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Using Tweedie distributions for fitting spike count data

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HIGHLIGHTS

- Variance of the spike counts distributions often depends supra-linearly on the mean.
- We used Tweedie distributions, that have this property, to fit spike count data.
- We show how to estimate the Tweedie distributions parameters from the data.
- Tweedie distributions often fit the data better than Poisson distributions.
- Tweedie distributions increase the reliability of tests for stimulus dependence.

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ABSTRACT

Background: The nature of spike count distributions is of great practical concern for the analysis of neural data. These distributions often have a tendency for 'failures' and a long tail of large counts, and may show a strong dependence of variance on the mean. Furthermore, spike count distributions often show multiplicative rather than additive effects of covariates. We analyzed the responses of neurons in primary auditory cortex to transposed stimuli as a function of interaural time differences (ITD). In more than half of the cases, the variance of neuronal responses showed a supralinear dependence on the mean spike count.
New method: We explored the use of the Tweedie family of distributions, which has a supralinear dependence of means on variances. To quantify the effects of ITD on neuronal responses, we used generalized linear models (GLMs), and developed methods for significance testing under the Tweedie assumption.
Results: We found the Tweedie distribution to be generally a better fit to the data than the Poisson distribution for over-dispersed responses.
Comparison with existing methods: Standard analysis of variance wrongly assumes Gaussian distributions with fixed variance and additive effects, but even generalized models under Poisson assumptions may be hampered by the over-dispersion of spike counts. The use of GLMs assuming Tweedie distributions increased the reliability of tests of sensitivity to ITD in our data.
Conclusions: When spike count variance depends strongly on the mean, the use of Tweedie distributions for analyzing the data is advised.

1. Introduction

The nature of spike count distributions in response to repeated presentations of the same stimulus is of great practical concern for the analysis of neural data. The variability of spike counts, which is usually attributed to the inevitable uncontrolled variables that occur in all neurophysiological experiments, reduces the information on stimulus identity carried by the neuronal responses. Spike count data are often assumed to have a Poisson distribution. This assumption is most often tested, if at all, by calculating the 'Fano factor' (Buracas et al., 1998), defined as the ratio of the variance to the mean spike count over trials. A perfectly repeatable neural response has a Fano factor equal to zero, and a Poisson distribution has a Fano factor equal to one. In fact, a large number of studies have reported Fano factors that are greater than one (e.g. Heggelund and Albus, 1978 among others), although several exceptions to this rule showing low variability of the response have also been reported (e.g. DeWeese et al., 2003).

Standard statistical tests that are often used for spike counts may be severely hampered by such effects. The standard analysis of variance (ANOVA) tests require spike count distributions to be

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Gaussian, as well as homoscedastic – having equal variance at all experimental conditions, independent of their means. ANOVA also assumes additive effects of covariates. These assumptions often fail with spike count data. Spike count distributions are often non-Gaussian, with a tendency for 'failures' (high probability of 0 counts even for relatively high average spike counts, e.g. Ulanovsky et al. (2004)) and may have a long tail of large counts due to bursting. Furthermore, spike count data often show a strong dependence of variance on the mean. This is already true for Poisson data, where the variance is equal to the mean. Over-dispersion relative to Poisson exaggerates such effects. Finally, spike count distributions often show multiplicative rather than additive effects of covariates.

Recently, some of these issues have been addressed by adopting the framework of *Generalized Linear Models* (GLM, Nelder and Wedderburn, 1972). GLMs generalize linear regression (which implicitly underlies ANOVAs), but allow non-normal error distributions (one parameter exponential families, including Poisson, binomial, and gamma) and a non-linear transformation between the linear sum of covariates and the model parameter, encoding for example multiplicative rather than additive effects. However, most applications of GLMs in the literature do not deal with the over-dispersion of the spike count distributions and their tendency to appear as mixtures of failures and successes.

We present here an analysis framework based on GLMs that is appropriate for data which is over-dispersed relative to Poisson. This framework is illustrated by analyzing the responses of high best frequency (BF) neurons in cat primary auditory cortex to transposed stimuli (van de Par and Kohlrausch, 1997) as a function of interaural time differences (ITD). The transposed stimuli are generated by multiplying a high-frequency carrier with a low-frequency envelope. The envelope of the transposed stimuli is generated by applying a simple hair cell model (half-wave rectification followed by lowpass filter) to a low-frequency stimulus. Transposed stimuli are perceptually lateralized as a function of ITD in a way that is comparable to their low frequency counterparts (Bernstein and Trahiotis, 2003), and have been used in these experiments to study the coding of the interaural time differences of sound envelopes in high-frequency auditory cortex. Most importantly for this paper, the neuronal responses showed a wide range of Fano factors, including a substantial population of neurons with over-dispersion of spike counts relative to the Poisson assumption. For many of these neurons, the variance depended on a power of the mean, $\text{var} = \phi\mu^p$, with μ being the mean and $p > 1$. We therefore used the family of Tweedie distributions (Tweedie, 1984), which have this type of dependence. In the spirit of ANOVA, we implemented a sequence of successively more complex statistical models in order to test for the significance of the effects of ITD and its interaction with the dynamics of the response during sound presentation.

2. Materials and methods

2.1. Animal preparation

The data were collected from 9 healthy adult cats. The joint ethics committee (IACUC) of the Hebrew University and Hadassah Medical Center approved the study protocol for animal welfare. The Hebrew University is an AAALAC International accredited institute. Anesthesia was induced with medetomidine (Domitor, Orion Pharma; 0.2 mg, i.m.) and ketamine (100 mg, i.m., Fort Dodge) and maintained with halothane (0.2–1.5% as needed). Extracellular recordings were performed in the left primary auditory cortex. We used up to four individually moveable glass-coated tungsten microelectrodes. Spike waveforms were sampled and stored for offline analysis (AlphaMap, Alpha-Omega). Spikes were sorted either online (MSD, Alpha-Omega, Nazareth Illit, Israel: template-based sorting) or offline under manual control using an adaptation of the Wave-Clus algorithm (using wavelet analysis of the spike shapes, Quiroga et al., 2004). Spikes were assigned to three quality levels: well separated spikes representing the activity of single neurons, partially separated spike shapes representing the activity of small clusters of neurons, and Multi Unit Activity (MUA). More details on animal preparation, spike sorting and the criteria used to assign quality level to spikes are available in Moshitch et al. (2006).

2.2. The stimuli

All stimuli were generated digitally. The sounds were presented to the animal through sealed earphones (designed by G. Sokolich) that were calibrated in each ear. Pure tones and broad-band noise bursts were generated online (AP2, Tucker-Davis Technologies, Alachua, FL), converted to analog voltage (DA3-4, Tucker-Davis), attenuated (PA4, Tucker-Davis) and switched with onset and offset ramps of 10 ms (SW2, Tucker-Davis). The transposed stimuli were generated as the product of an envelope with a carrier. The envelopes were derived from a 1/3 or 2/3 octave wide noise band centered at one of four frequencies, 32, 64, 128 or 256 Hz. These were half-wave rectified and filtered to remove frequencies below 2 kHz. The carriers were either pure tones close to the characteristic frequency (CF) of the neuron, or a noise band centered at CF with a width of CF Hz. The envelopes were generated offline and stored as disk files, while the carriers were generated online. The sound level was set to 30 dB above minimal threshold of the pure tone carrier (mean ± std of 53 ± 12.7 dB SPL) or 30 dB above noise threshold for the stimuli with a noise carrier (70 ± 11.7 dB SPL). ITD was generated by shifting the whole stimulus in one ear (the right ear) relative to the other. Stimulus duration was 400 ms, and we typically presented 5 repetitions of each of 21 different ITDs in a pseudo-random order (a total of 105 trials) at a presentation rate of about 0.45 Hz. ITD values usually ranged between 1.5 ms left ear leading and 1.5 ms right ear leading. All neurons were tested with all combinations of the two carriers (pure-tone or noise) and the four modulation frequencies (a total of 8 carrier-envelope combinations). The best combination of carrier type and modulation of the envelope was selected for a control study with 10 repetitions of 11 different ITDs in the same range as the previous protocol. This protocol included also measurements of the responses to right- and left-ear presentations, and a test of ITD sensitivity evoked by the carrier alone. In the monaural presentations to the left ear alone there were 55 repetitions of the same transposed stimulus. The right ear presentation included the same small shifts in time that were used to create the ITDs of the dichotic presentations, and was used to verify that these small shifts of the stimulus in the right ear did not affect the neuronal responses by themselves (10 repetitions of 11 different shifts).

2.3. Data analysis

2.3.1. Response significance

The significance of the responses to the transposed stimuli was tested for each envelope-carrier combination by a paired t-test between the spike rate during stimulus presentation and the spike rate just preceding each stimulus presentation ($p < 0.05$). A response onset was defined for each significant response as the beginning of the first 5 ms window (following stimulus onset) that showed a significant increase in spike counts. This was done by comparing the spike counts in each such window with the Poisson distribution whose expectation was equal to the mean number of spontaneous counts in the same window duration (using a conservative significance level of $5^{*}10^{-5}$, to correct for the high number of comparisons). To be included in the final database, the