Multifrequency Forcing of a Hopf Oscillator Model of the Inner Ear

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ABSTRACT In response to a sound stimulus, the inner ear emits sounds called otoacoustic emissions. While the exact mechanism for the production of otoacoustic emissions is not known, active motion of individual hair cells is thought to play a role. Two possible sources for otoacoustic emissions, both localized within individual hair cells, include somatic motility and hair bundle motility. Because physiological models of each of these systems are thought to be poised near a Hopf bifurcation, the dynamics of each can be described by the normal form for a system near a Hopf bifurcation. Here we demonstrate that experimental results from three-frequency suppression experiments can be predicted based on the response of an array of noninteracting Hopf oscillators tuned at different frequencies. This supports the idea that active motion of individual hair cells contributes to active processing of sounds in the ear. Interestingly, the model suggests an explanation for differing results recorded in mammals and nonmammals.

INTRODUCTION

The inner ear is more than a passive recorder of sounds. It also actively processes sounds using metabolic energy to spectrally analyze and amplify the stimulus (1–5). One consequence of the inner ear's active sound processing is that it produces sounds called otoacoustic emissions. Otoacoustic emissions, which consist of combinations of sounds at discrete frequencies, can occur either in the absence or in the presence of a sound stimulus (6). The exact mechanism responsible for the active processing of sounds and the related production of otoacoustic emissions within the ear is not well known (2,4,7). Recording the emissions spectrum provoked by a stimulus provides a way to probe the physiological systems responsible for active processing of sound.

In nonmammals, active sound processing is thought to occur within individual hair cells (8,9). Hair cells are mechanotransduction cells responsible for translating sound-induced mechanical motion into an electrical signal that is received by the auditory nerve (1,7). Each hair cell consists of a cell body which is contacted by the auditory nerve and a bundle of actin-supported fibers called stereocilia. When sound stimulates the auditory organ, the hair bundle is set into motion, causing transduction channels to be mechanically pulled open. Potassium ions flow through the transduction channels depolarizing the cell and ultimately causing the firing of the auditory nerve. In nonmammals, each hair cell responds preferentially at a specific frequency, a quality that makes the hair cell a prime suspect in the search for the source of the discrete-frequency otoacoustic emissions.

Active motion of the hair bundle is considered to be a possible mechanism for active sound processing in both the mammalian and nonmammalian ear (10–17). Experiments have shown that the hair bundle responds with more energy than the stimulus energy if stimulated near its resonance frequency (18). It has been proposed that when the hair bundle is displaced, calcium enters through the transduction channels and binds to a site inside the hair bundle (18,19). This binding causes a change in the tension of the transduction channels which results in the motion of the hair bundle. In mammals, there is another source of active hair cell motion. In response to depolarization, the cell bodies of outer hair cells contract due to the action of the protein prestin (20–22).

Either the hair bundle motility or the outer hair cell somatic motility could be involved in the production of otoacoustic emissions. Interestingly, a physiologically based model for hair bundle motion has been shown to be poised near a Hopf bifurcation for physiologically reasonable parameters (14). The motion of the outer hair cells also displays a resonance response (23) that is suspected to arise from a physiological system that is tuned near a Hopf bifurcation (24).

Assuming both the hair cell bundle motion and the outer hair cell motion is produced by a system poised near a Hopf bifurcation, the dynamics either system can be described by the normal form for a system near a Hopf bifurcation (25),

$$\frac{dA}{dt} = (a + ib)A - (c + id)|A|^2 A. \tag{1}$$

The response properties of Eq. 1 have been shown to reproduce qualitatively many of the amplification and tuning properties of the inner ear (26,27).

The otoacoustic emissions produced by the ear in response to multifrequency stimuli provide ample data concerning the active processing properties of the inner ear (6). Here, we consider the predictions of the Hopf oscillator model for three-frequency forcing experiments. It is of interest to determine whether observed otoacoustic emissions can be explained by an array of Hopf oscillators, each modeled by Eq. 1 and, if so, whether coupling between the motion of the

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oscillators is required to obtain observed otoacoustic emissions results. We find that an array of noninteracting Hopf oscillators, perhaps describing the motion of the hair bundles or outer hair cells, is adequate to qualitatively explain the results of the three-frequency forcing experiments in both nonmammals and mammals.

ANALYSIS

Assuming both the motion of the hair bundle and the motion of the outer hair cell body can be modeled by a system tuned near a Hopf bifurcation, the dynamics of each can be described by the normal form for a system near a Hopf bifurcation (see Eq. 1). In the normal form, the parameter a is a measure of proximity to the bifurcation point. When a is small in magnitude and negative, the cell is tuned slightly below the Hopf bifurcation and responds to brief disturbances with decaying oscillations. If $a > 0$, the cell is tuned above the Hopf bifurcation and the hair bundle oscillates spontaneously. The parameter b is the natural frequency of the cell at the onset of oscillation and d is a measure of the shift in the frequency of the cell as the response amplitude increases. The parameter c determines whether the system is supercritical ($c > 0$) or subcritical ($c < 0$). Here, we will concentrate on the supercritical case because it allows for small amplitude, spontaneous oscillations near the bifurcation point similar to the spontaneous hair bundle oscillations that are observed experimentally (28). If a small time-dependent forcing is applied the system (27,29,30), the normal form must be modified to include a forcing term, F,

$$\frac{dA}{dt} = (a + ib)A - (c + id)|A|^2 A + F. \tag{2}$$

In the case of single-frequency forcing, $F = fe^{i\omega t}$, the system can be analyzed by considering hair bundle motions responding at the same frequency as the forcing frequency. Substituting $A = Re^{i\omega t + i\phi}$ into Eq. 2 yields the following simple relationship between forcing amplitude and response amplitude,

$$(aR - cR^3)^2 + ([b - \omega]R - dR^3)^2 = f^2. \tag{3}$$

Using this relationship, Eguíluz et al. (26) and Camalet et al. (27) each demonstrated that a generic system poised near a Hopf bifurcation displays many of the amplification and tuning properties that are observed in the auditory system.

Two-frequency forcing experiments have been useful in studying the properties of otoacoustic emissions and determining their source. In suppression experiments (31,32), the cochlea is stimulated by a primary tone as well as a second softer tone, referred to as a suppressor tone. The addition of the softer tone has an effect on the magnitude of the cochlear response at the primary frequency. Specifically, as the frequency of the suppressor tone approaches the frequency of the primary tone, the magnitude of the component of the otoacoustic emission at the primary tone decreases. The biological interpretation of this is that since the maximum suppression occurs when the suppressor tone is near the primary frequency, it is likely that the otoacoustic emission originates near the part of the cochlea tuned at the primary frequency. Analysis of a Hopf oscillator tuned at the primary frequency and forced by a primary and suppressor tone supports the biological interpretation. Recently, Stoop et al. (33), by analyzing a Hopf oscillator model showed that the effect of adding a second frequency close to the primary frequency is to increase the effective damping of the oscillator's response at the primary frequency. Thus, a single cell, tuned near a Hopf bifurcation point and near the primary frequency, is adequate to reproduce the main qualitative features of two-frequency suppression experiments.

When the ear is stimulated by sound containing a linear combination of two primary frequencies ω_1 and ω_2, the otoacoustic emissions spectrum is more complicated to analyze because distortion product otoacoustic emissions (DPOAEs) occur at linear combinations of the stimulus frequencies (6,34,35). In experiments, the largest DPOAE response is observed to occur at the $2\omega_1 - \omega_2$ and $2\omega_2 - \omega_1$ frequency components. The presence of DPOAEs allows for more complicated multifrequency forcing experiments in which the amplitudes of the distortion products are considered. For instance, suppression experiments can be performed in which the cochlea is stimulated at a combination of two primary frequencies as well as a smaller amplitude suppressor tone. Then the effect of the suppressor tone on the response at each of the primary frequencies and the distortion product frequencies can be recorded.

In nonmammals, multifrequency forcing experiments, including two primary frequencies ω_1 and ω_2 ($\omega_1 < \omega_2$) and a suppressor frequency, indicate that maximum suppression of the $2\omega_1 - \omega_2$ distortion product frequency occurs when the suppressor tone is near the ω_1 frequency (36–38). Oddly, in mammals, the reverse trend is observed and maximum suppression of $2\omega_1 - \omega_2$ occurs when the suppressor frequency is near the ω_2 frequency (39,40). If active hair cell motion is responsible for the production of otoacoustic emissions, there must be an explanation for the discrepancy between emissions in mammals and nonmammals.

Here, we consider the response properties of a Hopf oscillator under three-frequency forcing, $F = F_1 e^{i\omega_1 t} + F_2 e^{i\omega_2 t} + F_3 e^{i\omega_3 t}$. Because the system is nonlinear, the response contains an infinite number of frequencies, a small number of which will be represented prominently. If one substitutes $A = A_1 e^{i\omega_1 t} + A_2 e^{i\omega_2 t} + A_3 e^{i\omega_3 t}$ into the nonlinear term from the normal form, $|A|^2 A$, the result contains only certain frequency combinations. We will assume that those frequencies dominate the response, and thus consider a response, A, that is a linear combination of those frequency components,

$$A = R_1 e^{i\omega_1 t + i\phi_1} + R_2 e^{i\omega_2 t + i\phi_2} + R_3 e^{i\omega_3 t + i\phi_3} + R_{112} e^{i(2\omega_1 - \omega_2)t + i\phi_{112}} + R_{221} e^{i(2\omega_2 - \omega_1)t + i\phi_{221}} + R_{113} e^{i(2\omega_1 - \omega_3)t + i\phi_{113}} + R_{223} e^{i(2\omega_2 - \omega_3)t + i\phi_{223}} + R_{332} e^{i(2\omega_3 - \omega_2)t + i\phi_{332}} + R_{331} e^{i(2\omega_3 - \omega_1)t + i\phi_{331}} + R_{123} e^{i(\omega_1 + \omega_2 - \omega_3)t + i\phi_{123}} + R_{231} e^{i(\omega_2 + \omega_3 - \omega_1)t + i\phi_{231}} + R_{312} e^{i(\omega_3 + \omega_1 - \omega_2)t + i\phi_{312}}. \quad (4)$$

Substituting Eq. 4 into Eq. 2 yields algebraic expressions relating the response amplitudes, response phases, and the forcing amplitudes, F_1, F_2, and F_3. Frequency components not represented in Eq. 4 are neglected. This provides an analytical description for the response of the Hopf oscillator to three-frequency forcing.

Under the assumption that the cells tuned near the primary frequencies, ω_1 and ω_2 and the distortion product frequencies, $2\omega_1 - \omega_2$ and $2\omega_2 - \omega_1$, are likely to produce the greatest response at $2\omega_1 - \omega_2$, we concentrate on the response of those four cells. Fig. 1 considers the response of the Hopf oscillator model to a suppression experiment in which the two primary frequencies were fixed at $\omega_1 = 300$ and $\omega_2 = 330$. Each plot shows the change in the magnitude of the $2\omega_1 - \omega_2$ frequency component of the response, R_{112}, as the suppressor tone, ω_3, was varied. In Fig. 1, *A* and *B*, the responses of single Hopf oscillators tuned at $2\omega_1 - \omega_2 = 270$ and $\omega_1 = 300$ are considered. As observed in the two-frequency suppression case, maximum suppression occurred when the suppressor frequency was tuned near the natural frequency of the cell, 270 in Fig. 1 *A* and 300 in Fig. 1 *B*. In this example, the component of the response of the ω_1 cell at the distortion product frequency is much louder than the distortion product component of the response for the other three cells. So, a plot of the total response of the four cells shows that maximum suppression occurs when the suppressor tone is tuned near ω_1 (Fig. 1 *C*). For larger values of the suppressor amplitude, or larger values of the nonlinear coefficients c and d, the distortion product component of the response of the $2\omega_1 - \omega_2$ cell can be louder than that of the ω_1 cell—in which case, substantial suppression may also occur at the $2\omega_1 - \omega_2$ frequency (Fig. 1 *D*). This result is consistent with suppression curve experiments in nonmammals which indicate that maximum suppression of the response at the distortion product frequency, $2\omega_1 - \omega_2$, occurs when the suppressor frequency is near the ω_1 frequency (6,34–36). Some experiments also show a secondary dip near the distortion product frequency, as predicted by the model (36).

Actual experimental suppression data differs from that shown in Fig. 1, *C* and *D*, where the forcing amplitude was held constant for each curve. Typically in suppression experiments, the magnitude of forcing needed to reduce the component of the response at $2\omega_1 - \omega_2$ by a specified amount is recorded as the suppressor frequency is changed. Repeating this experimental procedure for a single Hopf oscillator tuned at $\omega_1 = 300$ yields results similar to suppression experiments, again with maximum suppression occurring near ω_1 (Fig. 2) (6,34–36).

While the Hopf oscillator model qualitatively predicts the response properties for three-frequency suppression experiments in nonmammals, it does not reproduce mammalian suppression results. Recall, in mammals, it is observed that maximum suppression of the $2\omega_1 - \omega_2$ frequency occurs when the suppressor tone is tuned near the ω_2 frequency, not the ω_1 frequency, as in nonmammals. Over many trials, the Hopf oscillator model never predicted maximum suppression

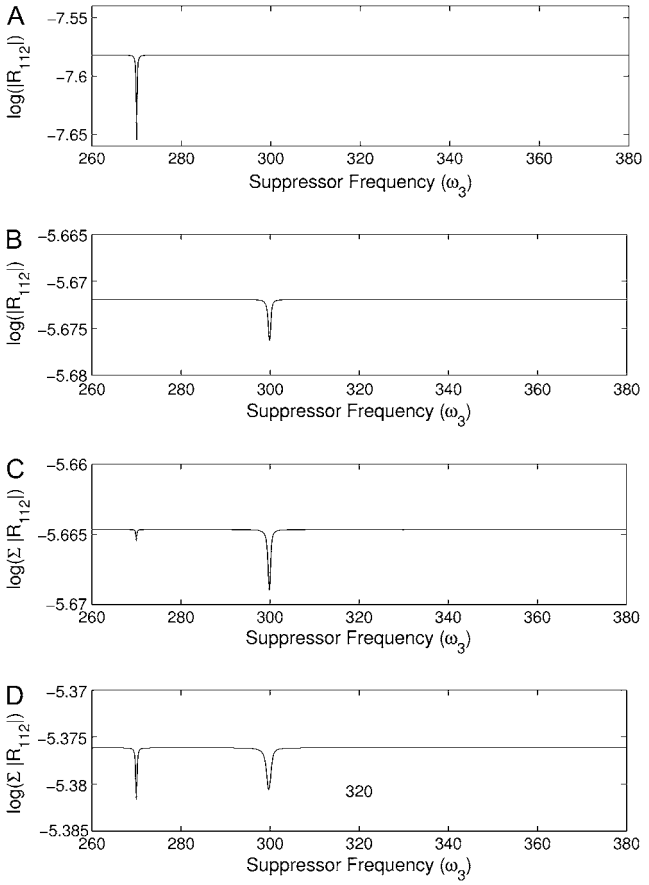

FIGURE 1 The response of the Hopf oscillator model (Eq. 2) subject to three-frequency forcing, $F = F_1 e^{i\omega_1 t} + F_2 e^{i\omega_2 t} + F_3 e^{i\omega_3 t}$, was estimated algebraically, as described in the main text. Each figure shows the change in the amplitude of the $2\omega_1 - \omega_2$ component of the Hopf oscillator response, R_{112}, as the suppressor frequency, ω_3, was varied. Panels *A* and *B* show the response of a single cell while panels *C* and *D* show the combined response for four cells tuned at different frequencies. For panels *A–C*, the Hopf oscillator parameter values were set at $a = -0.1$, $c = 100$, $d = 100$, $F_1 = 0.01$, $F_2 = 0.01$, and $F_3 = 0.001$. (*A*) The distortion product component of the response for a cell with a natural frequency of $b = 2\omega_1 - \omega_2 = 270$. (*B*) The distortion product component of the response for a cell with a natural frequency of $b = \omega_1 = 300$. (*C*) The total $2\omega_1 - \omega_2$ component of the response for four cells tuned at 270, 300, 330, and 360. (*D*) The total $2\omega_1 - \omega_2$ component of the response for the four cells tuned at 270, 300, 330, and 360, with $c = d = 500$ and other parameters the same as panels *A–C*.

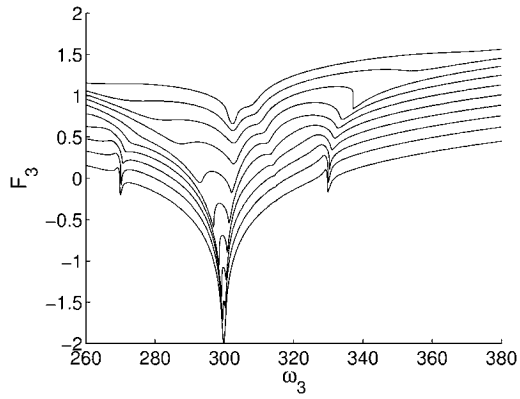

FIGURE 2 Each curve shows the amplitude of the suppressor tone, F_3, needed to suppress the response of a single Hopf oscillator at the distortion product frequency, R_{112}, by a fixed amount. For the lowest curve in the diagram, the response, $\log(R_{112})$, is reduced by 0.5 from its unsuppressed value. Each consecutive curve shows the forcing needed to reduce the response by an additional 0.5. Parameters were set at $a = -0.1$, $b = 300$, $c = 100$, $d = 100$, $F_1 = 0.01$, and $F_2 = 0.01$.

near the ω_2 frequency. The probable reason for the discrepancy lies in differences in physiology between mammals and nonmammals. In nonmammals, the hair cells are embedded in a membrane that lacks tuning properties, while in mammals, the hair cells are embedded in the basilar membrane (1). The basilar membrane performs much of the frequency filtering in the mammalian inner ear. When sound of a given frequency strikes the inner ear, a traveling wave is set into motion along the basilar membrane. This traveling wave reaches its maximum amplitude at different places along the membrane depending upon the frequency of the stimulus. For a high frequency stimulus, the wave reaches its maximum amplitude closer to the base of the cochlea than it would for lower frequency stimulus. After the wave passes through its preferred frequency, vibrations at that frequency are damped.

If the mammalian cochlea is forced at two frequencies, ω_1 and ω_2 with $\omega_1 < \omega_2$, the hair cells tuned near the higher frequency, ω_2 will feel both frequency components of the stimuli. Because higher frequency stimuli will have dissipated by the time the traveling wave reaches the hair cell tuned at ω_1, that cell will feel mainly the ω_1 component of the stimulus. Although in nonmammals, the cell tuned near ω_1 is responsible for generating the largest portion of the distortion product otoacoustic emission, in mammals the cell tuned near the ω_1 frequency does not receive the full stimulus at both frequency components and cannot produce as great a response at the distortion product frequency. Therefore, it would not be surprising if most of the $2\omega_1 - \omega_2$ distortion product frequency was generated at the ω_2 cell and not the ω_1 cell in mammals, causing maximum suppression to occur near ω_2.

CONCLUSIONS

A model consisting of a set of noninteracting oscillators tuned near a Hopf bifurcation was successful in qualitatively predicting the results of three-frequency forcing experiments observed in mammals and nonmammals. In the case of nonmammals, only two Hopf oscillators tuned near ω_1 and $2\omega_1 - \omega_2$ were necessary to predict the results of three-tone suppression experiments. In mammals, a single Hopf oscillator tuned near the ω_2 frequency correctly predicted experimental results. Which cell contributes the most is dictated by important differences in mammalian and nonmammalian physiology. In nonmammals, each cell receives the same stimulus so its response to a two-frequency stimulus depends wholly on the properties of the individual cell. Depending on the model parameter values, either the cell tuned near the primary frequency, ω_1, or the cell tuned near the distortion product frequency, $2\omega_1 - \omega_2$, produced the largest response at the $2\omega_1 - \omega_2$ component. The suppressor tone was most effective in suppressing the $2\omega_1 - \omega_2$ component when it was tuned near the natural frequency of the cell that had the loudest response at $2\omega_1 - \omega_2$. Hence maximum suppression in nonmammals occurred when the suppressor tone was near ω_1 or $2\omega_1 - \omega_2$. In mammals, the basilar membrane filters the forcing frequency, such that not every cell receives the same stimulus. While the cell tuned near ω_2 sees both frequency components of the stimulus, the cells tuned near ω_1 and $2\omega_1 - \omega_2$ see mainly the ω_1 component of the stimulus. Thus cells tuned near ω_1 and $2\omega_1 - \omega_2$ would be expected to produce little response at the $2\omega_1 - \omega_2$ frequency compared with the cell tuned near ω_2. It follows that in mammals, the suppressor tone would be expected to most effectively damp the distortion product component when tuned near the ω_2 frequency.

Notably, it was not necessary to assume coupling between cells of different frequencies to qualitatively reproduce experimental data. Though more complicated biophysically based models would be needed to produce a more quantitative agreement with the experiments, it is interesting that such a simple model can explain the main experimental features. These results lend support to the idea that an array of oscillators tuned near a Hopf bifurcation could be responsible for otoacoustic emissions and active sound processing in the ear. Because both the somatic motility of the outer hair cell and the motion of the hair bundle are thought to be well described by models poised near a Hopf bifurcation, either could play the role of the Hopf oscillator.

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