MODELING OF MOTOR NEURONAL STRUCTURES VIA TRANSCRANIAL MAGNETIC STIMULATION

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Abstract: Transcranial Magnetic Stimulation (TMS) of human motor area can evoke different biological waves in the epidural space of patients. These waves can evoke different muscle responses according to different types and amplitudes of stimuli. In this paper we analyze the different types of epidural waves and we propose a neuronal model for the biological structures involved in the experiments.

1 INTRODUCTION

Human nervous system is something much complex and its operation is still rather obscure to scientists. Nevertheless, more and more emerging techniques are helping scientists in examining the human brain in detail and making hypotheses on its operation. For example, the use of transcranial cerebral stimulations, such as the *Transcranial Magnetic Stimulation* (TMS), allows us to understand some cerebral mechanisms and identify several cerebral areas. Pioneering studies on brain stimulation through the intact scalp were carried out in the early 80s (Merton and Morton 1980) by stimulating the brain through an electric field. This stimulation technique is called *Transcranial Electrical Stimulation* (TES). Unfortunately, it has been found that TES is quite uncomfortable to the patient, because only a small fraction of the applied current flows through the resistance of the skull and scalp into the brain, while the rest travels between the electrodes on the surface, causing local pain and contraction of scalp muscles. The development of TMS (Barker et al., 1985) overcame these problems of discomfort by using a magnetic field to carry the electrical stimulus across the scalp and skull to the brain. Opposite to the TES, TMS is painless and lacking in harmful effects to the human nervous system. TMS has also been exploited with success in the treatment of mental illness and depression (Wasserman, 1998). The first magnetic stimulators were very heavy and they could reach low stimulation frequencies. Recently, novel stimulators with lower weight and smaller size have been designed. The stimulator used in the experiments is the *Magstim 200*® (Jalinous 1997). The magnetic stimulation adopted in the experiment is provided by a 70mm (internal diameter), eight-shaped coil, placed above the cerebral motor area responsible of the left hand movements. Different levels of stimulation have been used, from 20% to 53% of the maximum stimulator output, using a 3% increasing step. The experimental data are collected from patients who have spinal chord stimulators implanted in the epidural space at C1-C2 vertebras for the treatment of intractable dorsolumbar pain (V. Di Lazzaro, 1998). Two different types of data are available: the recordings from the patient's epidural space and the EMG recordings. The former is important for the understanding of the nature of brain waves; the latter is important for the understanding of the effects of the voluntary muscle contraction on the recorded muscle potentials. In particular, the effects of voluntary contraction are important at motoneuronal level, but they do not influence the corticospinal volleys, as it will be shown in the following. The paper is structured as follows: in the next section we analyze the epidural recordings of the biological waves, and the artifacts due to the stimulus and the measurement method. Moreover, we propose a first-attempt linear model. In the third section we exploit the Izhikevich nonlinear neuron model to build a model of the neuronal structure under investigation. In the fourth section we show the results. Finally, we draw our conclusions in the fifth section.

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2 DATA ANALYSIS

The data analyzed in this paper have been collected in experiments carried out by Prof. V. Di Lazzaro and co-workers at the Neurological Institute at *Cattolica* University in Rome, Italy. The recordings have been collected from a patient with epidural electrodes implanted at C1-C2 vertebras level. The left hand motor area of the patient's brain has been stimulated by TMS. Consequently, brain potentials have been evoked and recorded by a differential amplifier from the epidural electrodes, and by an EMG recorder from the First Dorsal Interosseus muscle (FDI) of the left hand. Experimental data have been recorded with different amplitudes of magnetic stimulation and different levels of voluntary muscle contractions.

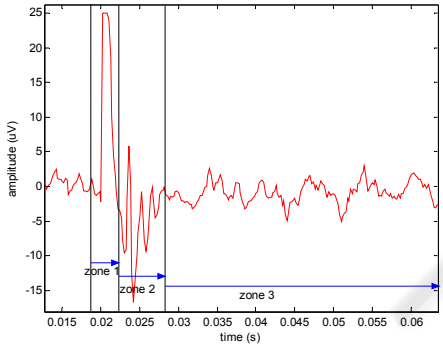

Figure 1: Typical recording taken at the epidural electrodes

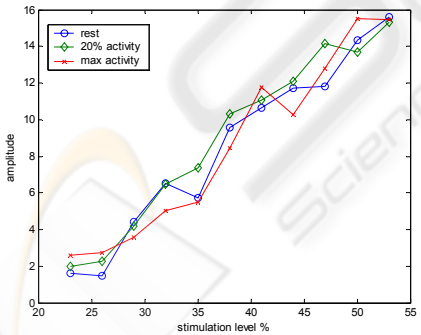

Figure 2: Amplitude of the first I wave evoked by TMS for different muscle contractions levels.

Figure 1 shows a typical recording taken at the epidural electrodes. Three different zones can be clearly distinguished:

- Zone one: stimulus artifact;
- Zone two: actual biological waves;
- Zone three: noise.

Biological waves evoked by TMS are of two kinds (Di Lazzaro, 2004). The first one, called *D wave* (Direct wave) is supposed to be produced by direct stimulation of the pyramidal tract axons. The second one is called *I wave* (Indirect wave), and is supposed to be produced by synaptic activation of the pyramidal neurons of the same tract. With TMS, a D wave is present only if the stimulus amplitude is greater than a threshold, whereas I waves are always present. If a D wave is present, it precedes the I waves. In the recorded data, I waves are numbered according to their temporal sequence. The recordings have been collected using a differential method; therefore, for each volley recorded, two peaks (a positive and a negative one) are present .
Figure 2 shows the amplitude of the I1 wave (computed on the experimental data as the half-peak-to-peak amplitude) for different voluntary muscle contraction at different stimulation levels. As it is seen from Figure 2 the amplitude of the I1 wave increases linearly with the stimulation level and it is independent from the voluntary contraction level. In fact, muscle contraction increases motoneuronal excitability and has no effect at the corticospinal level. On the other hand, voluntary contraction makes the recordings more noisy and lowers the signal to noise ratio.
In our recordings there is always a saturated peak which occurs at the same instant (0.02s) of application of the magnetic stimulus. This saturated peak is biologically implausible, and systematically occurs in every experimental recording. Thus, we can conclude that this is a stimulus artifact due to both the electromagnetic coupling and the displacement current (O'Keffe et al., 2001), (McLean et al., 1996). To analyze the actual biological waves we have reconstructed the stimulus artifact for different stimulation amplitudes. In particular we have developed 4 different stimulus artifact models according to the stimulus amplitude. Figure 3 shows, in clockwise direction from top-left, the stimulus artifacts from low to high stimulation intensity. In our modeling, the reconstructed stimulus artifact is subtracted from the experimental data to obtain the experimental biological waves to be modeled. Subsequently, the artifact is added again to the modeled waves to rebuild the modeled signal.
For the particular case of this patient it has been found that the amplitudes of subsequent I waves are well modeled by an exponential decreasing law. As stated before, the amplitude of I1 wave increases almost linearly with the stimulus amplitude. Therefore, a first-attempt model has been carried out

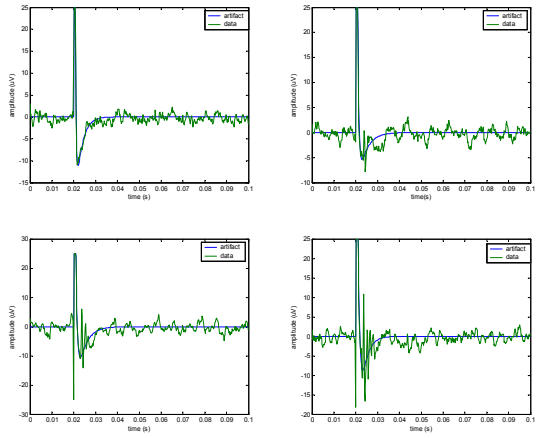

Figure 3: Reconstructed stimulus artifacts versus experimental data for different stimulation levels.

by considering a second order linear system, described by the following transfer function:

$$G(s) = b \cdot e^{-s \cdot rit} \cdot \frac{1}{s^2 + a \cdot s + b}$$

The Laplace transform of the input stimulus, as the monophasic current produced by the eight-shaped coil (Kammer et al., 2001), is:

$$i(s) = \frac{K}{\tau} \cdot \frac{1}{s^2 + \frac{3s}{\tau} + \frac{2}{\tau^2}}$$

The K parameter changes linearly with the stimulation amplitude and simulates the stimulus increase. In Figures 3 and 4 we show some results achieved with the linear model described above.
This model gave good results for this experiment but is not suitable for experimental data collected in other patients, nor for other similar experiments reported in literature (Houlden,1999). In fact, the use of a linear model implies the periodicity of I waves. An in-depth analysis on the latency of the I waves shows that in fact they are not periodic and each wave has a fixed latency for all the stimulation levels. We remind that the recordings are the results of different mechanisms: the stimulus artifact, the artifact due to the propagation of the nervous potentials through the fibers and the artifact due to the differential measurement method. Therefore, the aspect of the recordings is not entirely due to the action potentials generating in the fiber, and only amplitude and latency of I waves can be considered as biologically plausible, and useful, data.

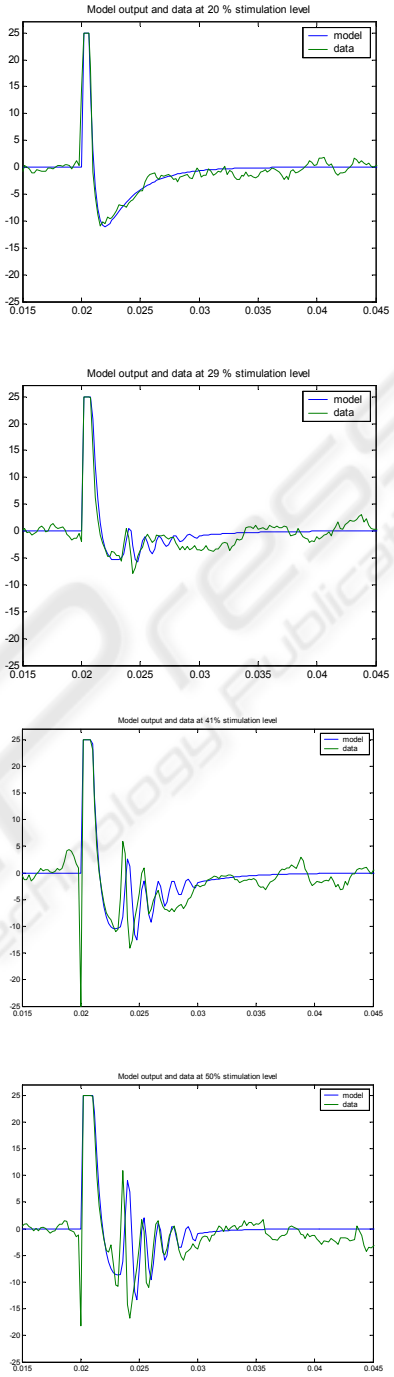

Figure 4: model output and data for different stimulation level

Therefore, we have developed another model based on a neuronal network of spiking neurons. The facts on which we base our hypotheses is that the potential recorded at the electrodes comes from the output of a huge number of spinal fibers, and the

greater the stimulation amplitude is, the higher the number of stimulated fibers is. This hypothesis is supported by the biological law of "nothing or all" which states that neurons produce a fixed voltage level when they are excited above a threshold. If the stimulation is under the threshold the action potential is not generated and, correspondently, a descending wave at the electrodes is not revealed.

3 NEURONAL MODELS

The neuronal network developed in this section consists of Izhikevich spiking neurons (Izhikevich, 2003). It is described by the equation system:

$$v' = 0.04v^2 + 5v + 140 - u + I$$
$$u' = a(bv - u)$$

With the reset condition:

If $v \geq 30$ mV then $v \leftarrow c$

$u \leftarrow u + d$

where v is the membrane potential, u is a recovery variable which considers the refractory period and the K^+ current activation after the action potential. The mechanism of iperpolarization is considered by the c parameter which has the -64 mV value. We can now analyze the meaning of the parameters.

- a describes the time scale of the recovery variable u. Smaller values result in slower recovery;
- b describes the sensitivity of the recovery variable u to the fluctuations of the membrane potential v;
- c describes the after-spike reset value of the membrane potential v;
- d describes after-spike reset of the recovery variable u.

The parameters of the neuron model have been fixed to: a=0.4, b=0.26, c=-65, d=6. This choice makes the neuron spiking and with a latency comparable to that of the experimental recordings.

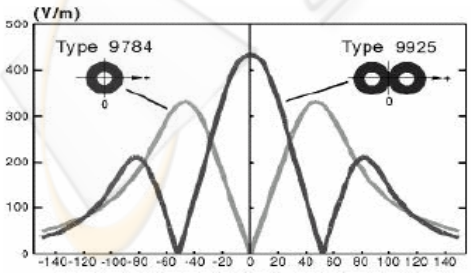

Figure 5: Electric field shape for circular and eight-shaped stimulation coils

The experimental recordings cannot reveal the action potentials of the single neuron activated by the stimulation, so we have studied the global behavior of the network, by simulating an appropriate inducted current at different neuronal areas, produced by the eight-shaped coil.

The amplitude of each I wave is proportional to the number of corticospinal neurons transinaptically activated by the stimulation. The generation of a D wave is due to the direct stimulation of the corticospinal neurons for high stimulation levels, as the inducted current activates the deep brainstem and activates cortical neurons directly. Nevertheless, for the generation of the simulated I waves, the number of neurons actually involved is unknown. We assumed that each stimulated neuron contributes to the formation of the I wave with a 1μV spike and consequently we estimated the number of neurons involved in the stimulation process.

Based on these considerations, we have simulated a 500 cortical neurons network connected to a 100 corticospinal neurons network. Both networks are considered within a regular topology. Each corticospinal neuron is synaptically connected to five cortical neurons. As it is illustrated in Figure 5, an eight-shaped coil induces an electric field with the highest peaks located in three main areas: one located immediately below the coil with the maximum intensity, the other two on the two sides of the coil, with a peak of intensity which is about a half of the highest one. The hypothesis made in this paper is that the electric field mainly stimulates groups of neurons located under the highest field peaks (Rosler, 2001 – Sakay). Therefore, an I wave consists of the sum of the outputs of many neurons which fires at the same time, because they are essentially stimulated by the same field. This hypotesis is supported by the following facts, which can be observed in the experimental data:

- In these experiments a maximum of three waves is generated, and there are three main areas in which a peak of electric field exists.
- For high intensities, the field peaks are higher and more spread in space. Consequently, more neurons are activated and the correspondent I wave is larger.
- For low intensities, the electric field has only one peak located under the coil. Correspondently, only one I wave is generated for low intensity field.

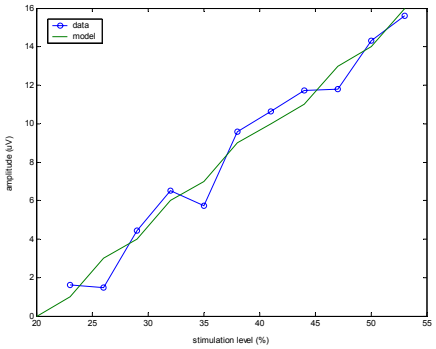

Figure 6: amplitude of the I1 waves for different stimulation levels.

Therefore, the cortical network (and consequently the corticospinal one) has been partitioned in three areas, each responsible for the generation of one of the three I waves. When the stimulation intensity increases, the number of activated neurons increases and larger waves are produced. This simulates the spatial spreading of the stimulus at higher intensity of stimulation. Therefore, different I waves are generated because a different current for each neuronal area is inducted by the magnetic field. Figures. 6, 7 and 8 show a comparison between the amplitude of simulated I1, I2 and I3 waves and the experimental ones, versus the stimulus intensity. Once amplitudes and latencies have been modeled, the signal shape must be reconstructed. We already dealt with the fact that the differential measurement configuration introduces an artifact in the measurements, producing a sequence of one positive and one negative volley for each cerebral I wave.

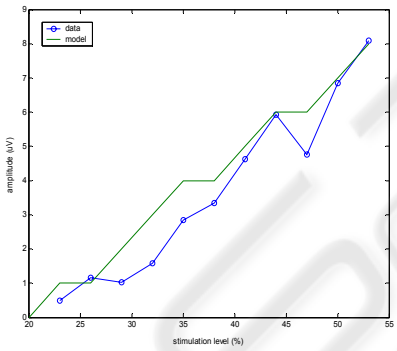

Figure 7: Amplitude of the I2 waves for different stimulation levels.

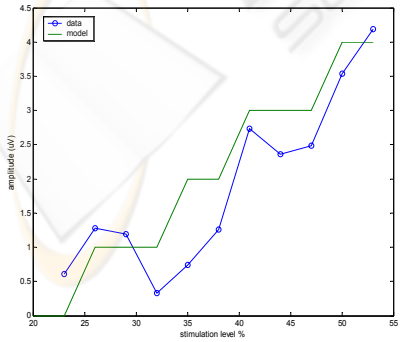

Figure 8: Amplitude of the I3 waves for different stimulation levels.

The propagation velocity of the impulse has been calculated in about 50 m/s. The propagation delay for the I1 wave is about 2.2 ms. For I waves, due to their synaptic nature, an approximately 1 ms delay due to the synaptic mechanism must be added. Therefore, a total latency for the I1 wave equal to 3.6 ms has been reckoned, which is coherent with the distance of 12 cm between stimulation and recording site.

Therefore, taking into account the propagation velocity of the waves and the distance between the electrodes, the artifact can be reconstructed.

4 RESULTS

A good fitting of the experimental data for all the stimulation levels has been obtained with the neuronal structure explained above.

To fit the experimental data we have reproduced the stimulus artifact, the measure setup and the propagation artifacts.

Figures 9, 10 and 11 illustrate a comparison between the output of the model and the experimental data. It can be clearly noticed that the neuronal network gives better results than the linear model. It respects

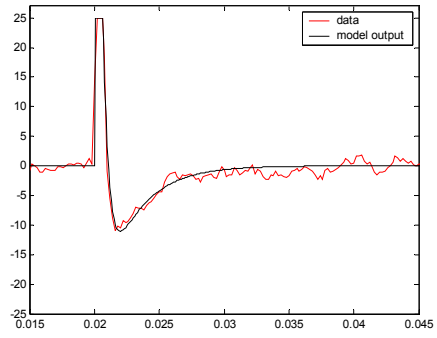

Figure 9: Model output and data for a 20% stimulation level.

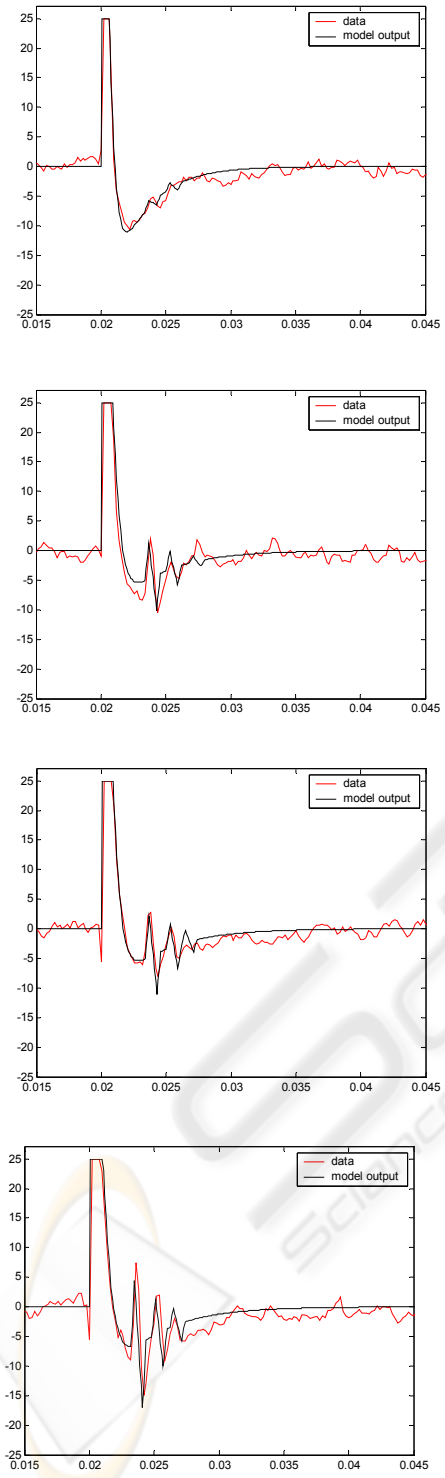

Figure 10: Model output and data for 23%, 32%, 35%, 44% stimulation level.

the aperiodicity of the response, taking into account the different latencies of I waves, and provides a better fitting for wave amplitudes.

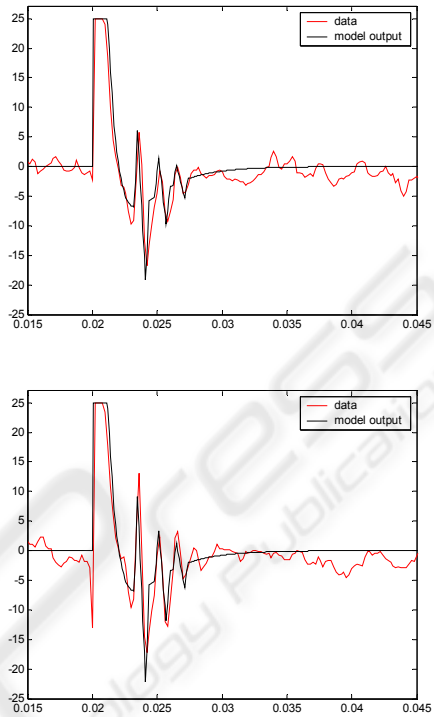

Figure 11: Model output and data for 47%, 53% stimulation level.

5 CONCLUSIONS

In this paper a model of motor neuronal structures has been built and validated on the basis of experimental recordings obtained via Transcranial Magnetic Stimulation (TMS). With this technique, the brain of the patient is stimulated by a suitable magnetic field placed above the cerebral motor area responsible of the left hand movements. The stimulation evokes different biological waves in the brain which are transmitted from the motor cortex, through the pyramidal neurons via synaptic connection, to the spinal chord, where signals are collected by a couple of electrodes implanted in the epidural space at C1-C2 vertebras level.

After a thorough data analysis phase, the motor neuronal structure has been modeled by a neural network based on Izhikevich neurons, for both the motor cortex and the pyramidal neuron areas. Moreover, stimulus and measurement artifacts have been reconstructed and considered in the modeling phase. The results are fully satisfactory, model

output and experimental recordings match for each available experiment.

Further research will involve a more accurate modeling of the motor cortex and its connections with the pyramidal tracts. At present, an hypothesis of a five-to-one local connection between cortex and pyramidal neurons has been made. In the future, optimization strategies will be considered to find an adequate connection scheme between cortex and pyramidal tracts, and with different topologies, involving also the plasticity mechanism (i.e. time-variant connections). Moreover, the model is being validated on several recordings coming from different patients, with different stimulation protocols.

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