An Empirical Model for Reliable Spiking Activity

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Abstract

Understanding a neuron’s transfer function, which relates a neuron’s inputs to its outputs, is essential for understanding the computational role of single neurons. Recently, statistical models, based on point processes and using generalized linear model (GLM) technology, have been widely applied to predict dynamic neuronal transfer functions. However, the standard version of these models fail to capture important features of neural activity, such as responses to stimuli that elicit highly reliable trial-to-trial spiking. Here, we consider a generalization of the usual GLM that incorporates nonlinearity by modeling reliable and non-reliable spikes as being generated by distinct stimulus features. We develop and apply these models to spike trains from olfactory bulb mitral cells recorded in vitro. We find that spike generation in these neurons is better modeled by these models that consider reliable and unreliable spikes separately and that this effect is most pronounced for neurons with a large number of both reliable and unreliable spikes.

1 Introduction

Neuronal input-output functions relate membrane biophysical properties to the specific computations each neuron performs [Koch, 1999, Izhikevich, 2010]. Recently, there has been interest in using statistical models to capture and describe neuronal transfer functions [Kass and Ventura, 2001, Paninski, 2004, Badel et al.,]
Despite the application of these models in numerous contexts [Tripathy et al., 2013, Mensi et al., 2012], a feature of neural activity that these models often fail to capture is the most temporally precise trial-to-trial reliable spiking [Butts et al., 2007, Calabrese et al., 2011]. Such reliable spiking has been shown in a number of contexts and systems, including as a general feature of neuronal membranes stimulated using somatic current injection in vitro [Bryant and Segundo, 1976, Mainen and Sejnowski, 1995, Padmanabhan and Urban, 2010], as well as resulting from multiple stages of neuronal circuit processing in vivo [Butts et al., 2007, Kelly et al., 2010]. Reliable spiking is thought important for computation as it has been shown to be especially effective in driving downstream neural activity [Tiesinga et al., 2008, Giridhar et al., 2011].

Here, we extend previous approaches and develop statistical models designed to better capture temporally precise and reliable spiking activity. We apply these models to data collected from olfactory bulb mitral cells (MCs) recorded in vitro [Padmanabhan and Urban, 2010, Tripathy et al., 2013], neurons which display extensive electrophysiological heterogeneity and varying degrees of spiking reliability [Padmanabhan and Urban, 2010, Angelo et al., 2012, Padmanabhan and Urban, 2014].

2 Methods

We begin by considering each neuron’s spike train as a point process with time-varying intensity function $\lambda_i$, as in [Kass and Ventura, 2001, Paninski et al., 2004, Pillow et al., 2008, Doya, 2011, Kass et al., 2014]. In discrete time, with time bins
of width $\Delta t$, the spike train likelihood function is

$$p(y|x, \theta) = (\Delta t)^n \prod_i \frac{\lambda_i^n e^{-(\Delta t)\lambda_i}}{y_i!},$$

where $y_i$ is 1 if there is a spike in the $i$th time bin, and 0 otherwise, $n$ is the number of spikes, $x_i$ represents any covariates that are assumed to drive spiking, here the stimulus and spiking history prior to the $i$th time bin, and the firing rate $\lambda_i$ is suitably defined in terms of $x$. The simplest generalized linear model (GLM) is

$$\lambda_i = \exp(\vec{k} \cdot \vec{x}_i + \vec{h} \cdot y_{[i-m:i]} + b),$$ \hspace{1cm} (1)$$

where $\vec{k}$ is the neuron’s stimulus filter; $\vec{h}$ is the post-spike or spike-history filter; $b$ is the bias term; $i$ indicates the $i$th time bin; and $x_i$ is the portion of the stimulus considered potentially relevant to spiking probability in the $i$th time bin. We extend this GLM by defining a nonlinear version, which we call the current-thresholded model (CT model), in which the stimulus filter is allowed to be different for stimuli that produce reliable and unreliable spikes. These reliable-spike and unreliable-spike stimulus are found from two pre-processing steps. First, the neuron’s trial-averaged peri-stimulus time histogram (PSTH) is examined to determine a set of narrow segments or "PSTH peaks" in which the spikes across trials are highly reliable, defined by having $>90\%$ of trials containing a spike within this peak. Second, the 20 ms of input stimulus prior to each peak is found, the positive-going part of the mean of these (actually, a trimmed mean, see the Appendix) is computed as a template, and then all snippets of stimulus
are defined as either reliable-spike stimulus snippets or unreliable-spike stimulus snippets, according to their correlation with this template. In the CT model, the neuron’s firing rate $\lambda_i$ is defined as

$$\lambda_i = \begin{cases} 
\exp((\vec{k}_{rel} \cdot \vec{x}_{i,rel})^a + \vec{h} \cdot y_{[i-m:i-1]} + b_1), & \text{reliable-spike stimulus} \\
\exp(\vec{k}_{unrel} \cdot \vec{x}_{i,unrel} + \vec{h} \cdot y_{[i-m:i-1]} + b_2), & \text{unreliable-spike stimulus}
\end{cases}$$

(2)

where $\vec{k}_{rel}$ and $\vec{x}_{i,rel}$ denotes the stimulus filter and the stimulus preceding reliable spikes (respectively) and similarly for $\vec{k}_{unrel}$ and $\vec{x}_{i,unrel}$ which denotes the stimulus filter and stimulus preceding unreliable spikes. When $a = 1$ (the default, unless otherwise specified), this is a “switching” model, where two different stimulus filters are used based on classifying the preceding the input stimulus (the stimulus) as either a reliable-spike stimulus or an unreliable-spike stimulus. In both the simple GLM in Equation (1) and the CT model in (2) we define $m = 60$ and $\vec{x}_i$ as 50 ms of input stimulus prior to $i_{th}$ time bin, and use a time bin size $\Delta t = 1$ ms. Details are given in the Appendix.

3 Results

We used equations (1) and (2) to model the spiking activity of olfactory bulb MCs recorded in vitro (Fig. 1A). As described in Padmanabhan and Urban, 2010, Tripathy et al., 2013, MCs were stimulated using somatic current injection of repeated trials of frozen noise plus a DC bias while fast synaptic activity was blocked pharmacologically ($n = 44$ MCs, ~40 trials per neuron). The CT model,
which treats temporally-reliable spikes (based on the trial-averaged PSTH) as occurring due to a different stimulus waveform than temporally-unreliable spikes (Fig. 1B), was better able to account for dynamic MC activity than the standard GLM model. We found this to be especially true for neurons with epochs of highly precise spiking (Fig. 1A, inset). Specifically, based on the PSTH error for reliable spikes (quantified as the sum of squared errors in the spike timing of reliable PSTH peaks, see Appendix), we found that on average, the CT model reduces the PSTH error relative to the GLM model by 7.5%, but in some neurons the error reduction was as high as 37% of PSTH error; Fig. 1C. Applying a likelihood ratio test to both the GLM and CT model, we found that the CT model was significantly improved for nearly all neurons, as shown in Figure 5 in the Appendix. (P-values for 40 of 44 where less than .05 and most were much smaller; 8 degrees of freedom difference between the two models.)

Furthermore, by allowing the parameter $a$ in equation (2) to vary, an additional 16% reduction of the PSTH error was obtained for the CT model on average (e.g. an additional 33% reduction of the PSTH error was found for the neuron in Fig. 1A, for $a = 1.4$.) While introducing the parameter $a$ to the GLM also facilitates further model improvement (e.g., 23% improvement for the neuron in Fig. 1A), the CT model still outperformed the GLM model.

Moreover, a nonlinear model incorporating an explicit additional interaction term between the stimulus and spike history filter (in lieu of the 2-filter CT model) showed no improvement over the standard GLM (mean improvement = -11%), suggesting that temporally-reliable spikes do not occur due to the interaction of
stimulus and spike-history based effects (e.g., stimulus-specific bursting effects).

Note that both the GLM and CT model contain a linear post-spike history term, which we previously found to be essential in capturing membrane resonance-like properties of MCs [Tripathy et al., 2013]. For example, a spike-triggered covariance model is similar to the CT model in that both incorporate two stimulus filters [Schwartz et al., 2006] but the STC model does not have a post-spike history term. We found the STC model to be qualitatively less effective for modeling the MC in Fig. 1A than either the GLM or CT model (Fig. 6 in the Appendix), again highlighting the importance of capturing spike-history effects for these neurons.

We found that specific MCs were considerably better modeled using the CT model over the GLM. Investigating these neurons, we found that the neurons most improved were those with relatively low firing rates (\(\sim 10-35\) Hz), and intermediate values of trial-to-trial reliability (Fig. 1D). In other words, the CT model was most influential for neurons which displayed a number of both reliable spikes as well as unreliable spikes. One biological explanation for this finding of differential explanatory benefits of the CT model may the inherent biophysical heterogeneity among MCs [Padmanabhan and Urban, 2010, Angelo and Margrie, 2011, Angelo et al., 2012, Burton and Urban, 2014, Padmanabhan and Urban, 2014].

4 Discussion

We contrast the statistical approach used here to the more common Hodgkin-Huxley dynamical systems based methodology for modeling intrinsic membrane responses [Hodgkin and Huxley, 1952]. Whereas Hodgkin-Huxley models are use-
Figure 1: Comparison of generalized linear model (GLM) and current thresholded model (CT model) in capturing dynamic mitral cell (MC) spiking activity. (A) MC intrinsic properties are probed using filtered broadband frozen noise (1st row) injected into the soma. MC spike rasters (2nd row; black) and PSTH (3rd row; black) for repeated stimulus presentations (n = 40 trials). Corresponding model-based rasters and PSTHs for GLM (green) and CT model (red) show that the CT model better captures temporally precise MC spiking activity. PSTH smoothed with Gaussian with \( \sigma = 2\text{ms} \) and are slightly offset for visual clarity. Inset on right indicates boxed segment on left. Data shown here only includes test data not used train model parameters. (B) Model stimulus filters for GLM (green) and CT model (unreliable stimulus filter, light red; reliable stimulus filter, dark red) for a representative MC. \( t = 0\text{ms} \) indicates current time bin. (C) Relative improvement of CT model (with \( a = 1 \)) compared to GLM. Improvement quantified by first calculating sum of squared errors between MC and model PSTHs and then calculating the ratio between GLM and CT model SSE. Higher ratios indicate that the CT model is a better model for MC activity than GLM. X-axis indicates MC identity (n = 44 MCs). Circle indicates MC shown in A. (D) Analysis of MC features compared to CT model improvement relative to GLM. x-axis indicates neuron trial-to-trial reliability, computed as the proportion of PSTH peaks defined as reliable relative to all PSTH peaks. MCs split into 4 categories based on CT model improvement (with \( a = 1 \)) relative to standard GLM model: no improvement (white; ratio of SSE < 1.0), slight improvement (black; 1.0 \( \leq \) ratio of SSE < 1.05); some improvement (red; 1.05 \( \leq \) ratio of SSE < 1.2); and large improvement (green; ratio of SSE \( \geq \) 1.2).
ful and attractive for their direct comparison to neuronal membranes and ion channels, point processes provide the natural probabilistic framework for analyzing noisy neural spiking behavior.

An interesting shortcoming of the standard stimulus-response GLM in Equation (1) is its failure to adequately account for spike timing reliability. We have shown that the nonlinear CT model in Equation (2) can improve on the standard GLM, specifically, when applied to spike trains elicited in vitro during dynamic current injection. The CT model is conceptually similar to linear models which incorporate multiple stimulus filters, such as spike-triggered covariance methods (STC) [Schwartz et al., 2006]. However, the CT model differs in that it dynamically switches between 1 of 2 stimulus filters, and critically, allows for a spike-history term which captures refractory and burst firing which governs much of the precise spiking timing of mitral cells. Thus our approach extends earlier efforts to mitigate the influence of spike-history effects by separately analyzing spikes well isolated in time from preceding spikes using a multi-filter approach [Agüera y Arcas and Fairhall, 2003, Agüera y Arcas et al., 2003].

However, we do not intend to propose this model as either realistic or empirically definitive. In the first place, additional nonlinearities are clearly needed to capture more of the spike reliability. Secondly, the CT model does not appear to be obviously close to any biophysical or dynamical model. Moreover, the specific methodology for fitting the CT model is admittedly somewhat ad hoc. It would be possible to define model hyperparameters and learn them through appropriate cross-validation.
An alternative to setting a hard threshold for reliable spiking would be to take a conceptually similar approach to that in [Escola et al., 2011] and use a Hidden Markov Model to determine whether each epoch of MC spiking activity most corresponded that of 2 states: a reliable state or unreliable state. However, since we were injecting current directly into each MC’s soma, it seemed more natural to classify the neuron’s effective state using the stimulus waveform directly.

While our focus here was to better model reliable MC spiking elicited during somatic current injection, our approach could likely also be extended to capture reliable spiking occurring during stimulation via naturalistic sensory stimuli, such as visual scenes or auditory stimuli [Butts et al., 2007, Calabrese et al., 2011]. However, we expect that as the dimensionality of the stimulus increases, a greater amount of data will be required to adequately parameterize each of the two stimulus filters used here. Our two-filter approach could also be applied in conjunction with other approaches for modeling reliable spiking, such as those which explicitly model the effects of threshold non-linearities of afferent presynaptic neurons [Butts et al., 2011].

Given the above caveats, our intention with the CT model is to use it to stimulate additional research. Perhaps a point process regression model, based on GLM methodology but again incorporating nonlinearity, might be based on ideas such as the adaptive timescale rate version of the exponential LIF model of [Ostojic and Brunel, 2011]. By working at the interface between statistical and dynamical system modeling it may be possible to gain further insight into reliable spiking.
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References


6 Appendix

6.1 Experimental methods and data collection

Whole cell patch clamp recordings of mitral cells were obtained in vitro from mouse olfactory bulb slices using methods described previously [Padmanabhan and Urban, 2010]. Mitral cells were identified under infrared differential interference contrast optics on the basis of their laminar position in the olfactory bulb and their morphology. All experiments were performed at 35 °C in standard Ringer’s solution with excitatory (25 μM AP5 and 10 μM CNQX) and inhibitory (10 μM bicuculline) synaptic activity blocked.

Current-clamp recordings were performed while injecting neurons with a filtered white noise current stimulus. Noise traces were generated by convolving a 2.5-s white noise current with an alpha function of the form \( t \cdot \exp(-t/\tau) \), where \( \tau = 3 \) ms. We chose this spectral structure as it generates reliable spiking in these neurons and corresponds to the time-scale of fast synapses afferent to MCs [Galán et al., 2008]. Each neuron received one of a small number of stimuli generated via this method (most neurons received 1 of 3 stimulus templates) and was presented \( \sim 40 \) stimulus repeats. The amplitude (variance) of the noise used was between 5% and 40% of the direct current (100-800 pA, \( \sigma = 20-80 \) pA) offset for each cell, with the majority of cells receiving 10-20% of the DC offset. The variance of the noise was selected as previously described [Galán et al., 2008], to induce reliable firing without large input fluctuations. For all recordings, a 25 or 50 pA hyperpolarizing pulse was injected before stimuli were delivered to measure input resistance and membrane time constant, allowing us to track the stability of recordings over multiple trials. As described in [Tripathy et al., 2013] only neurons whose firing patterns were stable across trials and fired a sufficient number of spikes in each trial (>5 Hz) were used in this study. Upon stimulation most neurons usually underwent a brief non-spiking adaptation period (111 +/- 14 ms) which was assessed visually and excluded from the analysis.

6.2 Fitting Procedure

In outline, for each neuron, our procedure may be summarized as follows:

1. Use the PSTH to identify reliable and unreliable peaks in the PSTH.

2. Define a reliable-spike current template as the longest positive part to the end of the trimmed mean of the 20 ms snippets of current preceding the reliable peaks, which is \( l \) ms.

3. Consider all \( l \) ms snippets of current and separate these into two categories: (1) those immediately preceding the reliable peaks and (2) all others. Find the correlation of each snippet with the reliable-spike current template and take its Fisher z transformation; this produces two distributions of values, one for category (1) and one for category (2). Then use a Bayes classifier to
determine a threshold for classifying each current snippet as either a reliable-spike current or an unreliable-spike current. Also, take the snippets that has high correlation but small inner-product with current template as unreliable.

**Step 1.** The PSTH was examined. First, we thresholded the PSTH and only considered time points within the PSTH which contained a spike in at least 3 trials (from among approximately 40 trials total). For convenience, we define such PSTH time points as 'PSTH peaks'. Second, for all the PSTH peaks, we combined the neighboring peaks with time difference less than 5 ms. This step is to make sure there is no temporal separation of one PSTH big peak into multiple smaller peaks. Finally, for each PSTH peak, we recorded the temporal range of the peak and calculate the percentage of trials that spike in that range. If the percentage was bigger than 90% (e.g. 36 of 40 trials), and the temporal range was smaller than 12 ms, then we regarded that peak as reliable. Otherwise, we called it unreliable. When we report neuron reliability, it is defined as the proportion of reliable peaks among all the peaks for the neuron.

**Step 2:** Considering the set of 20 ms current snippets immediately preceding these reliable PSTH peaks, we computed the mean 20 ms snippet (the mean across all these peaks). Because a positive current is required to drive each neuron to spike, we take only the positive portion of this snippet. We next computed the correlation of each snippet with the mean and excluded as outliers any snippets that have correlation greater than 1.5 times standard deviations from the mean correlation. We then re-computed the mean snippet to get the reliable-spike current template.

In Figure 3 we display the reliable-spike current templates computed for each of the mitral cells. In Figure 4 we show how the reliable-spike current template varies as a function of trials and peri-stimulus time used for model fitting. It may be seen that the parameter fits for the reliable spike template stabilize with a relatively small amount of trials \((n > 10\) trials). Similarly, for \(n > 10\) trials, more than 90% of the reliable PSTH peaks are recovered relative to when all trials are used to identify the reliable PSTH peaks. With respect to stimulus time, the reliable spike template converges when at least 30% of the total stimulus is used for training data relative to the 70% used previously (i.e., .75s vs 1.75 seconds).

**Step 3:** We computed the correlation of each snippet with the reliable-spike current template, applied the Fisher z transformation \(f(r) = \log \frac{1+r}{1-r}\), and thereby obtained z-transformed correlations for the snippets within each of two categories: (1) those immediately preceding the reliable peaks (termed \(R2\)) and (2) all others (termed \(R1\)). We then applied a Bayes classifier ([Kass et al., 2014, Hastie et al., 2011]) to find the threshold, as the intersection of the density functions for the correlations under both cases, that best discriminated these transformed coefficients (Fig. 2).

Also, we computed the inner-product of each snippet with reliable current template, and take the snippets with inner-product larger than \(mean(Inner-products) - sd(Inner-products)\). This ensures that classified reliable current snippets are those which have high correlation with the reliable current template and those which have large absolute current magnitude that could inspire a spike.
Figure 2: Finding the threshold using distributions of $R_1$ and $R_2$. In this figure, the solid black line is the fitted pdf of $\log((1 + R_1)/(1 - R_1))$, and the solid purple line is the corresponding fitted pdf of $\log((1 + R_2)/(1 - R_2))$. The threshold can be taken at the intersection of the two fitted pdfs.

After these steps, we finally have the classification of stimulus, and can define our two stimulus kernel $k_1$ and $k_2$ in the model. If time $t$ was regarded as a reliable-spike time, we used the convolution of $k_1$ and 50 ms before $t$ in the stimulus term; if unreliable, we used the convolution of $k_2$ and 50 ms before $t$ in the stimulus term. Model fitting proceeded by maximizing the likelihood function, as usual. We used 7 non-linearly spaced spline knots to fit $\hat{k}$ and 6 knots to fit $\hat{h}$ [Pillow et al., 2008, Tripathy et al., 2013]. In practice, we replace $(k_{rel} \cdot x_{i,rel})^a$ with $\text{sign}(k_{rel} \cdot x_{i,rel})|k_{rel} \cdot x_{i,rel}|^a$.

6.3 Assessing model goodness of fit

We used the summation of squared errors (SSE) as the goodness of fit measure for the models used here. Specifically, we used the difference between the PSTH for data and simulated spike trains. With the initial 70% of original data (with respect to peri-stimulus time, but including all trials) as training data, we fit each model and found model parameters. With these fitted filters and given stimuli, we next simulated 300 spike trains for each neuron. The simulated spike trains were used as simulated data.

For each reliable peak from test data, we compared the mean spike time of this peak and of the simulated PSTH. The summation of the squared difference between the mean time of both real and simulated PSTH peaks is denoted as SSE for reliable spikes.

To define the likelihood ratio test to compare the GLM and CT models, we use the first 50% of the stimulus and spike train data to train the reliable current
template for the CT model, and the last 50% data to fit both models.

Figure 3: Reliable stimulus current templates shown for all of the mitral cells. N = 44 mitral cells.
Figure 4: Convergence of reliable current stimulus template as a function of number of trials used to fit model (left) or amount of training data with respect to time for model fitting (right). Stimulus filter template shown for the neuron highlighted in Figure 1A. In both cases, a relatively small amount of training data, both with respect to trials, or peri-stimulus time, is needed for stimulus filter template to empirically converge.

Figure 5: Loglikelihood ratio p-values for testing CT vs. GLM model, on scale of log_{10}(p), for N = 44 mitral cells.
Figure 6: Comparison of spike-triggered covariance model to CT model and GLM for the example neuron highlighted in Figure 1A. (A) Rasters and PSTHs comparing each model to MC spike trains. Note that STC rasters are a much poorer model for MC activity relative to either the GLM and CT model. (B) Stimulus filters for the STC model. STC filter corresponds to the filter with the largest eigenvalue. (C) Eigenvalues for STC eigenvectors. A single STC eigenvector with the largest eigenvalue was chosen for the STC model, in addition to the STA. (D) Density plot for stimulus snippet projection onto STA and STC bases for all stimuli (Raw Stimuli) and only those preceding spikes (Spike-triggered Stimuli). This 2D density plot was used for calculating the firing rate nonlinearity.