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A Model of Auditory Nerve Responses to Electrical Stimulation with Pulse Train

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Background

Cochlear implants (CI) infuse electrical charge in the cochlea through multiple electrodes using symmetric, charge-balanced, biphasic pulses. A cathodic phase is believed to depolarize the auditory nerve (AN) neurons, producing an action potential (AP); an anodic phase to neutralizes the charge within the cochlea. Single neuron recordings in cat AN show, however, that both anodic and cathodic phases, in isolation can generate an AP. The site of AP generation differs for both phases, being more central for the anodic phase and more peripheral for the cathodic phase. This results in an average difference of 200 μs in spike latency for AP generated by anodic or cathodic pulses (Miller et al., 1999; for review - Joshi et al., 2014). Based on these observations, Joshi et al. 2015 proposed a two neuron model of the AN responsiveness for electrical stimulation. The model consisted of two point neurons, each representing a peripheral and central nodes along the AN. The model was parametrized using statistics of responses for monophasic stimulation and was also able predict response statistics including probabilistic thresholds, spike latencies, and jitter for various pulse shapes. Their model, however, was only concerned with stimulation with single pulses. This report extends the model for stimulation with pulse trains by including a variable that represents the adaptation current. The model is further tested for it's ability to predict responses for various pulse train stimuli.

Model

The model consists of two adaptive-exponential-integrate-and-fire type neurons (Brette and Gerstner, 2005). Each neuron in the model is defined by two differential equations, one that calculates changes in membrane potential in response to the stimulus and second that calculates two stimulus triggered adaptive currents. In this model, the strict threshold voltage criterion has been replaced by a more realistic smooth spike initiation zone. After crossing the threshold, membrane potential grows exponentially and an AP is marked when this potential reaches the peak potential. This peak potential represents height of an AP. After a spike is fired, the membrane voltage for both the neurons is reset to the resting membrane potential and the second adaptive current (equation 3) is changed by value of 'b', resulting in 'spike-triggered adaptation'. The adaptive current in this model is dependent on the membrane voltage, and not directly the stimulus. This allows the model to calculate the adaptive current for both, depolarizing and hyperpolarizing phases of the stimulus.

$$C\frac{dV}{dt} = -g_L(V-E_L) + g_L\Delta_T \exp\left(\frac{V-V_T}{\Delta_T}\right) - w_1 - w_2 + I \quad (1)$$

$$\tau_w(1)\frac{dw}{dt} = a1(V-E_L) - w1 \quad (2)$$

$$\tau_w(2)\frac{dw}{dt} = a2(V-E_L) - w2; \quad (3)$$

$$at \quad t = t^f \quad reset \qquad v \rightarrow El \quad and \quad w(2) \rightarrow w + b \quad (4)$$

In equation (1), C and g_L are the membrane capacitance and conductance, E_L is the resting membrane potential, Δ_T is parameter that defines exponential slope of the change in neural membrane voltage and V_T is the threshold. w_1 and w_2 in equation (2) and (3) are the stimulus triggered adaptive currents with corresponding adaptation time constants $\tau_w(1)$ and $\tau_w(2)$. Equation (4) shows that the membrane voltage for both, central and peripheral neurons is reset to the resting membrane potential (E_L) when a spike is fired and the adaptation current w(2) is changed by a value of 'b'.

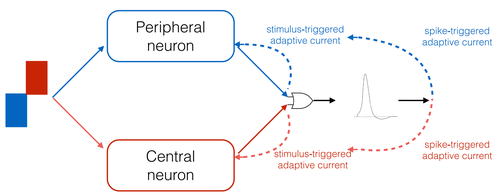

Fig.1 A block diagram showing the model structure. Red color is used for anodic phase, and neuron that is excitatory to anodic phase of the pulse. Blue indicates the cathodic phase and the neuron excitatory for a cathodic pulse.

Summary of parametrization

- Chronaxie and Rheobase is obtained from strength-duration relationships for monophasic pulses reported in Miller et al, 1999.
- The membrance resistance is calculated using rheobase.
- The membrane capacitance is calculated using chronaxie and the membrane resistance.
- Relative spread (RS) and threshold reported in Miller et al. 1999 are used to calculate the standard deviation of the membrane noise distribution.
- Value of α is adjusted to predict the correct RS for monophasic stimulation.
- Δ_T is adjusted to predict correct spike latencies for monophasic pulses.
- A value of $\tau_w(1)$ is fixed to the summation time constants reported by Cartee et al., 2006 for peripheral and central neuron.
- A value of $\tau_w(2)$ is fixed to the adaptation time constants reported by Ramekers et al., 2015.

Monophasic stimulation

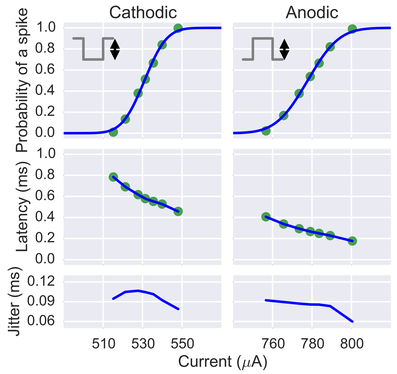

Fig.2 FE curve, spike latencies, and jitter from the model responses to stimulation with monophasic cathodic and anodic pulse of 39 μs duration. The model can correctly predict the latency and threshold difference between anodic and cathodic observed by Miller et al. 1999. Model can successfully predict decrease in spike latency and jitter with increasing stimulus level.

Effect of Anodic Phase Width

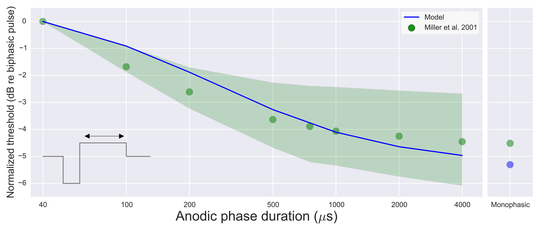

Fig.3 Thresholds for charge balanced biphasic (cathodic-anodic) pulses with varying anodic phase duration. The data and model predictions have been normalized re threshold for symmetric biphasic pulse. The model can quantitatively predict the trend of decreasing threshold with increase in anodic phase duration.

Effect of Inter Phase Gap (IPG)

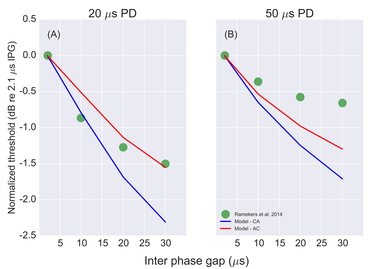

Fig.4 Interaction between inter-phase gap (IPG) and pulse-phase duration (PPD). The threshold data (circles) is derived from ECAPs recorded from guinea pigs implanted with CI. The model (shown with lines) can predict the trends in the data, suggesting larger effect of increasing IPG for shorter phase duration. Whether the absolute differences between the model and the data are due to the different animal species, or because of differences in ECAP and single neuron responses is unclear.

Sub-threshold response

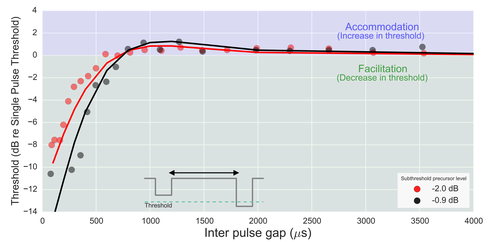

Fig.5 Immediately following a sub-threshold stimulus, the threshold decreases (known as 'facilitation'), and over time it increase (known as 'accommodation') relative to a threshold for a single pulse. The amplitude of such a change in threshold is dependent on the sub-threshold stimulus level. The data (re-plotted from Dynes, 1996) shows effect of two levels of pre-pulse stimulus on threshold for a second pulse. The model predictions (shown with lines) can quantitatively predict the effect of level on facilitation and accommodation.

Supra-threshold response

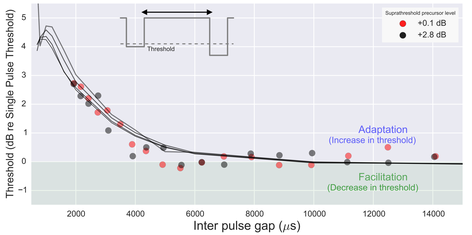

Fig.6 After an AP has been fired, the neuron goes through the 'absolute refractory period' during which no AP could be fired again. Following this, a threshold for firing a second AP is substantially higher, and reduces back to normal over the period known as the 'relative refractory period'. This effect is known as 'adaptation'. The rate of change in threshold during the relative refractory period shows a little dependence on a level of the first pulse, which produced an AP. The data for two pre-pulse levels is shown (re-plotted from Dynes, 1996) along with model responses for pre-pulse stimulus levels +1, +2, +4 and +6 dB relative to a single pulse threshold.

Polarity specific adaptation

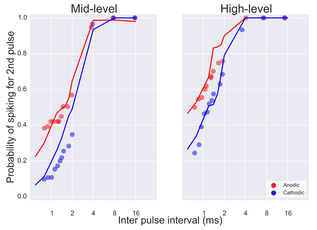

Fig.7 The rate of change in threshold during a relative refractory period shows dependence on stimulus polarity. This difference is possibly due to differences in the neural membrane properties at two different sites of excitation (Peripheral vs Central) along the AN. This effect is shown by Matsuoka et al., (2000) by measuring change in threshold as function of gap duration between a pre-pulse and the second pulse, for two polarities at two levels. Model can quantitatively predict this level as well as polarity dependence in adaptation.

Spike-rate adaptation

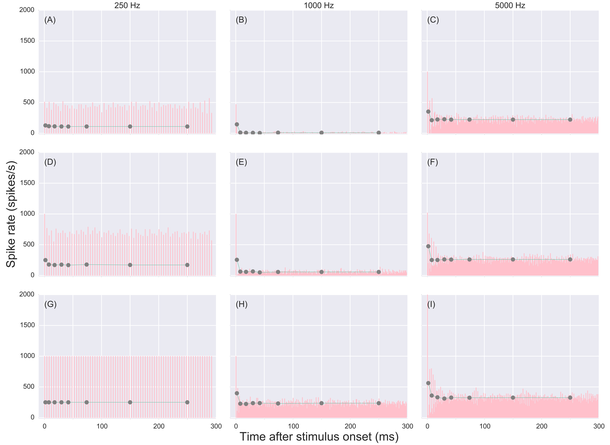

Fig.8 The figure shows a peri-stimulus time histogram (PSTH) predicted by the model for three pulse rates. PSTH is obtained for at low level (0.2 dB, A, B, C), mid level (0.8 dB, D, E, F) and high level (1.4 dB, G, H, I) relative to a threshold for a single pulse. Line joined by circles is an adaptive PSTH calculated with increasing bin width as described by Zhang et al., (2007) to quantify the spike rate adaptation. The levels are specified relative to threshold for a single pulse. The model can quantitatively predict the effect of level as well as stimulation rate on responsiveness of the AN over time.

Summary

A phenomenological model of AN for electrical stimulation (Joshi et al., 2015) is extended by addition of adaptation variable, and is tested for its ability to predict the responses to sub-threshold and supra-threshold stimulation. The model can quantitatively predict -

✓effect of pulse shapes
✓effect of sub-threshold stimulation
✓effect of supra-threshold stimulation
✓effect of stimulation pulse rates and stimulation level

With these features, the model presented here can be used to predict responses of the AN to various electrical stimulation paradigms used in clinical CIs, in order to quantify the information transfer in the AN. The model can also be used to model the degeneration of AN and its effect on responsiveness of the AN to various CI stimulation strategies.

Acknowledgements

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