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# Signal Detection by Active, Noisy Hair Bundles

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**Abstract.** Vertebrate ears employ hair bundles to transduce mechanical movements into electrical signals, but their performance is limited by noise. Hair bundles are substantially more sensitive to periodic stimulation when they are mechanically active, however, than when they are passive. We developed a model of active hair-bundle mechanics that predicts the conditions under which a bundle is most sensitive to periodic stimulation. The model relies only on the existence of mechanotransduction channels and an active adaptation mechanism that recloses the channels. For a frequency-detuned stimulus, a noisy hair bundle's phase-locked response and degree of entrainment as well as its detection bandwidth are maximized when the bundle exhibits low-amplitude spontaneous oscillations. The phase-locked response and entrainment of a bundle are predicted to peak as functions of the noise level. We confirmed several of these predictions experimentally by periodically forcing hair bundles held near the onset of self-oscillation. A hair bundle's active process amplifies the stimulus preferentially over the noise, allowing the bundle to detect periodic forces less than 1 pN in amplitude. Moreover, the addition of noise can improve a bundle's ability to detect the stimulus. Although, mechanical activity has not yet been observed in mammalian hair bundles, a related model predicts that active but quiescent bundles can oscillate spontaneously when they are loaded by a sufficiently massive object such as the tectorial membrane. Overall, this work indicates that auditory systems rely on active elements, composed of hair cells and their mechanical environment, that operate on the brink of self-oscillation.

## INTRODUCTION

Our ears employ an active process to amplify their responsiveness to low-intensity sounds. The mechanical response of the inner ear to a faint sound can be over a thousand times greater in a living animal than immediately after death [1]. Activity also sharpens the ear's frequency selectivity and broadens its dynamic range. To achieve a broader dynamic range, an active ear nonlinearly compresses the input. In contrast, the response of a passive ear to sound is linear.

Hair cells convert electrical and chemical energy into mechanical energy that can be used to power the active process. This process is inherently nonlinear, however, owing to the gating of a hair cell's mechanotransduction channels [2]. We seek to understand how an active ear achieves enhanced sensitivity, sharp tuning, and a highly nonlinear response to sound in comparison to the insensitive, broadly tuned, and linear response exhibited by a passive ear.

Activity and nonlinearity can together produce a system that oscillates spontaneously, depending on the parameter values that define its operating point. A quiescent oscillator operating on the brink of self-oscillation is highly sensitive to weak sinusoidal stimulation at frequencies close to the self-oscillation frequency [3]. Moreover, the oscillator's frequency selectivity and dynamic range are large when it is near the boundary of spontaneous oscillation [4, 5]. Reducing the system's activity moves the oscillator away from the self-oscillation zone. Consequently, the oscillator's sensitivity, frequency selectivity, and nonlinearity decline. These parallels between the ear's behavior and that of an active oscillator suggest that the auditory system comprises a set of active oscillators operating near the region of spontaneous oscillation.

The transition from one qualitative behavior to another as a parameter is changed is known as a bifurcation [6]. A bifurcation point partitions the self-oscillatory and quiescent regimes in parameter space. Many different types of bifurcation exist, but all systems exhibit similar dynamics when they are close to the same type of bifurcation. A supercritical Hopf bifurcation is the simplest type of bifurcation separating a zone of spontaneous oscillation from a quiescent region. Hopf bifurcations are ubiquitous in nature, from chemical oscillators to neurons [6, 7]. Owing to its

simplicity and ubiquity, the auditory system's active oscillators has been conjectured to operate near a supercritical Hopf bifurcation [3].

The idea that the auditory system is composed of a set of oscillators operating close to a Hopf bifurcation is further supported by experimental observations of hair bundles. Under the right conditions, hair bundles spontaneously oscillate [8]. These oscillations may be suppressed by changing the mechanical load on the hair bundles or the extracellular  $\text{Ca}^{2+}$  concentration [9, 10, 11]. Observations show that the sensitivity, sharpness of frequency tuning, and dynamic range of hair bundles is larger when they operate close to a Hopf bifurcation than when they function further away [11, 12].

Thermal fluctuations limit the ear's sensitivity to weak sounds. It is unclear whether operation near a Hopf bifurcation is generally advantageous for sinusoidal-signal detection in the presence of noise. Here we study the response to sinusoidal forcing of a noisy active oscillator poised near a supercritical Hopf bifurcation. Observations of hair cells confirm several predictions stemming from our analysis.

## A Noisy Hopf Oscillator

The dynamics of any system operating near a Hopf bifurcation is two-dimensional and is described by a universal equation known as the Hopf normal form. Rather than using two real variables to describe the system, it is convenient to use a single complex variable  $z$ . Small perturbations of the system's original variables from their steady-state values are proportional to  $|z|$  and therefore the dynamics of any component of the original system is qualitatively similar to the dynamics of  $|z|$ . In the presence of sinusoidal forcing and additive white noise, the Hopf normal form is

$$\dot{z} = (\mu + i\omega_0)z + b|z|^2z + fe^{i(\omega t + \theta)} + \eta, \quad (1)$$

in which  $\mu$  is the control parameter,  $\omega_0$  is the Hopf frequency, and  $b < 0$  is a coefficient defining the system's non-linearity. The complex forcing term  $fe^{i(\omega t + \theta)}$  has amplitude  $f$ , frequency  $\omega$ , and phase  $\theta$ . The noise  $\eta(t)$  is complex and white and satisfies  $\langle \eta(t) \rangle = 0$ ,  $\langle \eta(t)\eta(t') \rangle = 0$ , and  $\langle \eta(t)\eta^\dagger(t') \rangle = 4d\delta(t - t')$ , in which  $\langle \rangle$  represents the ensemble average,  $\eta^\dagger(t)$  is the complex conjugate of  $\eta(t)$ , and  $d$  is the strength of the noise [13, 14, 15]. In the case of complex Gaussian noise, the real and imaginary components of the noise are Gaussian distributed with variance  $2d$ . An oscillator for which the resonant frequency is independent of the forcing  $f$  and the control parameter  $\mu$  is said to be isochronous [16]. Equation 1 defines a noisy, isochronous, supercritical Hopf oscillator whose resonant frequency is  $\omega_0$ .

The control parameter  $\mu$  accounts for changes in a Hopf oscillator's operating point. In the unforced, deterministic limit, a Hopf bifurcation occurs when  $\mu = 0$ ; the system oscillates spontaneously when  $\mu > 0$  and is quiescent for  $\mu < 0$ . Equation 1 can be integrated directly to generate time series from which the average response to forcing can be calculated. This approach is impractical, however, for the study of forcing near the limit of detection ( $f < \sqrt{2d}$ ).

Equation 1 is equivalent to a Fokker-Planck equation describing the probability density  $P(y, t)$  in a frame rotating at the stimulus frequency  $\omega$ :

$$\partial_t P = -\partial_R \left[ (\mu y_R + \delta\omega y_I + by_R\rho^2 + f)P - d\partial_R P \right] - \partial_I \left[ (\mu y_I - \delta\omega y_R + by_I\rho^2)P - d\partial_I P \right], \quad (2)$$

in which  $y \equiv ze^{-i(\omega t + \theta)}$ ,  $\delta\omega \equiv \omega - \omega_0$ ,  $y \equiv y_R + iy_I$ ,  $\partial_R \equiv \partial/\partial y_R$ ,  $\partial_I \equiv \partial/\partial y_I$ , and the radial coordinate  $\rho(y_R, y_I) \equiv \sqrt{y_R^2 + y_I^2}$  [13, 17]. The steady-state solution to Eq. 2 permits us to find the average responsiveness of an oscillator to sinusoidal forcing in the long-time limit.

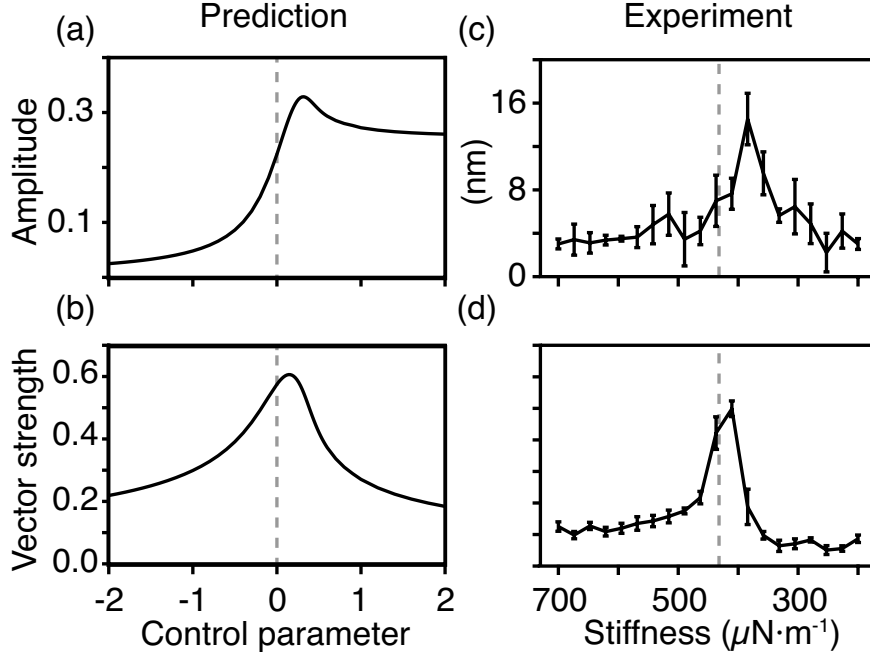
To determine how well an oscillator detects sinusoidal input we employ the phase-locked response

$$\frac{|\langle \tilde{z}(\omega) \rangle_{zs}|}{2\pi\delta(0)} = |\langle y \rangle_s| \quad (3)$$

and the vector strength

$$V \equiv \left| \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T e^{i\psi(t)} dt \right| = |\langle e^{i\psi} \rangle_s|, \quad (4)$$

in which  $\tilde{z}$  is the Fourier transform of  $z$ ,  $\psi \equiv \phi - \omega t - \theta$  is the phase difference between the response and driving, and  $\langle \rangle_{zs}$  and  $\langle \rangle_s$  denote long-time ensemble averages in the respectively non-rotating and rotating frames. The rightmost expressions in Eqs. 3 and 4 are employed to calculate the response measures from solutions to Eq. 2.



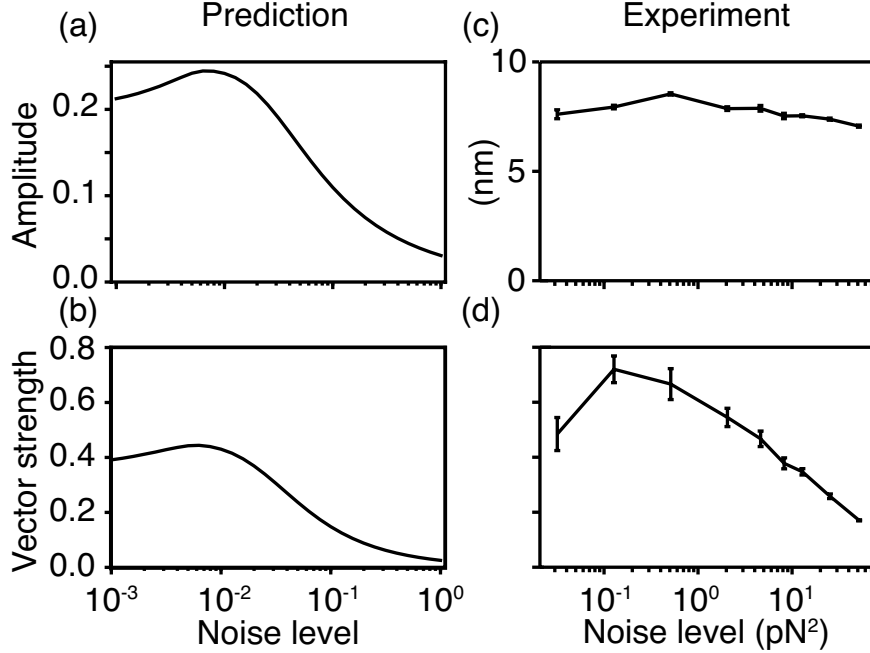
**FIGURE 1.** The phase-locked response and vector strength are shown as functions of control parameters for detuned forcing. Spontaneous oscillations occur to the right of the vertical dashed lines. (a, b) Near a supercritical Hopf bifurcation (dashed gray lines), both response measures are predicted to peak near the bifurcation when noise is taken into account. The forcing amplitude  $f = 0.05$ , detuning  $|\delta\omega| = 0.1$ , and noise level  $d = 0.01$ . For all theoretical calculations in this study,  $\omega_0 = 1$  and  $b = -1$ . (c, d) The responses measured for an experimentally observed hair bundle peak near the onset of self-oscillation (dashed gray lines) as functions of the hair bundle’s load stiffness. The hair bundle is controlled and stimulated with a glass fiber of stiffness  $600 \mu\text{N}\cdot\text{m}^{-1}$  and drag coefficient  $250 \text{ nN}\cdot\text{s}\cdot\text{m}^{-1}$ . The imposed load force is zero. Sinusoidal stimuli  $2 \text{ pN}$  in amplitude and  $6 \text{ Hz}$  in frequency are repeatedly applied for  $3 \text{ s}$ . Error bars show the standard error of the mean from five trials.

The phase-locked response and vector strength signify two different aspects of a system’s response to periodic driving. The phase-locked response increases as entrainment to the stimulus grows, but can rise without limit after perfect entrainment has been achieved. Perfect entrainment is equivalent to a constant phase difference between the stimulus and the response. The vector strength is a bounded measure of entrainment, in which a value of unity indicates perfect entrainment and a value of zero implies none.

We note that we can also calculate the average amplitude at the frequency of driving  $\langle |\tilde{z}(\omega)| \rangle_{\text{zs}} / 2\pi\delta(0) \geq |\langle \tilde{z}(\omega) \rangle_{\text{zs}}| / 2\pi\delta(0)$  from the probability density. Like a peak in the power spectrum, this amplitude can be nonzero in the absence of forcing. To capture only the response to sinusoidal forcing, we focus on the phase-locked response and the vector strength, which are zero in the absence of forcing.

## EXPERIMENTAL METHODS

The experimental procedure has been described in detail [11, 12]. Experiments were performed on spontaneously active hair bundles from the saccular maculae of adult bullfrogs, *Rana catesbeiana*. Mechanical stimuli were delivered by flexible glass fibers fabricated from borosilicate capillaries. A magnified image of the fiber’s tip attached to a hair bundle was projected onto a dual photodiode that transmitted the position information to a computer. A piezoelectric actuator served to displace the base of the stimulus fiber. We employed a feedback system with a real-time interface to update the position of the actuator based on the hair bundle’s displacement. This system allowed us to control the load stiffness and constant force applied to an individual hair bundle. These control parameters were varied to hold the hair bundle at difference distances from a supercritical Hopf bifurcation. A statistical test was used to determine the boundary of spontaneous oscillation. We used the glass fiber to apply sinusoidal stimuli to a hair bundle at each



**FIGURE 2.** The sensitivity and vector strength are shown as functions of the noise level. (a, b) The predicted responses of a supercritical Hopf oscillator at  $\mu = 0.27$ ,  $f = 0.05$ , and  $|\delta\omega| = 0.15$ . (c, d) For an experimentally observed hair bundle, the sensitivity and vector strength peak as functions of the noise level at an operating point near a supercritical Hopf bifurcation,  $K = 450 \mu\text{N}\cdot\text{m}^{-1}$ . The bundle is classified as quiescent. The value of the constant load force is zero. Sinusoidal stimuli 5 pN in amplitude and 10 Hz in frequency are repeatedly applied for 3 s. The noise level  $d$  corresponds to noise added by stimulating a hair bundle with a Gaussian white-noise force with variance  $2d$  that is flat in frequency up to 5 kHz. The stimulus fiber's stiffness is  $300 \mu\text{N}\cdot\text{m}^{-1}$  and its drag coefficient is  $200 \text{ nN}\cdot\text{s}\cdot\text{m}^{-1}$ . Error bars represent the standard errors of the means from ten trials.

operating point. The leftmost expressions in Eqs. 3 and 4 were used to compute the relevant quantities from time series of bundle displacements.

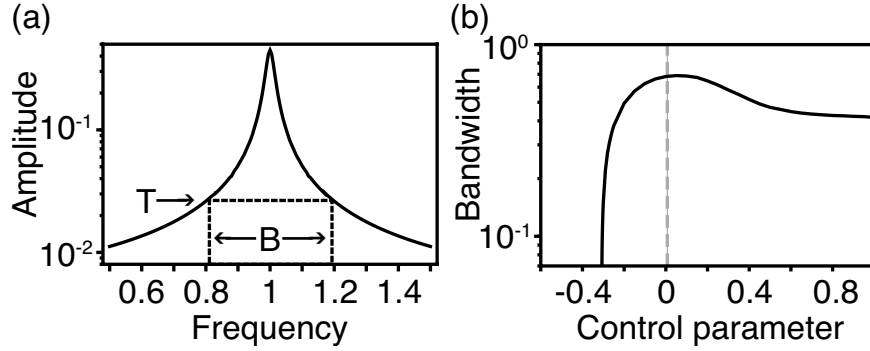
## RESULTS

When there is a mismatch between the stimulus frequency  $\omega$  and the resonant frequency  $\omega_0$ , the phase-locked response and the vector strength are predicted to peak on the oscillatory side of a supercritical Hopf bifurcation (Fig. 1). Because the stimulus frequency is never perfectly aligned with a hair bundle's resonant frequency in experiments, an actual bundle's phase-locked response and the vector strength also peak as a function of a control parameter, the load stiffness.

The further a quiescent bundle operates from the Hopf bifurcation, the more noise reduces its responsiveness. As the system progresses further into the oscillatory region, however, the magnitude of spontaneous oscillation increases and the influence of the stimulus on the bundle diminishes. Consequently, both of the response measures decline owing to frequency detuning between the forcing and the oscillator. Noisy hair bundles evidently perform best as sinusoidal-signal detectors when they oscillate spontaneously near but not at the bifurcation.

We next examine sinusoidal-signal detection for increasing levels of noise. We raise the level of noise experimentally by stimulating a hair bundle with a Gaussian white-noise force of variance  $2d$ , in which  $d$  is the noise level. The total noise level is then the sum of the intrinsic noise and this added noise.

The responsiveness of a system spontaneously oscillating near a supercritical Hopf bifurcation is predicted to peak as a function of the noise level (Fig. 2), a phenomenon known as *stochastic resonance* [18]. Experimental observations accord with theory. Although the phase-locked response's peak is quite small, the vector strength clearly peaks as a function of the noise level. Because of the conservative criterion used to detect spontaneous oscillations,



**FIGURE 3.** The threshold bandwidth peaks as a function of the control parameter. (a) The phase-locked amplitude for a supercritical Hopf oscillator depends on the stimulus frequency for a control-parameter value of  $\mu = 1$ . The threshold bandwidth  $B$  is the range of frequencies for which the phase-locked amplitude exceeds a threshold  $T$ . (b) The threshold bandwidth peaks near a supercritical Hopf bifurcation (gray, dashed) when the noise level  $d = 0.01$  for a threshold of 0.025. The stimulus force  $f = 0.01$  for all panels.

however, the hair bundle may be misclassified as quiescent at the operating point for which stochastic resonance occurs [12].

A hair bundle must detect sinusoidal stimuli within a range of frequencies around its resonant frequency. We suppose that an oscillator detects a stimulus if the magnitude of its phase-locked response exceeds a threshold  $|\langle \tilde{z}(\omega) \rangle_s| / 2\pi\delta(0) \geq T$ . We define the *threshold bandwidth*  $B$  to be the frequency range for which detection occurs, that is,  $B \equiv |\{\omega : |\langle \tilde{z}(\omega) \rangle_s| / 2\pi\delta(0) \geq T\}|$  (Fig. 3a).

In the presence or absence of noise, the threshold bandwidth is greatest when a supercritical Hopf oscillator operates close to and on the oscillatory side of the bifurcation (Fig. 3b). The threshold bandwidth is very sensitive to changes in the control parameter on the side of the peak closer to the quiescent region. This sensitivity arises from the failure of the system to achieve threshold for any stimulus frequency when it operates on the quiescent side of and far from a Hopf bifurcation. The gradual drop on the oscillatory side of the peak reflects the loss of entrainment that occurs as the system's spontaneous oscillations grow in amplitude. To maximize the threshold bandwidth while maintaining robustness of the bandwidth to parameter changes, it is consequently best to position the operating point of a Hopf system near but on the oscillatory side of the bandwidth's peak.

## DISCUSSION

Stochastic resonance has been observed in the mechanotransduction current of hair cells [19, 20]. It is unclear, however, whether this phenomenon arises from the transduction channels' bistable passive mechanics [19], the active hair-bundle motility discussed here, spontaneous electrical oscillations in hair cells [21], or a combination of the three.

Here we show that a hair bundle amplifies detuned, sinusoidal signals preferentially over noise when the bundle spontaneously oscillates near a Hopf bifurcation. A hair bundle in the auditory system must detect mechanical stimuli over a band of frequencies around its resonant frequency. This detection bandwidth is maximized on the oscillatory side of a Hopf bifurcation. The hair bundle's function depends on its control parameter, the load stiffness, which reflects its mechanical environment. A hair cell's function can be understood only in the context of the organ in which it resides.

Mammalian bundles have not been observed to oscillate spontaneously, possibly because experimental conditions have not yet replicated conditions *in vivo* sufficiently well. Spontaneous oscillations in the sacculus of the bullfrog are commonly seen only when the hair bundle is exposed to endolymph while the hair cell's basolateral surface is surrounded by perilymph [22]. These oscillations may allow the bullfrog sacculus to detect periodic seismic signals [23]. Additionally, mathematical models of bundle mechanics indicate that mammalian bundles would self-oscillate if they were loaded by a mass, such as that of the tectorial membrane, which is removed to facilitate experimental

observations [10, 24]. Finally, mammalian bundles also appear to lack the coherence of stereociliary motion seen in nonmammals [25, 26]. The overlying tectorial membrane may allow for coherent hair-bundle motion.

Spontaneous oscillations in the mammalian cochlea are likely facilitated by somatic motility and active hair-bundle motility. Modeling indicates that longitudinal slices of the organ of Corti could operate near a supercritical Hopf bifurcation [27]. Therefore, the analysis described here is relevant for signal detection within the mammalian cochlea. Sets of longitudinally coupled Hopf oscillators might constitute the active gain medium that has been proposed to generate spontaneous otoacoustic emissions in the cochlea [28]. How to relate the nonlinear dynamics of the local oscillators to the global vibrational modes of the cochlea remains an open question.

## ACKNOWLEDGMENTS

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## COMMENTS & QUESTIONS

[Online Forum]

**Steve Elliott:** The possibility of stochastic resonance in hair cells is certainly very interesting. As you say, it is not clear how the response of a local oscillator is related to the global vibration in the coupled cochlea. Do you think that one could devise tests of whether stochastic resonance really did play a role in mammalian hearing? Are there any psychoacoustic experiments that one could perform?

Author: Thanks for the questions Steve. There is some psychophysical evidence for stochastic resonance in mammalian hearing. Auditory thresholds and frequency discrimination limens were found to be lower in humans when noise was added to the input signal (Zeng, Fu, and Morse, *Brain Res* **869**, 251 (2000)).

**Steve Elliott (cont.):** It is also interesting to note that stochastic resonance has been proposed as a method of enhancing the perception of vowels in signal processing for cochlear implant users, e.g. by Morse and Evans, *Nat Med* **2**, 928 (1996).

Author: This is an interesting idea. We show that the existence of stochastic resonance depends on a system's parameter values. Whether the cochlea takes advantage of stochastic resonance will be determined by its operating point.

**John Stockie:** For a mathematician like me, this is really a fascinating application of bifurcation theory in stochastic dynamical systems. I'm curious how to connect this simple Hopf bifurcation model to actual cochlear physics. The key here seems to me to be the cubic form of the nonlinearity and the corresponding coefficient  $b$ . Is there any "typical" cochlear interpretation for the two components of  $z$  (your different "aspects" of the system)?

Author: Thanks for your comments John. There is no typical interpretation for the two components of  $z$ . For example, a published model of a cochlear cross section possesses a line of Hopf bifurcations as a function of two parameters (Ó Maoiléidigh and Jülicher, *J Acoust Soc Am* **128**, 1175 (2010)). It is possible to reduce the dynamics of this system to the normal form of a Hopf bifurcation for operating points near the line. The coefficients in the normal form are different, however, at each operating point. For this reason, we choose to study the generic response of the normal form to additive forcing.

**John Stockie (cont.):** For the right choice of  $z$ , is there a simple forcing coming from the cochlear physics that one could, say, do a small-amplitude approximation that leads to a first (nonlinear) correction term that's cubic in  $z$ ?

Author: It seems that you are referring to a correction to the forcing term that is cubic in  $z$ . The normal form of a weakly forced and weakly frequency detuned system is approximately equal to the normal form of the unforced system with additive forcing (Zhang and Golubitsky, *SIAM J Appl Dynam Sys* **10**, 1272 (2011)). For large forcing and detuning, all coefficients in the normal form of the forced system depend on the forcing. There are Hopf bifurcations of the forced system that differ from the bifurcations of the unforced system. Near the Hopf bifurcations of the forced system, the leading nonlinear term in the normal form is cubic.

**John Stockie (cont.):** Then, is there any way to connect the actual value of  $b$  (or the sign, I notice you take this to be  $b = -1$ ) for the "nonlinearity coefficient"?

Author: To understand the most basic effects of noise and forcing on a system near a supercritical Hopf bifurcation, we have chosen  $b = -1$ . When the imaginary part of this coefficient is sufficiently large, the response of the deterministic system to sinusoidal forcing is multivalued (Zhang and Golubitsky, *SIAM J Appl Dynam Sys* **10**, 1272 (2011)). In the presence of noise, the system now exhibits a large variety of behaviors depending on the forcing, the noise level, the control parameter, and the cubic coefficient.

**Alessandro Altoè:** Dear Dáibhid, thank you for this elegant study! There are a couple of points in your paper that I am not sure I fully understood.

Author: Thanks Alessandro!



**Alessandro Altoè (cont.):** First, is the threshold bandwidth independent on the noise level?

**Author:** No. Because the phase-locked response decreases with increasing noise, the threshold bandwidth declines as the noise level rises.

**Alessandro Altoè (cont.):** Second, the vector strength of the response depends on the noise level when the amplitude of the forcing term is constant. If the forcing term amplitude is increased, would the curves in Fig. 2 result as a shifted version of those presented? In other words, is the relationship between vector strength and noise level invariant to the driving amplitude when the noise level is normalized to the driving amplitude?

**Author:** The oscillator responds in a qualitatively different manner to the deterministic stimulus than it does to the noise. The curves in Fig. 2 are not simply shifted by increasing the stimulus level and instead lose their peaks for sufficiently large forcing amplitudes.

**Alessandro Altoè (cont.):** You conclude that sets of coupled Hopf oscillators might be the gain medium for the standing wave model of SOAE. I found very interesting that, because of the noise, the cochlear oscillators might not be perfectly phase locked with their driving force and therefore with the SOAE. How do you think this would affect SOAE generation theories?

**Author:** SOAEs are produced in the absence of an external driving force. We're suggesting that sets of coupled oscillators contribute to the production of SOAEs. The more synchronous and the larger a set of oscillators is, the larger the corresponding SOAE. Noise generally reduces synchronization between coupled oscillators. Consequently, noise may limit the number and the intensity of SOAE peaks produced by an auditory system.

**Alessandro Altoè (cont.):** In SOAE models a compressive nonlinearity operating at very low vibration magnitude is required to maintain the SOAE stable. On the other hand, at very low SPLs the cochlea is thought to exhibit responses similar to those of a linear system. Do you think that the non-perfect entrainment of "noisy" cochlear oscillators with the SOAE could provide a mechanism that maintains the SOAE amplitude within certain bounds?

**Author:** If an SOAE is produced by a limit-cycle oscillator, a nonlinearity is required to limit the amplitude of the SOAE. Noise can reduce the amplitude of the emission, but cannot ensure the system's stability.

**Joe Santos-Sacchi:** Hi Daib. Wanted to repeat my question during your talk. Can you comment on the dispersion of maximal regions of excitation (white boxes)? Shouldn't the "hot" data localize towards the periphery where the bifurcation arises? Joe.

**Author:** Thanks for the question Joe. You're referring to Fig. 1D from reference 12, which I showed during the talk. When a hair bundle oscillates spontaneously, its position distribution is multimodal such that there is at least one dip in the distribution. The larger the value of the distribution's dip statistic the more likely the distribution is not unimodal. To find the regime of self-oscillation, were plotting the value of the dip statistic for different operating points. Large values for the dip statistic correspond to the region of excitation you describe. The amplitude of spontaneous oscillation decreases as the load stiffness increases and thus in the absence of any other effects, the dip statistic should be largest near the low-stiffness boundary of the area of self-oscillation. Near this boundary, however, the spontaneous oscillations are spike-like such that the position distribution has a large primary peak and a tiny secondary peak. Because the dip between the peaks is small, the dip statistic is small near the low-stiffness border. In contrast, spontaneous oscillations are large and most symmetric in the center of the region of self-oscillation and consequently the dip statistic has its largest values at these operating points.