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Research Paper

A simple model of the inner-hair-cell ribbon synapse accounts for mammalian auditory-nerve-fiber spontaneous spike times

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ABSTRACT

The initial neural encoding of acoustic information occurs by means of spikes in primary auditory afferents. Each mammalian primary auditory afferent (type-I auditory-nerve fiber; ANF) is associated with only one ribbon synapse in one receptor cell (inner hair cell; IHC). The properties of ANF spike trains therefore provide an indirect view of the operation of individual IHC synapses. We showed previously that a point process model of presynaptic vesicle pool depletion and deterministic exponential replenishment, combined with short postsynaptic neural refractoriness, accounts for the interspike interval (ISI) distributions, serial ISI correlations, and spike-count statistics of a population of cat-ANF spontaneous spike trains. Here, we demonstrate that this previous synapse model produces unrealistic properties when spike rates are high and show that this problem can be resolved if the replenishment of each release site is stochastic and independent. We assume that the depletion probability varies between synapses to produce differences in spontaneous rate and that the other model parameters are constant across synapses. We find that this model fits best with only four release sites per IHC synapse, a mean replenishment time of 17 ms, and absolute and mean relative refractory periods of 0.6 ms each. This model accounts for ANF spontaneous spike timing better than two influential, comprehensive models of the auditory periphery. It also reproduces ISI distributions from spontaneous and steady-state driven activity from other studies and other mammalian species. Adding fractal noise to the rate of depletion of each release site can yield long-range correlations as typically observed in long spike trains. We also examine two model variants having more complex vesicle cycles, but neither variant yields a markedly improved fit or a different estimate of the number of release sites. In addition, we examine a model variant having both short and long relative refractory components and find that it cannot account for all aspects of the data. These model results will be beneficial for understanding ribbon synapses and ANF responses to acoustic stimulation.

1. Introduction

Acoustic information from the auditory periphery is relayed to the brain via primary auditory afferents and encoded in the timing of the spikes generated by them. In the mammalian cochlea, the peripheral axon of each primary auditory afferent (type-I auditory-nerve fiber; ANF) usually contacts only one sensory receptor cell (inner hair cell; IHC) at one private ribbon synapse, which converts the graded IHC membrane potential to a train of ANF spikes via the release of glutamate (Matthews and Fuchs, 2010). Release events also occur spontaneously in the absence of acoustic stimulation, and nearly all cause a spike unless the ANF is refractory (Siegel, 1992; Rutherford et al., 2012; Zhang-Hooks et al., 2016). Spike timing in ANF spontaneous activity therefore provides an indirect view of ribbon synapse function in vivo.

Spontaneous activity has been modeled by point processes in which stochastic trains of excitatory events are modified by postsynaptic refractoriness to yield spike trains (e.g., Kiang et al., 1965; Gaumond et al., 1983; Bibikov and Ivanitskii, 1985; Teich and Khanna, 1985; Young and Barta, 1986; Teich et al., 1990a,b; Lowen and Teich, 1992; Carney, 1993; Li and Young, 1993; Miller and Wang, 1993; Prijs et al., 1993; Delgutte, 1996; Johnson, 1996; Zhang et al., 2001; Jackson and Carney, 2005; Heil et al., 2007; Peterson et al., 2014; for review, see Heil and Peterson, 2015,

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2017). Event trains were often assumed to be Poisson renewal point processes, with all history effects in the subsequent spike trains being attributed to postsynaptic refractoriness. Several observations contradict such an assumption. First, mean refractory periods are short (~1 ms; Brown, 1994; Cartee et al., 2000; Miller et al., 2001; Shepherd et al., 2004; Morsnowski et al., 2006; Joshi et al., 2017), whereas interspike interval (ISI) distributions deviate over tens of milliseconds from the exponential distribution expected for a Poisson process. Second, similar deviations were also reported for distributions of intervals between excitatory postsynaptic currents (EPSCs), which occur prior to postsynaptic refractoriness (Wu et al., 2016). Third, predominantly negative serial correlations exist between low-order (e.g., adjacent) ISIs (Prijs et al., 1993; Peterson et al., 2014), and positive correlations exist between higher-order ISIs (Lowen and Teich, 1992; Teich and Lowen, 1994). These history effects in the distribution and ordering of ISIs manifest in the Fano factor, which measures spike-count variability (Teich and Khanna, 1985; Lowen and Teich, 1992; Peterson et al., 2014). The spike trains are less variable than a Poisson process over short time scales, due to refractoriness and negative serial ISI correlations, but more variable than a Poisson process over long time scales, due to rate fluctuations that generate positive long-range correlations and cause the Fano factor to grow in a power-law-like fashion with increasing counting time (Teich, 1989; Teich et al., 1990a,b; Lowen and Teich, 1992; Teich and Lowen, 1994; Delgutte, 1996; Kelly et al., 1996; Chacron et al., 2001; Jackson and Carney, 2005; Moezzi et al., 2014, 2016). Such fluctuations likely originate presynaptically (Wu et al., 2016).

Here, we describe an alternative to the point process model used by Peterson et al. (2014) to account for the major history effects in cat-ANF spontaneous spike trains. Each train of excitatory release events is generated via the depletion and replenishment of a small number of presynaptic release sites and is then modified by ANF refractoriness to yield a spike train. Unlike in the previous model, each release site is depleted and replenished independently and stochastically, which enables the model to better account for spontaneous (and even steady-state sound-driven) activity having a high spike rate and allows for interevent interval (IEI) distributions to be derived analytically. The structure of the model is nearly identical (see 2.3) to that proposed by Frank et al. (2010), but our estimates of the model parameters differ markedly from theirs. We demonstrate that the model, with our parameter estimates, accounts for the major properties of a population of cat-ANF spontaneous spike trains much better than popular comprehensive models of the auditory periphery (Meddis, 1986; Zilany et al., 2014). We show that the model also accounts for the IEI distributions of individual EPSC trains and the ISI distributions of individual spike trains from several mammalian species, and that the effects of long-range correlations on spike-count variability can be reproduced using fractional Gaussian noise. We also explore more complex model variants having an additional rate-limiting step in the vesicle cycle, but find no reason to prefer them to the simpler version. Finally, we explore a more complex variant having both short and long relative refractory components and find that it cannot account for all aspects of the data.

2. Materials and methods

2.1. Data

Most of the data for this study were used in two previous studies of the first-order ISI distributions from spontaneous spike trains of cat ANFs (Heil et al., 2007; Peterson et al., 2014), with the details of data acquisition given in the former. Briefly, in five barbiturate-anesthetized adult cats (three females, two males), spikes of 171 individual ANFs were recorded extracellularly, with microelectrodes, from the left auditory nerve near its exit from the internal auditory meatus. Continuous samples of spontaneous activity (470 samples between 12.5 and 134.4 s long) were recorded, along with responses to various stimuli for other purposes (e.g., Heil et al., 2008, 2011). Spike times were taken as the instants at which the amplified and filtered electrode signal crossed a Schmitt trigger level. They were stored digitally with a precision of 1 μs.

The rat-ANF EPSC data used in this study were provided by Jingjing Sherry Wu and Elisabeth Glowatzki and are the same as those reported in Wu et al. (2016). The gerbil-ANF spike data used in this study were provided by Antoine Huet, Jérôme Bourien, and Jean-Luc Puel and were obtained using methods described in Huet et al. (2016). The chinchilla-ANF spike data used in this study were provided by Robert E. Wickesberg and were obtained from chinchillas anesthetized with ketamine and acepromazine. When multiple samples of spontaneous activity existed for a single chinchilla ANF, we pooled the ISIs across them to obtain a smoother ISI distribution.

The guinea-pig-ANF spike data and the remaining cat-ANF spike data used in this study were extracted from figures in the literature. Specifically, we extracted ISI distributions (histograms, probability densities, or hazard rates; see 2.2.2) from guinea pig ANFs in Figs. 2 and 5 of Manley and Robertson (1976) and cat ANFs in Fig. 5 of Gaumond et al. (1982) and Fig. 4 of Li and Young (1993). The extracted distributions were then compared to corresponding distributions generated from spike trains simulated with the model, some of which are shown in Results. In addition, standard deviations and means of ISIs from cat-ANF spontaneous and sound-driven spike trains were extracted from Fig. 3A and B of Li and Young (1993) and used to compute coefficients of variation. All data were extracted manually using WebPlotDigitizer developed by Ankit Rohatgi and available online.[1]

2.2. Data analysis

All data analysis was performed using MATLAB R2015a and R2016a (The MathWorks, Inc., Natick, MA, USA). Samples from our database of cat-ANF spontaneous spike trains were considered for analysis only if they had at least 500 ISIs (180 of 470 samples). Because all but one sample meeting this criterion came from high-spontaneous-rate (high-SR) ANFs (>18 spikes/s; Liberman, 1978), we only considered those samples here (179 of 180 samples, with durations from 12.5 to 50 s). For each spike train, first-order ISIs were calculated with a precision of 1 μs.

2.2.1. Stationarity of interspike intervals

The Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test was used to assess the null hypothesis that the ISIs of each spike train were generated by a stationary process, as opposed to being generated by a nonstationary unit-root process (Kwiatkowski et al., 1992). In this test, a time series is expressed as the sum of a deterministic trend, a random walk, and a stationary error (Kwiatkowski et al., 1992). Because the ISIs as a function of ISI number would have a slope of zero for a stationary spike train, the deterministic trend was omitted to test for level-stationarity rather than trend-stationarity. The test requires a calculation of the long-run variance for a specified lag truncation value. Kwiatkowski et al. (1992) recommend using lag truncations on the order of $\sqrt{n}$, where n is the sample size (here, the number of ISIs in the spike train). We performed the test using five consecutive lag truncations centered on the integer nearest to $\sqrt{n}$ and deemed the spike train stationary if the null

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[1] http://www.arohatgi.info/WebPlotDigitizer.

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