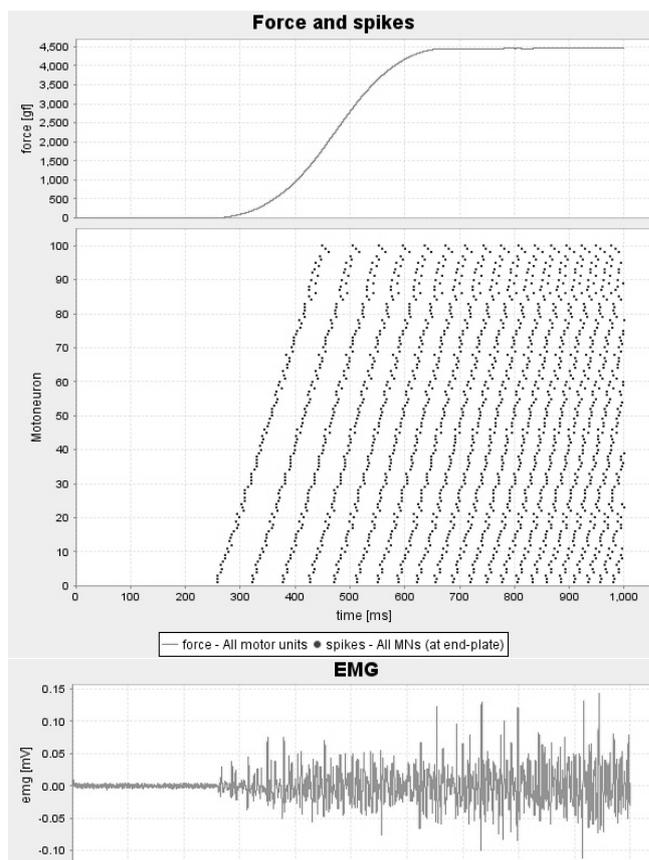


Fig 7 Same current injection as for Fig 6, now showing the force developed by a muscle (upper panel) innervated by 100 motoneurons. The middle panel shows the firing times (each point indicates an action potential firing) of the motoneurons ordered in the ordinate by their size. The lower panel shows the corresponding muscle EMG as recorded by surface electrodes, referred to the same abscissa as in the middle panel.

IV. CONCLUSION

A versatile Web-based simulator of the spinal cord neuronal networks associated with muscle control has been developed. The examples showed that it may be a useful tool also in the teaching of neuroscience because many concepts may be studied with great ease through the interactive windows. Although other simulators of the mammalian spinal cord are available in the literature [9-11] the present simulator has some advantages, such as: 1) close reproduction of many motoneuron properties; 2) the inclusion of nerve stimulation, which is relevant to clinical neurophysiology and studies with human subjects; 3) the interactivity by means of windows; 4) ready access through the Web.

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The last simulation example presented here is that of an electrophysiological experiment to obtain a human H reflex and an M wave from the soleus muscle (recordings are done in humans using surface electrodes positioned below the junction of the two heads of the gastrocnemii muscles). These waveforms are elicited through the stimulation of the posterior tibial nerve (PTN) at the popliteal fossa which activates Ia sensory fibers as well as motor fibers. The latter will be responsible for the generation of a small latency M wave (see Fig 8, waveform with latency about 5 ms). The Ia sensory fibers are also discharged by the nerve stimulus and will cause large EPSPs in the motoneurons. Many of these will fire, but only those motoneurons that did not have their axons fired antidromically by the electrical stimulus will be able to activate their respective motor units, therefore generating the H reflex (waveform in Fig 8 at latency around 30 ms) [6]. These waveforms are easily obtainable from the human soleus muscle. However, the detailed information of the firings of all the motor units, as shown in the lower panel of Fig 8, is technically unfeasible with today's technology.

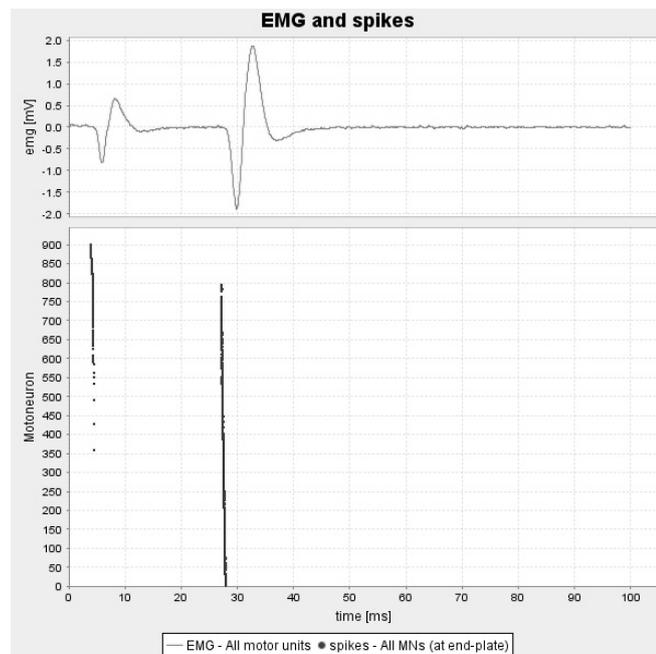


Fig 8 The upper panel show an M wave (latency around 5 ms) followed by an H reflex. These were elicited by a PTN stimulation of 13 mA (1 ms pulse duration). The lower panel shows the firing times of the motoneurons, ordered by size from the bottom to the top. The M wave is attributed mostly to the largest motor units and the H reflex is caused mainly by the smaller and medium-sized motor units. Although not visible, there is no double-firing of a given motor unit, i.e., each will contribute either to the M or to the H (or to none).

In a previous communication, these authors have studied the phenomenon of H reflex depression in response to trains of stimuli [7]. The data from the simulator suggested an alternative hypothesis to that originally put forward when the experiments were done in humans [8].