Improved Parameterization of a Hybrid Phenomenological-Biophysical Model of Cochlear Implant Stimulation of the Auditory Nerve

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ABSTRACT

Background: Computational models of electrical stimulation of auditory nerve fibers (ANFs) extend from simple phenomenological models describing ANF spiking statistics through to detailed biophysical models describing the membrane potential and the activity of voltage-gated ion channels along the length of ANFs. Phenomenological models have the advantage of computational speed and a smaller set of parameters, but they may lack accuracy. The hybrid model of Joshi et al. (2017) aims to incorporate the best of both phenomenological and biophysical models. This model can accurately describe many response characteristics observed in cat ANF data, such as the increase in the dynamic range of an ANF's response with increasing pulse phase duration (PPD) of a biphasic stimulating pulse. However, preliminary simulations indicate that, with its default parameterization, the model's spontaneous firing rate is much higher than that observed in deafened cat ears, which could influence the dynamic range versus PPD behavior.

Methods: Simulations were run with single biphasic current pulses at a range of current levels to map out the model's discharge probability versus level function. From each probability versus level function, the relative spread (RS) was estimated as a measure of the model ANF's dynamic range. The onset time of the pulse and the PPD were systematically varied to determine how these affected the estimated RS. For each set of onset times and PPDs, the model parameters p_RS and c_RS were scaled by a range of factors to establish how these parameter values map onto the estimated RS values.

Results: The simulation results indicate that the model only produces RS values matching the cat ANF data, including the RS vs PPD effect, if i) the membrane potential is always initialized to the same resting potential and ii) the pulse onset time is close to zero, which are the defaults in the public release of the code. To obtain estimated RS values similar to cat ANFs for short PPDs, the parameters p_RS and c_RS had to be reduced by a factor of 3. This parameter scaling also reduced the spontaneous rate to zero, more consistent with the physiological data. However, the RS vs PPD effect is then greatly reduced, demonstrating that this effect was indeed influenced by the abnormally high spontaneous rate.

Conclusions: This study showed that the default parameterization of the Joshi et al. (2017) model does not generate appropriate dynamic ranges or rates of spontaneous activity in general. A new parameterization fixes these shortcomings, but further modifications will need to be made to the model to produce an appropriate increase in the dynamic range with increasing pulse phase duration. The code should also be modified so that the initial membrane potential is randomized with an appropriate probability distribution.

I. INTRODUCTION

- The different types of models of electrical stimulation of ANFs by cochlear implants (CIs) proposed in the literature span a large range of complexity and physiological detail, from simple phenomenological models with a small number of parameters (Takanen et al., 2016) through to biophysical models describing the activity of a single node of Ranvier or an entire axon (O'Brien and Rubinstein, 2016).
- The hybrid phenomenological-biophysical model of Joshi et al. (2017), shown in Fig. 1, aims to achieve a reasonable compromise between simplicity and accuracy.

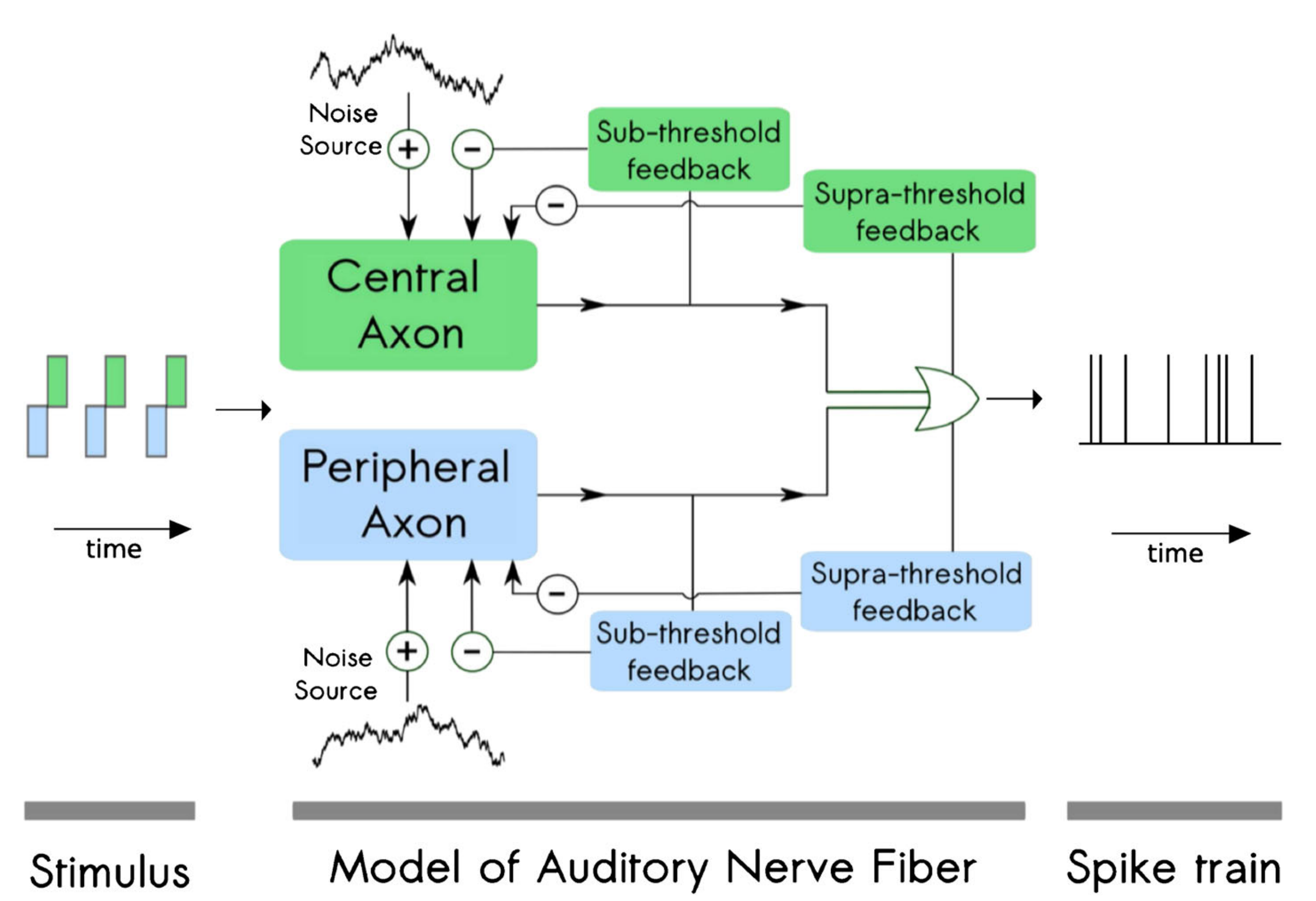

Figure 1: Schematic of the two-compartment neural model developed by Joshi et al. (2017), reprinted from Fig. 1 of that article. The model takes an extracellular stimulating current waveform as the input and produces spike instances as its output.

- Cathodic (negative) stimulating currents depolarize the peripheral axon compartment and hyperpolarize the central axon compartment, whereas anodic (positive) stimulating currents do the converse. The compartments have separate noise sources producing stochastic activity, subthreshold feedback producing accommodation (subthreshold adaptation), and suprathreshold feedback producing refractoriness and spike-rate adaptation. The first compartment to reach the threshold potential generates a spike.
- Each compartment is described by an exponential integrate-and-fire (eIAF) model, with the stimulating current, noise sources and subthreshold & suprathreshold feedback mechanisms all contributing to the change in the compartments' membrane potentials V over time, according to:

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = h(V) - I_{\mathrm{sub}} - I_{\mathrm{supra}} + I_{\mathrm{noise}} + I_{\mathrm{stim}} \tag{1}$$

where C is the membrane capacitance, and the filtering of the membrane potential is given by:

$$h(V) = -g_L(V - E_L) + g_L \Delta T\, e^{\frac{V - V_{thr}}{\Delta T}} \tag{2}$$

where g_L is the membrane conductance, E_L is the resting potential, ΔT is the slope factor for the exponential term, and V_{thr} is the threshold potential.

- The firing efficiency (FE) of an ANF for a given stimulus is defined as the number of neural spikes divided by the number of stimulating pulses and the number of stimulus repetitions, providing an estimate of the spiking probability per pulse.
- As shown in Fig. 2A, FE versus stimulating current level curves tend to be well fit by the equation:

$$\mathrm{FE} = \frac{1}{2}\left(1 + \mathrm{erf}\left(\frac{I_{\mathrm{stim}} - I_{\mathrm{thr}}}{\sqrt{2}\sigma}\right)\right) \tag{3}$$

where erf is the "error" (integrated-Gaussian) function, I_{thr} is the threshold current (corresponding to FE = 0.5), and σ is the standard deviation of the integrated-Gaussian function.

- The relative noise level of the integrated-Gaussian function is quantified by the *relative spread* (RS), which is the noise standard deviation σ divided by the threshold current I_{thr}.

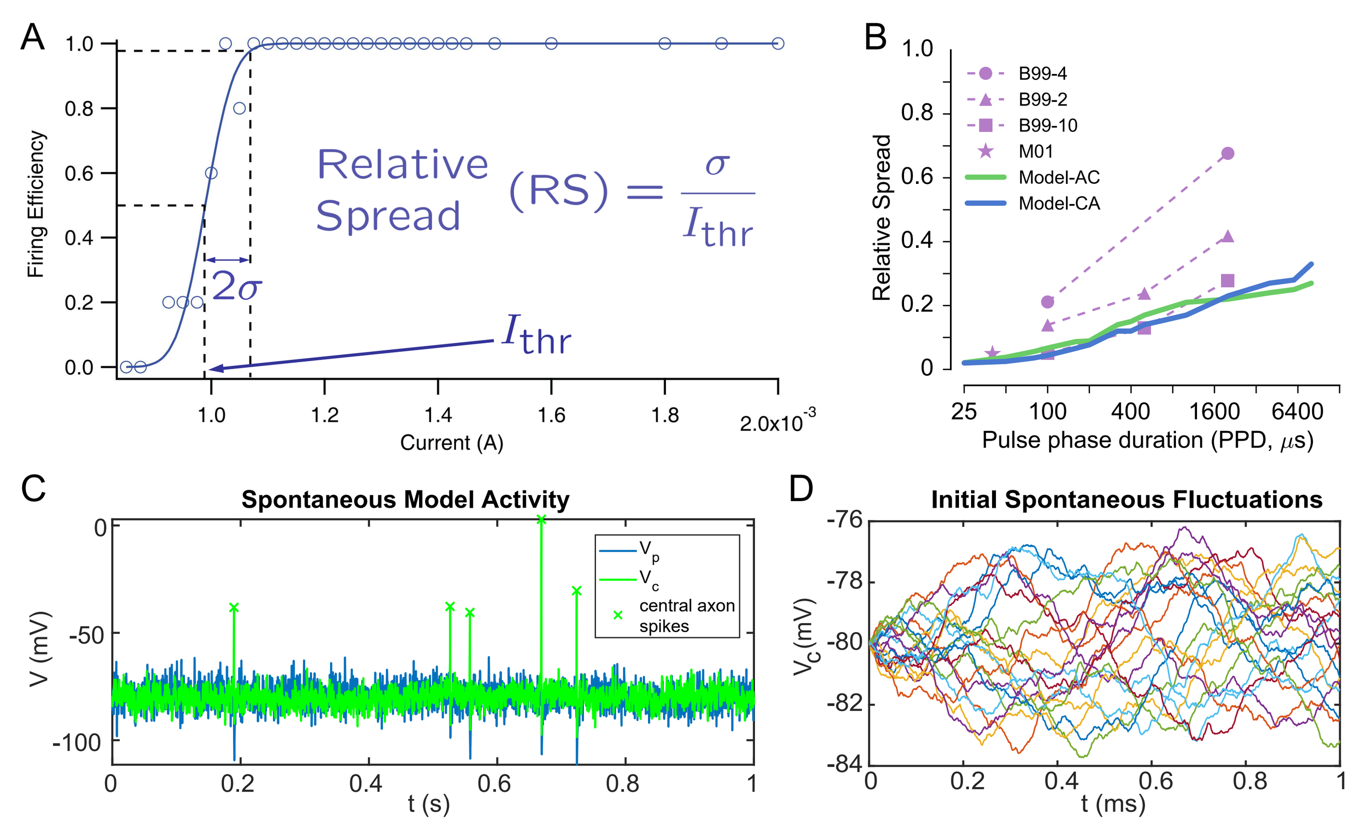

Figure 2: A: An example FE versus I_{stim} plot (open circles), fit by Eq. 3 (solid curve). B: Relative spread versus pulse phase duration data and model predictions for biphasic stimulation. Dashed magenta curves (B99-4, B99-2, B99-10) are cat ANF data from Bruce et al. (1999), while the magenta star (M01) is the average RS value for a population of cat ANFs from Miller et al. (2001). Model predictions are for anodic-phase first (green curve) and cathodic-phase first (blue curve) stimulation. Panel B reprinted from Fig. 4e of Joshi et al. (2017). C: Example of spontaneous activity for the model over a simulation period of 1 second. The membrane potential of the peripheral axon (blue curve) and central axon (green curve) are shown. It can be observed that spontaneous spikes (x) tend to occur in the central axon compartment rather than the peripheral axon. D: 20 simulations showing spontaneous fluctuations in the central axon's membrane potential over the first 1 millisecond after being initialized at the resting potential value E_L.

- As shown by the magenta dashed curves in Fig. 2B, cat ANFs exhibit an increase in RS with increasing pulse phase duration (PPD) for a single stimulating pulse.
- Earlier models describing this RS vs PPD effect required either an *ad hoc* phenomenological mechanism (Bruce et al., 1999) or a biophysical low-threshold potassium channel (Negm and Bruce, 2008).
- In contrast, the Joshi et al. model has a *fixed scaling of the noise sources*, determined by the parameters p_RS and c_RS, set to values of 0.062 and 0.075, respectively, in the public release of the code.
- Despite these fixed noise scaling parameters, the model is still able to produce the increasing RS versus PPD behavior (blue and green solid curves in Fig. 2B) observed in the data. This is likely because the noise sources have a $^1/_f$ frequency spectrum, such that there are larger random fluctuations on longer time scales than on shorter time scales.
- However, the model also produces more spontaneous spikes than is typical for ANFs in deafened ears (see Fig. 2C), the model's membrane potential is always initialized exactly to the resting potential parameter value E_L (see Fig. 2D), and the simulation duration increased with increasing PPD for the simulation results in Fig. 2B, potentially confounding the estimates of RS.
- This prompts a more thorough investigation of: i) the parameterization of the noise sources in the model, ii) the RS versus PPD effect, and iii) initialization of the membrane potential.

II. METHODS

- Simulations were performed using the public release of the code with the default parameters and with the relative spread parameters p_RS and c_RS scaled by ½, ⅓, and ¼.
- FE versus I_{stim} curves were obtain for 1,000 repetitions of a single biphasic pulse at each current level. The pulses had zero interphase gap, and both cathodic-phase first (CA) and anodic-phase first (AC) pulses were tested. Eq. 3 was fit to each FE vs I_{stim} curve and the RS value calculated.
- RS values were obtained for 20 pulse phase durations (PPDs) logarithmically spaced between 25 μs and 10 ms and pulse onset times of 0, 0.1, 0.2, and 0.3 ms.
- The spontaneous activity of each model variant was evaluated by running 1,000 simulations of duration 1 s with zero stimulating current, from which the mean spontaneous spike rate was calculated. 20 membrane traces in which no spikes occurred were randomly selected and the amplitude distributions of the membrane potentials in the second half of all of those traces computed.
- A version of the model was then created in which the peripheral and central axons' membrane potentials are initialized based on the computed amplitude distributions from the above analysis. The RS vs PPD and onset time simulations were then repeated with this model version.

III. RESULTS

- Figure 3 shows that the RS vs PPD curves change as a function of the pulse onset time for the default RS parameters (panel A), indicating that initializing the model's membrane potential at a fixed value is problematic. Scaling down the RS parameters (panels B–D) reduces the effect of the onset time but also gives unrealistically low RS vs PPD curves.

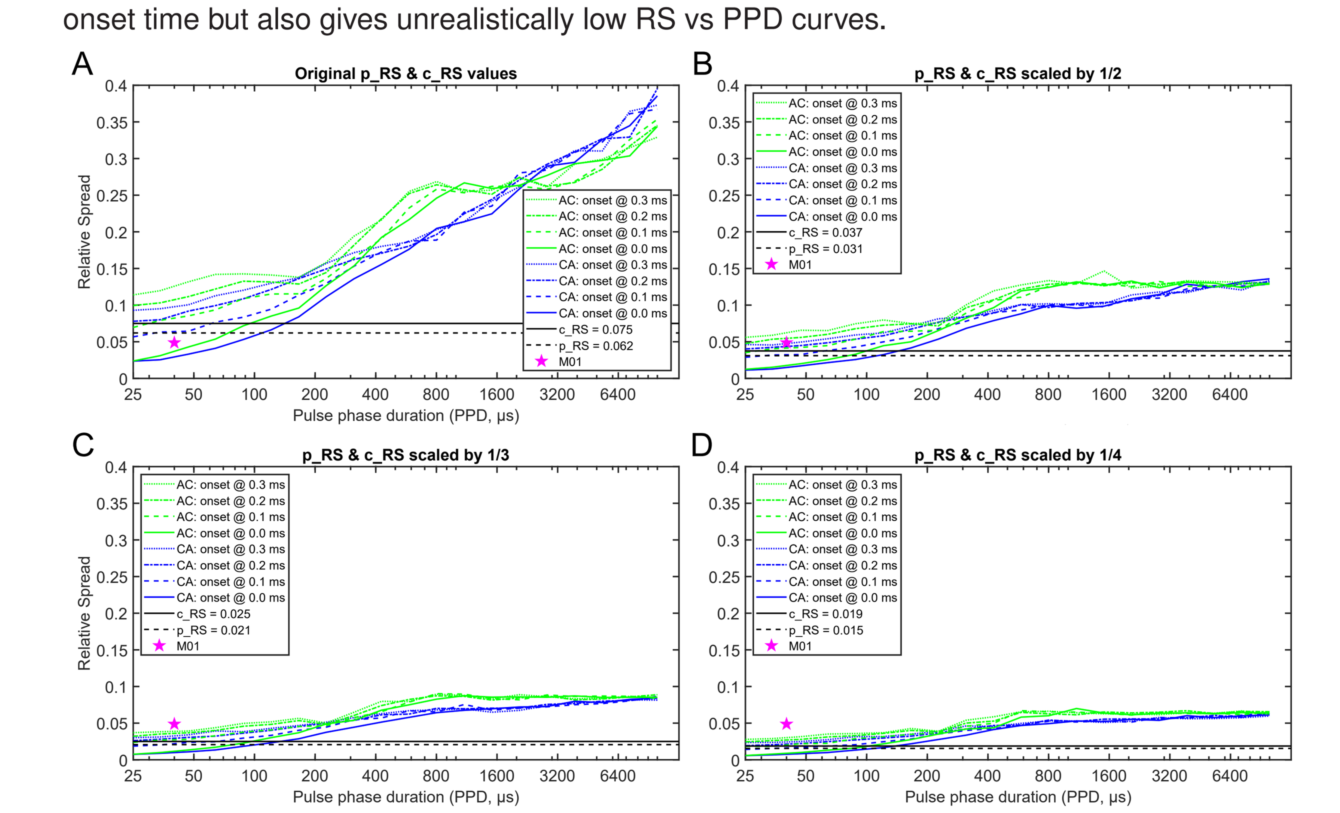

Figure 3: Model RS vs PPD curves for A) the original model RS parameter values, and scaling of these parameters by B) ½, C) ⅓, and D) ¼. The legend indicates the phase order (AC: anodic first, green curves; CA: cathodic first, blue curves) and the pulse onset time. The black horizontal lines show the model parameter values, and the magenta star is the data point from Miller et al. (2001).

- Figure 4 indicates that the spontaneous amplitude distributions of the peripheral and central axons' membrane potentials have Gaussian distributions and that the standard deviations of these distributions scale linearly with the RS-parameter scaling.

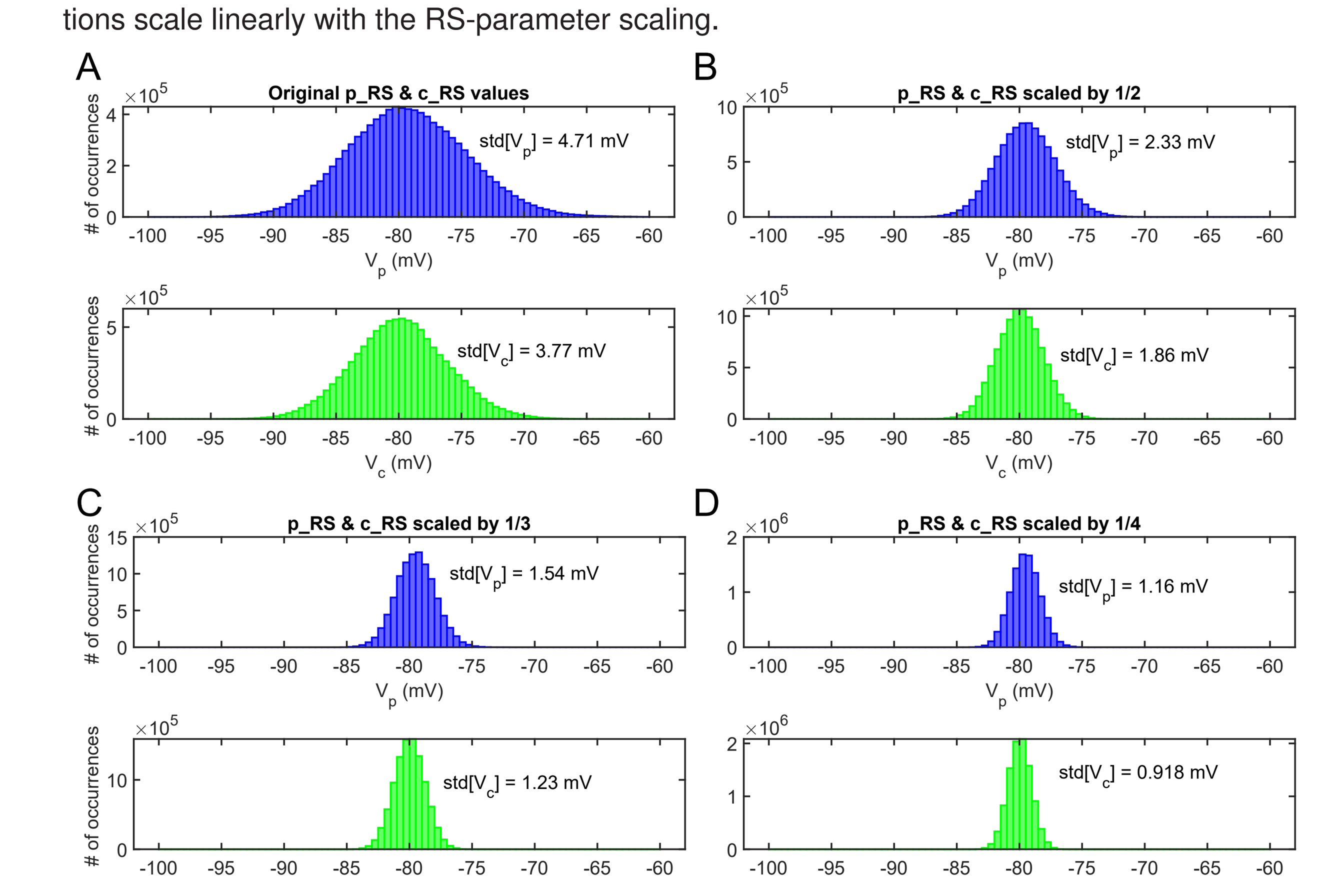

Figure 4: Steady-state membrane potential distributions for 0.5 s of spontaneous fluctuations for A) the original model RS parameter values, and scaling of these parameters by B) ½, C) ⅓, and D) ¼.

- Table 1 shows that the model with default parameters has a mean spontaneous spike rate of just under one spike per second, while reducing the RS parameters by a factor of 2 or more causes the spont rate to drop to zero, more consistent with ANF data from deafened ears.

Table 1: Estimates of mean spontaneous spike rate.

RS Parameter Scaling	1	½	⅓	¼
Mean spont rate (spikes/s)	0.878	0	0	0

- Figure 5 shows RS vs PPD curves for the version of the model that has randomized initial membrane potential values, which are set to be equal to the resting potential plus a normally-distributed pseudo-random number with appropriate standard deviation as given in Fig. 4.
- Using this randomized initialization produces RS vs PPD curves that are largely independent of the pulse onset time, but the default parameters produce RS values that are too large for shorter PPDs (Fig. 5A). Reducing the RS parameter values by a factor of 3 gives the correct magnitude of RS values for shorter PPDs (Fig. 5C), but the overall effect of PPD on RS values is greatly reduced.

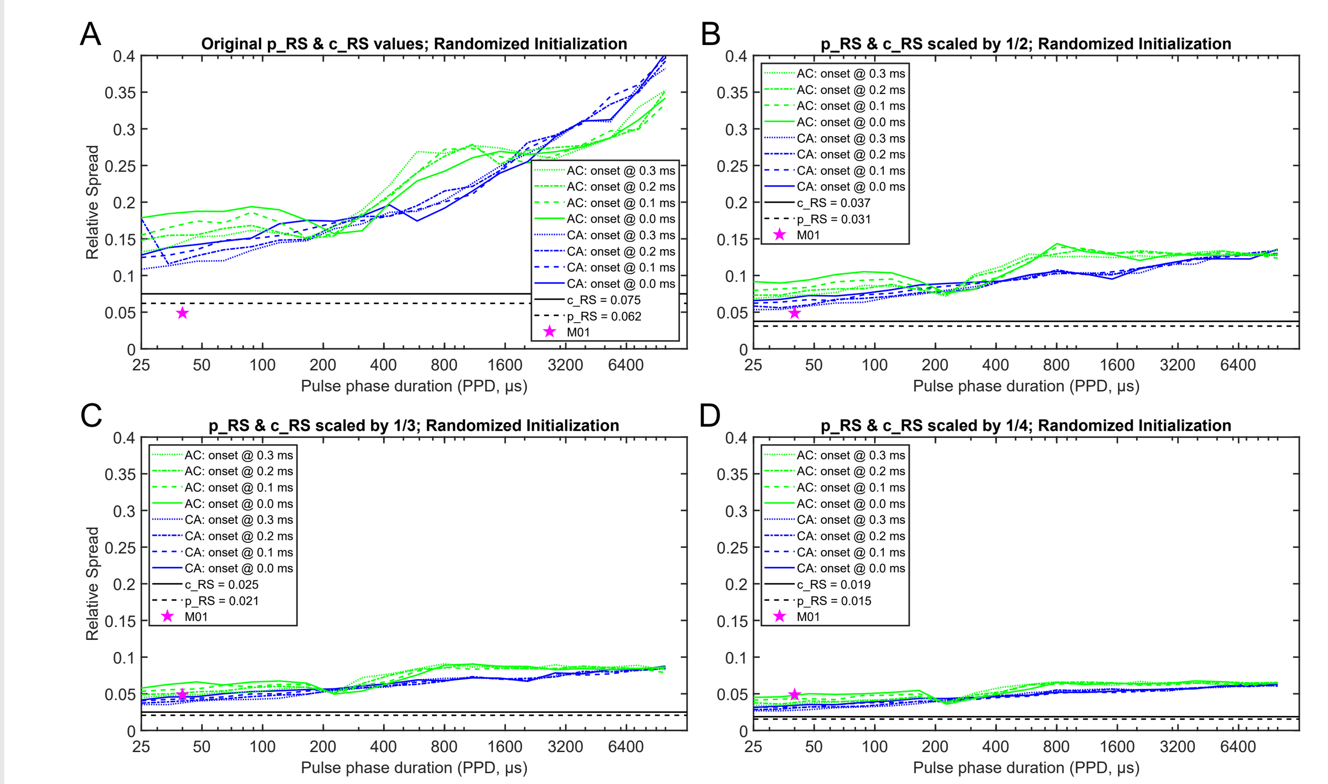

Figure 5: Model RS vs PPD curves for the modified model with randomized initialization of the membrane potential values, based on the distributions shown in Fig. 4. The plotting conventions are as for Fig. 3.

IV. DISCUSSION AND CONCLUSIONS

- The simulation results from this study indicate that the original parameterization and membrane potential initialization method of the Joshi et al. (2017) model lead to response properties that do not well match CI physiological data.
- Reducing the parameters p_RS and c_RS by a factor of 3 and appropriately randomizing the initial membrane potentials of the peripheral and central axon compartments produces more realistic spontaneous spike rates for auditory nerve fibers in a deafened ear and relative spread values for short pulse phase durations. However, this also reduces the predicted rate of increase in RS with increasing PPD.
- One approach to addressing this deficiency would be to investigate modifications of the statistics of the noise sources used in the model.
- Another avenue to pursue is substituting the model's subthreshold and suprathreshold adaptation mechanisms with more physiologically-realistic ion channels (Boulet and Bruce, 2017; Negm and Bruce, 2008, 2014). A likely additional benefit of this modification is that these voltage-gated ion channels predict the strong adaptation behavior observed in ANFs for stimulation rates above 1,000 pulses per second, which the Joshi model cannot explain.

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