Subthreshold K⁺ channel dynamics interact with stimulus spectrum to influence temporal coding in an auditory brainstem model

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Running head:

K⁺ dynamics and stimulus spectrum shape auditory coding

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ABSTRACT

Neurons in the auditory brainstem encode signals with exceptional temporal precision. A low-threshold potassium current, $I_{KLT}$, present in many auditory brainstem structures and thought to enhance temporal encoding, facilitates spike selection of rapid input current transients through an associated dynamic gate. Whether the dynamic nature of $I_{KLT}$ interacts with the timescales in spectrally-rich input to influence spike encoding remains unclear. We examine the general influence of $I_{KLT}$ on spike encoding of stochastic stimuli using a pattern classification analysis between spike responses from a ventral cochlear nucleus (VCN) model containing $I_{KLT}$ (Rothman and Manis 2003b), and the same model with the $I_{KLT}$ dynamics removed. The influence of $I_{KLT}$ on spike encoding depended on the spectral content of the current stimulus such that maximal $I_{KLT}$ influence occurred for stimuli with power concentrated at frequencies low enough ($<500$ Hz) to allow $I_{KLT}$ activation. Further, broadband stimuli significantly decreased the influence of $I_{KLT}$ on spike encoding suggesting that broadband stimuli are not well-suited for investigating the influence of some dynamic membrane nonlinearities. Finally, pattern classification on spike responses was performed for physiologically-realistic conductance stimuli created from various sounds filtered through an auditory nerve (AN) model. Regardless of the sound, the synaptic input arriving at VCN had similar low-pass power spectra, which led to a large influence of $I_{KLT}$ on spike encoding, suggesting that the subthreshold dynamics of $I_{KLT}$ play a significant role in shaping the response of real auditory brainstem neurons.
INTRODUCTION

Auditory brainstem neurons encode signals with exceptional temporal precision. The relaying of precise temporal information is important for birds and low-frequency-hearing mammals in localizing sounds based on the encoding of very small interaural time differences of acoustic signals arriving at the two ears (Goldberg and Brown 1969; Moiseff and Konishi 1981; Spitzer and Semple 1995; Yin and Chan 1990). Several biophysical mechanisms in the auditory brainstem enable high temporal precision, including calyceal synaptic inputs (Jhaveri and Morest 1982), fast, adapting synaptic currents (Gardner et al. 1999; Raman and Trussell 1992; Smith et al. 2000), short (<1 ms) membrane time constants (Scott et al. 2005), and the subject of our study—the fast, low-threshold potassium current ($I_{KLT}$) (Manis and Marx 1991; Rathouz and Trussell 1998; Reyes et al. 1994). Neurons with large densities of $I_{KLT}$ have been found to fire phasically in response to step current stimuli (Manis and Marx 1991; Reyes et al. 1994; Smith 1995); have increased phase-locking to strong sinusoidal current stimuli (Oertel 1983; Reyes et al. 1996; Rothman and Young 1996); and have an increased signal-to-noise ratio for detecting small current signals in noise (Svirskis et al. 2002). Some of these phenomena, including the ability to enhance detection of coincident synaptic input, may be attributed, in part, to the simple passive properties associated with $I_{KLT}$ decreasing the resting membrane time constant. However, it remains unclear to what extent the active, dynamic properties of $I_{KLT}$ influence spike train encoding in the auditory brainstem.
The influence of $I_{\text{KLT}}$ has been investigated by observing the voltage response of cells and models of cells to simple current stimuli such as steps, ramps, pulse trains, and sinusoids in the presence and absence of $I_{\text{KLT}}$ channel-blockers (Brew and Forsythe 1995; Cai et al. 2000; Ferragamo and Oertel 2002; Svirskis et al. 2002; 2004). Alternatively, $I_{\text{KLT}}$ has also been investigated by observing changes in spike encoding of a dynamic stimulus with application of $I_{\text{KLT}}$ channel-blockers (Slee et al. 2005; Svirskis et al. 2002; 2004). These latter studies have employed spike-triggered reverse correlation on stochastic current signals—such as summated excitatory and inhibitory post-synaptic currents, and broadband stochastic currents—to characterize spike encoding. Here, the influence of $I_{\text{KLT}}$ has been assessed with a qualitative comparison of the shape of the spike-triggered average (STA) (Svirskis et al. 2002; 2004) or the principal components of the spike-triggered covariance (STC) (Slee et al. 2005) in the presence and absence of $I_{\text{KLT}}$ channel-blockers. Furthermore, since these studies do not correct for any change in passive membrane properties after a pharmacological $I_{\text{KLT}}$ block, and do not vary the spectral content of stimuli in a systematic fashion, it is then difficult to quantify the exclusive influence that the dynamic nature of $I_{\text{KLT}}$ has on spike train coding.

In this study, we examine the influence of $I_{\text{KLT}}$ on spike encoding in a Hodgkin-Huxley-like model of VCN neurons (Rothman and Manis 2003b) using stochastic current stimuli. In contrast to the above cited STA/STC approaches, we use a linear pattern classifier (Duda et al. 2001) to more accurately quantify how much influence $I_{\text{KLT}}$ has on spike encoding, without assuming a specific representation of the code. We apply the pattern classifier in a novel way to assess the difference in spike encoding caused by the interaction of the spectral content of a stimulus and $I_{\text{KLT}}$ dynamics. By comparing a
model with dynamic $I_{KLT}$ to a model with $I_{KLT}$ conductance fixed to its level at resting membrane potential, we find that dynamic $I_{KLT}$ has a significant influence on the stimulus current selectivity of the spiking model only when the stimulus has sufficiently low-frequency power, or when a broadband stimulus is sufficiently weak. Further, we specifically investigate whether the spectral content of realistic synaptic input interacts with the dynamics of $I_{KLT}$ to effect spike encoding.

METHODS

Model

The model used to simulate neurons with $I_{KLT}$ was the same as the Type II VCN model developed by Rothman and Manis (2003b). The Rothman-Manis model (here abbreviated “RM03”) is a Hodgkin-Huxley-type point neuron model consisting of a standard fast-inactivating sodium current, $I_{Na}$, a high-threshold potassium current, $I_{KHT}$, and leak currents, $I_{Ik}$, as well as a low-threshold potassium current, $I_{KLT}$, and a hyperpolarization-activated cation current, $I_h$. These currents are combined in the current-balance equation

$$C_m \frac{dV}{dt} = -I_{Na} - I_{KHT} - I_{KLT} - I_h - I_{Ik} + s(t)$$

(1)

where $C_m$ is the membrane capacitance, $V$ is the membrane potential, and $s(t)$ is the external stimulating current. Expressing each current $I_x$ in terms of its activation and inactivation gating variables re-writes Eqn. 1 as

$$C_m \frac{dV}{dt} = -g_{Na} m^3 h (V - E_{Na}) - g_{KHT} (0.85 n^2 + 0.15 p) (V - E_K)$$
\(-g_{KLT}w^4z(V - E_K) - g_{h}r(V - E_h) - g_{l}r(V - E_l) + s(t)\)  \(\text{(2)}\)

where \(g_x\) and \(E_x\) are the respective maximal conductance and reversal potential for ionic species \(x\). For all simulations, \(C_m = 12\) pF, \(E_K = -70\) mV, \(E_{Na} = +55\) mV, \(E_h = -43\) mV, and \(E_l = -65\) mV. Maximal conductances are: \(g_{Na} = 1,000\) nS, \(g_{KHT} = 150\) nS, \(g_{KLT} = 200\) nS, \(g_{h} = 20\) nS, and \(g_{l} = 2\) nS. The voltage- and time-dependence of the activation/inactivation variables, \(x\), are described by the equation

\[
\frac{dx}{dt} = \left( x_s(V) - x \right) / \tau_x(V)
\]

where \(x_s(V)\) is the steady-state value of \(x\) at potential \(V\), and \(\tau_x(V)\) is the time constant of \(x\). The functions \(x_s(V)\) and \(\tau_x(V)\) are empirically-derived from voltage-clamped responses of cochlear nucleus neurons and may be found in Rothman and Manis (2003b). Additionally, all time constants were multiplied by 0.17 and maximal conductances were multiplied by 3.03 to adjust model dynamics to normal body temperature (38°C) (Rothman and Manis 2003b).

Integration of the above equations was carried out using the forward Euler method with a time step of 0.01 ms. This first-order, single-step integration scheme proved adequately efficient for our long simulations to collect many spikes and was accurate due to the small step size. Halving the time step produced no noticeable differences in voltage traces. Spike times were recorded when the membrane potential crossed upward through our selected threshold, \(V_{Th} = 0\) mV.

We examined responses of two versions of the RM03 model. The dynamic KLT model was the unaltered RM03 model, with no change in the dynamics of \(I_{KLT}\). The frozen KLT model had the activation and inactivation gating variables of \(I_{KLT}\), \(w\) and \(z\),
fixed to their resting values. This eliminated the voltage- and time-dependence of $I_{KLT}$ in the frozen KLT model, yet maintained the same resting conductance and membrane time constant in both models.

Stimuli

All random stimuli, $s(t)$, were filtered Gaussian white noise currents digitized at the integration time step. We implemented a fourth-order Butterworth filter (MATLAB, Mathworks) to create narrowband (approximately rectangular power spectrum) and broadband stimuli (Fig. 1). For narrowband stimuli, upper and lower cutoff frequencies were chosen to create a bandwidth of 100 Hz. The center frequency of the narrowband was chosen to create signals that spanned non-overlapping intervals $0 - 100$ Hz, $100 - 200$ Hz, and so on up to $1,100 - 1,200$ Hz. For broadband stimuli the spectrum was uniform between 0 and 2,000 Hz. Stimulus currents were scaled such that the standard deviation of the stimulus amplitude was set to a value chosen between $0.3 - 0.8$ nA. Simulations were continued long enough to obtain 10,000 spikes for a given stimulus.

Pattern classification analysis

For every stimulus, 10,000 spike times were collected each from the dynamic and frozen KLT models. To develop a putative spike code we employed reverse correlation techniques (Rieke et al. 1997; Slee et al. 2005) on the simulated data. Specifically, for every spike time, $t_{sp}$, we recorded the preceding stimulus as the vector $s(tsp-(K-1)\Delta t), s(tsp-(K-2)\Delta t), ..., s(tsp-\Delta t), s(tsp))$ where $K = T/\Delta t$, with $T$ being the time interval of the reverse correlation and $\Delta t$ the time discretization (Fig. 2A). In practice $\Delta t = 0.2$ ms and $T$
= 30 ms. The collection of these spike-triggered stimulus vectors for a given model—the spike-triggered ensemble (STE)—formed a cloud of points in 150-dimensional stimulus space. The STE was a finite sample of all possible stimuli which caused the model to spike. The spike-triggered average, $\mathbf{m}$, is the mean of the STE:

$$m_{d,f} = \langle s \rangle_{d,f}$$

(4)

where the subscripts $d$ and $f$ represent the dynamic and frozen KLT models, respectively, and the brackets $\langle \cdot \rangle$ represent an average over the corresponding ensemble, not over time.

STAs were compared between the dynamic and frozen KLT models as a means of visually observing the difference in stimulus selection (or equivalently, spike encoding). However, STAs assume a mean representation of stimulus selection and, further, do not themselves quantify the difference in stimulus selection between the two models. The problem of quantifying stimulus selection difference between models was addressed as a standard pattern classification problem (Duda et al. 2001). Given large samples of two pattern classes (e.g., STEs), the question was posed as to how accurately a classifier could correctly classify a given spike-triggered stimulus as either causing the dynamic KLT model to spike or the frozen KLT model to spike. The accuracy of such a classifier depended on how distinct the STEs from each model were from one another. If the STEs largely overlapped, meaning most spike-triggered stimuli caused spiking in both models, then the classifier would have poor accuracy in correctly classifying a stimulus.

In $K$-dimensional stimulus space, the STEs exist as two partially overlapping clouds of points. A linear classifier attempts to optimally separate the two STE clouds with an appropriate hyperplane. This hyperplane may be defined by its normal vector $\mathbf{f}$. We used a linear discriminant classifier function, $h(s)$, of the form
\[ h(s) = f \cdot s - \theta \]  

(5)

where the projection of the stimulus vector \( s \) onto \( f \) is compared to a threshold value \( \theta \). Spike-triggered stimuli which gave a positive value of \( h(s) \) were classified as causing the dynamic KLT model to spike. Otherwise, the stimulus was classified as causing the frozen KLT model to spike.

The separating hyperplane was chosen using the Fisher method (Metzner et al. 1998). This method chooses \( f \) such that when the STEs are projected onto it, creating two distributions of projected values, the ratio of the squared difference of means of the distributions to the sum of the variances of the distributions is maximized (see Fig. 2B for a schematic illustration). The Fisher ratio \( F(f) \) takes the form

\[
F(f) = \frac{[f \cdot (m_f - m_d)]^2}{f^T \left( \frac{1}{2} \Sigma_d + \frac{1}{2} \Sigma_f \right) f}
\]

(6)

where \( m_d \) and \( m_f \) are the STAs of the dynamic and frozen KLT models, respectively, and \( \Sigma_d \) and \( \Sigma_f \) are the covariance matrices. The covariance matrix is

\[
\Sigma_{d,f} = \left\langle (s - m_{d,f}) (s - m_{d,f})^T \right\rangle_{d,f}
\]

(7)

where the vector product is averaged over the STE. The \( f \) which maximizes the Fisher ratio has a relatively simple closed-form solution (Duda et al. 2001, Sec 3.8.2):

\[
f_{\text{max}} = 2(\Sigma_d + \Sigma_f)^{-1}(m_f - m_d)
\]

(8)

Most often, the sum of the covariance matrices in Eqn. 8 was not invertible, therefore, the inverse was replaced with the pseudoinverse using the MATLAB function `pinv`.

After solving for \( f_{\text{max}} \), both STEs were projected onto it, creating two probability densities of projected values (e.g., Fig. 4A(a,b)). Each probability density was approximated by combining projected values into a histogram with 200 bins, then
dividing by the total number of spike-triggered stimuli. The misclassification error $\varepsilon(\theta)$ of the classifier was determined by

$$\varepsilon(\theta) = \frac{1}{2} P_{Fd}(\theta) + \frac{1}{2} P_{Ff}(\theta)$$

(9)

where $P_{Fd}(\theta)$ is the probability that, for a fixed $\theta$, a stimulus is falsely classified with the dynamic KLT model, and $P_{Ff}(\theta)$ is the probability that it is falsely classified with the frozen KLT model. The threshold was varied through the complete range of projected values, effectively parameterizing $\varepsilon$. The optimal linear classifier was constructed using the $\theta$ which minimized $\varepsilon$, denoted $\varepsilon_{\text{min}}$. A linear transformation of $\varepsilon_{\text{min}}$ motivated a simple definition of the stimulus selection difference (SSD) between the two models:

$$SSD = 1 - 2\varepsilon_{\text{min}}.$$ 

(10)

The SSD takes a value between 0 and 1. A SSD of 0 occurs when the STEs of each model completely overlap, meaning that the dynamic and frozen KLT models spiked to the same stimulus waveforms. Conversely, a SSD of 1 occurs when the STEs are completely separable, in which case the dynamic and frozen KLT models spiked to distinctly different stimuli.

The Fisher method is ideal when the projection of the STEs along any $f$ forms two Gaussian distributions, however, the projection of the STEs in this study were not Gaussian. Nevertheless, projecting the STEs onto $f_{\text{max}}$ resulted in probability distributions which were unimodal and could be described largely by the first two moments (Fig. 4A(a,b)). Therefore, Fisher linear discrimination was assumed to be adequate in quantifying SSD. The accuracy of SSD computations was checked with a bootstrap procedure. The STEs collected in response to the narrowband stimulus with center frequency 150 Hz were re-sampled with replacement 100 times, creating 100
bootstrap estimates of the SSD. The 95 percent bootstrap confidence interval surrounding the SSD was ±0.0034.

Physiological conductance stimuli

The narrowband and broadband current stimuli described above were useful artificial stimuli to compare spike encoding between the dynamic and frozen KLT models. However, these stimuli were not physiologically realistic examples of the input that VCN neurons likely receive from convergent AN synapses. To compare the dynamic and frozen KLT model spike encoding of physiological stimuli, realistic inputs were approximated using the output of an appropriate AN model (Fig. 7A).

To this end, stochastic narrowband and broadband sound waveforms were created as described above for current stimuli (see Stimuli). Sound waveforms were scaled to have a standard deviation pressure level of 70 dB SPL. The waveforms were then input into an AN model (Tan and Carney 2003) with the characteristic frequency of the model set to match the center frequency of the input band. The AN model produced in response to the input waveform a post-stimulus time histogram (PSTH). Three separate spike trains were randomly extracted from the PSTH assuming an inhomogeneous Poisson process where the probability of spike occurrence in each time bin was set to the firing probability of the corresponding time in the PSTH. Spike times within a hard refractory period of 1 ms were eliminated, yielding the final AN spike trains. Each AN spike train was convolved with an \( \alpha \)-function with a time constant of 0.3 ms yielding an excitatory post-synaptic potential with a decay time of approximately 0.4 ms (Gardner et al. 1999). Furthermore, each synaptic event was randomly assigned a peak conductance from a
Gaussian distribution, modeling a strong reliability of event occurrence of the end bulb of Held synapse. Mean peak conductance was set to 15 nS with a standard deviation of 3.75 nS. The three conductance time courses were summated to produce a single conductance stimulus, $s(t)$. The summation of the three AN fibers modeled the synapsing of a small number of end bulbs of Held onto spherical bushy cells (Sento and Ryugo 1989). Globular bushy cells, on the other hand, receive a large number of convergent AN inputs (Spirou et al. 2005). This study focused on the case of spherical bushy cells, which are known to project to medial and lateral superior olive (MSO and LSO, respectively).

Finally, since $s(t)$ was a conductance stimulus, not a current stimulus, the current stimulus term in Eqn. 2 was replaced with $s(t) (V - E_{exc})$, where $E_{exc} = 0$ mV was the excitatory synaptic reversal potential. As with the artificial current stimuli, simulation was continued long enough to collect 10,000 spikes for each sound waveform.

RESULTS

We conducted this study to investigate whether subthreshold $I_{KLT}$ dynamics influences the stimulus selectivity exhibited by spike train responses. We compared the spike train responses of the RM03 model (dynamic KLT) to responses from an altered version of the model (frozen KLT) in which the time- and voltage-varying activation-gating of $I_{KLT}$ was removed, effectively freezing the gating variable to its value at the resting potential (see Methods). This alteration kept the input resistance and membrane time constant the same in the two models, ensuring any difference in response between
models would be due to the loss of time- and voltage-varying properties of $I_{KL T}$ and not due to the passive filtering that $I_{KL T}$ automatically adds just by increasing the resting conductance.

**Differential voltage response to current ramps and random stimuli of different timescales**

As an introduction to the dynamic stimulus selectivity that $I_{KL T}$ imparts to excitable membrane, we compared the dynamic and frozen KLT models’ voltage responses to two triangular current ramps (Fig. 3A). Each current ramp had the same peak current (1.5 nA), but different rates of rise up to peak (0.3 nA-ms$^{-1}$ and 2 nA-ms$^{-1}$). In response to the slow current ramp, the frozen KLT model spiked several times while the dynamic KLT model only responded with a subthreshold depolarization. In contrast, both models spiked in response to the fast current ramp.

Next, we compared the models’ membrane voltage responses to two random current stimuli—one with low-frequency content (100-200 Hz) and the other with high-frequency content (700-800 Hz) (Fig. 3B). In a sense, these stimuli were stochastic analogs of the slow and fast current ramps. The slow rate of rise of the current upswings in the low-frequency stimulus was similar to the rate of rise of the slow current ramp, and likewise for the high-frequency stimulus and fast current ramp. In response to the low-frequency stimulus, the models’ voltage responses were visibly different in the subthreshold regime, and the frozen KLT model fired more often than the dynamic KLT model. However, in response to the high-frequency stimulus, the frozen KLT model only fired slightly more often and the subthreshold voltage trajectories were almost identical.
Differential activation of $I_{KLT}$ in response to stimuli with slow and fast timescales can be understood from the dynamics of $I_{KLT}$’s activation gating variable (Svirskis and Rinzel 2003). As voltage rises, the steady-state value of the $I_{KLT}$ gate also rises. The dynamic gate approaches this new value with a time constant, $\tau_{KLT}$, which is also voltage-dependent. At resting potential, $\tau_{KLT} = 1.1$ ms and decreases to 0.25 ms near spike threshold. The membrane time constant, $\tau_m = 0.3$ ms, is faster than $\tau_{KLT}$ at rest, therefore allowing fast stimulus upswings, such as fast current ramps or high-frequency stochastic stimuli, to drive the membrane potential up to spike threshold before $I_{KLT}$ has time to fully activate. For slower stimulus fluctuations, the membrane potential changes at a slow enough rate to allow the $I_{KLT}$ gate to fully activate its rectifying current, making it more difficult to depolarize the cell to spike threshold.

*Differences in STAs*

We investigated $I_{KLT}$’s effect on spike encoding by comparing the stimulus waveforms that caused each model to spike. For each spike response to the random time-varying stimulus, we recorded the 30 ms of the stimulus waveform preceding the spike (see Methods). We collected a large number of these spike-triggered stimuli, yet due to the large dimension of the stimulus waveforms this still gave only a sparse sample of all possible stimuli that elicit spikes in a given model. One way to examine how $I_{KLT}$ changes spike encoding is to visually compare the *averages* of the STEs between dynamic and frozen KLT models (Slee et al. 2005; Svirskis et al. 2002). Fig. 3C shows the STAs of the two models in response to the same low- and high-frequency inputs of Fig. 3B. Upon comparison of the two model STAs two major observations are made:
1) In response to low-frequency inputs the dynamic KLT model spiked to stimuli with on-average sharper upswings than the frozen KLT model (Svirskis et al. 2002). In contrast, there was no discernable difference between the two models’ STAs in response to high-frequency stimuli. This conditional influence of $I_{\text{KLT}}$ on the STA shape is expected from the above voltage response results showing dynamic KLT model selectivity for fast current ramps.

2) The dynamic KLT model exhibited a larger preceding hyperpolarization in its STA than the frozen KLT model in response to low-frequency stimuli, yet not in response to high frequency stimuli. A preceding stimulus downswing before a stimulus upswing enhances the probability of the dynamic KLT model to fire. This enhancement is because the downswing temporarily hyperpolarizes the model below the resting potential, permitting a de-activation of the resting $I_{\text{KLT}}$ conductance before the subsequent upswing towards spike threshold. For high-frequency stimuli, upswings were fast enough to not require a de-activation of $I_{\text{KLT}}$ to enhance spike discharge probability, leading to no visible differences between STAs computed from frozen and dynamic KLT models.

We remark that both models display oscillatory STAs due to the correlative timescale inherent in the stimulus itself. Nevertheless, the preceding hyperpolarization is on average reduced for the frozen KLT model, similar to experimental STAs of MSO bathed in DTX (an $I_{\text{KLT}}$ channel-blocker) (Svirskis et al. 2002). Any preceding hyperpolarization in the frozen KLT model STA (beyond the one induced by a stimulus oscillation) is likely due to the spike probability-enhancing effect of removing latent $I_{\text{Na}}$ inactivation before a stimulus upswing (Svirskis et al. 2004). The timescale of $I_{\text{Na}}$
inactivation is 1.1 ms, the same as $\tau_{\text{KLT}}$, therefore, low-frequency stimuli contain downswings which are slow enough for $I_{\text{Na}}$ to de-inactivate, hence promoting spike discharge in either model.

The combination of these two observations qualitatively exposes the influence of $I_{\text{KLT}}$ on spike stimulus selectivity, conditional on the stimulus power spectrum being low-frequency dominated. However, a visual comparison of STAs of the two models, as mean representations of two ensembles of spike-triggered stimuli, may not accurately assess how different the two ensembles are from each other (or conversely, how similar). In the next section we offer a quantitative analysis to better expose the stimulus-dependence of $I_{\text{KLT}}$'s influence on spike encoding.

**Stimulus selection difference for narrowband stimuli**

We performed pattern classification on spike-triggered stimulus ensembles (STEs) collected from the dynamic and frozen KLT models using reverse correlation. To assess the amount of STE overlap we first project both STEs onto a vector determined by the Fisher ratio (see Methods). This transforms the task of measuring the amount of overlap between two multi-dimensional densities into the simpler task of measuring the overlap of two single-variable probability densities of projected values (see Methods; Fig. 2). The classifier sets a threshold between the two probability densities by which spike-triggered stimuli are classified as either causing the dynamic or frozen KLT models to spike. The SSD (see Methods) is a measure of how accurately the classifier performs, and equivalently a measure of the difference in spike encoding between the models. The SSD takes a value between 0 and 1: a SSD of 0 means the models fire to completely
distinguishable stimulus features; a SSD of 1 means the models fire to the same stimulus features.

In Fig. 4A, we show the SSD in response to narrowband stimuli (0.4 nA intensity) as the center frequency is shifted along the frequency axis. $I_{KLT}$ had a large influence on the spike train response to low-frequency stimuli, which lessened as the center frequency shifted to higher frequencies. This result confirmed our intuition gained from a visual comparison of the dynamic and frozen KLT model STAs for low- and high-frequency stimuli (Fig. 3).

A SSD value could not be computed for the narrowband stimulus with a center frequency of 50 Hz, even for large stimulus amplitudes. For this lowest-frequency content, stimulus fluctuations were always slow enough to allow time for $I_{KLT}$ to fully activate near spike threshold and reduce the spike probability to very low values (<< 1 spike/s). Without sufficient spike-triggered events from the dynamic KLT model, SSD could not be reliably computed. In contrast, the frozen KLT model did fire in response to narrowband stimuli with 50 Hz center frequency (Fig. 4B). This comparison again demonstrates that the phasic nature of the dynamic KLT model (i.e., no firing to lowest frequencies and phasic firing to current step onset) is due to the dynamic properties of $I_{KLT}$ (see Fig. 3). In terms of frequency-response, the dynamic KLT model is a band-pass filter, responding only to stimuli in an intermediate frequency range due to a combination of the phasic $I_{KLT}$ reducing the spike response to low-frequency stimuli and the passive membrane filtering reducing the spike response to high-frequency stimuli. However, the frozen KLT model is not completely band-pass due to its firing even at lowest frequencies. Both the frozen and dynamic KLT models had a resonance of firing
rate in the intermediate frequency range (Hutcheon and Yarom 2000; Izhikevich 2001).
At all frequencies, the dynamic KLT model fired less than the frozen KLT model.
Curiously, the quantitative relationship between SSD and center frequency was
maintained at three stimulus intensities: 0.3 nA, 0.4 nA, and 0.5 nA (Fig. 4B, inset). This
is true even though the range of stimulus intensities used was quite large given that Fig.
4B shows an increase of firing rate by up to a factor of 5. This demonstrates that the
influence of $I_{KLT}$ on spike encoding is very dependent on the center frequency of the
narrowband yet is roughly independent of the stimulus amplitude or firing rate.

Alternatively, while fixing the stimulus spectrum we observed that the SSD was
dependent on the time constant of the $I_{KLT}$ activation gate, $\tau_{KLT}$ (Fig. 5). Specifically, we
computed the response to a narrowband stimulus with a center frequency of 350 Hz for
dynamic KLT models having different values of $\tau_{KLT}$. When $\tau_{KLT}$ was reduced by a
factor of 4, the SSD rose from 0.70 to 0.99—a SSD value which represents nearly
complete distinction between model coding. When $\tau_{KLT}$ was reduced to zero (equivalent
to matching the $I_{KLT}$ activation gate instantaneously to its steady-state value at a given
voltage) the dynamic KLT model ceased to fire since for reasonable stimulus intensities
the membrane potential was not capable of escaping $I_{KLT}$ activation. Conversely, SSD
decreased when $\tau_{KLT}$ was increased. When $\tau_{KLT}$ was set to infinity, implying that the
dynamic and frozen KLT models are identical, the SSD settled to a lower limit of ~0.07.
In total, the smaller is $\tau_{KLT}$ the larger is the influence of $I_{KLT}$ on spike encoding. This is
because the faster $I_{KLT}$ activates, stimulus upswings must be faster and stronger to
overcome its dampening effect.
Stimulus selection difference for broadband stimuli

The stimulus-dependent influence of $I_{\text{KL}T}$ on spike encoding was evident as the center frequency of a narrowband stimulus was varied. We next examined the influence that $I_{\text{KL}T}$ had on the encoding of stimuli with more complex power spectra. As shown in Fig. 6, the SSD in response to a stimulus generated from the addition of two narrowband stimuli was 0.62 – a SSD value in-between the values for isolated presentation of the frequency bands. In other words, the addition of high-frequency components to the low-frequency stimulus deteriorated the influence of $I_{\text{KL}T}$ on spike encoding. This decrease in the influence of $I_{\text{KL}T}$ held true if the total power of the combined stimulus was allowed to increase, as in Fig. 6, or if the total power of the combined stimulus was normalized to that of the isolated narrowband presentation (SSD = 0.60).

A broadband stimulus is a linear combination of many narrowband stimuli with power spread equally over the components. The majority of these frequency components contain fluctuations that are too fast to allow $I_{\text{KL}T}$ time to influence the membrane potential, while a smaller amount of frequency components at the lowest end of the spectrum allow significant influence of $I_{\text{KL}T}$. In response to a broadband stimulus of an intensity of 0.4 nA we found the SSD to be 0.66 – a value significantly less than that in response to a lower-frequency narrowband of the same intensity (Fig. 4A), yet higher than that in response to a high-frequency narrowband. Unlike the SSD for narrowband stimuli, the SSD in response to the broadband stimulus was dependent on the intensity of the stimulus (Fig. 7). The tendency for the models to become more similar as the intensity of the broadband stimulus is increased is likely due to the “linearizing” effect of a strong broadband input on a weakly nonlinear system (see Discussion).
**Stimulus selection difference for physiological conductance stimuli**

Up to this point we have used rather artificial current stimuli to investigate $I_{\text{KL}}$’s influence on spike encoding: current ramps; narrowband and broadband stochastic currents with a Gaussian distribution. From the responses to artificial stimuli, one can predict how the system might respond to real synaptic input. Yet in reality, neurons receive conductance, not current stimuli, as well as stimuli shaped by a synaptic filter, not current steps, ramps, or flat-spectrum Gaussian noise. To investigate whether $I_{\text{KL}}$ could influence the spike train encoding of more realistic synaptic inputs in a similar manner as that found for artificial stimuli, we re-created synaptic stimuli based on what is known of the input feeding into VCN (Fig. 8A; see Methods). In brief, a sound pressure waveform was fed into an AN firing rate model (Tan and Carney 2003). This model produced a PSTH from which we created three separate spike trains (AN fibers) via an inhomogeneous Poisson process with a dynamic rate defined by the AN PSTH. Finally, the spike trains were convolved with an excitatory post-synaptic conductance waveform and summed to create the final conductance stimulus.

We performed pattern classification analysis on conductance stimuli derived from four sound waveforms: stochastic narrowband sounds centered at 500 Hz, 1 kHz and 4 kHz; and a broadband waveform (Fig. 8B). The power spectra of the corresponding conductance stimuli were all low-pass and nearly identical between all sound waveforms (Fig. 8C), being essentially dominated by the synaptic filter associated with the EPSP. Additionally, the AN model phase-locks to the 500 Hz narrowband, to a lesser extent to the 1 kHz narrowband, and not at all to the 4 kHz narrowband and broadband sound.
waveforms. Therefore, the power spectrum of the synaptic response to the 500 Hz narrowband waveform shows a slight additional increase of power at 500 Hz.

The SSD between dynamic and frozen KLT model responses was between 0.8 and 0.9 for all sound waveforms (Fig. 8D). This means that $I_{\text{KLT}}$ had a large influence on the spike encoding of synaptic stimuli derived from all of these very different sounds. The majority of spectral power of conductance stimuli derived from sound input came from frequencies well below $1/\tau_{\text{KLT}}$ (~1 kHz). As we showed in Fig. 4A, it is stimulus frequencies well below $1/\tau_{\text{KLT}}$ which best recruit $I_{\text{KLT}}$. Since the physiological conductance stimuli had spectra dominated at those frequencies, there then was a significant influence of $I_{\text{KLT}}$ on spike train encoding. Like the STAs in response to low-frequency current stimuli (Fig. 3C), the dynamic KLT model fired on average to a physiological conductance stimulus with a sharper upswing and greater preceding hyperpolarization (Fig. 8E). Further, the dynamic KLT model required a greater peak conductance to fire. Altogether, the resultant stimulus selectivity of the dynamic KLT model is near-equivalent to a detection of precisely coincident (monaural) AN fiber input.

Large influence of $I_{\text{KLT}}$ occurred when we drove the model with a reasonable strength of input (creating a dynamic KLT firing rate of ~35 spikes/s). When we increased the mean peak conductance of synaptic events by one third, the dynamic KLT model firing rate increased to ~100 spikes/s and the SSD lowered to 0.74 (1 kHz narrowband sound). This may, again, be interpreted in light of the stimulus power spectrum. While most power in the conductance stimulus was concentrated at frequencies well below $1/\tau_{\text{KLT}}$, there was a contribution of power near to and above $1/\tau_{\text{KLT}}$. In this respect the physiological conductance stimulus was similar to broadband
current in having some power at frequencies which activate $I_{\text{KL}}$, and some at those that do not. Like the broadband current stimulus (Fig. 7), the SSD of the physiological conductance stimulus was intensity-dependent because the model became input-driven when presented with strong stimuli which overwhelmed the weak $I_{\text{KL}}$ nonlinearity.

**DISCUSSION**

We employed a pattern classifier methodology to quantify the degree to which the dynamic properties of $I_{\text{KL}}$ influences the spike encoding of stimuli in an auditory brain stem neuron model. We compared STEs in response to various stochastic stimuli when the conductance for $I_{\text{KL}}$ was voltage- and time-dependent against when the conductance was frozen at its resting level. The classifier evidenced a significant encoding contribution by dynamic $I_{\text{KL}}$ for stimuli with dominant low-frequency content, including physiologically-realistic synaptic input. Conversely, $I_{\text{KL}}$’s contribution to spike encoding was diluted when substantial high-frequency power was present in the stimulus. In total, the influence of $I_{\text{KL}}$ on response to stochastic inputs was dependent on the spectrum of the stimulus.

*Comparison to previous experimental studies*

The selective recruitment of $I_{\text{KL}}$ in response to stimuli with slow fluctuations has been qualitatively shown previously. Like the dynamic KLT model’s response to current ramps (Fig. 3A), MSO cells (Svirskis et al. 2002) and VCN octopus cells (Ferragamo and Oertel 2002) fire selectively to fast current ramps, and will not fire to slow ramps of equal peak amplitude, due to the activation of low-threshold outward current. When $I_{\text{KL}}$
channel-blockers were applied the MSO cells (in gerbils, age P14-P17) and VCN cells fired to both stimuli, similar to the frozen KLT model. Gerbil MSO has also been shown to produce STAs similar to Fig. 3C (left) in response to a stimulus with high power at low frequencies (Svirskis et al. 2002). The STAs in that study demonstrated a decreased preceding hyperpolarization and a slower upswing when the cell was bathed in DTX.

We note that the difference between our dynamic and frozen KLT models is not equivalent to the blocking of $I_{KLT}$ in experimental studies. $I_{KLT}$ contributes a substantial conductance to cells at resting potential (Reyes et al. 1994; Rothman and Manis 2003a; Scott et al. 2005). The removal of this conductance with $I_{KLT}$ channel-block depolarizes the cell, decreases the resting membrane conductance, and increases the membrane time constant. In our comparison, by freezing $I_{KLT}$’s gating variables to their resting values, we ensure that the resting conductance and membrane time constant are unaltered as compared to the dynamic KLT model. The difference between the dynamic and frozen KLT models’ responsiveness therefore lies with the extra filtering properties in the dynamic KLT model conferred by a voltage- and time-dependent $I_{KLT}$. The frozen KLT model spiked to stimuli with slow or fast timescales (Fig. 3), similar to experimental performance of cells with $I_{KLT}$ channel-block. Therefore, the selectivity of cells with $I_{KLT}$ for stimuli with fast timescales is not solely dependent on these cells’ decreased membrane time constant, but crucially depends on the dynamic properties of $I_{KLT}$, as also noted in previous modeling studies (Cai et al. 2000; Svirskis et al. 2002). The specific effects of the dynamic properties of $I_{KLT}$ could be experimentally verified in vitro by comparing cell responses in control conditions with responses in the presence of $I_{KLT}$
channel-blockers while maintaining the control resting conductance by simulating a frozen $I_{KLT}$ with dynamic clamp.

$I_{KLT}$ influence on spike encoding is largely bypassed with broadband stimuli, especially for strong stimuli

Our pattern classification analysis showed that the dynamic properties of $I_{KLT}$ greatly altered spike encoding for stochastic input with dominant low-frequency spectral content. This effect of $I_{KLT}$ was eroded when high frequencies were introduced into the stimulus (Fig. 5). Moreover, the eroding effect of the broadband stimulus on $I_{KLT}$’s influence became more dramatic as the intensity of the stimulus increased. This can be understood by examining the current-balance equation (Eqn. 2) in the subthreshold potential regime. Only the currents $I_{KLT}$, $I_h$, $I_{ik}$, and $s(t)$ contribute to subthreshold integration. Further, the inactivation gate of $I_{KLT}$ and the activation gate of $I_h$ have very long time constants, and may be approximated as constant over the short time periods used in the reverse correlation analysis. Thus, in this regime, the right-hand side of Eqn. 2 may be reduced to three current terms: one which is linear with respect to voltage; the nonlinear $I_{KLT}$ term; and the stimulus $s(t)$. For weak-intensity broadband stimuli, the $I_{KLT}$ nonlinearity plays a role in shaping the distribution of output voltage. However, for strong broadband inputs, the $s(t)$ term becomes much more dominant in shaping output voltage than the weaker $I_{KLT}$ nonlinearity. It is known that strong broadband inputs effectively “linearize” the response of systems with weak nonlinearities (Chialvo et al. 1997). Therefore, strong broadband inputs make the dynamic KLT model more like the frozen KLT model, reducing the SSD between them.
The erosion of the influence of $I_{KLT}$ on spike encoding in response to broadband stimuli creates a problem for functional models of $I_{KLT}$-expressing cells derived from traditional reverse correlation using white noise stimuli (Slee et al. 2005). Our results suggest that such models should be more similar to our frozen KLT model – a model with a short membrane time constant but without the function conferred by a voltage- and time-dependent $I_{KLT}$. Further, our results from physiological conductance stimuli suggest that functional models constructed from reverse correlation on realistic synaptic input (instead of white noise currents) could more accurately exhibit the functional contribution of $I_{KLT}$. Consistent with this idea, a change in a functional model derived from an avian auditory brainstem neuron under pharmacological blockade of low-threshold K$^+$ current was demonstrable only when synaptic waveform-filtered currents were used, and not white noise currents (Slee et al. 2005).

**Pattern classification on spike-triggered stimuli**

Pattern classification has been used previously to analyze spike-triggered stimuli from periphery electrosensory processing in weakly electric fish. Gabbiani et al. (1996) performed Fisher linear discrimination to discriminate between stimuli which produced spikes (or bursts) versus stimuli which did not produce spikes (or bursts) as a means to assess the quality of coding of cells in the electrosensory pathway. Later, Oswald et al. (2007) used Fisher linear discrimination to discriminate between stimuli which created bursts of different lengths in current-driven *in vitro* electrosensory pyramidal neurons (see also Kepecs and Lisman (2003) for similar work in model cells). We demonstrate a
novel use for the Fisher linear discriminant by discriminating between spike-triggered events from different neuronal models (i.e., different membrane properties) in response to the same stimulus. This allowed us to quantify the influence that a particular biophysical mechanism (dynamic $I_{\text{KLT}}$) had on spike encoding. We mention that pattern classification did not give any information about how $I_{\text{KLT}}$ changed spike encoding. This information was obtained using various experimental paradigms such as response to current ramps and band-limited stochastic stimuli. Instead, pattern classification provided an answer as to how much $I_{\text{KLT}}$ changed spike encoding. This quantification of coding change through pattern classification was more sophisticated than a simple comparison of firing rates or STAs of the two models for a given stimulus. For instance, it is possible for two models to fire at the same rate to a given stochastic input, yet be firing to quite different features within the input. Further, it is possible for two models to have similar STAs, yet one model be more selective in its firing than the other.

Our pattern classification method could be adapted to investigate the effect on spike encoding of other ion channels in the nervous system. As an example, in vitro experiments on stellate cells in entorhinal cortex have shown how persistent Na$^+$ currents and the inward rectifier $I_h$ combine to influence spike encoding in a stimulus-dependent manner (Haas et al. 2007). Further, calcium-activated K$^+$ channels have been shown to change the frequency tuning of spike response in primary electrosensory neurons through an influence on the burst discharge in these cells (Ellis et al. 2007). In both of these examples, when the stimulus timescale is chosen appropriately, the channel dynamics are such that the measured spike train encoding is distinct from that when the channel is pharmacologically-blocked. It would be straightforward to use the pattern classification
methodology presented here to quantify the stimulus-dependent coding influence of the various ion channels in these, and many other, single neuron coding schemes.

**Generality of results, across auditory brainstem areas and models**

We computed all results in this study using the RM03 model, a Hodgkin-Huxley-like model of Type II cells in the guinea pig VCN (Rothman and Manis 2003b). Many studies have used VCN models for the MSO (Brand et al. 2002; Brughera et al. 1996; Zhou et al. 2005) because of the high prevalence of $I_{KLT}$ in both areas, similar firing characteristics between Type II VCN neurons and MSO neurons, as well as the absence of voltage-clamped kinetics data for currents in MSO. The RM03 model, when adjusted for a body temperature of 38°C, has a very fast membrane time constant of 0.3 ms, like that found in gerbil MSO (Scott et al. 2005). Other $I_{KLT}$-variants also exist in the avian nucleus magnocellularis (Rathouz and Trussell 1998; Reyes et al. 1994), in the mammalian MNTB (Brew and Forsythe 1995) and in VCN octopus cells (Cai et al. 2000), each of which transmits precise timing information. While our results were based on the RM03 model, we believe the finding that the dynamic properties of $I_{KLT}$ influence spike encoding dependent on stimulus spectrum is general for any auditory brainstem neuron which has a large density of currents in the $I_{KLT}$ family. Correspondingly, our approach if applied to other models which include phasic-firing properties would yield similar results. For example, contributions to spike encoding by other biophysical phasic-inducing mechanisms should demonstrate an interaction between the timescale of the mechanism and the power spectrum of the input. We have previously demonstrated such stimulus-dependent spike encoding for an idealized, phasic-spiking, leaky-integrate-
and-fire model with a dynamic $V$- and $t$-gated rectification (Day et al. 2006). Many of our conclusions about stimulus-dependent encoding should also generalize to other non-$I_{KLT}$, subthreshold, dynamic negative feedback mechanisms (such as the inactivation of sodium current) which contribute to phasic behavior (Svirskis et al. 2004; Svirskis and Rinzel 2003).
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GRANTS

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REFERENCES


FIGURE LEGENDS

FIG. 1. Current stimuli. Center: power spectra of the current stimuli used in the study. Narrowband stimuli were 100-Hz-wide with center frequency varied along the frequency axis. The broadband stimulus had a cutoff frequency off the axis at 2 kHz. Sample time courses are shown for two narrowband stimuli with center frequencies 150 Hz (a) and 950 Hz (b), respectively. c: sample time course of the broadband stimulus.

FIG. 2. Schematic of Fisher linear discrimination on spike-triggered stimulus waveforms. A: for every spike event in the spike train $x(t)$ the 30 ms of stimulus current $s(t)$ preceding the spike is collected as a spike-triggered current waveform. B: example of Fisher linear discrimination on dynamic and frozen KLT model STEs, idealized in two dimensions. Here, a line instead of a hyperplane may be visualized to separate the two ensembles, if oriented properly. The orientation of the normal vector $f$, perpendicular to the separating line, changes the Fisher ratio of the projected ensemble probability densities. $f$ is chosen to maximize the Fisher ratio.

FIG. 3. Comparison of model responses to stimuli with slow and fast timescales. A: response of the dynamic (black) and frozen (gray) KLT models (top) to triangular current ramps (bottom). Current ramps have equal peak amplitude but different ramp speeds (left, slow; right, fast). B: response of the two models to a narrowband stimulus with
center frequency 150 Hz (left) and a narrowband stimulus with center frequency 750 Hz (right). Note how the subthreshold voltage trajectories of the two models deviate from each other more in response to the low-frequency stimulus. C: STAs of the two models in response to low- (left) and high-frequency (right) narrowband stimuli, same as in B. The STAs are oscillatory due to temporal correlations inherent in the stochastic stimulus. Inset: STAs plotted at a finer timescale.

FIG. 4. Difference between dynamic and frozen KLT spike encoding to narrowband stimuli at different center frequencies. A: stimulus selection difference (SSD) between models in response to narrowband stimuli as a function of center frequency (100-Hz bandwidth; 0.4 nA intensity). The probability densities of the projected STEs are shown for two narrowband stimuli with center frequencies 150 Hz (a) and 650 Hz (b), respectively. B: firing rates of the dynamic (black) and frozen (gray dashed) KLT models in response to narrowband stimuli. Intensity of the stimulus was varied: 0.3 nA (thick lines); 0.4 nA (medium lines); 0.5 nA (thin lines). Inset: SSD curves for the same stimuli at 0.3 nA (thick), 0.4 nA (medium), and 0.5 nA (thin) intensities.

FIG. 5. The change in the influence of $I_{KLT}$ on spike encoding as the time constant of $I_{KLT}$ activation, $\tau_{KLT}$, is varied. SSDs were computed for model responses to a narrowband stimulus with a center frequency of 350 Hz (0.4 nA intensity) as $\tau_{KLT}$ was varied. A SSD measure could not be computed for $\tau_{KLT} = 0$ (*) because the instantaneous
activation of $I_{\text{KLT}}$ completely prevented the dynamic KLT model from firing at this stimulus intensity.

FIG. 6. Difference in spike encoding between dynamic and frozen KLT models to a stimulus with combined low and high frequency content. SSD was computed in response to a stimulus consisting of a combination of a narrowband stimulus with center frequency of 150 Hz and another narrowband with center frequency 750 Hz. Note that SSD decreases with the addition of high-frequency stimulus components in comparison to an exclusively low-frequency stimulus.

FIG. 7. Difference in spike encoding between dynamic and frozen KLT models to a broadband stimulus. SSD was computed in response to a broadband stimulus as intensity was varied. The firing rates of both models are listed for each stimulus intensity tested. Note that below 0.35 nA intensity the dynamic KLT model fired minimally (< 1 sp/s), therefore SSD could not be computed.

FIG. 8. Difference between dynamic and frozen KLT model responses to physiological conductance stimuli. A: schematic of the transformation of a sound into a conductance stimulus. A sound pressure waveform is input into an AN model to produce a PSTH. Three spike trains are randomly obtained from the PSTH via an inhomogeneous Poisson process. The spike trains are convolved with an EPSG waveform with randomized peak conductance, then summed to produce the conductance stimulus. B: power spectra of
the initial sounds. The sounds are narrowband waveforms centered at 500 Hz (black), 1 kHz (dark gray) and 4 kHz (light gray). The power spectrum of the broadband sound is flat and not visible at this scale. C: power spectra of the conductance stimuli. Regardless of the initial sound, the stimuli arriving at VCN have approximately the same power spectrum: 500 Hz (black); 1 kHz (dark gray); 4 kHz (medium gray); broadband (light gray). D: SSD between model responses to the different sounds. E: STAs of the dynamic KLT model (black) and the frozen KLT model (gray) in response to the broadband sound. STAs in response to the other sounds look similar. Inset: probability densities of the STEs projected onto the normal vector. These densities led to the SSD for broadband sound in D.
<table>
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<th>Summary of model properties</th>
<th>( \tau_m )</th>
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<td>Membrane time constant</td>
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<tr>
<td>Resting membrane resistance</td>
<td>( 65% )</td>
<td></td>
</tr>
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</table>
A

\[ s(t) \]

\[ x(t) \]

Time

B  Large Fisher ratio  Small Fisher ratio
A

Stimulus Selection Difference

Projection onto feature

Probability density

Center frequency (Hz)

B

Firing rate (sp/s)

SSD

Center frequency (Hz)

amplitude

Hz
Frequency (Hz)

- 200
- 400
- 600
- 800
- 1000
- 1200

Power

Low freq. only
SSD = 0.96

Low + high freq.
SSD = 0.62

High freq. only
SSD = 0.33
A sound AN PSTH

AN fibers conductance stimulus

Σ Poisson process

AN fibers

B

Frequency (kHz)

Power (Pa^2/Hz x 10^{-4})

0 1 2 3 4

0.5 kHz 1 kHz 4 kHz broad band

C

Frequency (kHz)

Power (nS^2/Hz)

0.06 0.12

D

SSD

0.5 kHz 1 kHz 4 kHz broad band

E

Time before spike (ms)

Conductance (nS)

Prob. density Projection

Page 45 of 45