Proceedings of the 29th Annual International
Conference of the IEEE EMBS
Cité Internationale, Lyon, France
August 23-26, 2007.

H-reflex depression simulated by a biologically realistic motoneuron network

Rogerio R. L. Cisi and André F. Kohn

Abstract — **The H-reflex is frequently used both in the clinic as well as in research, with the purpose of providing a better understanding of the spinal cord. For repetitive stimuli (e.g. at 1 Hz) the H-reflex depresses, probably due to synaptic depression. Experimental results from the literature provided the basis for the simulations presented here. A large network of motoneurons connected to muscle fibers was modeled and implemented as a computer simulator. Afferent fibers that excited synaptically the motoneurons fired in response to a programmable stimulus. After an initial fitting to the experimental results was achieved, the analysis of which motor units contributed to the H-reflex in two different paradigms pointed to an alternative interpretation of the human data.**

I. Introduction

The H-reflex is the homologue of the stretch reflex, obtained by the electrical stimulation of the appropriate nerve. It can be obtained from many muscles, but it is most commonly studied in the soleus and flexor carpi radialis muscles. The volley of action potentials from the activated sensory fibers reaches the spinal cord and activates the excitatory synapses on the motoneuron pool. The firing of a fraction of the pool generates an efferent volley, which causes a contraction of the innervated muscle. An experiment to obtain the soleus muscle H-reflex is performed by placing a stimulation electrode over the tibial nerve at the popliteal fossa, and recording the resulting soleus electromyographic signal generated by the soleus muscle. Despite its apparent simplicity, this technique presents some complexities that inhibit its broader use in clinical neurophysiology [1]. On the other hand, H-reflex experiments have been largely used in research on the normal or pathologic spinal cord, because specific dynamics of interneuronal pathways may be estimated by appropriate conditioning of the H-reflex [2, 3].

When successive reflexes are elicited repeatedly, the reflex amplitudes decline consistently if the next stimulus is applied at an interval less than about 10 s [4]. This phenomenon, called H-reflex depression, is useful to assess the dynamics of the Ia reflex loop. For example, spinal cord injured patients present lower H-reflex depression than normal subjects [5].

This article presents a simulation study of H-reflex depression. The simulation software used presents the following features: easy usage for spinal cord investigators, flexibility to simulate distinct neural circuits and experimental paradigms, good time performance and possibility of saving personal configurations in a database. The simulator was designed as a web-based object-oriented system. Users can customize neural circuits, run simulations and obtain graphic and raw data results for further analysis. Programming and installations procedures are not required.

Floeter and Kohn [6] conducted a series of H-reflex experiments, showing that the magnitude of the H-reflex decline is greater when the amplitude of the H-reflex is small. Using a novel paradigm of a low amplitude train of stimuli followed in the sequence by a higher amplitude train of stimuli, they showed that nearly all the depression of larger H-reflexes could be accounted for by the depression of the same motor units involved in the smaller amplitude H-reflexes. The present simulation work aimed to replicate these experiments and permit a more thorough analysis of some of the spinal cord mechanisms involved.

II. Methods

The simulation software used in this work was developed in our laboratory [7] and will be described in detail in a future publication. The software allows simulation of circuits composed of motoneurons (MN), interneurons, descending tracts, sensory fibers, muscle fibers and their force and electromyogram (EMG). Each motoneuron model has two compartments, the soma having a firing threshold and K and Na conductances following the simplified Hodgkin-Huxley model proposed by Destexhe [8], but adapted to present the afterhyperpolarization (AHP) phenomenon. Sensory and motor axons are simple models that fire an action potential whenever stimuli overcome their thresholds. Orthodromic and antidromic conduction are simulated, as well as collisions, allowing for more realistic results.

For the proposal of this work, simulations were carried out for the soleus motoneuron pool, containing 800 motoneurons, 90% identified as S type and the remaining as FR and FF types. MNs are ordered (indexed) according to their sizes. In addition, there were 100 Renshaw cell interneurons, 400 Ia sensory fibers and 200 Ib sensory fibers.

Manuscript received March 30, 2007. This work was supported by FAPESP and CNPq (Brasil). R. R. L. Cisi is a recipient of a fellowship from FAPESP.

R. R. L. Cisi and A. F. Kohn are with Laboratório de Engenharia Biomédica, Universidade de São Paulo, São Paulo - Brazil (phone: 55-11-3091-5541; e-mails: rcisi@leb.usp.br - andfkohn@leb.usp.br).

MN model parameters had been adjusted previously in accordance with single MN experimental data from the literature [9, 10]. They were not altered in the current simulations. Axonal conduction velocity distribution among the totality of sensory and motor axons was adjusted according to available data from humans [11]. The only adjustments made for this work on the H-reflex were related to the motor-unit potential (MUP) amplitudes, and the sensory and motor axon thresholds of the stimulated nerve. When motor axons are discharged by nerve stimulation, the volley of action potentials propagating orthodromically generates a muscle compound potential which is known as the M-wave. The corresponding antidromically propagated action potentials end up colliding with the reflexively generated action potentials resulting in annihilation.

The MUP was modeled as a bandpass-filtered second-order Hermite-Rodriguez function [12], multiplied by a scaling factor. Small motor-units have small scaling factors, and big motor-units have higher ones. Table I shows the range of the simulated MUP amplitudes as recorded by surface electrodes. As the motor-units were sorted according to the size-order, new MNs recruited by an increase in stimulation will result in a larger contribution to the H-reflex. This results in a nonlinear relation between the H-reflex amplitude and the number of MNs that contributed to the H-reflex.

TABLE I
RANGE OF MUP AMPLITUDES

MN type	MN index	Amplitude range [mV]
S	1 to 720	0.01 to 0.02
FR	721 to 780	0.02 to 0.04
FF	781 to 800	0.04 to 0.06

The experimentally observed H-reflex depression has been attributed to the Ia-MN synaptic depression [4], which reduces the number of reflexively recruited MNs. In the simulator, each Ia-MN synapse was modeled using a kinetic approach [13], depression being obtained as follows: every time a new synaptic transmission occurs, a variable that models the synaptic conductance is decreased by a constant percentage $\boldsymbol{p}$ and returns to its resting value with a given time constant $\boldsymbol{\tau}$ [14-17]. The parameters $\boldsymbol{p}$ and $\boldsymbol{\tau}$ were kept the same for every synapse between the Ia afferents and all the MNs in the simulated pool.

Applying a sequence of stimulus pulses with constant intensity, width and period, the H-reflex amplitude declines from the maximum value, related to the first pulse, to a plateau, after five or six pulses. The observed decrease in H-reflex amplitudes is called H-reflex depression, also known as low frequency depression.

Pulses of lower amplitude (I_{LA}) were adjusted to cause H-reflexes of 20% of M_{max} amplitude (the maximum electrical output of the muscle for a single stimulus), and higher pulses (I_{HA}) were selected to cause H-reflexes of 50% of M_{max}, the same percentages used in the real experiments [6].

Three major simulations were carried out: in the *first* one, a 1 Hz train of 10 pulses (each pulse with 1.0 ms duration and intensity I_{LA}) was applied over the simulated tibial nerve, reaching sensory and motor axons that innervate the soleus muscle; the *second* simulation was similar to the previous, but the pulse intensity was raised to I_{HA}; the *third* simulation, following the paradigm proposed by Floeter and Kohn [6], was composed by a train of 20 stimulation pulses, the first 10 at I_{LA} and the last 10 at I_{HA}.

III. RESULTS

The H-reflex and M-wave recruitment curves (Figure 1) were obtained in a first step, as also done in human experiments. Previously, axonal thresholds for external stimulation had been adjusted so that curves compatible with those obtained in humans would result from the simulations.

Figures 2, 4 and 6 present the H-reflexes evoked at every 1 s, declining from the maximum response (first stimulus) to a plateau (last 5 stimuli). Figures 3, 5 and 7 show the indexes of the MNs contributing to the H-reflex and M-wave, generated in response to each stimulus pulse. Points in blue represent the MNs that contributed to the H-reflex and points in red those MNs that contributed to the M-wave.

Table II summarizes results of the simulations, comparing them with results obtained in real experiments [6]. As shown in this table, the decline in the amplitude of the H-reflex in the real and simulated cases was very close.

Table III presents the numbers of MNs contributing to the first H-reflex in the train and to the H-reflex in the plateau. It is interesting that approximately the same number of MNs were unrecruited due to synaptic depression during the lower (164 MNs) and during the higher stimuli (180 MNs) when applied each at a time. There are no experimental data to compare with, as it is not trivial to assess how many and which MNs are reflexively recruited in an H-reflex experiment.

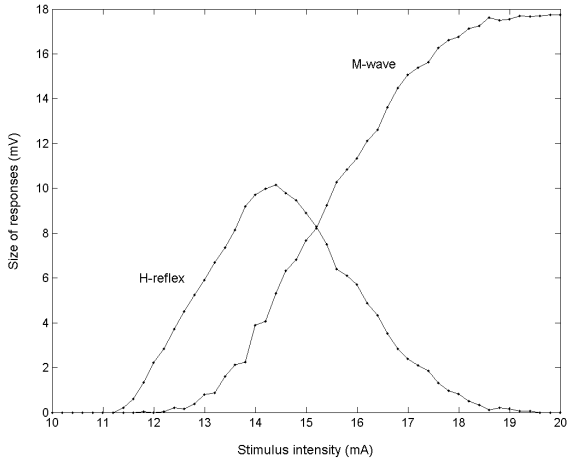

Fig. 1. H-reflex and M-wave recruitment curves. Peak-to-peak amplitudes are plotted against stimulus intensity.

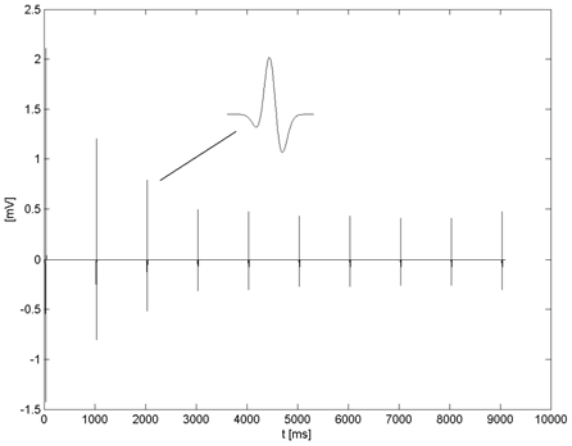

Fig. 2. H-reflexes evoked at every 1 s, with I_{LA} pulse intensity.

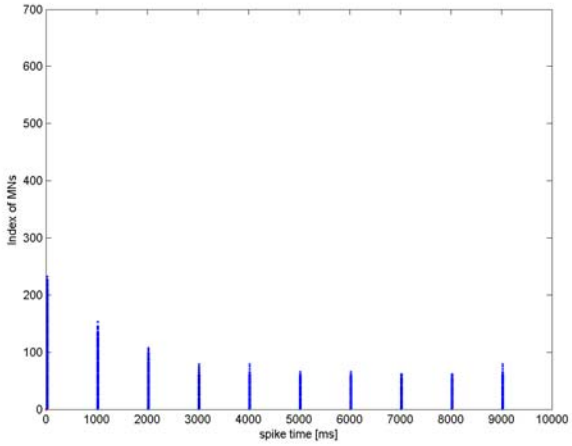

Fig. 3. Index of MNs recruited and their spike times, with I_{LA} pulse intensity. Blue points: H-reflex; Red points: M-wave.

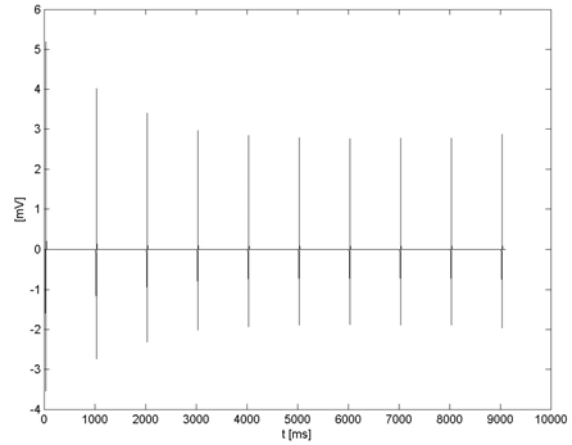

Fig. 4. H-reflexes evoked at every 1 s, with I_{HA} pulse intensity.

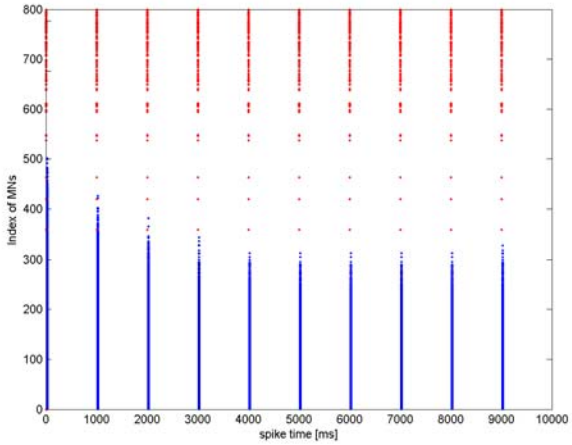

Fig. 5. Index of MNs recruited and their spike times, with I_{HA} pulse intensity. Blue points: H-reflex; Red points: M-wave.

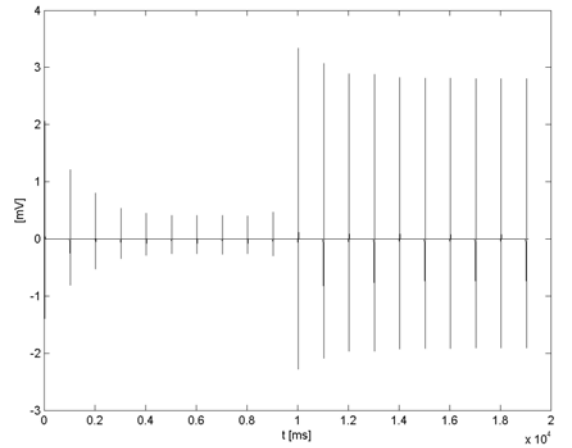

Fig. 6. H-reflexes evoked at every 1 s, with I_{LA} and I_{HA} pulse intensities.

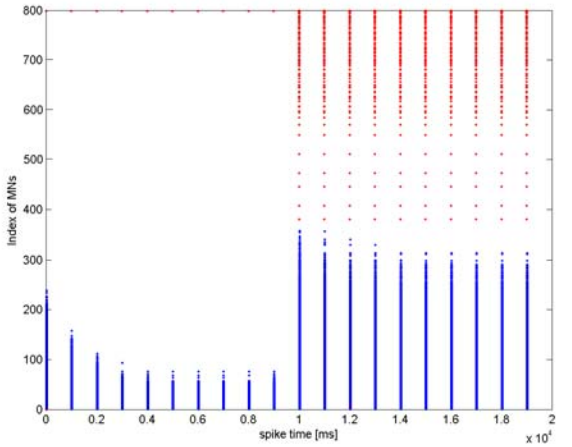

Fig. 7. MNs recruited and their spike times, with I_{LA} and I_{HA} pulse intensities. Blue points: H-reflex; Red points: M-wave.

TABLE II
H-REFLEX PEAK-TO-PEAK (% OF MMAX)

	Simulation		Experiment [6]	
Stimulus	1st pulse	plateau	1st pulse	plateau
lower	20.1	4.0	19.0	5.0
higher	49.6	26.4	50.0	22.0
both (1st – 10th pulse)	20.1	4.0	19.0	5.0
both (11th – 20th pulse)	31.9	26.7	25.0	20.0

TABLE III
NUMBER OF MNS CONTRIBUTING TO THE H-REFLEX – **SIMULATION**

Stimulus	1st pulse	plateau
lower	226	62
higher	468	288
both (1st – 10th pulse)	226	62
both (11th – 20th pulse)	330	287

IV. DISCUSSION

The simulations of the H-reflexes are capable of providing several measurements not available from the non-invasive human experiments. It is possible to characterize which motoneurons (indexed according to their sizes) discharged in the different experimental situations.

Focusing only on the decline of the H-reflex amplitude (the only data available in human experiments), a plausible hypothesis is that the depressibility of the earliest units is greater than that of the later activated units (Figs. 2, 4 and 6). However, *all* the synapses in the present simulations had the same depression dynamics. Therefore, the simulations results (third and fourth line of Table III and Figs. 6 and 7) suggest an alternative scenario, which could be occurring if the simulation parameters and hypotheses are not far from the physiological reality. The differential decrease in H-reflex amplitude between the two stimulation amplitudes (Table II: from 20.1 to 4.0 for the first 10 H-reflexes and from 31.9 to 26.7 for the last 10 H-reflexes) could be due to the fact that many medium or large sized motor units that could have been recruited by the first higher stimulation (11th pulse) were already with their input synapses in a depressed state. Comparing Figures 5 and 7, it is noticed that MNs with indexes in the range 360 through 500 have their synaptic inputs (from the Ia fibers) in a depressed state after the 10th pulse, and cannot be recruited when additional Ia fibers are discharged by the higher stimulus intensity.

It is expected that simulation results obtained from reasonably realistic models of the spinal cord neuronal network and the corresponding muscle(s) may prove to be valuable in the interpretation of electrophysiological data obtained from normal subjects or neurologic patients.

REFERENCES

[1] D. DUMITRU, *ELECTRODIAGNOSTIC MEDICINE*. PHILADELPHIA: HANLEY & BELFUS, 1995.

[2] J. P. A. DEWALD AND B. D. SCHMIT, "STRETCH REFLEX GAIN AND THRESHOLD CHANGES AS A FUNCTION OF ELBOW STRETCH VELOCITY IN HEMIPARETIC STROKE," PRESENTED AT INT. CONF. OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY, 2003.

[3] K. NAKAZAWA, T. MIYOSHI, H. SEKIGUCHI, D. NOZAKI, M. AKAI, AND H. YANO, "EFFECTS OF LOADING AND UNLOADING OF LOWER LIMB JOINTS ON THE SOLEUS H-REFLEX IN STANDING HUMANS," *CLIN NEUROPHYSIOL*, VOL. 115, PP. 1296-304, 2004.

[4] A. F. KOHN, M. K. FLOETER, AND M. HALLETT, "PRESYNAPTIC INHIBITION COMPARED WITH HOMOSYNAPTIC DEPRESSION AS AN EXPLANATION FOR SOLEUS H-REFLEX DEPRESSION IN HUMANS," *EXPERIMENTAL BRAIN RESEARCH*, VOL. 116, PP. 375-380, 1997.

[5] C. AYMARD, R. KATZ, C. LAFITTE, E. LO, A. PENICAUD, P. PRADAT-DIEHL, AND S. RAOUL, "PRESYNAPTIC INHIBITION AND HOMOSYNAPTIC DEPRESSION. A COMPARISON BETWEEN LOWER AND UPPER LIMBS IN NORMAL HUMAN SUBJECTS AND PATIENTS WITH HEMIPLEGIA," *BRAIN*, VOL. 123, PP. 1688-1702, 2000.

[6] M. K. FLOETER AND A. F. KOHN, "H-REFLEX OF DIFFERENT SIZES EXHIBIT DIFFERENTIAL SENSITIVITY TO LOW FREQUENCY DEPRESSION," *ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY*, VOL. 105, PP. 470-475, 1997.

[7] R. R. L. CISI AND A. F. KOHN, "SPINAL CORD NEURONAL NETWORK SIMULATOR," PRESENTED AT 28TH CONFERENCE OF THE CANADIAN MEDICAL AND BIOLOGICAL ENGINEERING SOCIETY, QUEBEC, CANADA, 2004.

[8] A. DESTEXHE, "CONDUCTANCE-BASED INTEGRATE-AND-FIRE MODELS," *NEURAL COMPUT*, VOL. 9, PP. 503-14, 1997.

[9] J. E. ZENGEL, S. A. REID, G. W. SYPERT, AND J. B. MUNSON, "MEMBRANE ELECTRICAL-PROPERTIES AND PREDICTION OF MOTOR-UNIT TYPE OF MEDIAL GASTROCNEMIUS MOTONEURONS IN THE CAT," *JOURNAL OF NEUROPHYSIOLOGY*, VOL. 53, PP. 1323-1344, 1985.

[10] J. W. FLESHMAN, I. SEGEV, AND R. E. BURKE, "ELECTROTONIC ARCHITECTURE OF TYPE-IDENTIFIED ALPHA-MOTONEURONS IN THE CAT SPINAL CORD," *JOURNAL OF NEUROPHYSIOLOGY*, VOL. 60, PP. 60-85, 1988.

[11] E. PIERROT-DESEILLIGNY AND D. BURKE, *THE CIRCUITRY OF THE HUMAN SPINAL CORD*. NEW YORK: CAMBRIDGE UNIVERSITY PRESS, 2005.

[12] L. R. LO CONTE, R. MERLETTI, AND G. V. SANDRI, "HERMITE EXPANSIONS OF COMPACT SUPPORT WAVEFORMS: APPLICATIONS TO MYOELECTRIC SIGNALS," *IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING*, VOL. 41, PP. 1147-1159, 1994.

[13] A. DESTEXHE, Z. F. MAINEN, AND T. J. SEJNOWSKI, "AN EFFICIENT METHOD FOR COMPUTING SYNAPTIC CONDUCTANCES BASED ON A KINETIC-MODEL OF RECEPTOR-BINDING," *NEURAL COMPUTATION*, VOL. 6, PP. 14-18, 1994.

[14] L. F. ABBOTT, J. A. VARELA, K. SEN, AND S. B. NELSON, "SYNAPTIC DEPRESSION AND CORTICAL GAIN CONTROL," *SCIENCE*, VOL. 275, PP. 220-4, 1997.

[15] M. GIUGLIANO, "SYNTHESIS OF GENERALIZED ALGORITHMS FOR THE FAST COMPUTATION OF SYNAPTIC CONDUCTANCES WITH MARKOV KINETIC MODELS IN LARGE NETWORK SIMULATIONS," *NEURAL COMPUTATION*, VOL. 12, PP. 903-931, 2000.

[16] A. F. KOHN, M. K. FLOETER, AND M. HALLET, "A MODEL-BASED APPROACH FOR THE QUANTIFICATION OF H REFLEX DEPRESSION IN HUMANS," PRESENTED AT INT. CONF. OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY, 1995.

[17] R. CAPEK AND B. ESPLIN, "HOMOSYNAPTIC DEPRESSION AND TRANSMITTER TURNOVER IN SPINAL MONOSYNAPTIC PATHWAY," *JOURNAL OF NEUROPHYSIOLOGY*, VOL. 40, PP. 95-105, 1977.