

The amplitude and phase responses of the firing rates of some motoneuron models

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Abstract

A vertebrate motoneuron receives an enormous amount of synaptic activity from descending pathways, from spinal cord interneurons and directly from mechanoreceptor afferents. The intrinsic characteristics of the motoneuron will determine how its output spike train will encode the activities of all its inputs. Therefore, the essence of the intrinsic motoneuron characteristics should be well studied and modelled if the roles of the motoneuron as a processing or encoding element are to be well understood. Mathematical models of motoneurons have been described in the literature and tested mostly under static conditions. To increase the reality of the validation of such models, the objective of the present work is to test a few selected models described in the literature using sinusoidal injected current of different frequencies. The resulting frequency responses are compared with data available in the literature from cat type F motoneurons. Discrepancies between some of the models' responses and real motoneuron data suggest that improvements are needed in the modelling of the afterhyperpolarization mechanism. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Motoneuron model validation; Frequency response of motoneuron models; Afterhyperpolarization and frequency response

1. Introduction

The control of motor behaviour is accomplished by the coordinated action of a multitude of neurons in the central nervous system, including those in the cortex (e.g. primary motor, supplementary motor, premotor, parietal), basal ganglia, cerebellum, brainstem and spinal cord. A motoneuron in the spinal cord receives an enormous amount of synaptic input from the central and peripheral nervous systems. It encodes the incoming spike trains into an outflow of action potentials that taken together with the spike trains of the other motoneurons in the same nucleus will determine how the target muscle will contract. The encoding effected by a motoneuron can be studied under static or dynamic conditions, both being useful to characterise the motoneuron behaviour. In terms of physiological actions, the static behaviour is relevant for the determination of, e.g. posture and prehension, while the dynamic

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behaviour is important in locomotion, grabbing, throwing, etc. A particular case of dynamic action involves rhythmic movements, such as walking, running, pedalling, swimming, chewing, tremor. In these cases there is a rhythmic excitatory drive acting on a motoneuron pool that causes the motoneurons to fire rhythmic bursts that will command rhythmic contractions of the target muscle. In these sorts of behaviour, a study of the response of the motoneurons to sinusoidal input currents is warranted.

On the other hand, for studies on the neural substrates of motor control it would be helpful to have available a simulator of the corresponding network of spinal cord motoneurons and interneurons. Therefore, ‘good’ models of those neurons are required, which means that any candidate model should pass several tests for its validation. In spite of the importance of frequency response analysis, the motoneuron models described in the literature have not been validated using sinusoidal input currents. Tests that have been used in the literature for the validation of motoneuron models include: $f \times I$ curve, action potential and afterhyperpolarization (AHP) characteristics, recruitment threshold, voltage transients for dendritic inputs, bistability, change in firing rate due to trains of short input pulses. In this work we present simulations of two rather complex motoneuron models described in the literature (Traub, 1977; Booth et al., 1997) as well as those of two simple models of the leaky integrator type. The responses to two inputs are analysed: a step current and a sinusoidal current (superimposed on a step current). In the former we study the adaptation time course and in the latter we study the sinusoidal steady state responses. Cat motoneuron data published by Baldissera et al. (1984, 1998) and by Schwindt and Crill (1984) are used as a reference for comparison.

2. Models chosen for evaluation by sinusoidal inputs

The first model chosen for evaluation using sinusoidal input signals is that of Traub (1977),

consisting of three dendritic compartments, a soma compartment and an initial segment compartment. There is a slow K channel to represent the calcium-dependent K channels found in motoneurons. To speed up the computations we merged the three dendritic compartments in a single one so that the whole model is now described by three compartments totalling ten ordinary differential equations. The parameter values were chosen so that the resulting neuronal model would represent a type F motoneuron. Parameters β_q and $g_{K,slow,tot}$ were taken as 0.035 and 0.005 to achieve a better approximation to real $f \times I$ curves but still without altering other characteristics such as rheobase. The second model we chose to test is that of Booth et al. (1997), composed of a somatic compartment and a dendritic compartment. The former includes an N type Ca channel and a Ca-dependent K channel, while the latter includes N and L type Ca channels and a Ca-dependent K channel. This model, to be referred simply as the Booth model, is described by 11 ordinary differential equations. As this model has an active dendrite, we decided to test also an equivalent model with a passive dendrite, which we shall call Booth PD model. The parameters for the passive dendrite were derived from the full dendritic model imposing resting conditions. This new model is described by seven ordinary differential equations. Both Booth models were simulated without denormalising the input current and the parameters. It should be pointed out that Booth et al. (1997) developed their model to represent turtle motoneurons. In spite of this, we thought it was an interesting model to test because its core is mostly based on the biophysics and mathematical modelling of cat motoneurons. An additional interesting feature of this model is that its active channels in the soma and dendrite provide a mechanism for bistability, something found in cat and turtle (e.g. motoneurons under certain experimental conditions).

In addition to the three models described above, which include a rather detailed description of several ionic channels and a dendritic compartment, we also decided to test a simple leaky integrator model. Its parameter values were chosen to approximate real motoneuron data:

threshold = 14.4 mV above membrane resting potential, membrane time constant = 5.0 ms. These parameter values are typical of cat FF type motoneurons (Zengel et al., 1985). When it was noticed that the frequency response of this model was quite different from that of real motoneurons, we decided to test a leaky integrator model with negative current feedback that would generate an AHP similar to that found in real motoneurons. For each action potential discharged by the standard leaky integrator model, a Dirac delta impulse is applied to a first order lowpass linear system whose output is subtracted from the input current to the leaky integrator model. The same values for the membrane time constant and threshold voltage used in the simple leaky integrator were also used for the leaky integrator with negative feedback. The AHP time constant was 20 ms and the AHP peak amplitude for a single activation was made equal to -3 mV, similar to values described in real motoneurons. Additional simulations of the leaky integrator with feedback investigated the effects of different AHP time constants (5 and 30 ms) on the frequency response. We took care to assure that each of these models still had the same values for the AHP peak amplitude (-3 mV), firing threshold (14.4 mV) and membrane time constant ($\tau_m = 5$ ms). To achieve an AHP peak amplitude of -3 mV the peak of the negative feedback current (a decreasing exponential signal) had a different value for different AHP time constants. To our knowledge, one of the first descriptions of such a negative feedback modelling in the context of an integrate and fire model was published by Sokolove (1972), with the objective of representing an adaptation mechanism in crayfish stretch receptors.

The steady state discharge rate of each motoneuron model was adjusted to 60.0/s for the adaptation simulations and to 52.0/s for the frequency response simulations (by choosing appropriate levels of the input step current), so that the experimental data from Baldissera et al. (1984) and Schwindt and Crill (1984) could be used as references.

Specific programs in C language were devel-

oped for the simulation of all the models. The differential equations were integrated using the fourth order Runge-Kutta method, with a fixed step size of 0.01 ms. The frequency responses were estimated with the help of programs written in the Matlab environment.

3. Method for obtaining the amplitude and phase responses

The motoneuron models described in the previous section were tested with an input current consisting of a sinusoidal signal superimposed on a step signal. At the start of a simulation, only the step current was applied until a steady state firing rate of 52/s was reached. After that, the sinusoidal current was injected superimposed on the step current, thereby modulating the firing rate of the motoneuron model. The amplitude and phase of the firing rate modulations for different input frequencies (1–30 Hz) yielded the amplitude and phase response graphs.

The spike train analysis followed in essence that described by Baldissera et al. (1984, 1998): (a) each interspike interval was localised in time as the midpoint between two consecutive spikes, this time location normalised with respect to the phase of the input sinusoid; (b) one cycle of the input was divided into 72 bins and each interspike interval time location was binned; (c) the mean interspike interval in each bin was computed and its inverse — a mean instantaneous rate — was the value associated with that bin; (d) a spline interpolation was applied to the *cycle histogram of the instantaneous rate* found in step (c); and (e) the fundamental component of the FFT of the interpolated cycle histogram of (d) gave the amplitude and phase of the response for the specific input. When at least one bin in the cycle histogram computed in (c) was empty, a linear interpolation was employed prior to the spline interpolation. Some of the steps above are required because the raw cycle histogram shows distortions, mainly when the input peak amplitude is not small enough or the modulating frequency is high with respect to the basal frequency of the neuron (the neuron's dis-

charge rate when just the step current is applied). The amplitude ranges of the sinusoidal modulating currents were smaller than in Baldissera et al. (1984) to avoid excessive distortions in the histograms. Typical sine amplitude to step current amplitude ratios were from 1/50 to 1/2 for the Booth and Traub models and from 1/200 to 1/10 for the leaky integrator models. Some ad-hoc criteria were employed to eliminate cycle histograms that were too distorted (e.g. when the phase value for a larger amplitude of the sinusoidal input jumped with respect to the phase values measured for smaller input amplitudes). For the computation of the amplitude response or gain, four different peak amplitudes of the input sine functions were employed and the slope of the curve defined by the corresponding amplitudes (of the resulting fundamental frequency) yielded the gain. The phase at each input frequency was measured using the response to the smallest input sine wave. Each analysed spike train had 10 000 action potentials. Before ending this section, it should be emphasised that the cycle histograms employed in the comparisons of the five models with real motoneuron data are different from the *cycle histogram of spike density*, which estimates an intensity function of a point process and is a sort of post-stimulus time histogram (where time 0 is, e.g. the upward zero crossing of the input sine wave and the histogram is computed for the duration of a sine period). For the purpose of interpreting the effects of frequency modulated spike trains on a target neurone, the cycle histogram of spike density is more relevant because it conveys information on spike discharge probability in any desired time interval. A recent work that illustrates the usage of the cycle histogram of spike density can be found in Shimokawa et al. (1999). On the other hand, the cycle histogram of the instantaneous rate was used by Baldissera et al. (1984) to quantify cat motoneuron behaviour and is, therefore, important for motoneuron model validation. Significant differences in amplitude and/or phase responses of a motoneuron model and real motoneurons obtained from the cycle histogram of the instantaneous rate would mean that improvements are required in the model structure or parameter values.

4. Results

An initial simulation was run to study the adaptation characteristics of each model as compared with those of a real motoneuron. Each of the three models (leaky integrator with feedback, Booth and Traub) had an input step current injected with an appropriate amplitude to yield a steady state discharge rate of 60.0/s, which was the steady state discharge rate of the cat motoneuron that was reported by Schwindt and Crill (1984).

The step response of each model is plotted in Fig. 1 (top three graphs) showing the instantaneous rate as a function of time together with the data from a real motoneuron. More specifically, Fig. 1 shows, from top to bottom, the instantaneous rates for the leaky integrator model with feedback (AHP time constant 20 ms), for the Booth model, for Traub's model, and for a cat motoneuron (Schwindt and Crill, 1984).

The Booth model and the leaky integrator with feedback ($\tau_{\text{AHP}} = 20$ ms) reach the steady state discharge rate after about the third interspike interval while Traub's model is already at the steady state rate at the second interspike interval (i.e. almost no adaptation). On the other hand, the real motoneuron reached the steady state discharge rate at about the fifth interspike interval following the input step current.

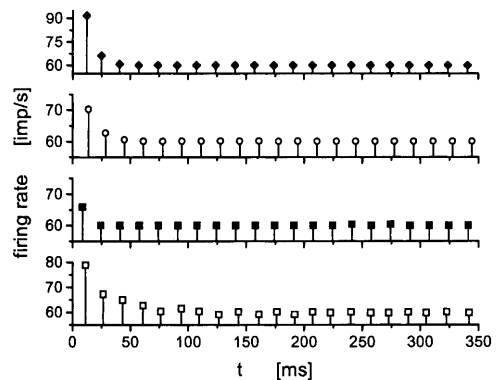


Fig. 1. Instantaneous frequency as a function of time for a step current input. From top to bottom: leaky integrator with feedback ($\tau_{\text{AHP}} = 20$ ms), Booth model, Traub model, and cat motoneuron (data redrawn from Schwindt and Crill, 1984).

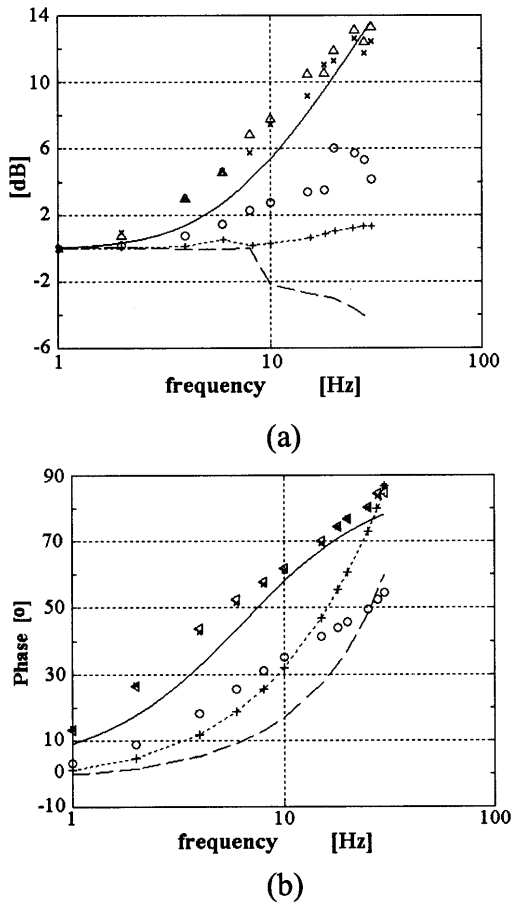


Fig. 2. (a) Amplitude responses (in dB); and (b) phase responses (in degrees) of real motoneurons (solid line, redrawn from Baldissera et al., 1984), and the following models: Booth et al. (1997) (\times), Booth PD (Δ), Traub (1977) (dashed line, small dashes with crosses), leaky integrator (dashed line, long dashes), leaky integrator with negative feedback and AHP time constant 20 ms (\circ).

The amplitude response (or gain) and the phase response graphs are seen in Fig. 2a and b, respectively. The real motoneuron data were fitted by Baldissera et al. (1984) using a proportional + derivative system and this fit is shown in continuous lines in Fig. 2 and in Fig. 3. Therefore, this will be the golden standard we shall use to evaluate the sinusoidal dynamic response of the five motoneuron models we chose to test. The main features of the real motoneuron data are the increasing gain and phase advance for higher frequencies, with a zero of the transfer function

occurring at about 6.3 Hz (i.e. the 3 dB point frequency is around 6.3 Hz).

The amplitude response (or gain) curves from the simulations (Fig. 2a) show that the leaky integrator behaves rather poorly, as does the Traub model. An improvement over the leaky integrator was achieved by the introduction of the negative feedback (measured values indicated by circles), mimicking the after-hyperpolarization found in motoneurons. However, the best fit of all was obtained by either of the two versions of the Booth model.

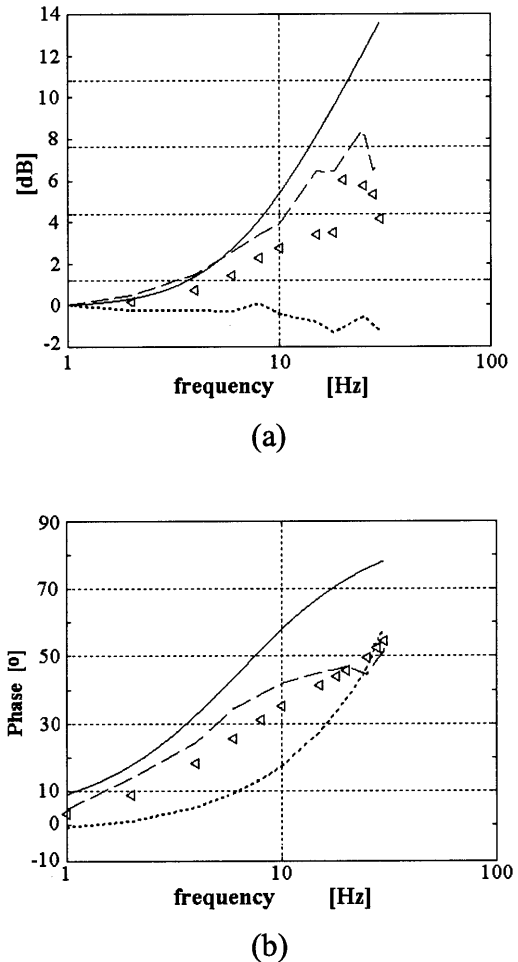


Fig. 3. (a) Amplitude responses (in dB); and (b) phase responses (in degrees) of three leaky integrator models, with membrane time constant 5 ms, discharging at 52.0/s but with different negative feedback time constants: 5 (short dashes), 20 (Δ) and 30 ms (longer dashes). Real motoneuron frequency response in solid line (redrawn from Baldissera et al., 1984).

The phase responses of both leaky integrator models and Traub's model (Fig. 2b) were quite in error with respect to the real motoneuron data. On the other hand, both versions of Booth's model gave a good fit. As the difference between the two leaky integrator models is the negative feedback, and it caused an improvement in the model's reality, we investigated if an increase of the AHP time constant could improve the fitting.

Next we simulated two additional leaky integrator models with negative feedback having AHP time constants 5 and 30 ms. The smaller time constant was made equal to the membrane time constant in order to check if a leaky integrator model with a simple negative reset following an action potential would work well (this model would be simpler to implement in a simulation because the decay of the hyperpolarization would be just the decay caused by the membrane time constant).

The larger time constant value was chosen to be still compatible with physiological data. Fig. 3 shows the gain and phase curves for three leaky integrator models with negative feedback and AHP time constants (τ_{AHP}) equal to 5, 20 and 30 ms. The relation between negative peak feedback current and injected current was 0.53 for the model with $\tau_{\text{AHP}} = 5$ ms ($\tau_{\text{m}} = \tau_{\text{AHP}}$), 0.21 for the model with $\tau_{\text{AHP}} = 30$ ms, and 0.25 for the model with $\tau_{\text{AHP}} = 20$ ms. Fig. 3 shows that the gain and phase curves for $\tau_{\text{AHP}} = 30$ ms are more similar to the data from Baldissera et al. (1984) than the other curves (5 and 20 ms). The model with 5 ms of AHP time constant showed almost no sign of the feedback effect (in the frequency response analysis) and behaved practically as a pure leaky integrator.

For the sake of completeness, we also simulated a leaky integrator model (without feedback) having a larger membrane time constant, equal to 15 ms, more typical of pyramidal neurons in the cortex. The same methodology as described before was used to determine the gain and phase responses to sinusoidal input currents. The results showed that the gain curve was quite near to that found for the leaky integrator with 5 ms membrane time constant. However, the phase curve was much below that obtained for the 5 ms leaky

integrator, for example, at 15 Hz the phase was 17° below and at 25 Hz it was 29° below.

5. Discussion

Our search for a 'good' motoneuron model actually started with an analysis of Traub's model (1977) as it appeared to include all the major aspects needed to represent a motoneuron. When the frequency response showed a poor performance, we decided to test a more recent model and chose the model by Booth et al. (1997), which ended up giving good frequency responses.

An important question then arose: what parameter values or what model sub-structure are directly relevant in the Booth model to justify its good dynamic performance for sinusoidal inputs? And what has to be changed in the Traub model? At the same time we were curious to see if a simple leaky integrator model with realistic parameter values would follow approximately the motoneuron frequency response data. When the results with the simple leaky integrator showed a poor fit, we decided to test a leaky integrator model with a negative feedback that generated an AHP (a conspicuous finding in motoneurons). The better results obtained using a negative feedback in the leaky integrator model indicated that we should look at the way the AHP dynamics were implemented in Traub's and Booth's model to understand why the latter gave much better results. Indeed, the proportional + derivative model fitting of real motoneuron data (Baldissera et al., 1984) suggests that an approximate transfer function between input injected current and motoneuron firing rate modulation would be $(s + a)/(s + b)$, with $b \gg a$. The step response of such a system shows adaptation, something that certainly the leaky integrator does not have and Traub's model has very little (Fig. 1). The leaky integrator model with negative feedback showed increasing levels of adaptation as the AHP time constant was increased, and at the same time the fitting of the frequency response curves improved. The Booth model has a somewhat more pronounced adaptation than Traub and at the same time has a more elaborate description of the dynamics of the

calcium dependent potassium channels. Nevertheless, it may well be that by a proper parameter adjustment Traub's model can exhibit a much better frequency response. But one has to always check if the resulting parameter values are realistic and if other model behaviours are still within the normal ranges.

One additional question raised by the simulations was if the good frequency response characteristics of the Booth model was due to the active dendritic model employed. Our simulations showed that an equivalent passive dendritic model gave a similar frequency response. Hence, voltage-dependent conductances in the dendrites are not necessary for the motoneuron model to represent well the gain and phase data described for real motoneurons.

In terms of simpler models, if the only criterion would be a reasonable fitting of the gain and phase curves of real motoneurons, then the leaky integrator with feedback having a higher AHP time constant could be an adequate model. Nevertheless, its behaviour for other types of tests (not covered here) would certainly fail and, therefore, the choice of this simpler model would be conditioned on the usage required for it (e.g. in a study of synchronisation in a network of such models).

As a conclusion, the model by Booth et al. (1997), shows a good dynamic response as compared with real motoneuron data and should be considered when choosing a reasonably realistic mathematical model for motoneurons. Nevertheless, as this model was originally proposed for turtle motoneurons (the authors used turtle, cat and rat data to determine parameter values), additional work needs to be done to check how its good dynamic behaviour can be reproduced when the parameters are changed to fit cat motoneuron morphological and biophysical data.

The relevance of studying the frequency responses of real motoneurons and motoneuron models transcends the mere testing of the models to check their adequacy. Compensation of the lowpass characteristics of muscle by the motoneuron frequency response is relevant to the high

frequency performance of movement (Baldissera et al., 1998). The motoneuron frequency response compensates partially the phase lags caused by axonal conduction and the sluggishness in muscle contraction in the stretch receptor loop. This is relevant for the reduction of tremor (Matthews, 1997).

Acknowledgements

This research was supported by FAPESP (São Paulo, Brazil). D.G. Goroso had a fellowship from FAPESP.

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