# Beneath the Tip of the Iceberg in Auditory Nerve Fibers: Subthreshold Dynamics for Cochlear Implants


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## Abstract

Refractoriness is a common neural phenomenon that has been shown to characterize some aspects of the auditory nerve fiber (ANF) spike-dependent response to cochlear implant (CI) stimulation. However, for high-rate pulse trains, a greater drop-off in spike rate over time is often observed than can be explained by refractoriness alone. This is typically assumed to be caused by ongoing spike-dependent neural adaptation, but mounting evidence suggests that subthreshold stimulus-response behaviors may also play a crucial role in ANF stimulus-response electrophysiology. In this study, we explore two such mechanisms: facilitation in which a subthreshold stimulus increases the subsequent excitability, and accommodation in which the excitability is decreased.

Progress has been made in the area of developing phenomenological models to predict the effects of several of the aforementioned behaviors. However, up until now, no model has combined all four of these stimulus-response behaviors: refractoriness, spike-rate adaptation, facilitation and accommodation. In this study, we present a stochastic integrate-and-fire model that simultaneously considers all four phenomena using parameters from fits to data from paired-pulse experiments to model facilitation, accommodation (Dynes 1996, PhD Thesis) and refractoriness (Miller et al 2001, JARO); and as well as spike-rate adaptation (Nourski et al 2006, NIH QPR). We observed that spike-rate adaptation behaved as expected by showing a slow decay in excitability measured by post-stimulus time histograms (PSTHs). However, under various stimulus regimes, including (1) current levels that elicit a low-probability of spiking and (2) time-scales that are relevant for accommodation, the model also predicts long-term drops in the ANF spike-rate due to accommodation without explicitly modeling spike-rate adaptation. Thus, care should be taken when interpreting experimental PSTHs, since using only spike-rate adaptation may be insufficient to explain the drop in excitability over the duration of the stimulus. The proposed model with all four mechanisms permits a systematic investigation of their contribution to ANF response properties under various stimulus conditions.



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## I. What Processes Explain the Reduction in Spike Rate Over Time?

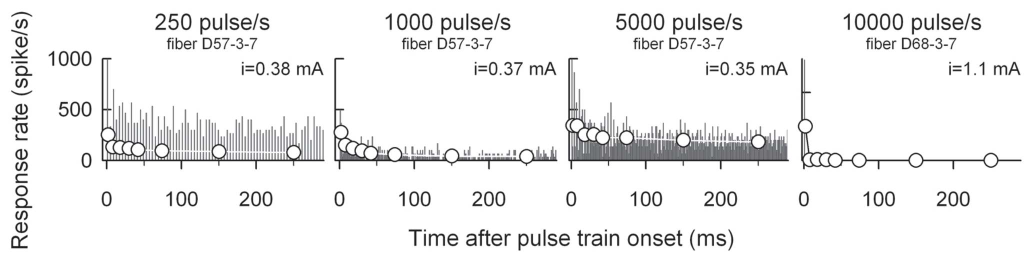


Figure 1: Post-Stimulus Time Histograms (PSTHs) from feline single ANF recordings (Zhang et al., 2007, see Fig. 2) for a constant amplitude biphasic pulse train.

## II. Single Pulse Response: The Threshold and the Noise

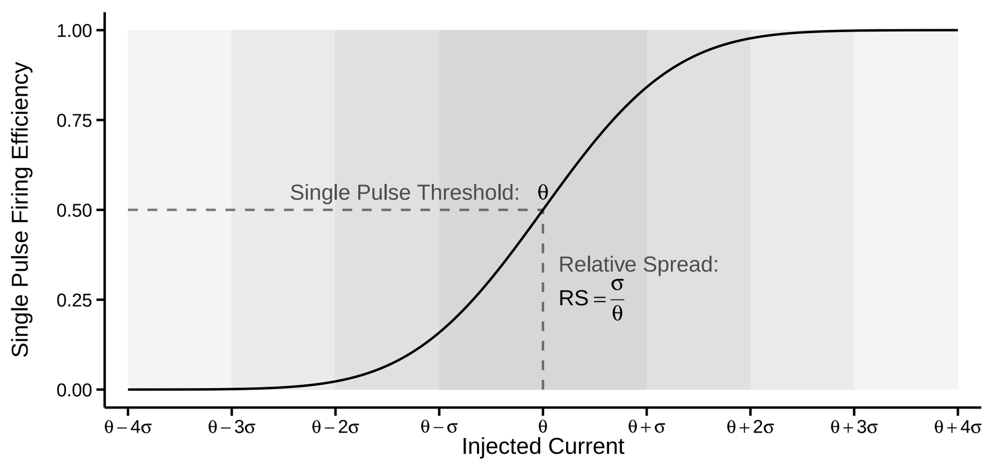


Figure 2: Single pulse firing efficiency (FE) as a function of the injected current. Single pulse threshold current ($\theta$) and relative spread (RS) characterize the FE with an integrated Gaussian function (Bruce et al., 1999b). RS is a normalized measure of a neuron's dynamic range given membrane fluctuations (Verveen, 1962; Verveen and Derksen, 1968).

## III. The Stimulus-Response Phenomena

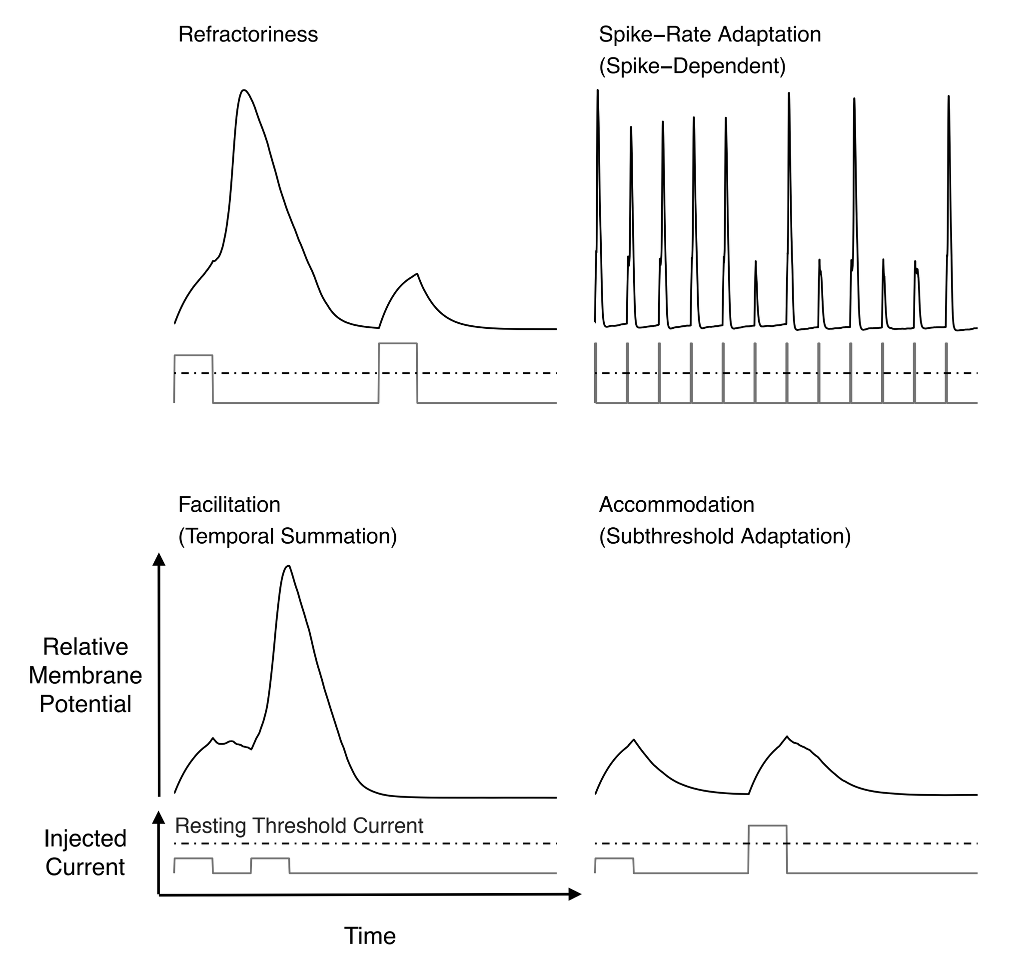


Figure 3: Single-trial voltage traces were generated from an augmented Hodgkin–Huxley ANF membrane model (Negm and Bruce, 2014) with updated hyperpolarization-activated cyclic nucleotide-gated cation (HCN) kinetics (Liu et al., 2014).

## IV. The Data: Refractoriness

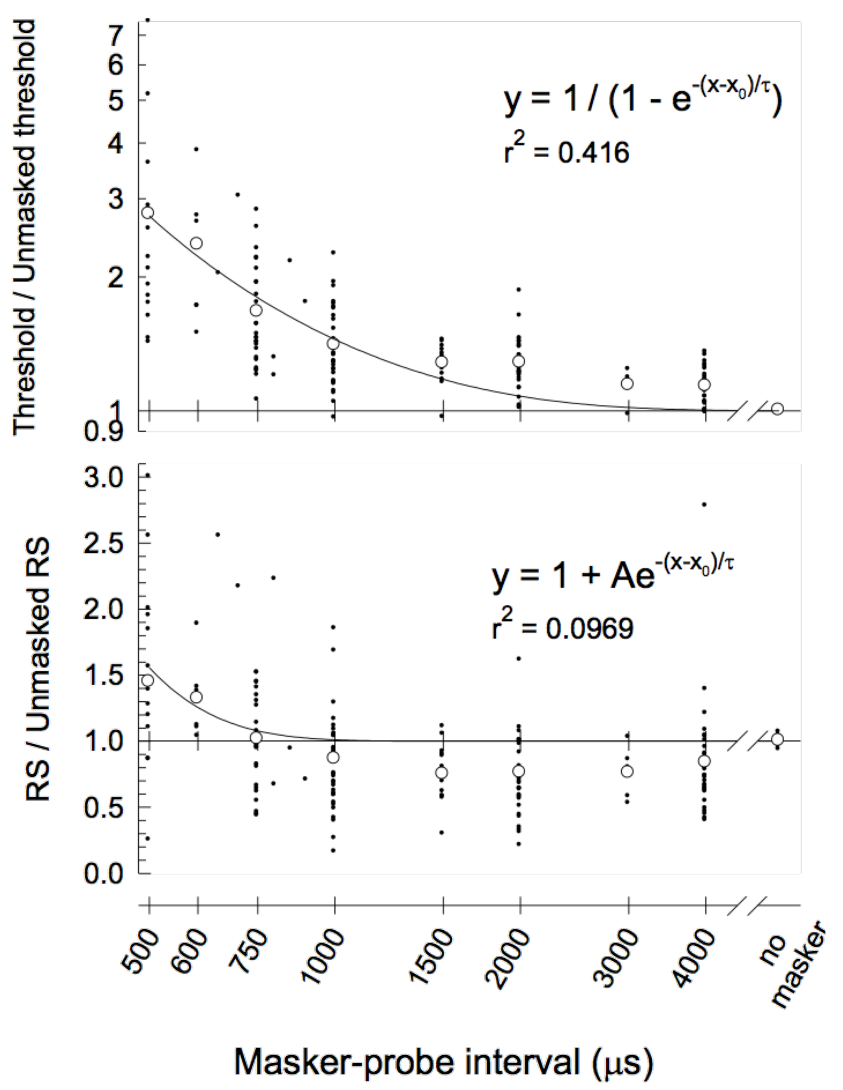


Figure 4: Changes to the threshold and RS following one spike (Miller et al., 2001, see Fig. 7). ANF feline stimulation with monophasic pulses.

## V. The Data: Facilitation and Accommodation

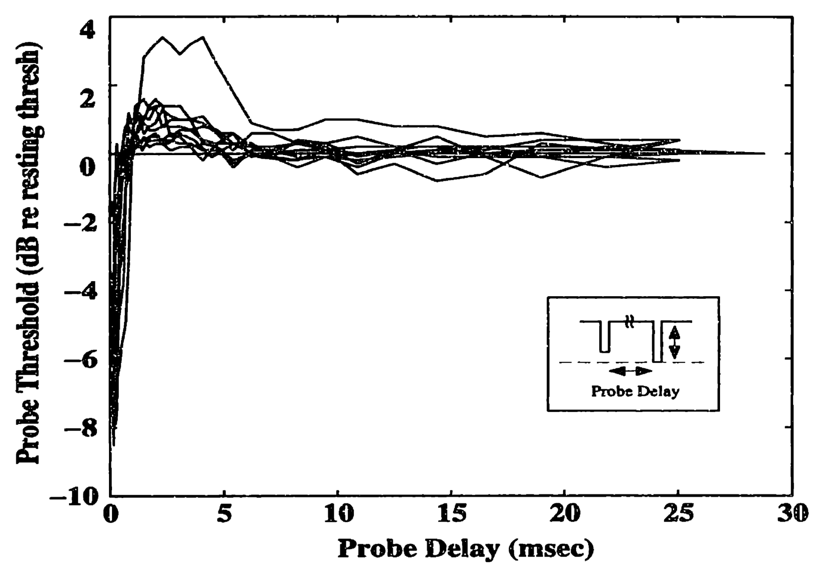


Figure 5: A subthreshold masker pulse alters the threshold for the probe pulse depending on the inter-pulse interval (IPI) (Dynes, 1996, see Fig. 3-2).

## VI. Facilitation: Passive and Active Contributions

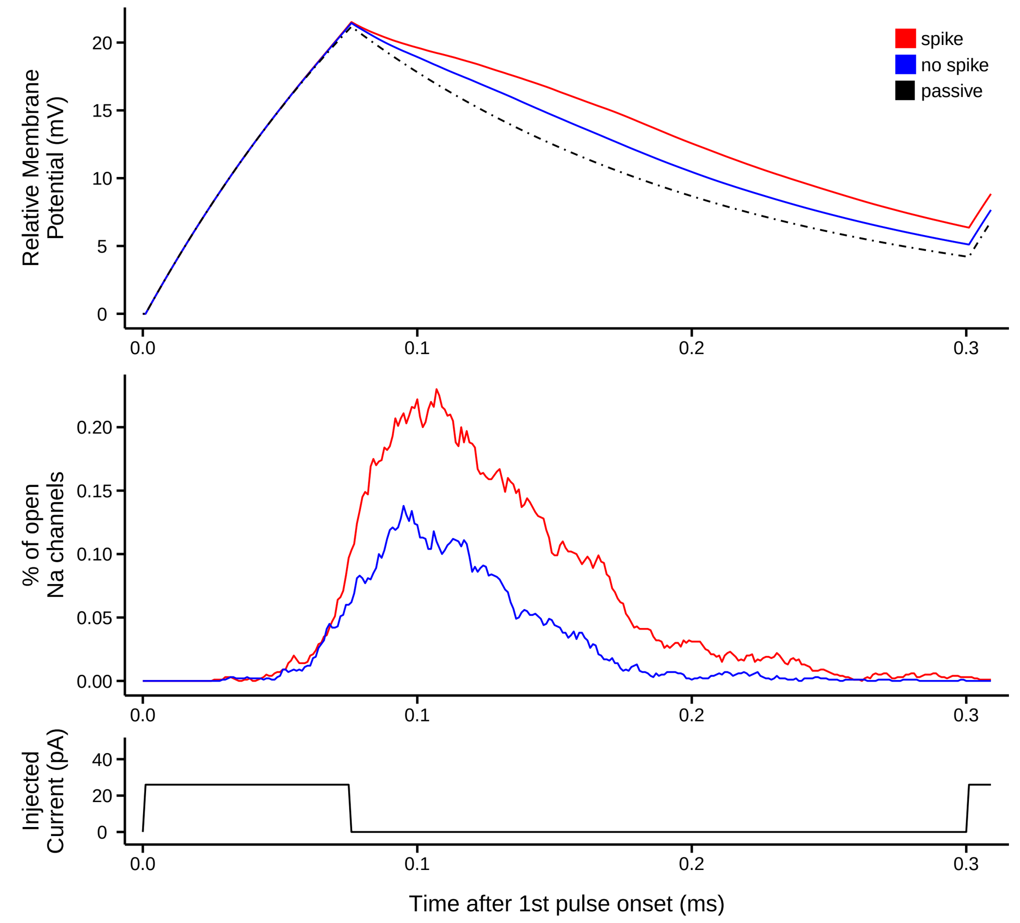


Figure 6: Passive facilitation can occur due to residual charge on the neural membrane at the time of a pulse. This can be augmented by active facilitation where large fluctuations in sodium activation sustain the membrane potential at a higher amplitude until the next pulse. Simulation results averaged over 100 trials of the stochastic Hodgkin–Huxley model (Hodgkin and Huxley, 1952; Mino et al., 2002). Red curves are for trials where the second pulse generated a spike, while blue curves are for trials where no spike was generated.

## VII. Stochastic IAF model with F+A, ref, and SRA

**Previous model version components**

- Stochastic single pulse model (Bruce et al., 1999b)
- ref: refractoriness threshold (Bruce et al., 2000, 1999a)
- SRA: spike-rate adaptation (Nourski et al., 2006)
- IAF: Integrate-and-fire membrane model (Lapicque, 1907; Nourski et al., 2006)

**New components in this model**

- F+A: active facilitation + accommodation threshold (Dynes, 1996)
- ref: refractoriness RS (Miller et al., 2001)
- membrane noise: $1/f$ spectrum (Verveen and Derksen, 1968)

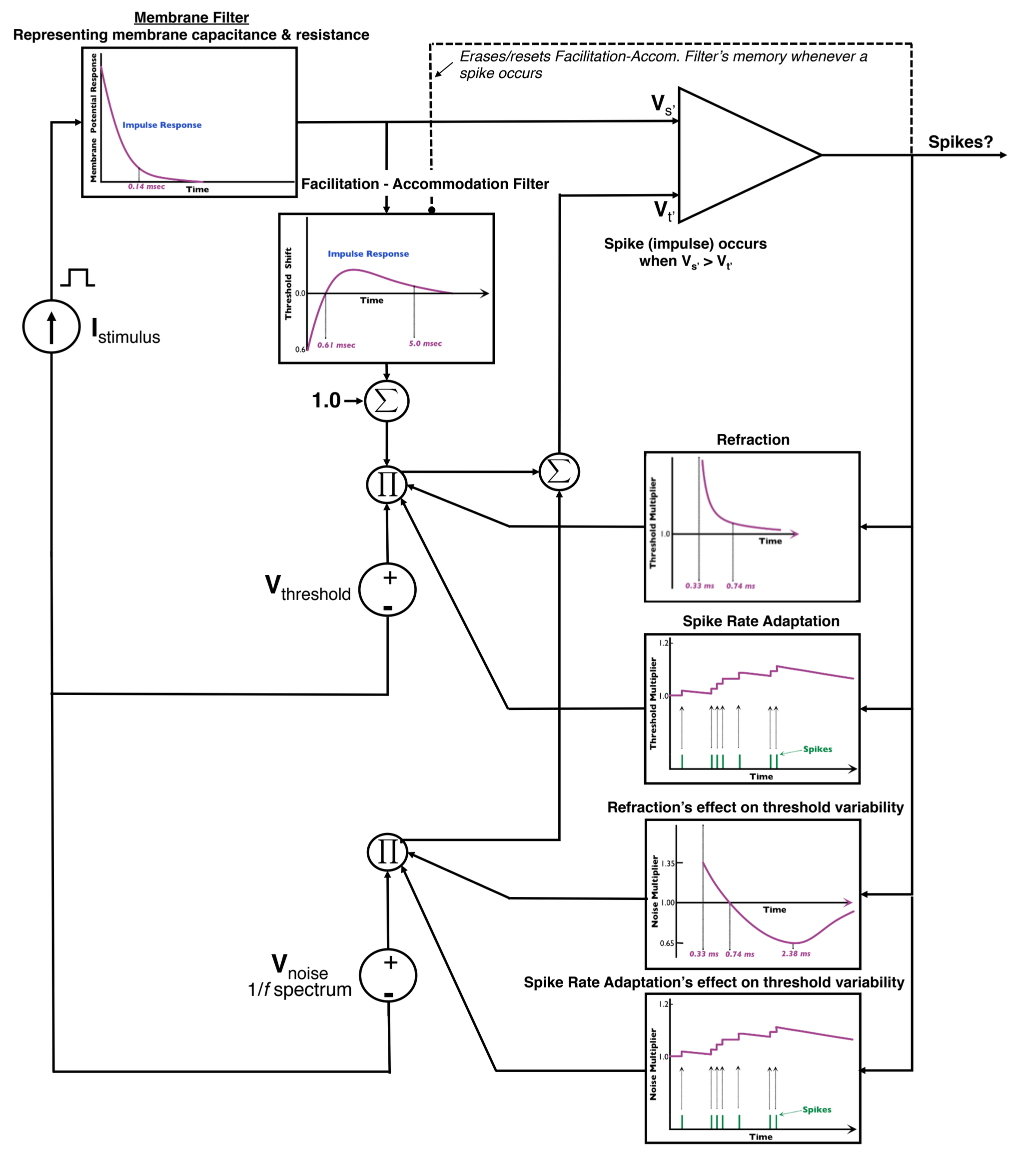


Figure 7: Model schematic.

## VIII. Model Responses to Monophasic Paired-Pulse Stimulation

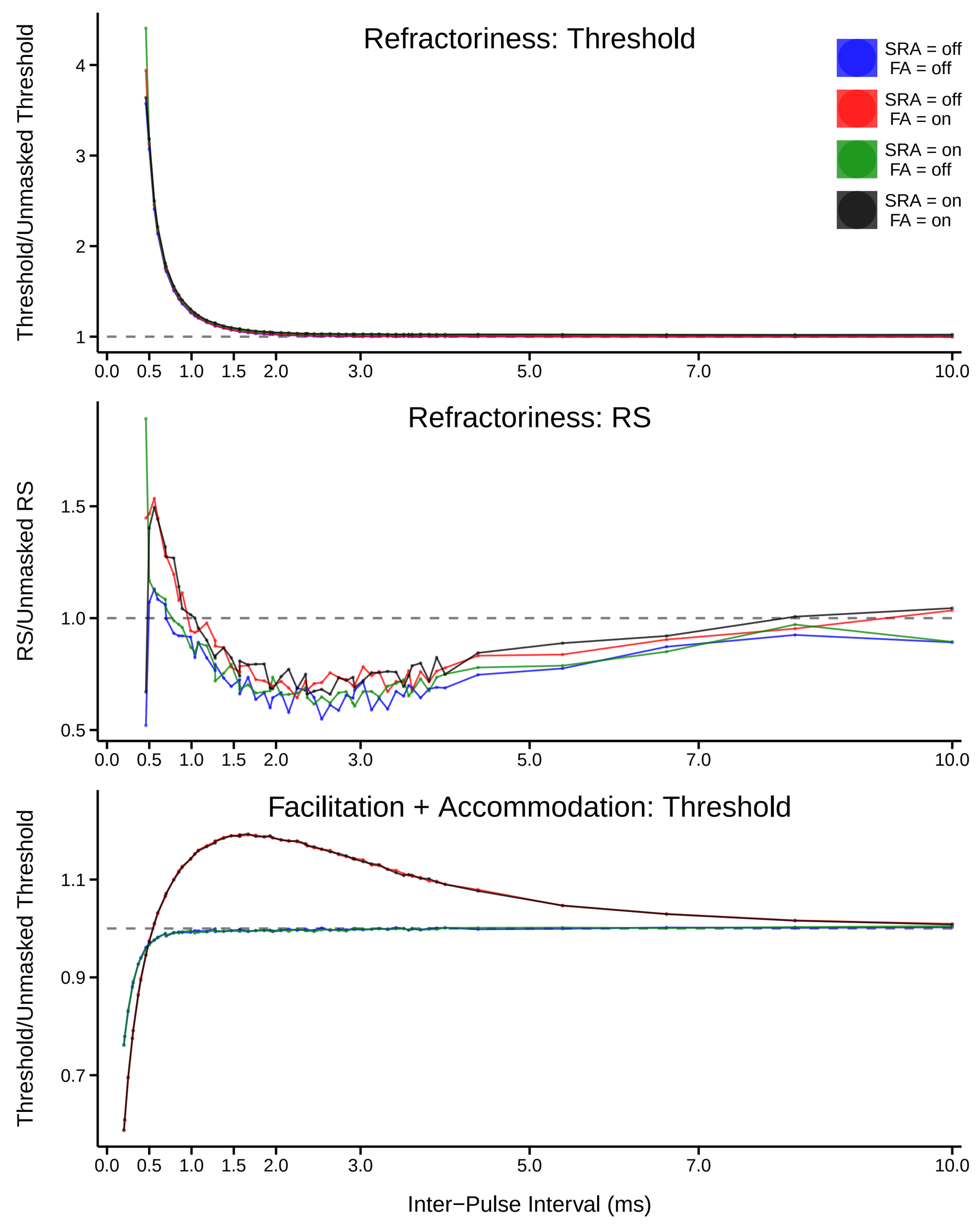


Figure 8: Responses of a paired-pulse paradigm classified for the cases when (1) the masker pulse generated a spike (possible refractoriness) or (2) the masker pulse did not elicit a spike (facilitation and accommodation). Both pulses were delivered at the single pulse threshold current level. Dashed line represents the single pulse threshold or RS.

## IX. PSTH Responses at 1,000 pulses/s and Varying Current Level

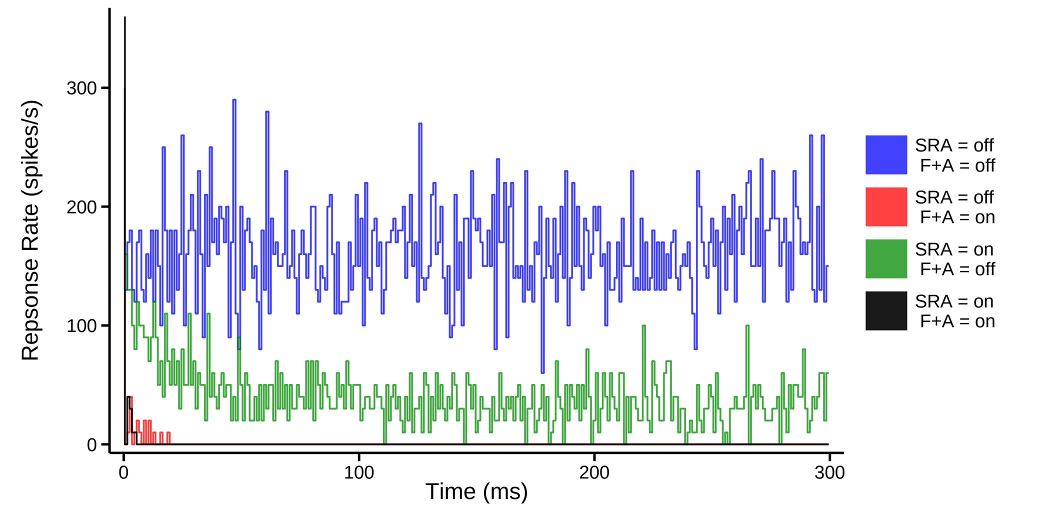

Figure 9: Pulse rate: 1,000 pulses/s, current level: single-pulse FE = 30.85%.

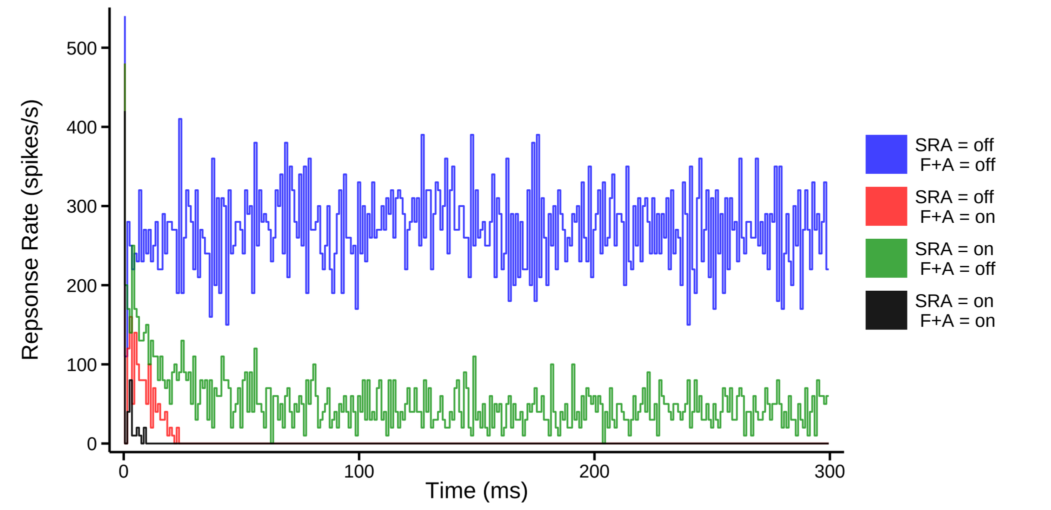

Figure 10: Pulse rate: 1,000 pulses/s, current level: single-pulse FE = 50%.

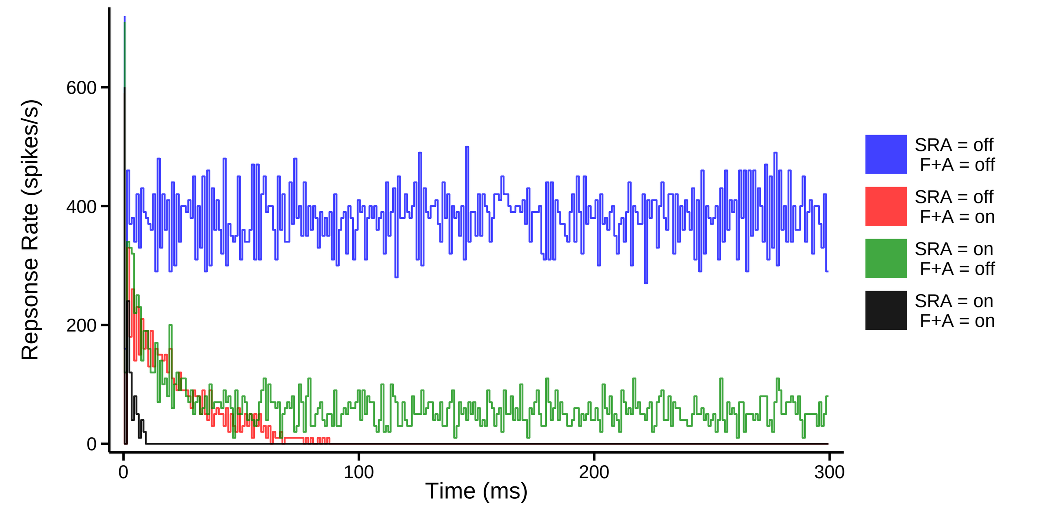

Figure 11: Pulse rate: 1,000 pulses/s, current level: single-pulse FE = 69.15%.

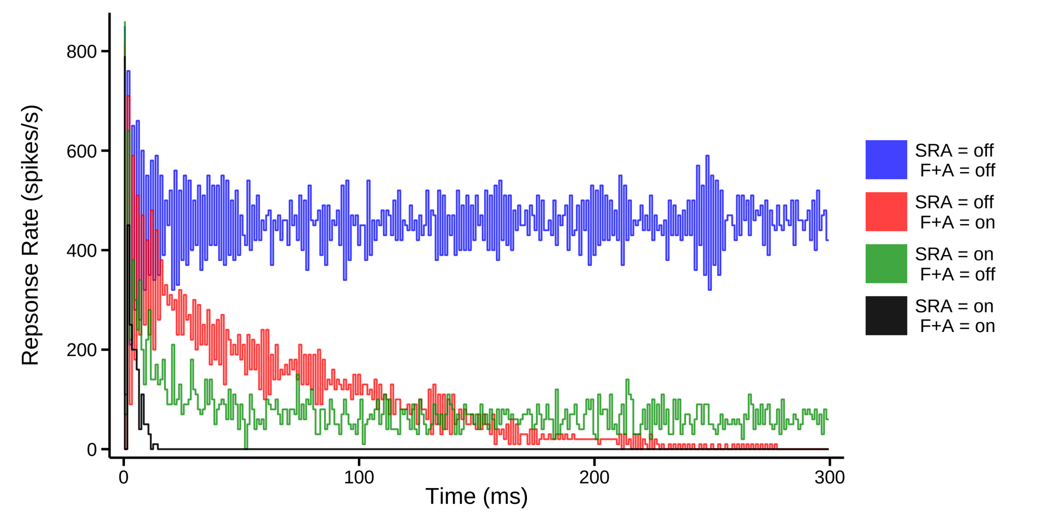

Figure 12: Pulse rate: 1,000 pulses/s, current level: single-pulse FE = 84.13%.

## X. PSTH Responses at 10,000 pulses/s

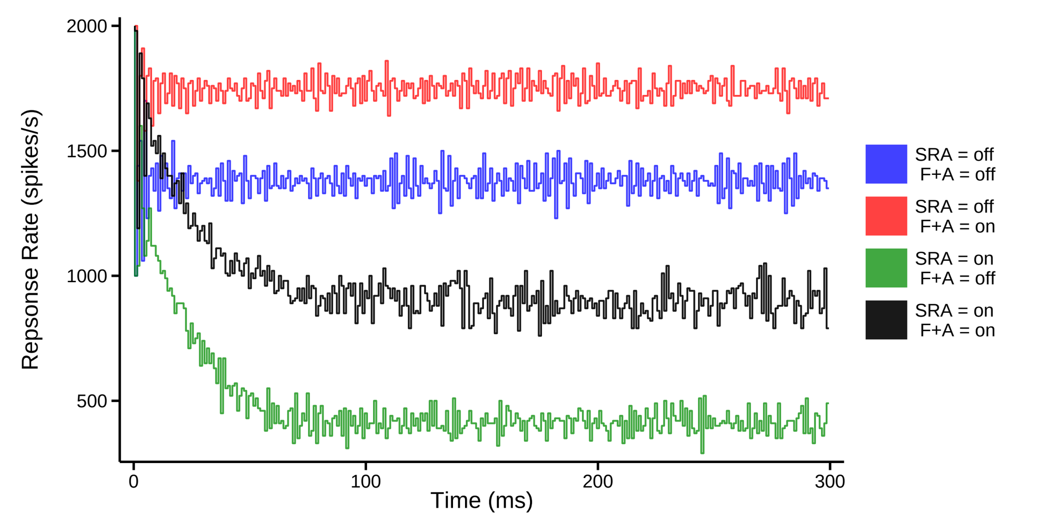

Figure 13: Pulse rate: 10,000 pulses/s, current level: single-pulse FE = 2.28%.

## XI. Rate-Level Functions at End of Pulse Train

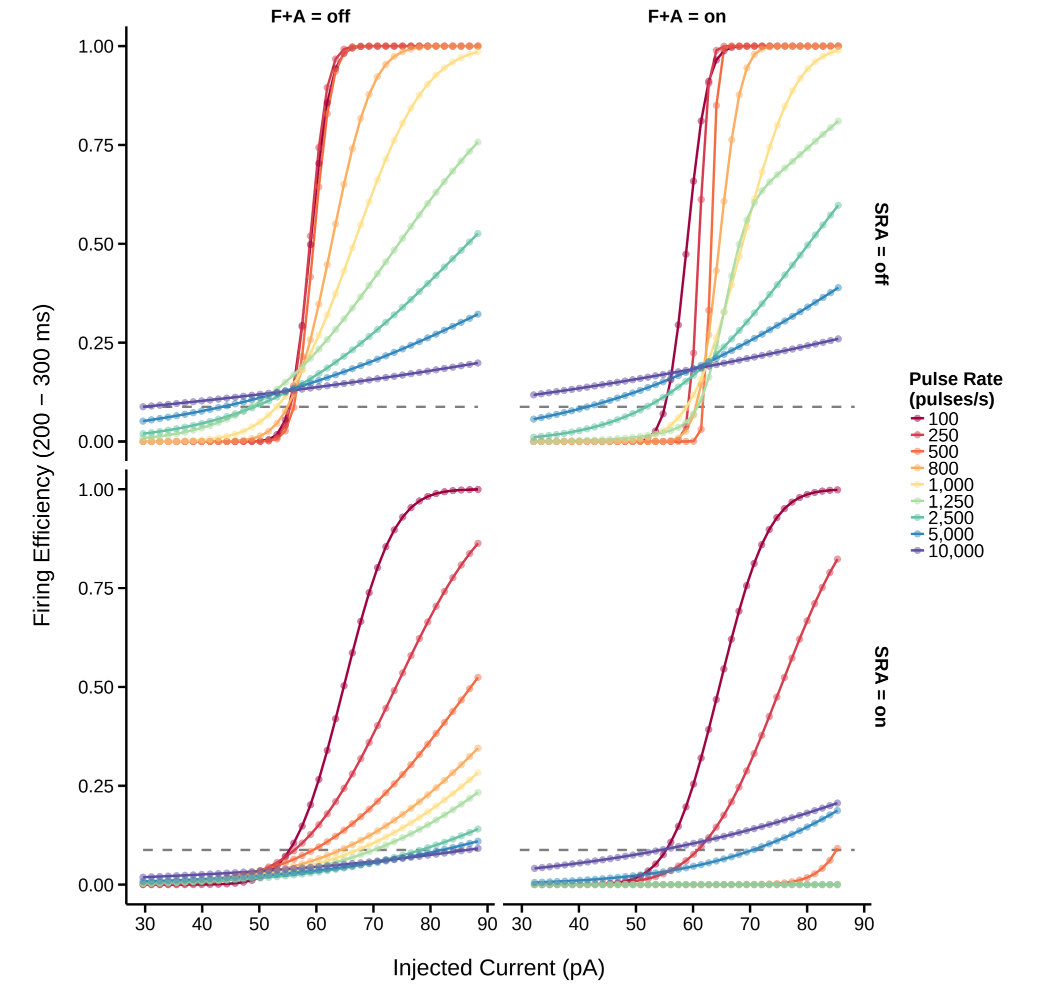


Figure 14: FE of responses to pulse trains over the 200 to 300 ms interval. Dashed line represents the FE at the lowest current level for the 10,000 pulses/s curve and SRA = off and F+A = off model.

## XII. Conclusions

### Results Summary

- Accommodation alone is capable of progressively reducing spike rates down to 0 spikes/s at moderate stimulation rates (≈1,000 pulses/s).
- Accommodation works synergistically with spike-rate adaptation to more rapidly stop spiking at moderate pulse train rates.
- Passive facilitation imposes a relatively high floor on the long-term pulse train firing efficiency at high stimulus rates (≈5,000 to 10,000 pulses/s).
- Active facilitation boosts this phenomenon.
- Thus, facilitation dominates over accommodation at ≈5,000 to 10,000 pulses/s in the model results, whereas in the data from Zhang et al. (2007) shown in Fig. 1 accommodation appears to dominate at 10,000 pulses/s.

### Future Directions

- One possible explanation of the difference between the data and the model results at 10,000 pulses/s is that the pulse train data were responses to biphasic pulses, and facilitation is reduced is cases of biphasic stimulation (not shown). This is consistent with results from multicompartmental biophysical models.
- Alternatively, active facilitation and accommodation may need to be modeled as separate processes, because the neural membrane mechanisms are thought to be different for these phenomena:
  - Passive facilitation: charging from membrane capacitance and resistance.
  - Active facilitation: subthreshold fluctuations of Na activation can sustain the membrane potential between pulses.
  - Accommodation: slow kinetics and regulation of the resting membrane potential by hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels can impart long-lasting reductions in subthreshold excitability (Liu et al., 2014; Negm and Bruce, 2014; Yi et al., 2010).
- It will be valuable to determine multiple accurate combinations of refractoriness, spike-rate adaptation, accommodation and facilitation that explain variation in PSTHs.
- The initial model is based on monophasic pulses. It will be important to generalize the model to explain single pulse and pulse train responses to multiple pulse shapes including (1) biphasic with and without interphase gaps and (2) different pulse widths since the effect of facilitation and accommodation interacts with the output of the membrane-filtered pulse.

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