Adaptation and Inhibition Underlie Responses to Time-Varying Interaural Phase Cues in a Model of Inferior Colliculus Neurons

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Borisyuk, Alla, Malcolm N. Semple, and John Rinzel. Adaptation and inhibition underlie responses to time-varying interaural phase cues in a model of inferior colliculus neurons. J Neurophysiol 88: 2134–2146, 2002; 10.1152/jn.00073.2002. A mathematical model was developed for exploring the sensitivity of low-frequency inferior colliculus (IC) neurons to interaural phase disparity (IPD). The formulation involves a firing-rate-type model that does not include spikes per se. The model IC neuron receives IPD-tuned excitatory and inhibitory inputs (viewed as the output of a collection of cells in the medial superior olive). The model cell possesses cellular properties of firing rate adaptation and postinhibitory rebound (PIR). The descriptions of these mechanisms are biophysically reasonable, but only semi-quantitative. We seek to explain within a minimal model the experimentally observed mismatch between responses to IPD stimuli delivered dynamically and those delivered statically (McAlpine et al. 2000; Spitzer and Semple 1993). The model reproduces many features of the responses to static IPD presentations, binaural beat, and partial range sweep stimuli. These features include differences in responses to a stimulus presented in static or dynamic context: sharper tuning and phase shifts in response to binaural beats, and hysteresis and “rise-from-nowhere” in response to partial range sweeps. Our results suggest that dynamic response features are due to the structure of inputs and the presence of firing rate adaptation and PIR mechanism in IC cells, but do not depend on a specific biophysical mechanism. We demonstrate how the model’s various components contribute to shaping the observed phenomena. For example, adaptation, PIR, and transmission delay shape phase advances and delays in responses to binaural beats, adaptation and PIR shape hysteresis in different ranges of IPD, and tuned inhibition underlies asymmetry in dynamic tuning properties. We also suggest experiments to test our modeling predictions: in vitro simulation of the binaural beat (phase advance at low beat frequencies, its dependence on firing rate), in vivo partial range sweep experiments (dependence of the hysteresis curve on parameters), and inhibition blocking experiments (to study inhibitory tuning properties by observation of phase shifts).

INTRODUCTION

Many neurons in the inferior colliculus (IC) exhibit displaced tuning to auditory stimuli presented under static or dynamic conditions. Recent studies have shown that tuning to interaural delay (McAlpine et al. 2000; Spitzer and Semple 1991a, 1993, 1998), interaural level difference (Sanes et al. 1998), simulated free-field motion (Wilson and O’Neill 1998), and monaural frequency (Malone and Semple 2001) may be different when the tuning curve is generated by continuously varying the stimulus parameter rather than by testing a range of discrete parameter values.

These dynamic conditioning effects have been particularly well studied with manipulation of the interaural phase difference (IPD)—a binaural cue for low-frequency sound localization. Temporal variation of IPD simulates the binaural cue produced by a moving sound source, and the variable may be manipulated across its entire range (i.e., 360°). Although IC responses to IPD modulation depend on the recent stimulus-response history (McAlpine et al. 2000; Spitzer and Semple 1991a, 1993, 1998), responses in the medial superior olive (MSO, where IPD is initially encoded) reflect a coincidence-detection process that effectively tracks the instantaneous value of IPD (Spitzer and Semple 1995, 1998; Yin and Chan 1990).

One explanation for this transformation of response properties between MSO and IC is that it reflects “adaptation of excitation” (firing rate adaptation) (Cai et al. 1998b; McAlpine et al. 2000; Spitzer and Semple 1998). Alternatively (Spitzer and Semple 1998), motion sensitivity could be the result of interaction between excitatory and inhibitory inputs, aided by firing rate adaptation and postinhibitory rebound. However, McAlpine and Palmer (2002) argued that leaving the key role to inhibition contradicts their data. They showed that sensitivity to the apparent motion cues is decreased in the presence of the inhibitory transmitter, GABA, and increased in the presence of bicuculline.

In this study, we propose a framework that unifies these different ideas. We explore how intrinsic cellular mechanisms, such as adaptation and rebound, together with the interaction of excitatory and inhibitory inputs, can contribute to the shaping of dynamic conditioning. We suggest that each of these mechanisms has a specific influence on response features. To examine the role of various mechanisms in shaping IC response properties, we developed a mathematical model of an IC cell that receives IPD-tuned excitatory and inhibitory inputs and possesses the properties of adaptation and postinhibitory rebound. In earlier modeling studies of the role of adaptation and inhibition in IC, Cai et al. (1998a,b) developed detailed cell-based spike-generating models, involving multiple stages of auditory processing. In contrast, our model is minimal in that it only involves the components whose role we want to test and
does not explicitly include spikes (firing-rate-type models). This approach (extending the prototype version of Borisyuk et al. 2001a) greatly facilitates examination of computations that can be performed with rate-coded inputs (spike-timing precision on the order of 10 ms), consistent with the type of input information available to neurons at higher levels of processing (such as the inferior colliculus compared with the superior olive). In addition, our model is computationally efficient, can be easily implemented, and requires minimal assumptions about the underlying neural system.

First, we explore the extent to which our model, using the experiment-based hypotheses of firing rate adaptation and IPD tuned excitatory and inhibitory inputs, satisfactorily accounts for experimental findings. Next, the novel feature of a post-inhibitory rebound mechanism (modeled as a transient membrane current activated by release from prolonged hyperpolarization) allows us to explain the strong excitatory dynamic response to sweeps in the silent portion of the static tuning curve (“rise-from-nowhere”). Preliminary reports of some aspects of these results have been presented in abstract form (Borisyuk et al. 2001b).

METHODS

Cellular properties

Our model cell represents a low-frequency-tuned IC neuron that responds to interaural phase cues. Since phase-locking to the carrier frequency among such cells is infrequent and not tight (Kuwada et al. 1984), our model assumes that binaural input is rate-encoded. We adopt the idealization of our earlier model (Borisyuk et al. 2001a), i.e., we eliminate spikes by implicitly averaging over a short time scale (say, 10 ms). Here, we take as the cell’s observable state variable its averaged voltage relative to rest ($V$). Our formulation is in the spirit of previous rate models (e.g., Grossberg 1973), but extended to include intrinsic cellular mechanisms such as adaptation and rebound. Parameter values are not optimized, most of them are chosen to have representative values within physiological constraints, as specified in this section.

The current-balance equation for our IC cell is

$$CV = -g_L(V - V_L) - \bar{g}_a (V - V_a) - I_{m}(t) - I_m + I$$

The terms on the right-hand side of the equation represent (in this order) the leakage, adaptation, synaptic, post-inhibitory rebound, and applied currents. The applied current $I$ is zero except in Fig. 8B, and all other terms are defined below.

Leakage current has reversal potential $V_L = 0$ mV and conductance $g_L = 0.2$ mS/cm$^2$. Thus with $C = \mu F/cm^2$, the membrane time constant $\tau_V = C/g_L$ is 5 ms.

We model adaptation by a slowly-activating voltage-gated potassium current $\bar{g}_a (V - V_a)$. Its gating variable $a$ satisfies

$$\tau_a = a_0 (V - a).$$

Here $a_0(V) = 1/(1 + \exp(-(V - \theta_a)/k_a))$, time constant $\tau_a = 150$ ms, $k_a = 5$ mV, $\theta_a = 30$ mV, maximal conductance $\bar{g}_a = 0.4$ mS/cm$^2$, and reversal potential $V_a = -30$ mV. The parameters $k_a$ and $\theta_a$ were chosen so that little adaptation occurs below firing threshold, and $\bar{g}_a$ so that when fully adapted for large inputs, the firing rate is reduced by 67%. The value of $\tau_a$, assumed to be voltage-independent, matches the adaptation time scale range seen in spike trains (Semple, unpublished observations), and it leads to dynamic effects that provide good comparison with results over the range of stimulus rates used in experiments.

The model’s readout variable, $r$, represents firing rate, normalized by an arbitrary constant. It is an instantaneous threshold-linear function of $V$: $r = 0$ for $V < V_{\text{th}}$ and $r = K \cdot (V - V_{\text{th}})$ for $V \geq V_{\text{th}}$, where $V_{\text{th}} = 10$ mV. We set (arbitrarily) $K = 0.04075$ mV$^{-1}$. Its value does not influence the cell’s responsiveness, only setting the scale for $r$.

Synaptic inputs

As proposed in Spitzer and Semple (1998) and implemented in the spike-based model of Cai et al. (1998a,b), our model IC cell receives binaural excitatory input from neurons in ipsilateral MSO (e.g., Adams 1979; Oliver et al. 1995) and indirect (via dorsal nucleus of lateral lemniscus (DNLL)); Shneiderman and Oliver 1989) binaural inhibitory input from the contralateral MSO (Fig. 1). Thus DNLL, although it is not specifically included in the model, is assumed (as in Cai et al. 1998a) to serve as an instantaneous converter of excitation to inhibition.

The afferent input from MSO is assumed to be tonotopically organized and IPD-tuned. Typical tuning curves of MSO neurons are approximately sinusoidal with preferred (maximum) phases in contralateral space (Spitzer and Semple 1995; Yin and Chan 1990). We use a sign convention that the IPD is positive if the phase is leading in the ear contralateral to the IC cell, to choose the preferred phases $\phi_+ = 40^\circ$ for excitation and $\phi_- = -100^\circ$ for inhibition. Preferred phases of MSO cells are broadly distributed (Malone et al. 2002; McAlpine et al. 2001). Similar ranges work in the model, and in that sense, the particular values that we picked are arbitrary.

While individual MSO cells are phase-locked to the carrier frequency (Spitzer and Semple 1995; Yin and Chan 1990), we assume that the effective input to an IC neuron is rate-encoded. That is, the convergent afferents from MSO represent a distribution of preferred phases and phase-locking properties so that, either through filtering by the IC cell or dispersion among the inputs, spike-timing information is not of critical importance to these IC cells, for the issues under consideration here. Under these assumptions, the synaptic conductance transients from incoming MSO spikes are smeared into a smooth time course that traces the tuning curve of the respective presynaptic population (Fig. 1). We define $g_{E}$ and $g_{I}$ to be these smoothed synaptic conductances, averaged over input lines and short time scales. They are proportional to the firing rates of the respective MSO populations and they depend on $t$ if IPD is dynamic

$$I_{\text{syn}} = -g_{E}(V - V_E) - g_{I}(V - V_I) - g_{\text{tonic}}(V - V_t)$$

$$g_{E} = g_{E}(0.55 + 0.45 \cos(\text{IPD}(t) - \phi_+))$$

In some cases we consider IPD-insensitive inhibition; and then $g_{\text{tonic}} \neq 0$. Reversal potentials are $V_E = 100$ mV and $V_I = -30$ mV.

**FIG. 1.** Schematic of the model. A neuron in the inferior colliculus (IC), receiving excitatory input from ipsilateral medial superior olive (MSO); contralateral input is inhibitory. Each of the MSO-labeled units represents an average of several MSO cells with similar response properties. Dorsal nucleus of lateral lemniscus (DNLL) is a relay nucleus and is not included in the model. Interaural phase difference (IPD) is the parameter whose value at any time defines the stimulus. The tuning curves show the stimulus (IPD) tuning of the MSO populations. They also represent dependence of synaptic conductances ($g_{E}$ and $g_{I}$) on IPD.
For these maximum conductance values: \( g_{\text{K}} = 0.3 \text{ mS/cm}^2 \), \( g_{\text{Na}} = 0.43 \text{ mS/cm}^2 \), total membrane conductance doubles or triples when the stimulus is maximal. Similar conductance changes have been shown in other parts of the CNS (e.g., Anderson et al. 2000). All of our qualitative results are robust with respect to the input parameters.

Rebound mechanism

The postinhibitory rebound (PIR) mechanism (motivated and described in the corresponding subsection of RESULTS) is implemented as a transient inward current \( I_{\text{PIR}} \) in the Eq.1

\[
I_{\text{PIR}} = g_{\text{PIR}} \cdot m \cdot h \cdot (V - V_{\text{PIR}})
\]

The current’s gating variables, fast (instantaneous) activation, \( m \), and slow inactivation, \( h \) satisfy

\[
m = m(V)
\]

\[
r_\text{h} = h(V) - h
\]

where \( m(V) = 1/[1 + \exp(-(V - \theta_m)/k_m)] \), \( h_\text{s}(V) = 1/[1 + \exp(-(V - \theta_h)/k_h)] \). The parameter values \( k_m = 4.55 \text{ mV} \), \( \theta_m = 9 \text{ mV} \), \( k_h = 0.11 \text{ mV} \), and \( \theta_h = -11 \text{ mV} \) are chosen to provide only small current at steady state for any constant \( V \) and maximum responsiveness for voltages near rest. We set \( r_\text{h} = 150 \text{ ms} \) and \( V_{\text{PIR}} = 100 \text{ mV} \). Maximum conductance \( g_{\text{PIR}} \) equals 0.35 mS/cm² in the subsection on PIR and zero elsewhere. We treat \( r_\text{h}, V_{\text{PIR}}, \text{ and } g_{\text{PIR}} \) as parameters and discuss their values in Fig. 10 and the accompanying text.

Stimuli

The only sound input parameter that we vary is IPD as represented in Eqs. 3 and 4; the sound’s carrier frequency and pressure level are fixed. The static tuning curve is generated by presentation of constant-IPD stimuli for 500 ms. The dynamic stimuli are from two classes. First, the binaural beat stimulus is generated as:

\[
P_{\text{b}}(t) = P_{\text{b}}(t) + P_{\text{d}}(t)
\]

Second, the parametric sweep is generated by IPD(t) = \( P_{\text{b}} + P_{\text{d}} \) for 0 ≤ t ≤ T (mod 360°).

Simulation data analysis

The response’s relative phase (Figs. 5 and 11) is the mean phase of the response to a binaural beat stimulus minus the mean phase of the static tuning curve. The mean phase is the direction of the vector that determines the response’s vector strength (Goldberg and Brown 1969). To compute the mean phase, we collect a number of response values \( r(t) \) and corresponding stimulus values \( IPD(t) \) in radians. The average phase \( \phi \) is such that \( tan(\phi) = [\sum r(t) \sin(IPD(t))] / [\sum r(t) \cos(IPD(t))] \).

For the static tuning curve, the responses were collected at IPDs ranging from −180° to 180° in 10° intervals. For the binaural beat we used the response to the last stimulus cycle recorded with 1-ms steps in time.

We compute a hysteresis measure (Figs. 6, 7, and 11) by using the up-sweep \( r_{\text{up}} \) and the down-sweep \( r_{\text{down}} \) responses, recorded with 1-ms time increments during the final stimulus cycle. They are normalized by the maximum response over the period to yield \( r_{\text{up}} \) and \( r_{\text{down}} \). The hysteresis measure is then the area of the hysteresis loop formed by the normalized responses approximated by the sum \( \sum [r_{\text{up}} - r_{\text{down}}] \cdot dt \cdot P/360 \), where \( dt \) is the time step (0.001 s) and \( P \) is the rate of the sweep (in degrees per second). Similar measures were used by Spitzer and Semple (1993) and McAlpine and Palmer (2002).

Transmission delays

In its essence, our model deals with information processing in the IC as represented by a transformation between rate-coded inputs and rate-coded output. (The rate-coding means that the timing information is only represented with accuracy on the order of 10 ms). Therefore most of our qualitative results do not depend on the presence or absence of the short (5–10 ms) delays that exist in the transmission of signal from ear to IC (transmission delay). Moreover, in most of the paper (as in the experiments), we use periodic stimuli with frequencies of only 1 or 2 Hz. Inclusion of the transmission delay would shift the observed response, relative to the stimulus, only by a small fraction of the cycle, resulting in a very slight modification of the results. Therefore for clarity of presentation, we only consider transmission delay in the binaural beats section, where higher frequency stimuli are used. Of course, the discussion on the role of the delays would be more complicated had we varied the carrier frequency.

Simulations

The model is implemented in MATLAB. The system of ordinary differential equations is integrated by the low-order stiff solver “ode23s.” Numerical simulations were run under Solaris on a Sun Ultra10 workstation. To check accuracy, the error tolerance was decreased until no noticeable differences were observed.

Experimental procedures

In selected instances, model properties are compared directly with physiological response properties recorded extracellularly from single cells in the IC of anesthetized gerbils. These neural responses derive from a database that has formed the basis of prior published reports (Spitzer and Semple 1993, 1995, 1998) in which methods are described in full detail. All procedures concerning the use of animals were approved by the institutional animal care and use committee. Adult gerbils (Meriones unguiculatus) were anesthetized (pentobarbital sodium, 60 mg/kg ip) for surgical preparation, and anesthesia was maintained throughout the recording session with supplemental injections of ketamine (30 mg/kg/h, im). Single neurons were recorded at histologically confirmed sites in the IC. Digitally synthesized stimuli were presented dichotically through calibrated sealed sound-delivery systems. Sound pressure level (SPL) was calculated in dB (approximately 20 μPa). Static IPDs were generated by dichotic presentation of tone pips differing only in starting phase. Dynamic IPDs were in the form of binaural beats or IPD sweeps generated by triangular modulation of the phase at one ear.

RESULTS

Static tuning curve

SHAPING OF STATIC TUNING CURVE BY SYNAPTIC CONDUCTANCES AND CURRENTS. Static IPD tuning of the model IC neuron is determined by the sharpness of tuning, preferred IPDs and mutual strengths of the incoming excitatory and inhibitory inputs from MSO (Fig. 1), and by the cell’s intrinsic properties. Figure 2A shows the tuning of model MSO populations as well as the resulting adapted response of the IC neuron for statically presented inputs. The peak of the model IC cell’s tuning curve is close to that of the excitatory MSO population. However, because for our choice of parameters excitation and inhibition are neither in-phase nor exactly in anti-phase, inhibition shifts the peak of the IC curve closer to the minimum of inhibition.
A sequence of nonlinearity, we repeat the IC tuning curve, in terms of excitation and inhibition determines the width of the tuning curve. Given a certain tuning width for excitation, the tuned inhibition provides a shift in the position of the peak (unless inhibition is exactly in antiphase with excitation) and a mechanism for narrowing the tuning curve (Fig. 3A). Narrower tuning (at the given level of excitation) can also be achieved by application of the IPD-insensitive inhibition or by raising the threshold of the cell (Fig. 3B), at the expense of substantially decreasing firing rates. Comparison between Fig. 3, A and B, leads to a prediction that tuning properties of major inhibitory input in IC may be determined by observation of phase shifts in inhibition blocking experiments (see Discussion).

So far we have discussed the case when excitation and inhibition tuning curves were both sinusoidal of the same period. Different tuning properties of excitation and inhibition can produce different results. For example, if inhibition is more narrowly tuned than excitation, and phase-shifted, it can provide a trough at the slope of the tuning curve, resulting in a two-peaked tuning curve as in Fig. 2 of Cal et al. 1998a.

**Binaural beats**

The binaural beat stimulus has been used widely in experimental studies (e.g., Kuwada et al. 1979; McAlpine et al. 1998; Spitzer and Semple 1993; Wernick and Starr 1968) to create interaural phase modulation: a linear sweep through a full range of phases (Fig. 4A). Positive beat frequency means IPD increases during each cycle; negative beat frequency means IPD decreases (Fig. 4A). Using the linear form of $IPD(t)$ to represent a binaural beat stimulus in the model, we obtain responses whose time courses are shown in Fig. 4A (bottom).

To compare responses between different beat stimuli and also with the static response, we plot the instantaneous firing rate versus the corresponding IPD. Figure 4B shows an example that is typical of many experimentally recorded responses (e.g., Kuwada et al. 1979; Spitzer and Semple 1991a, 1993).

**FIG. 2.** Static tuning curves of the model neurons. $A$: black curves represent, as functions of IPD, the synaptic conductances $(g_E, g_I)$ that are delivered to an IC neuron due to the activity of the excitatory (thick) and inhibitory (thin) MSO populations. Gray line is the steady (normalized) firing rate of the IC cell (computed as the steady-state solution of Eqs. 1–4)—the IC static tuning curve. $B$: gray line is the same static IC response as in $A$, in terms of voltage. Black curves are the synaptic currents $I = g(V - V_{th})$, corresponding to the conductances in $A$. Horizontal dotted lines are the resting potential ($V_{rest} = 0$ mV) and the threshold potential ($V_{th} = 10$ mV).

Recall that the static tuning curve is the steady-state solution of Eqs. 1–7

$$V = \frac{g_E(V - V_g) + g_I(IPD)V_i + g_{\mu_e}(V)V_i}{g_E + g_I(IPD) + g_{\mu_e}(V)}$$

**FIG. 3.** A: static (fully adapted) tuning curve at different levels of IPD-tuned inhibition ($g_I = 0, 0.2, 0.43 \text{ mS/cm}^2; g_{I_{tonic}} = 0 \text{ mS/cm}^2$). $B$: static (fully adapted) tuning curve at different levels of IPD-insensitive inhibition ($g_I = 0 \text{ mS/cm}^2; g_{I_{tonic}} = 0, 0.1, 0.2 \text{ mS/cm}^2$).
Replotting our computed response from Fig. 4A in Fig. 4C reveals features in accord with the experimental data (compare Fig. 4, B and C): dynamic IPD modulation increases the sharpness of tuning, preferred phases of responses to the two directions of the beat are shifted in opposite directions from the static tuning curve, and maximum dynamic responses are significantly higher than maximum static responses. These features, especially the phase shift, depend on beat frequency (Fig. 4, C and D).

DEPENDENCE OF PHASE ON THE BEAT FREQUENCY. In Fig. 4D, the direction of phase shift is what one would expect from a lag in response. In Fig. 4C, it is what would be expected in the presence of adaptation (e.g., Smith et al. 2001; as the firing rate rises, the response is “chopped off” by adaptation at the later part of the cycle—this shifts the average of the response to earlier phases). In particular, if we interpret the IPD change as an acoustic motion, then for a stimulus moving in a given direction (e.g., solid curve in Fig. 4, C and D), there can be a phase advance or phase-lag, depending on the speed of the simulated motion (beat frequency).

To characterize the dependence of the phase shift on parameters, we define the response phase \( \phi'_{j} \) as a vector-strength computation (see METHODS). We take the average phase of the static response as a reference (\( \phi_{0} = 0.1623 \)). Figure 5A shows the relative phase of the response \( \phi'_{j} - \phi_{0} \) versus beat frequency \( f_{b} \). At the smallest beat frequencies, the tuning is close to the static case and the relative phase is close to zero. As the absolute value of beat frequency increases, so does the phase advance. The phase-advance is due to the firing rate adaptation (see above). At yet higher frequencies, a phase lag develops. This reflects the resistance-capacitive properties of the cell membrane—the membrane time constant prevents the cell from responding fast enough to follow the high-frequency phase modulation.

Plots such as in Fig. 5A have been published for two IC recordings (Spitzer and Semple 1998). A sample of results for several different neurons is shown in Fig. 5B. Whereas we do not have a goal of quantitative match between our modeling results and experimental data, there are two qualitative differences between Fig. 5, A and B. First, the range of values of the phase shift is considerably larger in the experimental recordings, particularly, the phase lag at higher beat frequencies. Second, it has been reported in the experimental data that there is no appreciable phase advance at lower beat frequencies. Figure 5B suggests that the phase remains approximately constant before shifting in the positive direction. Only in the close-up view of the phase at low beat frequencies (Fig. 5B, inset) can the phase-advance be detected, and this has not been reported previously. It is a surprising observation, given that the firing rate, or spike frequency, adaptation has been reported in IC cells on many occasions (e.g., McAlpine et al. 2000; Spitzer and Semple 1993) and that, as we noted above, the phase advance is a generic feature of cells with adapting spike trains.

ROLE OF TRANSMISSION DELAY. We propose that the absence of phase advance and high values of phase lag should be attributed to the transmission delay (5 to tens of milliseconds) that exists in transmission of the stimulus to the IC. This delay was not included in our model up to this point, as outlined in METHODS. In fact, we can find its contribution analytically (Fig. 5C, inset). Consider the response without transmission delay to the beat of positive frequency \( f_{b} \). In the phase computation, the response at each of the chosen times (each bin of poststimulus time histogram) is considered as a vector from the origin with length proportional to the recorded firing rate and pointing at the corresponding value of IPD. In polar coordinates \( r_{j} = (r_{j}, IPD_{j}) \), \( r_{j} \) is the jth recorded data point (normalized firing rate) and \( IPD_{j} \) is the corresponding IPD. The average phase of response \( \langle \phi' \rangle \) can be found as a phase of the sum of these vectors. If the response is delayed, then the vectors should be \( r_{j} = (r_{j}, IPD_{j} + d \cdot f_{b} \cdot 360^\circ) \), because the same firing rates would correspond to different IPDs (see Fig. 5C, inset). The vectors are the same as without transmission delay, just rotated by \( d \cdot f_{b} \) fractions of the cycle. Therefore the phase with
transmission delay $\varphi_t = \varphi'_f + d \cdot f_o$. If we plot the relative phase with the transmission delay, it will be $\varphi_t - \varphi_0 = (\varphi'_f - \varphi_f) + d \cdot f_o$. The phase of the static tuning curve ($\varphi_f$) does not depend on the transmission delay. Figure 5C shows the graph from Fig. 5A (right), modified by various transmission delays (thick curve is without delay—same as in Fig. 5A, right). With transmission delay included in the model, the range of observed phase shifts increases dramatically, and the phase-advance is masked. In practice, neurons are expected to have various transmission delays, which would result in a variety of phase-frequency curves, even if the cellular parameters were similar.

**MEAN FIRING RATE.** Another interesting property of response to binaural beats is that the mean firing rate stays approximately constant over a wide range of beat frequencies (Fig. 5D and Spitzer and Semple 1998). The particular value, however, is different for different cells. The same is valid for the model system (Fig. 5E). The thick curve is the firing rate for the standard parameter values. It is nearly constant across all tested beat frequencies (0.1–100 Hz). The constant value can be modified by change in other parameters of the system e.g., $g_I$ (shown).

**DEPENDENCE ON MODEL PARAMETERS.** We have illustrated in Fig. 5C that variability in phase-frequency curves can be created by introduction of the transmission delay. Additional variability arises from changes in cellular and input parameters of the system. For example, decreased level of inhibition will increase phase-advance (shift the phase curve downwards) by increasing the effect of adaptation through the increase in firing rates; slower adaptation processes (larger $\tau_a$) would narrow the range of beat frequencies where phase advance is observed, due to the slowing in the system’s response. These parameter dependencies are not shown here.

**Partial range sweeps**

Spitzer and Semple (1991a) pointed out that the physiologically realistic range of IPDs for small mammals (such as cats and gerbils) at low carrier frequencies is restricted. Therefore they elected to use restricted range IPD modulations as an alternative to binaural beats (Spitzer and Semple 1991a, 1993). We call it partial range sweep stimulus (see METHODS). This stimulation can be crudely interpreted as a motion of a sound source back and forth on an arc in the azimuthal plane around the head of the animal (Spitzer and Semple 1993). An example of IPD time course is shown in Fig. 7A (top).

As in the case of binaural beats, we plot the instantaneous firing rate (averaged over all periods) versus IPD. Figure 6A shows three examples of responses of the model neuron to sweep stimuli with different sweep centers. Figure 6B shows an example of experimental recording. Both in the model and
in the data, dynamic responses deviate from the static tuning curve and responses to two different directions of motion in IPD space form hysteresis loops. These are the properties of IPD-sensitive cells in inferior colliculus, as previously reported (e.g., McAlpine and Palmer 2002; McAlpine et al. 2000; Spitzer and Semple 1993, 1998). Such properties are not usually observed for cells at lower levels of processing, such as MSO (Spitzer and Semple 1995, 1998) but are even more pronounced in auditory cortex (Malone et al. 2002).

Using the shaded areas (Fig. 6A) to quantify the degree of hysteresis (see METHODS), we plot the hysteresis measure versus sweep center in Fig. 6C. The hysteresis measure curve or, for short, hysteresis curve, readily demonstrates multiple properties of dynamic responses, some of which have been described experimentally. First, there is a local minimum at the neuron’s best phase, consistent with the observation that dynamic response properties are less evident near the peak of the static curve. Next, the dynamic effects increase as the static tuning curve steepens. Notice that there is a local maximum near 0° IPD (midline). The physiological range of IPDs lies around that point and the dynamic effect is strong there. The hysteresis measure falls to zero at some range of IPD as there are no static or dynamic responses at those IPDs.

An important feature of the hysteresis curve is its asymmetry. It has been noted before (Spitzer and Semple 1991b) that dynamic effects are stronger on one side from the best phase of the neuron than on the other (asymmetric). Our model reveals that the asymmetry can be due to IPD-tuned inhibition that is neither in-phase nor in anti-phase with excitation. If the tuned inhibition is blocked or replaced with nontuned inhibition, the asymmetry in the model disappears. This leads to another model prediction distinguishing effects of tuned inhibition (see DISCUSSION).

McAlpine and Palmer (2002) studied the effect of blockade and induction of inhibition on hysteresis. The thin curves in Fig. 6C illustrate qualitatively similar effects in the model, because IPD insensitive inhibition is varied (as modeled by changing $g_{I,t}$(see METHODS)). As more inhibition is added (which corresponds to an increase in concentration of local GABA application in experiments), the overall hysteresis level is decreased, less asymmetry is observed, the region of nonzero hysteresis measure becomes narrower, and the dip near the best phase disappears.

VARYING SWEEP PARAMETERS. McAlpine et al. (2000) and Spitzer and Semple (1993) reported that variation of sweep parameters does not dramatically affect the response dynamics. We explored the changes using the hysteresis measure curve and varying in the model modulation depth and rate.

Varying sweep rate while keeping the depth constant (Fig. 7A, bottom left) leads to a family of hysteresis curves shown in Fig. 7B. If the rate is close to the control value of 360°/s, then the hysteresis properties are similar (compare 360°/s curve with 180°/s). However if the sweep is too slow (90°/s), then the system is adapted most of the time, dynamic responses fall close to the static tuning curve, and as a result, the hysteresis measure is reduced. On the other hand, if the sweep is too fast (720°/s), then the adaptation hardly has time to turn on during a cycle and the curve is lowered again. Particular values of what is a “slow” or “fast” rate are likely to be highly variable among cells, but the model’s prediction is that there is an intermediate range of sweep rates that are most effective in producing hysteresis.

Figure 7C demonstrates how hysteresis depends on modulation depth while sweep rate is kept constant (stimulus in Fig. 7A, bottom right). Notice change in scale from Fig. 7 B to C: the control case (thick curve) is the same in both panels. As one
expects, the hysteresis measure increases with depth for all positions of the sweep. Moreover, if the sweep depth is large enough, then the local decrease of hysteresis near the best phase is lost, and in fact, the hysteresis there becomes larger than elsewhere. This happens because best-phase-centered sweeps with large range include the large hysteresis effects associated with the steepest slopes on both sides of the tuning curve.

Now we summarize our observations of the model hysteresis curves. First, the shape of the curve is generic, it is robust with respect to the cell and stimulus parameters, and it is defined by the presence of firing rate adaptation. Second, the overall level of inhibition determines the average hysteresis level and width of the hysteresis curve (by defining the range of observed firing rates). Third, IPD tuned inhibition can be potentially detected from the asymmetry of the curve. Fourth, at a fixed center IPD, the hysteresis increases with the depth of the sweep, and there is an intermediate range of sweep rates where the hysteresis is maximal.

PIR

In in vivo IC recordings, the sweep stimuli sometimes evoke a strong excitatory response over the zero-response portion of the static tuning curve (Spitzer and Semple 1998; Fig. 9A of this paper). We call this type of response a “rise-from-nowhere.” We set out to test the hypothesis that the “rise-from-nowhere” can be explained by the presence of an intrinsic PIR mechanism. To do this, we have developed and included a voltage-gated postinhibitory rebound (PIR) current in our model ($I_{PIR}$, see METHODS). It is meant to give a qualitative/semi-quantitative match with the experimental observations. We do not consider it as a biophysically identified current. We also investigate how the features of dynamic responses, as described in the previous two sections, are modified by PIR.

IMPLEMENTATION AND PROPERTIES OF PIR. In accordance with our hypothesis that dynamic response properties of IC cells
primarily depend on intrinsic mechanisms, we implement the rebound mechanism as a transient inward current ($I_{\text{PIR}}$; see METHODS). The steady-state PIR current is very small at any constant value of voltage, $V$, as evident from the lack of overlap in the steady state gating functions (Fig. 8A). This means that $I_{\text{PIR}}$ does not contribute significantly to the cell’s static response properties, such as the static tuning curve. On the other hand, when the membrane is hyperpolarized for a sufficient duration, the current deinactivates ($h$ grows). If the membrane is abruptly released from hyperpolarization, then the cell can begin to depolarize. $I_{\text{PIR}}$ activates instantaneously and it contributes to regeneratively depolarizing the membrane until $h$ decreases again, inactivating $I_{\text{PIR}}$ on the time scale $\tau_h$. This current behaves in a manner analogous to the Hodgkin-Huxley Na current (Hodgkin and Huxley 1952), but on different time scales and at different voltage ranges, resembling more closely a transient Ca current (Jahnsen and Llinas 1984; Zhan et al. 1999). Figure 8B shows how the model cell with $I_{\text{PIR}}$ responds to release from hyperpolarizing current steps of different amplitudes. From modest hyperpolarization $V$ returns to rest soon after release. If the hyperpolarizing current is strong enough, there is a large, but saturating, rebound response.

“RISE-FROM-NOWHERE”, DEPENDENCE ON PARAMETERS. For IC cells, the inhibitory input presumably dominates at the lowest portion of the static IPD tuning curve. The membrane, therefore might be hyperpolarized. As the stimulus moves to adjacent regions of IPD (toward the peak), the cell is released from inhibition. This suggests that if the cell possesses a mechanism of postinhibitory rebound, it can be engaged to produce a dynamic response at the zero portion of the static tuning curve (“rise-from-nowhere,” Fig. 9A, arrow). Essentially, due to PIR, dynamic stimuli can produce responses beyond the statically determined excitatory receptive field limits. The above scenario is robustly realized in the model with parameter values given in METHODS and the sweep rate of 360°/s. It is illustrated in Fig. 9B (the “rise-from-nowhere” is marked with an arrow). A less dramatic rebound occurs on the “left side” of the tuning curve.

One advantage of having a conductance-based model is the ability to dissect the mechanisms that underlie dynamic phenomena like the rebound response seen here. We carry out this dissection in Fig. 9C by examining the time courses of several variables in the model. First, notice the macroscopic features. The sawtooth-shaped IPD(t) (Fig. 9C1) leads to the $g_I$ and $g_E$ time courses (Fig. 9C4). $g_I$ is dominant throughout most of the cycle so the model cell is hyperpolarized (Fig. 9C2); this constitutes phase 1. The rebound event occurs during phases 2 and 3 with the rapid V-upstroke and then prolonged depolarization (Fig. 9C2). Phase 3 involves contributions from both the intrinsic properties of $I_{\text{PIR}}$ and the time-dependent synaptic driving influences, when $g_E$ is smallest and $g_I$ is peaking. Of course, during phases 2 and 3 is when $I_{\text{PIR}}$ is active (Fig. 9C3). Perhaps unexpected is the time course of the net synaptic input (Fig. 9C5, heavy curve). For example, notice the rounded local maximum of $I_{\text{syn}}$ near $t = 1,250$, when $g_I$ has the sawtooth peak; a sharp peak of $I_{\text{syn}}$ in phase 2 when $g_E$ and $g_I$ are changing smoothly. The explanations are based on understanding that synaptic input is modeled here as due to time dependent conductance changes. The synaptic currents are, therefore, $V$ dependent through their driving forces. So, for example, the outward spike in $I_{\text{syn}}$ of phase 2 reflects the rapid rise in driving force of the inhibitory current $I_e$ coming from the rebound’s upstroke.

FIG. 9. “RISE-FROM-NOWHERE.” A: experimentally observed response arising in silent region of the static tuning curve (marked with an arrow). Carrier frequency, 1,050 Hz; binaural SPL, 40 Hz. Notations are the same as in Fig. 7A. B: model responses to various sweeps. The rightmost sweep produces “rise-from-nowhere” (arrow). C: model variables during stimulation marked with an arrow in B. C1: stimulus (IPD). Two periods are shown. C2: voltage time course, showing 4 main phases, marked with numbers: 1, hyperpolarization; 2, rebound; 3, removal of inhibition; 4, relaxation. C3: time course of $I_{\text{syn}}$ current (solid line) and its inactivation gating variable $h$ (dotted line). C4: firing rates of excitatory (MSO) excitatory and inhibitory (MSO) afferent populations, proportional to corresponding synaptic conductances. C5: excitatory, inhibitory, and total synaptic currents.
A closer look enables us to gain more insight into the dynamic features, although some readers may wish to bypass this paragraph. During phase 1, the voltage stays nearly constant at a hyperpolarized value. The PIR current (\(I_{\text{PIR}}\)), therefore, is near zero (solid curve in Fig. 9C3), because its activation gating variable \(m = m_{\text{a}}(V)\) has a very small value (see Fig. 8A). But its inactivation gating variable \((h)\) is slow growing during phase one (dotted curve in Fig. 9C3), i.e., the current deinactivates. At the same time, the inhibitory synaptic conductance (solid curve in Fig. 9C4) changes quite significantly, but the inhibitory current (thin solid curve in Fig. 9C5) does not. This is due to the fact that the conductance change is compensated by the opposite change of the driving force of inhibition \(V - V_I\). By the end of phase one the voltage grows due to increase in excitatory conductance (dashed curve in Fig. 9C4). The small excitatory conductance creates strong excitatory current \(I_E\) (dashed curve in Fig. 9C5), due to the large value of \(V - V_E\). The total outward synaptic current \((I_{\text{syn}}\) thick curve in Fig. 9C5) reduces its value and the voltage is moved into values where the PIR activation \(m\) is turned on. This begins phase two, rebound, where \(I_{\text{PIR}}\) grows rapidly, bringing voltage above the threshold (10 mV), which in turn, increases the driving force for inhibition and produces sharp increases in inhibitory and total synaptic currents. During phase three the voltage still increases, due to continuing removal of inhibition and increase in excitation (Fig. 9, C4 and C5) and also due to the integration of the inward PIR current. However, the PIR current is decreasing at this phase, as its activation variable is nearly constant \(m_{\text{a}}(V)\) is close to one] and inactivation variable is decreasing (Fig. 9C3). At the end of the phase 3, the stimulus is reversed, which leads to an increase in inhibitory and a decrease in excitatory conductance (also reflected in the synaptic currents). The voltage decreases, speeding up the decay of the PIR current by changing \(m_{\text{a}}(V)\). By the end of phase 4 the PIR current is back to zero and the membrane is hyperpolarized.

The rebound responses depicted in Fig. 9B are robust with respect to most parameters of the stimulus and the model. Changing the sweep’s center (\(=30^\circ\) in either direction) shifts the position and the amplitude of the response, but the rebound persists. Also, the rebound response persists for a variety of sweep rates. The particular range of the effective sweep rates depends on the balance between the rate of the sweep and the inactivation time constant \(\tau_h\). We chose \(\tau_h = 150\) ms, so that the most effective rate of sweep is \(360^\circ/s\), which is what is usually used experimentally. Rise-from-nowhere is also observed for rates such as \(180^\circ/s\) and \(720^\circ/s\), but starts to fail at \(90^\circ/s\). It is also possible to produce the rebound response with smaller values of \(\tau_h\). For the control stimulus rate \(360^\circ/s\), the rebound disappears if inactivation is too fast (60 ms; Fig. 10A). However, the critical value of \(\tau_h\) will decrease for faster sweeps (30 ms for \(720^\circ/s\) sweep). Also, the critical value of \(\tau_h\) at a particular sweep rate can be lowered by requiring sharper tuning of the MSO populations. Then a sweep over the slopes of MSO tuning curves would produce sharper change in input current, which means an increase in the effective stimulus rate.

Increase in PIR reversal potential \((V_{\text{PIR}})\) and maximum conductance \((g_{\text{PIR}})\) increases the rebound (curves 1–3 in Fig. 10B), but introduces a nonmonotonicity in response. The nonmonotonicity (curve 3) is due to the fact that the inhibition is removed slower than the PIR current deactivates. This effect can be reduced (or removed) by slowing the inactivation of the PIR current (increasing \(\tau_h\)—curve 4 in Fig. 10B) or by speeding up the removal of inhibition (for example, by having the inhibitory MSO population sharper tuned).

**PIR EFFECT ON DYNAMIC RESPONSE: PHASE AND HYSTERESIS.** We have shown that the presence of PIR can explain the “rise-from-nowhere” phenomenon. In this section, we show how it modifies the dynamic properties of responses described earlier in the paper.

We have shown in our simulation of binaural beats that the presence of firing rate adaptation creates a phase advance of the response to some beat frequencies. The addition of the rebound mechanism increases the phase advance (Fig. 11A). If the IPD modulation rate (beat frequency) is too low, then there is no rebound and the two curves in Fig. 11A are indistinguishable. If the beat frequency is too high, then the PIR current does not have time to deinactivate and does not change the phase either. However, at the intermediate values of beat frequency, due to rebound, the response can rise before the statically determined excitatory receptive field (as in “rise-from-nowhere”), which further advances the response.

Due to the “rise-from-nowhere” phenomenon, PIR will introduce additional hysteresis in responses to sweeps at the tails of the hysteresis curve. Notice in Fig. 11B that the previously bimodal hysteresis curve gains additional extrema. The spike in the hysteresis curve (asterisk in Fig. 11B) appears when the PIR current is not strong enough to cause firing during the sweep toward the peak, but it persists long enough to produce firing on the return sweep.

The rebound current also changes the way in which the hysteresis curve is modified by additional inhibition (compare Figs. 11C and 6C). The overall hysteresis level is still reduced, but at the tails of the hysteresis curve (away from best phase)
it happens slower than in other regions, reflecting the fact that increase in inhibition makes PIR more effective.

**Discussion**

We have developed an idealized firing-rate-type model for interaural phase sensitive IC cells. This minimal model reproduces many features of physiological responses to simulated acoustic motion and suggests underlying mechanisms. For example, adaptation, PIR and transmission delay shape phase advance and phase lag for beat stimuli; adaptation or PIR shape hysteresis loops (including “rise from nowhere”) at different sweep center locations; tuned inhibition provides asymmetry of the hysteresis curve; and overall level of inhibition determines the average hysteresis value. We also propose additional experiments, both in vitro and in vivo, to test our predictions.

**Advantages and limitations of averaged voltage model**

In contrast to typical firing rate models (e.g., Grossberg 1973; Wilson and Cowan 1972), our model includes intrinsic mechanisms. On one hand, their presence allows us to study a broader repertoire of dynamic behaviors, in which these mechanisms are directly involved. On the other hand, the model is simple enough so that we can discriminate the mechanistic contributions to individual properties. Also, our results show that many of the dynamic response properties can be reproduced without consideration of spike timing or individual synaptic events.

Even though we find the use of an activity model appropriate in this study, it does impose some limitations on the types of questions that we can address. For example, we cannot explore the dependence of response on fast synaptic time scales (say, 10 ms or less) or emergence of loosely phase-locked IC response from convergent tightly phase-locked MSO inputs. Also, the simulation of responses to brief stimuli or responses that are manifested with only a few spikes occurring over a short period of time, is beyond the scope of this study.

**Inhibitory inputs to the IC**

Still under debate (McAlpine et al. 2000) are the properties of inhibitory inputs to IPD-sensitive IC neurons and the role of inhibition in shaping IC cells’ dynamic responses. If the principal inhibition comes from DNLL (Li and Kelly 1992; Shneiderman and Oliver 1989), it could be IPD-tuned (Brugge et al. 1970), as in our model. It is also possible that the inhibition is IPD-insensitive (tonic). Our results suggest experiments that can help to characterize the nature of inhibitory inputs.

It was previously suggested (Cai et al. 1998b; McAlpine et al. 2000; Spitzer and Semple 1998) that firing rate adaptation (firing rate decrease with time) may be responsible for the dynamic response properties in IC. Several different sources can contribute to the firing rate decrease, e.g., adapting excitatory or facilitating inhibitory input, synaptic depression, or intrinsic cellular mechanisms. Recent data show the following: first, the major source for creation of dynamic response properties seen in IC must reside above the level of MSO (Spitzer and Semple 1998); and second, 25% of the intracellularly recorded cells in IC slice show adapting spike patterns in response to depolarizing current injection (Peruzzi et al. 2000; Sivaramakrishnan and Oliver 2001). In our view, these data argue in favor of intrinsic cellular mechanism of adaptation. It may be mediated in part by an apamin-sensitive, voltage-independent Ca2+-activated potassium current found in adapting IC cells (Sivaramakrishnan and Oliver 2001). Other mechanisms are likely to be additional to the intrinsic factors, and cannot be excluded without further investigation.

**Postinhibitory rebound**

We have shown that the excitatory and inhibitory inputs, coupled with a postinhibitory rebound mechanism, can explain some of the response properties not generated by adaptation, including the “rise-from-nowhere” phenomena. The purpose of

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**Fig. 11.** Change of dynamic response properties in presence of PIR. A: increase of phase advance in response to binaural beats. Thick curve, same as in Fig. 5A, right. B: increase in hysteresis level in responses to sweeps. Thick curve is the same as in Fig. 6C. C: hysteresis level decreases with added inhibition, but less so in presence of PIR. Thick curve is the same as the thin curve in B; thin curves correspond to successively increased levels of IPD-insensitive inhibition: \( g_{ionic} \) is 0, 0.1, 0.2, 0.3 mS/cm².
our modeling was to show that a fairly generic rebound mechanism suffices. There are not enough intracellular electrophysiological data for us to interpret this aspect of the model as a quantitative match or prediction of a specific current.

Recently it was found in vitro that 57% (59 of 104) of IC cells exhibited rebound responses to release from hyperpolarization (Sivaramakrishnan and Oliver 2001). Rebound responses consist of a Ca\(^{2+}\)-dependent rapid rising and then slowly decaying depolarization, crowned by a few spikes. Qualitatively similar PIR responses have been observed and characterized in thalamic relay neurons (Jahnsen and Llinas 1984; Sherman 2001). There, the release from hyperpolarization activates a low-threshold transient Ca\(^{2+}\) current that underlies a depolarizing event with 10- to 50-ms duration. It is not known if the rebound depolarization in IC (Sivaramakrishnan and Oliver 2001) is caused by the same current.

**Tests of the model and model predictions**

Our modeling results predict phase advance in responses to binaural beats at low and intermediate beat frequencies. Further, we suggest that in vivo transmission delay significantly increases the phase lag at high frequencies, making it hard to observe the phase advance without magnification (Fig. 5C). In vitro, the phase advance prediction can potentially be tested by simulating the binaural beats by current injection in dynamic clamp mode, with conductances tracing sinusoidal curves, specified just as in our modeling of binaural beats. If these simulated “binaural beats” are delivered to an IC cell that exhibits dynamic response properties, phase advance of the response should be observed as the beat frequency increases. Furthermore, the phase advance should diminish if one of the currents responsible for PIR or adaptation is blocked; and abolished if both currents are blocked simultaneously.

Predictions, regarding the shape and the dependence of the hysteresis curve on parameters (Figs. 6, 7, 11B, and C), can be tested in vivo or in vitro experiments and by re-examining the existing data (McAlpine et al. 2000; Spitzer and Semple 1993).

If in vivo intracellular recordings were available, it would be possible to suggest experiments to distinguish cellular and synaptic mechanisms of adaptation. For example, if the mechanism of adaptation is synaptic, one should be able to hyperpolarize the cell that does not exhibit strong PIR (to prevent it from spiking) and still see the hysteresis (in voltage values) in response to sweeps.

Depending on the principal source of inhibitory input in IC, the inhibition could be IPD-sensitive or not. One way to distinguish between these possibilities would be to perform in vivo intracellular recordings similar to what is done in V1 (in studying the possible push/pull arrangement of connections: e.g., Anderson et al. 2000; Troyer et al. 1998). With extracellular in vivo recordings, one possibility is to examine a cell’s hysteresis curve. In the model, the curve’s asymmetry is due to the tuning of inhibition. If the hysteresis curves of IC neurons in vivo are found to be asymmetric and the asymmetry goes away when the inhibition is blocked (by local application of bicuculline; McAlpine and Palmer 2002; or by suppression of DNLL input; Kelly and Kidd 2000), it would be evidence for IPD-tuning of inhibitory afferents. Of course, it is also possible that asymmetry is inherited from the pattern of excitatory inputs, but in that case it should not be altered by changes in inhibition level. Additional evidence for tuned inhibition would be a phase shift of tuning properties (e.g., a shift of the maximum of the static tuning curve), induced by blockade of inhibition (Fig. 3). These types of data analyses, to our knowledge, have not been performed.

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**REFERENCES**


