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A phenomenological model of myelinated nerve with a dynamic threshold

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HIGHLIGHTS

- We validate the standard leaky integrate-and-fire model with myelinated nerve data.
- Rate-level functions were not accurately predicted with a single set of parameters.
- Inclusion of a dynamic threshold into the standard model led to better predictions.

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ABSTRACT

To evaluate coding strategies for cochlear implants a model of the human cochlear nerve is required. Nerve models based on voltage-clamp experiments, such as the Frankenhaeuser–Huxley model of myelinated nerve, can have over forty parameters and are not amenable for fitting to physiological data from a different animal or type of nerve. Phenomenological nerve models, such as leaky integrate-and-fire (LIF) models, have fewer parameters but have not been validated with a wide range of stimuli. In the absence of substantial cochlear nerve data, we have used data from a toad sciatic nerve for validation (50 Hz to 2 kHz with levels up to 20 dB above threshold). We show that the standard LIF model with fixed refractory properties and a single set of parameters cannot adequately predict the toad rate-level functions. Given the deficiency of this standard model, we have abstracted the dynamics of the sodium inactivation variable in the Frankenhaeuser–Huxley model to develop a phenomenological LIF model with a dynamic threshold. This nine-parameter model predicts the physiological rate-level functions much more accurately than the standard LIF model. Because of the low number of parameters, we expect to be able to optimize the model parameters so that the model is more appropriate for cochlear implant simulations.

1. Introduction

Although cochlear implantation has become a standard option for many children born deaf and for those who have become deaf later in life, there is still much uncertainty about how sound should be coded by a cochlear implant. To enable the evaluation of coding strategies a computational model of the human cochlear nerve is required. Initially this could be a generic model, but the physiological properties of the cochlear nerve are known to depend on the condition of the cochlea (Shepherd and Javel, 1997) and will therefore depend on the etiology and duration of deafness. A useful model for the evaluation of coding strategies should therefore contain few parameters to enable rapid and robust fitting to patient data.

Several models of nerve fibres have been developed based on voltage-clamp experiments on nerves from a particular animal species, e.g. squid (Hodgkin and Huxley, 1952), toad (Frankenhaeuser and Huxley, 1964), rat (Schwarz and Eikhof, 1987), rabbit (Chiu et al., 1979), and human (Schwarz et al., 1995). These model the conductance or permeability of various ion channels, particularly sodium and potassium, in response to an electrical stimulus, and enable the membrane voltage to be calculated. This type of model is particularly useful for investigating the influence of specific ion channels on emergent nerve properties such as action potential duration, refractoriness, facilitation, accommodation and adaptation (e.g. Negm and Bruce, 2014; Rattay et al., 2013). Because of differences in ion channel expression, however, the systems of equations and parameters for the squid, amphibian and mammalian nerve models differ; the predicted responses to electrical stimulation therefore also differ. To date, there is no ion-channel Q3

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model of the cochlear nerve based solely on cochlear-nerve recordings, although whole-cell patch clamping has enabled some ion-channels in the cochlear nerve to be identified and characterized (e.g. Santos-Sacchi, 1993; Mo and Davis, 1997; Hossain et al., 2005). Moreover, there are many morphological differences between the human cochlear nerve and the cochlear nerves used in animal studies (Ota and Kimura, 1980), and these would be expected to lead substantial physiological differences (Rattay et al., 2001, 2013). Nonetheless, classical ion-channel models and modified ion-channel models that incorporate classical ion-channel model have enabled a greater understanding of how the human cochlear nerve might respond to cochlear implant stimulation (e.g. Motz and Rattay, 1986; Westen et al., 2011; Imennov et al., 2013). Ion-channel models, however, are not intended to be predictive models in the sense that they are not intended to predict the response of a particular fibre, or group of fibres. Fibres from the sciatic nerve of the toad, for example, exhibit a wide range of responses to a single stimulus (Morse and Evans, 2003) and this cannot be captured by the Frankenhaeuser–Huxley model with the single set of standard parameters. Moreover, with over forty parameters, an enormous amount of data would be required to adequately constrain the optimization of new parameter values. While ion-channel models remain useful, there is also a need for less complex models for predictive modelling.

We therefore considered using a phenomenological nerve model in which the relationships between the variables relate to observed phenomena from physiological experiments, such as the recovery from a suprathreshold pulse and the relationship between the width of a pulsatile stimulus and its threshold. Because phenomenological models generally have few parameters the parameters can be constrained by a moderate amount of data. A further advantage is that because they contain fewer equations, the computation time for phenomenological nerve models is substantially less than that for ion-channel models.

The most common phenomenological nerve model is the leaky integrate-and-fire (LIF) model, which models the membrane properties by a differential equation with a single time-constant (Lapicque, 1907). An improvement is to model the absolute refractory period following an action potential and the subsequent relative refractory period during which the threshold is elevated but gradually returns to its resting value (e.g. White, 1985); classically, the absolute refractory period is taken to be the period during which a second action potential cannot be evoked irrespective of stimulus amplitude (effectively infinite threshold), but we discuss later that this definition may need to be refined. The recovery functions are typically exponential, but different forms, such as hyperbolic, have been used (Holden, 1976). Although the basic LIF model does not account for the probabilistic nature of the neural response this can be modelled by the addition of Gaussian noise to the threshold (Verveen and Derksen, 1968).

A few cochlear implant studies have used phenomenological models (e.g. Bruce et al., 1999a, 1999b; Morse and Meyer, 2000; White, 1985; Wilson et al., 1994) and have attempted to model the phenomena described above to varying degrees. None of these models, however, have been extensively tested against cochlear nerve data. In part, this is because the technical difficulty of microelectrode recording in vivo has precluded the recording of responses from a single fibre to a wide variety of frequencies and amplitudes; the difficulty arises because the cochlea contains conductive fluids and the direct current between the stimulating electrodes and the recording electrode leads to a stimulus artefact that masks the neural response. If such recordings were available, it would enable much more rigorous evaluation of the cochlear nerve models.

To date, the most rigorous evaluation has been performed on the model by Bruce et al. (1999a, 1999b). The Bruce model is a stochastic model in which the input stimulus is compared with a stochastic threshold. Each spike is followed by an absolute refractory period and subsequent fixed (stimulus-independent) relative refractory period during which the threshold returns exponentially to its resting value. The model was used to predict the response to a train of biphasic pulses (100 μs per phase) presented at rates from 100 to 800 pulses per second. The Bruce model is able to accurately predict the response of single cochlear nerve fibres to these stimuli, which demonstrates the importance of including both a stochastic threshold and refractory effects in models of the cochlear nerve.

The Bruce model, however, does not model leaky charge-integration by the nerve membrane and therefore does not include a membrane time constant. The stimuli used for validation were slowly varying compared with the time scales of the nerve being modelled, and so the inclusion of a membrane time-constant would not have greatly affected the predicted response to these particular stimuli. Without leaky charge-integration, the model would not be expected to predict the increased threshold to high-frequency sinusoids, or the effect of pulse width on the threshold to pulsatile stimulation, that have been observed in cochlear nerve experiments (Dynes and Delgutte, 1992; Kiang and Moxon, 1972). We have therefore extended the Bruce model and use a leaky integrate-and-fire neuron with a stochastic threshold. The initial model was similar to the unvalidated models by Wilson et al. (1994), Morse and Meyer (2000).

Although extensive cochlear nerve data from a single fibre is not available, we have previously recorded single-fibre data from the sciatic nerve of the toad *Xenopus laevis* in response to a wide range of stimulus frequencies and levels (Morse and Evans, 2003): frequencies were from 50 Hz to 2 kHz at levels from threshold to 20 dB above threshold. Given this data, we are adopting a three-stage approach. First, we assume that the cochlear nerve and sciatic nerve are ordinary nerves and that they share similar dynamics. This assumption is supported by our previous study, in which we measured the properties of the sciatic nerve such its excitation (strength-duration) time constant, refractory time constants, and relative spread—a measure of the internal noise level (Morse and Evans, 2003). The differences between the sciatic nerve and cochlear nerve appear to be in terms of the speed of the response and not in the intrinsic nature of the response. Based on the assumption of shared dynamics, we here develop a phenomenological model that predicts the response of the sciatic nerve to sinusoidal stimulation. Our focus is on the application of the model to predict responses to cochlear implant stimulation and the second stage of our approach will therefore be to show that the same model (i.e. the same dynamics), but with different parameters, can adequately model the more limited cochlear nerve data. The model developed here, however, is not restricted to cochlear implants and may find application for more general studies where the predicted firing rate of a nerve fibre is required, particularly in response to high-frequency stimuli. The final stage will be to optimize the model parameters based on the compound response of the cochlear nerve to electrical stimulation by a cochlear implant (Abbas et al., 1999; Brown et al., 1996).

We first show that the standard leaky-integrate and fire model with a fixed (stimulus-independent) recovery from threshold cannot adequately predict the sciatic nerve data.

2. Leaky-integrate and fire model with fixed threshold recovery

2.1. Initial model

Our initial model was a stochastic leaky integrate-and-fire model with stimulus-independent refractory properties. The