Cellular adaptation shapes spike train covariability: theory and application to tinnitus.

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Introduction

Tinnitus, a disease characterized by the persistent perception of a subjective sound, is accompanied by **increased firing rates** and **hypersynchrony** in many auditory areas (Eggermont & Roberts 2004). The mechanisms that underly tinnitus-related changes in neural activity are ill understood. In a mouse model of tinnitus, the principal cells of the dorsal cochlear nucleus (DCN) have significantly weaker after-hyperpolarization (AHP) currents in tinnitus mice. A reduction in AHP current will lead to increased firing activity. It remains, however, to consider how AHP currents affects the synchronization of pairs of neurons. Using a combination of **simulations** and **linear response theory** we show that **weakened AHP currents**, consistent with those of DCN principal cells of mice with behavioral evidence of tinnitus, **increase both the firing rate and covariability** of spike train responses. Furthermore, we show that the **increase in long-timescale covariability is not a rate effect**. We show that these results are not obvious from past theories linking firing rate and correlation (de la Rocha et al., 2007) and uncover a novel relationship between cellular biophysics and pairwise spiking statistics, **linking intrinsic negative feedback and covariability**.

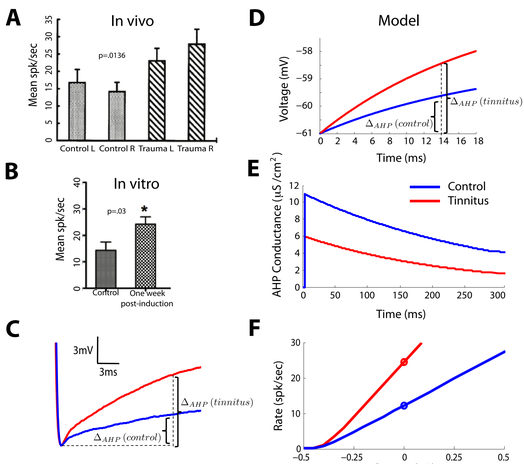
Weak-AHP tinnitus model

In rodent models of acoustic trauma-induced tinnitus, elevated spontaneous firing rates are report in the DCN both *in vivo* (Fig. 1A) and *in vitro* (Fig. 1B) preparations. *In vitro* work has established that reduced AHP current recruitment is a biophysical correlate of these changes (Fig. 1C).

Based on past work (Doiron et al., 2011; Leao et al., 2012), we model a DCN principal cell as an exponential integrate-and-fire neuron with a spike-activated AHP conductance:

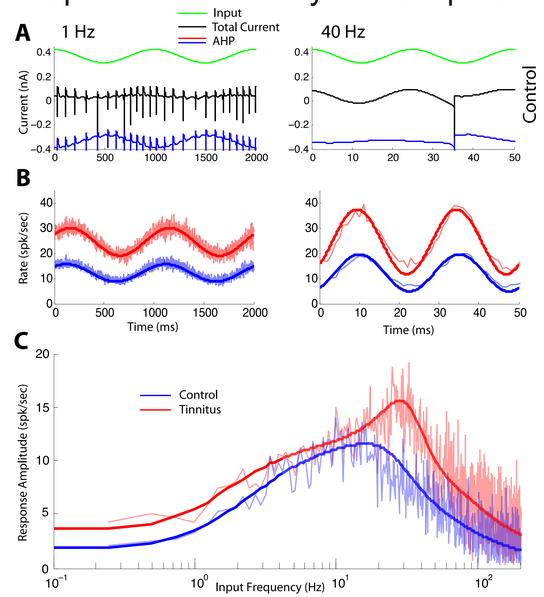
$$C\frac{dV_i}{dt} = g_L\left(V_L - V\right) + g_x x\left(V_x - V\right) + g_L\Delta\exp\frac{V-V_T}{\Delta} + \mu + \sqrt{1-c}\xi_i\left(t\right) + \sqrt{c}\xi_c\left(t\right)$$

$$\frac{dx}{dt} = -\frac{x}{\tau_x} + \sum_{j=1}^{\infty}\delta\left(t - t_j\right)$$



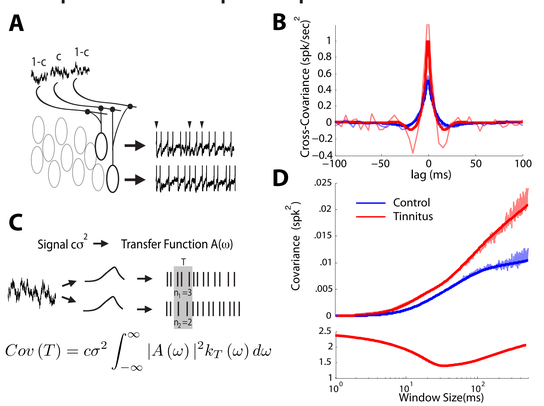
AHP Conductance controls the post-spike membrane dynamics and gain of the f-I curve. (A) DCN principal cell firing rates are decreased in an in vivo chinchilla model of noise-induced tinnitus (Brozoski et al, 2002). (B) This finding is replicated in an vitro mouse model (Li & Tzounopoulos, personal communication). (C) The afterhyperpolarization of DCN principal cells from mice with behavioral evidence of tinnitus is half as strong as that of control mice. (D) The model membrane dynamics exhibit a slow afterhyperpolarization, of the same size and time course as the in vitro data. With the neuron hyper-polarized to rest, one spike was evoked to show the post-spike membrane dynamics. (E) The AHP conductance is kicked by g_x when a spike occurs. Consistent with the weakened AHP observed in tinnitus, the tinnitus model is characterized by an AHP half as strong as the control. (F) f-I curves for the control and tinnitus models, obtained by solving the 2-D Fokker-Planck equation for the steady-state rate (Richardson, 2009). Circles mark the spontaneous firing rates, at 0 injected current. The change in AHP leads to a change in firing rate matching the in vitro change.

Adaptation cancels dynamic inputs



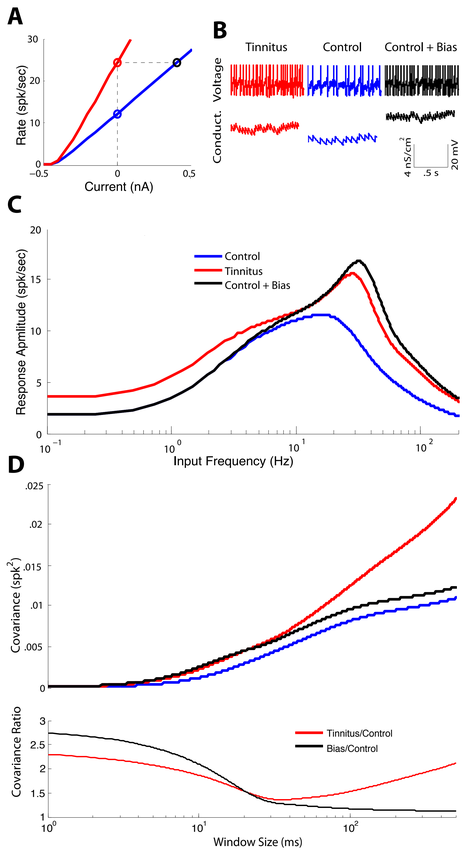
AHP current cancels dynamic inputs in a frequency-dependent fashion, shaping the single cell firing rate response. (A) Left: we inject a sinusoidal current at 1 Hz (green). The AHP current elicited (blue) cancels off the input, yielding a net current near 0 nA (black). Right: we inject a sinusoid at 40 Hz, and the AHP is less able to track and cancel this faster input. (B) The firing rate responses to those same inputs reflect how well the AHP cancells off the injected current. The tinnitus neuron responds more strongly than the control to a dynamic input. (C) The transfer function for each type of neuron describes how strongly an input at a given frequency will modulate the firing rate, analogously to the f-I curve (which is the transfer at 0 Hz). Lines: theory obtained by solving the Fokker-Planck equation (Richardson, 2007; 2008; 2009), shaded lines: simulation.

Adaptation shapes spike-train covariability



Adaptation shapes spike-train covariance and correlation. (A) In the dorsal cochlear nucleus, parallel fibers are a source of partially correlated fluctuating inputs to the principal cells. (B) The cross-correlogram of two tinnitus neurons exhibits a stronger peak and sharper resonance than that of control neurons. Lines: theory obtained from the inverse Fourier transform of the transfer function, circles: simulation. (C) A linear response theory (de la Rocha et al., 2007) allows us to predict the spike train covariance of a pair of neurons, using only knowledge of the single-cell transfer function. (D) The weaker AHP of the tinnitus model yields increased spike train covariance on both short and long timescales. Lines: theory, shaded lines: simulation.

Gain, not rate, determines long-timescale covariability.



Firing rate does not account for the long-timescale hyper-covariance of the tinnitus neurons. (A) We propose an alternative, simple hyperexcitability model for the DCN correlates of tinnitus. With control adaptation strength, a high bias injection yields the same firing rate as the tinnitus case (black circle), modeling a change in the resting membrane potential or the mean synaptic input (the latter consistent to 0th order with DCN disinhibition seen in tinnitus (Middleton et al, 2012)). (B) Voltage and conductance traces for each of the three cases. (C) At low frequencies, the transfer function of the control+bias model is equal to the control, because the two have the same adaptation dynamics and strength canceling slow fluctuations. The high frequency transfer is dominated by the firing rate effect, and the control+bias and tinnitus cases approach each other. (D) At short time-scales, the control+bias model exhibits increased covariability even greater than in the tinnitus case. At long timescales, however, it fails to exhibit the long timescale increased covariance of the weak-adaptation tinnitus model. These properties are inherited from the transfer functions.

AHP conductance linearizes and controls gain of long-timescale responses.

Focusing on the large T limit, we have that $A\left(\omega\right) \to \frac{\partial r}{\partial \mu}$.

Now, to uncover how the AHP conductance sets gain and covariability, we define an effective bias (Ermentrout, 1998; Sutherland, Doiron & Longtin, 2009) and self-consistently relate mean adaptation and steady-state firing rate r_0:

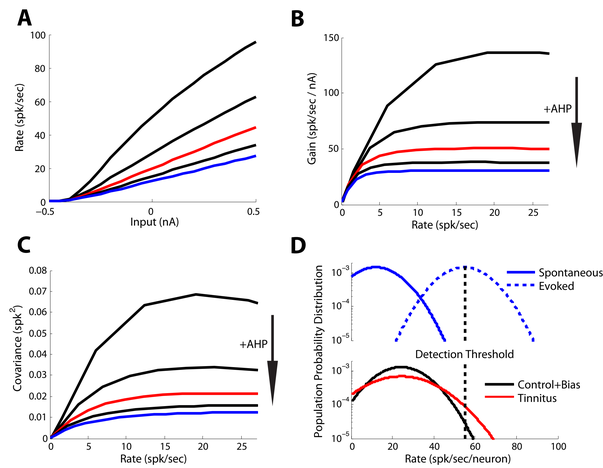
$$\mu_{eff} = \mu + \langle g_x x\left(V_x - V\right)\rangle$$
$$= \mu + g_x r_0 \tau_x\left(V_x - \langle V_0\rangle\right)$$

Applying the chain rule to $\frac{\partial r_0}{\partial \mu}$ and simplifying, we see that for large g_x:

$$\frac{\partial r_0}{\partial \mu} = \frac{1}{g_x\tau_x\left(\langle V_0\rangle - V_x\right)}$$

We see that the firing rate gain is inversely proportional to g_x and independent of the drive μ, showing why the tinnitus model and not the control+bias model can shape co-variability.

AHP conductance shapes pairwise and population statistics



Gain, not rate, determines covariance. (A) f-I curves as g_x is varied. The control and tinnitus models of the previous figures are marked blue and red, respectively. As the AHP becomes stronger, the gain of the f-I curve decreases. (B) As g_x increases, the f-I curve becomes more linear over a wider input domain. (C) As g_x increases, the (long-timescale) spike-train covariance both decreases and becomes less dependent on firing rate. It inherits both properties from the gain-rate curve of (B). (D) The variability of population responses is determined by pairwise covariability. We speculate that changes in covariability could shift spontaneous population activity above a sound detection threshold and cause downstream auditory neurons to spike as if in response to sound, propagating tinnitus-like activity.

Conclusion

- Afterhyperpolarizing conductances shape the input-output gain of a neuron by cancelling off slow inputs.
- This gain control shapes the long-timescale covariability of neurons, in a manner that depends on the strength and timescale of the adaptation.
- Increased firing rate of DCN principal cells in tinnitus due to a weakened AHP will lead to increased long-timescale synchrony, but simple hyperexcitability would not.

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