Phase-locked spiking of inner ear hair cells and the driven noisy Adler equation

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The inner ear constitutes a remarkably sensitive mechanical detector. This detection occurs in a noisy and highly viscous environment, as the sensory cells—the hair cells—are immersed in a fluid-filled compartment and operate at room or higher temperatures. We model the active motility of hair cell bundles of the vestibular system with the Adler equation, which describes the phase degree of freedom of bundle motion. We explore both analytically and numerically the response of the system to external signals, in the presence of white noise. The theoretical model predicts that hair bundles poised in the quiescent regime can exhibit sporadic spikes—sudden excursions in the position of the bundle. In this spiking regime, the system exhibits stochastic resonance, with the spiking rate peaking at an optimal level of noise. Upon the application of a very weak signal, the spikes occur at a preferential phase of the stimulus cycle. We compare the theoretical predictions of our model to experimental measurements obtained in vitro from individual hair cells. Finally, we show that an array of uncoupled hair cells could provide a sensitive detector that encodes the frequency of the applied signal.

1. Introduction

The problem of detecting weak signals in a noisy environment is a challenge familiar to most physicists and engineers. Sensory organs of living organisms face a similar challenge: heat, light, touch and sound emanating from the surrounding environment must be detected against a noisy background. The inner ear is an example of an extremely sensitive biological signal detector. The human cochlea can detect over six orders of magnitude in sound pressure and signals below 1 nm in amplitude [1]. Sound detection in the inner ear relies on active amplification mechanisms residing in specialized mechano-sensory cells called hair cells [2,3]. Signal detection by a hair cell is performed by an array of stereocilia protruding from its surface, which comprise the hair bundle. These stereocilia contain mechanically sensitive ion channels and are interconnected by tip links. Motor proteins are believed to actively maintain tension in the tip links [2,3]. When the tension in a tip link exceeds a threshold, mechano-sensitive ion channels open, allowing an inflow of ionic current, a small fraction of which is carried by Ca²⁺. The influx of calcium ions into the cell causes the motor proteins to slip, releasing tension and allowing the channels to re-close and the process to repeat. Studies performed in vitro on the mechanical properties of individual hair cells, obtained from the bullfrog sacculus, showed that stereociliary bundles exhibit spontaneous oscillations [4–7] with rather large amplitudes—in the range of 20–100 nm—and frequencies in the 10–80 Hz range.

A number of mathematical frameworks can describe the development of spontaneous oscillations in active systems. Examples are the normal form equation for the supercritical [8–10] and subcritical [11] Hopf bifurcations, the FitzHugh–Nagumo model [12] and others [13]. The dynamics of hair cells of the inner ear have been described in terms of the Hopf bifurcation. When this bifurcation is crossed, a quiescent system develops a limit cycle oscillation, with a fixed
characteristic frequency $\omega_0$ and an amplitude that grows continuously from zero as a control parameter changes sign [8,9]. In the vicinity of a Hopf bifurcation, with the control parameter slightly negative, the system exhibits a large dynamic susceptibility, for stimulus frequencies close to $\omega_0$.

Under in vitro conditions, stereociliary bundles of the bullfrog sacculus exhibit large-amplitude spontaneous oscillations. Such cells should be tuned away from the critical point with a positive control parameter. It is not apparent that a system in this oscillatory regime would be particularly sensitive to external stimuli. In fact, hair bundles performing large-amplitude spontaneous oscillations have been shown to be exquisitely sensitive to very weak external perturbations [4,5]. It was demonstrated [14,15] that this sensitivity is due to phase-locking of the spontaneous motility to a weak periodic stimulus. For weak stimuli, the amplitude of the innate oscillation is not much affected by the stimulus. In this regime, a different type of bifurcation is observed: a saddle-node bifurcation on an invariant circle (SNIC), also known as an infinite-period bifurcation. At the critical point, an infinite-period bifurcation is characterized by the development of a finite-amplitude limit cycle, in the form of a regular temporal sequence of spikes. A saddle located on the limit cycle splits off into a node pair of fixed points, with the spiking frequency going to zero at the critical point. In contrast to the supercritical Hopf bifurcation, the amplitude of the spontaneous oscillation remains finite at the critical point. In the regime of very weak stimuli, where the amplitude of oscillation remains constant, loss of phase-locking as the stimulus frequency is detuned from the natural frequency is characterized by the appearance of phase slips [16]. The experimentally observed phase-locking phenomena were quantitatively captured by a mathematical description based on the noisy Adler equation [17].

Although spontaneous otoacoustic emissions have been detected in a number of species [18], it is not known whether spontaneous hair cell activity occurs inside the vertebrate inner ear in vitro and—if it does—whether this plays a role in sound detection. It has however been demonstrated that hair cells of the bullfrog sacculus do not show much spontaneous activity under in vitro conditions when the overlying otolithic membrane is preserved [19]. It was proposed that this is due to mechanical loading of the hair bundle by the otolithic membrane. Single hair bundles indeed lose their spontaneous activity when subject to mechanical loads in excess of a few hundred piconewtons [20].

In this article, we propose the driven noisy Adler equation as a phase equation that can describe the dynamics of hair bundles subject to a steady mechanical load and a weak periodic stimulus:

$$\dot{\phi} = \omega_0 + F \sin \phi + \epsilon \sin(\phi - \omega_0 t) + \sqrt{2D} \eta(t).$$

(2.1)

Here, $\phi$ denotes the phase of the oscillator, $\omega_0$ the natural frequency, $F$ the magnitude of a steady load and $\epsilon$ the magnitude of a periodic stimulus of frequency $\omega_0$. The last term describes white noise with $\langle \eta(t) \eta(0) \rangle = \delta(t)$. Finally, $D$ is the phase diffusion coefficient (note that $F, \epsilon$ and $D$ all have the dimension of inverse time in our units). The motivation for this equation is first that its predictions have been verified in one limiting case. In an experimental study of the phase response of a spontaneously oscillating hair bundle subject to weak periodic stimuli, we found that equation (2.1) with $F = 0$ could account very well for the observations [16]. Separately, in an experimental study [20], we found that an increasing mechanical load suppresses spontaneous oscillations through an infinite-period bifurcation. Equation (2.1) with $\epsilon = D = 0$ is the simplest mathematical form describing such a bifurcation.

Returning to the general case, equation (2.1) can be viewed as the Langevin equation of motion for a Brownian particle with ‘position’ $\phi(t)$, sliding with friction along a tilted washboard potential $U(\phi) = -\omega_0 \phi + F \cos \phi$ (see figure 1). It can also be viewed as the equation for time evolution of the phase of a Josephson junction in a dissipative electrical circuit [27], or that of the angle of a pendulum rotating with friction subject to a time-dependent torque. We first consider some limiting cases.

2.1. $D = 0, \epsilon = 0$

The properties of the infinite-period bifurcation of equation (2.1) are well known for $\epsilon = D = 0$ [17]. For $F = 0$, the phase velocity equals $\omega_0$. As $F$ increases from zero, the phase no longer increases linearly in time but exhibits a periodic sequence of slips where the phase increases by almost $2\pi$, alternating with
time intervals where the phase grows slowly. The phase slips correspond to sudden spikes in the position of the stochastic bundle. For a particle moving along a tilted washboard, a phase slip corresponds to a rapid change in the particle position between adjacent plateaus. The mean phase velocity, which is proportional to the spike rate, is given by \( \langle \dot{\phi} \rangle = \frac{\omega_0^2 - F^2}{} \) for \( F < \omega_0 \). The point \( F = \omega_0 \), where the spike rate goes to zero, marks the infinite-period bifurcation. For \( F \) larger than \( \omega_0 \), the mean phase velocity is zero. In terms of the particle analogy, this corresponds to the particle being trapped in one of the metastable wells of the washboard potential. Before turning to the general case, we first consider two simple limiting regimes.

2.2. \( D = 0, \epsilon \neq 0 \)

For \( D = 0 \) and \( \epsilon \neq 0 \), the equation of motion can be directly integrated, either analytically or numerically. We will assume that \( F \) is larger than \( \omega_0 \), so that spontaneous oscillations are suppressed (the system is in the ‘subthreshold’ regime). Figure 2 shows examples of trajectories obtained by numerical integration (\( T = 2\pi/\omega_0 \) denotes the stimulus period, see appendix A for details). It follows from equation (2.1) that if the stimulus amplitude \( \epsilon \) is less than a critical value \( \epsilon_c \approx F - \omega_0 \), then \( \langle \dot{\phi} \rangle \) must remain zero because the particle cannot escape out of a metastable well, though it will exhibit small oscillations around a local minimum of \( U(\phi) \) in response to the periodic drive. The lowest trajectory (blue) is an example of the case where \( \epsilon \) is less than \( \epsilon_c \). The mean phase velocity \( \langle \dot{\phi} \rangle \) changes discontinuously from zero to \( \omega_0 \) at \( \epsilon = \epsilon_c \). The green trajectory is an example of the case where \( \epsilon \) is slightly above \( \epsilon_c \). The phase precesses, on average, with the angular velocity of the drive, so the oscillator is 1:1 mode-locked to the drive. If the stimulus amplitude is increased further, a second discontinuous increase occurs in \( \langle \dot{\phi} \rangle \), from \( \omega_0 \) to \( 2\omega_0 \). The oscillation remains mode-locked to the drive but now with a 2:1 frequency ratio. The red curve in figure 2 gives an example. In appendix A, we show that \( \langle \dot{\phi} \rangle \) is in general quantized as integer multiples of \( \omega_0 \). The phenomenon of an alternating stimulus producing a quantized steady ‘current’ is known in the field of Josephson junction physics as the ‘inverse AC Josephson effect’ [27]. In summary, for \( D = 0 \), the subthreshold system barely responds to stimuli with amplitudes less than a threshold, which is approximately \( |F - \omega_0| \).

2.3. \( D \neq 0, \epsilon = 0 \)

Another familiar case is encountered if one includes noise in the equation of motion but sets the drive amplitude \( \epsilon \) to zero.

Including the fluctuation term of equation (2.1) in the subthreshold regime \( (F > \omega_0) \) can be understood as producing the Langevin equation of motion for a Brownian particle moving along the washboard potential (figure 1). Thermal activation allows the particle to jump over the barrier separating adjacent minima of the washboard potential. This is a well-known problem of non-equilibrium statistical mechanics. Under steady-state conditions, the Kramers mean barrier transition rate \( \Gamma_0 \) is given by

\[
\Gamma_0 = \frac{\sqrt{\lambda_1\lambda_2}}{2\pi} \text{e}^{-\Delta U/D},
\]

where \( \lambda_1 \) and \( \lambda_2 \) are the curvatures of the washboard potential at a minimum \( (\phi_s) \) and maximum \( (\phi_u) \), respectively, while \( \Delta U \) is the activation energy barrier. Close to the SNIC, the energy barrier goes to zero as \( \Delta U \propto (F - \omega_0)^{1/2} \), while \( \lambda = \lambda_2 - \lambda_1 \) with \( \lambda \propto (F - \omega_0)^{1/2} \) (see appendix B for the exact expressions). If barrier crossing events (and thus spikes) are uncorrelated, it is easy to show that, in this limit, the ISI decays exponentially as \( p(t) = \Gamma_0 \text{e}^{-t/\Gamma_0} \).

2.4. \( D \neq 0, \epsilon \neq 0 \)

In appendix B, we discuss analytical methods that can be used to calculate the response of a system that is subject to both noise and a weak periodic stimulus with frequency \( \omega_0 \) and amplitude \( \epsilon \). As before, the system is modelled with a noisy Adler equation, poised in the quiescent regime by a steady load. The average rate of extra spiking events due to the imposed stimulus, defined as \( \Delta \Gamma(\epsilon, D) = \Gamma - \Gamma_0 \), yields a measure of the dynamical susceptibility. It is predicted to be

\[
\Delta \Gamma(\epsilon, D) \simeq \epsilon^2 \left( \frac{\lambda^2}{\omega^2 + \lambda^2} \right)^2 \frac{\Delta U}{2\pi D^2} \text{e}^{-\Delta U/D}.
\]

In figure 3, we compare this result with numerically computed mean transition rates (see appendix B for details). The computed curves exhibit a zero slope at \( \epsilon = 0 \) and a curvature that agrees with the analytical prediction. \( \Delta \Gamma(\epsilon, D) \) is indeed proportional to \( \epsilon^2 \) for small \( \epsilon \).

Equation (2.3) exhibits an interesting feature with respect to noise amplitude: \( \Delta \Gamma(\epsilon, D) \) has a maximum at \( D = \Delta U/2 \). It vanishes in the limit of both small and large noise amplitudes. In figure 4, we show the numerically computed \( \Delta \Gamma(\epsilon, D) \) as a function of \( D \), computed at different stimulus amplitudes: \( \Delta \Gamma(\epsilon, D) \) indeed has a maximum as a function of \( D \). This addition of noise thus increases the detection efficiency and range. This suggests that \( \Delta \Gamma(\epsilon, D) \) exhibits a form of stochastic
2.5. Spike statistics

Noise alters not only the mean spike rate but also the statistical distribution of spiking events. In appendix B, we show that the spike rate is time dependent, due to the periodic modulation of the activation energy barriers. We restrict ourselves to the adiabatic regime of low applied frequencies (for the general case, see [28,29]). The instantaneous spike rate is then given by

\[ \Gamma(\epsilon, t) = \Gamma_0 e^{(\phi(t) - \phi_u)} \exp(\omega t + \phi_0)/D, \tag{2.4} \]

where

\[ \lambda_u \phi_u' = \lambda_u \phi_u = \sqrt{\frac{2 \lambda_0 |\lambda_u|}{|\lambda_u| + \lambda_u}} \tag{2.5} \]

and where \( \phi_0 = 3\pi/2 \) is the phase of the drive at which the time-dependent energy barrier is minimal. The ISI is given by

\[ p(t) = \Gamma(\epsilon, t) \exp\left(-\int_0^t \Gamma(\epsilon, t') dt'\right). \tag{2.6} \]

Expanding in powers of \( \epsilon \) gives

\[ p(t) \approx \Gamma_0 \exp (-\Gamma_0 t) \left[ 1 + \epsilon \left( \frac{\phi_u' - \phi_u}{D} \right) \left( \sin(\omega t + \phi_0) - \int_0^\infty \frac{\Gamma_0}{\omega_0} \left( \cos(\omega t + \phi_0) - \cos(\phi_0) \right) + O(\epsilon^2) \right] \right]. \tag{2.7} \]

The stimulus thus affects the ISI to first order in \( \epsilon \). In figure 5, we show the numerically computed ISIs for \( \epsilon = 0 \) and \( \epsilon = 0.05 \). The effect of the stimulus on the ISI is quite dramatic compared to its effect on the mean spike rate for the same \( \epsilon \) (see figure 3). Spike generation is most likely at the specific phase \( \phi_0 \approx 3\pi/2 \), for which the activation barrier is lowest. In figure 6, we show...
the spike rates for events sampled at a particular phase of the stimulus for different stimulus amplitudes.

3. Experimental measurements of hair bundle response

3.1. Methods

Sacculus from the inner ear of the North American bullfrog (Rana catesbeiana) was excised in an artificial perilymph solution (110 mM Na+, 2 mM K+, 1.5 mM Ca2+, 113 mM Cl−, 3 mM D-glucose, 1 mM sodium pyruvate, 1 mM creatine and 5 mM HEPES). The epithelia were mounted in a two-compartment chamber, with the apical side immersed in an artificial endolymph solution (2 mM Na+, 118 mM K+, 0.25 mM Ca2+, 118 mM Cl, 3 mM D-glucose and 5 mM HEPES), and the basal side in perilymph. The otoëtic membrane was dissociated with an 8 min incubation in 50 µg ml−1 of Collagenase IV (Sigma Aldrich) and lifted off with an eyelash tool [20], allowing access to individual hair bundles. The bundles were deflected with a glass probe mounted on a piezoelectric stimulator and imaged with an upright optical microscope (Olympus B51X) with a water immersion objective (60×, 1.00 NA). Images were further magnified to approximately 500× and projected onto a CMOS (complementary metal oxide semiconductor) camera (Photron Fastcam SA1.1). Images of 124 pixels were recorded at 1000 frames s−1. Software written in Matlab was used to fit a Gaussian distribution through the intensity profile of a hair bundle in each frame of a recording. Time-dependent traces of bundle deflections were then obtained by plotting the centre position extracted for each frame of the record.

3.2. Results

Steady-state deflections were applied to hair bundles in the positive direction (by convention, defined to be the direction increasing the channel opening probability), leading to a suppression of spontaneous oscillation. Owing to the effects of adaptation, offsets in the positive direction typically do not fully suppress active motility unless very large deflections are imposed [20]. Before full suppression is reached, a number of hair bundles display a transition from spontaneous limit cycle oscillation to spiking, in which they undergo rapid excursions in the negative direction. Under increasing offset, the occurrence of spikes becomes more rare, leading to a higher interspike interval, while the spike amplitude decreases.

In figure 7a, we show the activity of a hair bundle subject to a steady deflection of approximately 500 nm applied to the tip of the stereocilia. The bundle displacement is shown in black and the applied stimulus in red. The first portion of the trace displays the spiking regime of the bundle in the absence of a periodic drive. In the second portion of the trace, a weak sinusoidal stimulus is superposed onto the constant offset. Figure 7b shows a histogram of the resulting ISI. The stimulus frequency was 10 Hz, and the stimulus amplitude was approximately 1 pN. In the presence of the sinusoidal drive, the ISI is peaked at intervals equal to the stimulus period (0.1 s). In the inset, we show the equivalent histogram, computed for a spiking hair bundle in the absence of an imposed drive. For large ISIs $\Delta t$, the ISI can be fit to an exponential with a decay time of 0.04 s (note however the peak for small $\Delta t$). The decay time observed in the presence of stimulus is comparable to that of the stimulus-free case, with the correlation lost after about four stimulus cycles.

3.3. Comparison between experimental and theoretical results

In the absence of a stimulus, a system poised below the threshold of a SNIC bifurcation should exhibit an ISI distribution showing an exponential decay, with a constant equal to the mean spike rate $\Gamma_b$. The ISI measured in the absence of an imposed stimulus (figure 7b, inset) indeed does have an exponential tail for large $\Delta t$, with a fitted decay constant $\Gamma_b \simeq 25$ Hz. The broad peak that arises around $\Delta t = 0.05$ s could be due to an effective refractory period following a spike or could indicate that the system is poised incrementally below the SNIC threshold ($F < a_0$). We focus on time intervals that are large compared to 0.05 s.

When a stimulus is applied, the ISI distribution is strongly affected (see figure 7b), whereas the spike rate remains roughly constant, within the statistical accuracy of the experiments. This is consistent with our theoretical prediction that the stimulus alters the temporal distribution of spikes to first order in the stimulus amplitude but the mean spike rate only to second order. According to equation (2.3), the ISI should be a modulated exponential, with the modulation following the period of the drive. Peaks were observed in the measured ISI, and the spacing between them indeed agrees with the period of the drive.

Finally, it can be seen from the trace in figure 7a that spike events preferentially occur at a particular phase of the stimulus. In order to compare theory and experiment more quantitatively, we show in figure 8 histograms of the spiking rate $\dot{F}$ as a function of the phase of the periodic stimulus. The stimulus frequency was 20 Hz, and the amplitudes were varied from 0 to 1 pN. In the absence of an applied stimulus, the probability of spiking was uniformly distributed, while a peak arose in the probability distribution as the stimulus increased. We performed a three-parameter fit of equation (2.4) to the data, with $I_{in} = e^\alpha$ and $\dot{F}_0$ as the fitting parameters for different stimulus levels. The parameters extracted from the fits were roughly constant for different stimulus levels, consistent with the theoretical prediction.

These experiments focused on hair cells that show a significant level of spontaneous spiking activity, despite the mechanical loading, which allowed the collection of a statistically significant dataset from a single cell. In §4, we consider the biologically interesting case when sacculus hair cells are well below the spiking threshold, so that they exhibit spikes only rarely.

4. Arrays of noisy Adler equation oscillators

As discussed in the Introduction, preparations of hair cell arrays with intact otoëtic membranes show no detectable spontaneous activity, presumably due to mechanical loading by the membrane. Results from the previous sections offer the possibility that an array of hair cells, rendered quiescent by the mechanical loading with only rare spontaneous spiking, might constitute a sensitive detector. The mechanism of detection would be the phase-locking of spiking events by uncoupled oscillators to the applied periodic stimulus [21].
As an example, we assume that \( N \) cells of a large array (\( N \gg 1 \)) are subject to the same mechanical load and the same weak periodic drive. For a given cell in this array, noise-induced firing events would be rare, because changes in the firing rate are a second-order effect in the stimulus amplitude. However, these rare spike events occur at a preferred phase of the stimulus. If the mean spike rate is of the order of \( 1/N \) times the stimulus frequency (or larger), then the array as a whole would be expected to have one or more simultaneous spiking events per period of the drive. The output of such an array would provide a record of the stimulus. Note that no coupling between the hair cells would be required for such a detection mechanism, merely a collective readout of the array. Individual hair cells do not always fire during any given stimulus cycle; there is only a statistical preference for a given phase when a spike does occur.

We simulated a population of 1000 decoupled oscillators described by the driven noisy Adler equation, all subject to a mechanical load sufficiently large to force each oscillator to be well below the infinite-period bifurcation threshold. The stochastic noise on different oscillators was uncorrelated. Results of the simulation are shown in figure 9, with traces of different hair cells shown in different colours. A few examples are highlighted (yellow, red and black) for clarity. The horizontal axis is labelled in units of the stimulus period. The stimulus level is set to be \( \epsilon = 0.1 \), with a threshold \( \epsilon_c = 0.15 \). The noise level \( D = 0.02 \) corresponds to that of the gold line in figure 3, which has a pronounced SR peak in figure 4. An individual oscillator, for example one indicated by the yellow line in figure 9, clearly would not be a reliable signal detector. There is a wide variation in the number and temporal spacing of spikes in the response of an individual cell to identical presentations of the signal (compare the yellow with the red and black curves). However, for the full array, a burst of spikes is visible at every period of the stimulus at a well-defined phase of the cycle. The array already bursts during the first stimulus period, and hence exhibits a fast response. If the frequency of the drive were to change by a small amount, the burst frequency would follow within one period of the drive. In appendix C, we show that a large array of this type has a clear linear response, whereas individual oscillators do not.

Figure 7. (a) Hair bundle position as a function of time, with the stimulus (red) superposed and rescaled for clarity. The applied stimulus was 2.36 pN (15 nm) at a frequency of 10 Hz. (b) Histogram of the ISI distribution, with 0.96 pN (15 nm) stimulus applied at 10 Hz. A fit of the form \( \exp \left[ -t/\tau + \delta \sin (\omega t + \phi) \right] \) is shown in black. In the inset, a histogram is shown for the ISI distribution obtained with no applied stimulus. A fit to a decaying exponential is superposed. (Online version in colour.)
5. Discussion and conclusion

We showed that a noisy oscillator described by the driven noisy Adler equation, poised in the quiescent regime by the application a steady load, exhibits stochastic spiking events. In the presence of even a weak periodic drive, the spiking events phase-lock to the stimulus. The dynamic susceptibility of the system shows stochastic resonance as a function of the noise amplitude, with a peak at a noise level that is comparable to the activation barrier. Measurements of phase-locking dynamics in hair bundles exhibiting spikes provide experimental results that are in agreement with the theoretical description. Numerical simulations further indicate that a large array of subthreshold driven noisy Adler equation oscillators could constitute an effective detector of weak signals. This requires integration of the response of different hair cells. Indeed, in the sacculus, different hair cells are connected to the same neuron.

Interestingly, records of the firing rate from the auditory nerve fibre in vivo, elicited in response to a pure tone [30], show a remarkable similarity to the driven noisy Adler equation response. In addition to an increase in the firing rate as the intensity of the tone increased, for low-frequency tones, the firing probability peaks at a preferred phase of the tone. For low-intensity stimuli, the firing probability exhibits sinusoidal modulation similar to that shown in figures 6 and 7.

The detector array described here generates, in effect, a ‘digital’ record of the drive. For a sinusoidal stimulus, the relation between the occurrence of a spike burst and the signal is obvious: it records the instant when the stimulus phase adopts a particular value. However, it is not so obvious how the detector would respond to more complex stimuli. In further studies, we will explore how the detector would respond to aperiodic signals.

It is not known how the observed mechanical spike events relate to the chemo-electrical firing events of neurons innervating the hair cells. However, there is a clear similarity between the formalism describing the mechanical spiking events of hair bundles and that of the firing events of neurons. Phase-locking of neuronal firing to weak periodic signals has been extensively studied in the context of so-called place cells [31]. It was shown that the position of an animal is encoded by the preferred phase of firing events (‘phase precession’). In the formalism presented in this paper, the preferred phase was fixed at $3\pi/2$. We are currently investigating extensions of this theoretical framework to allow for
modulation of the preferred phase, to test whether a form of phase-coding could play a role in hearing.

Ethics statement. Animals were euthanized according to protocols approved by the UCLA Chancellors Animal Research Committee, in accordance with federal and state guidelines.

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Appendix A. Deterministic limit

In this appendix, we show numerical solutions of equation (2.1) in the absence of noise. In figure 10a, we plot the real part of the complex displacement $z = R e^{i\phi}$ for the values of $\epsilon$ used in figure 2. If $\epsilon < F - \omega_0$, then the phase is restricted to one of the local minima of the washboard potential. The corresponding displacement is a small-amplitude oscillation with $|z| \ll R$. The displacement $z$ mode-locks to the drive when $\epsilon$ exceeds a critical value $\epsilon_c$. In the adiabatic limit $\omega_0 \to 0$, $\epsilon_c = F - \omega_0$, while $\epsilon_c$ increases with increasing $\omega_0$. In figure 10b, we plot the average phase velocity as a function of $\epsilon$ for different drive frequencies. For $\omega_0 = 0.3\omega_0$, one recovers simple 1:1 mode-locking behaviour. Higher-order mode-locking appears as the drive amplitudes are increased, with 2:1 mode-locking for $\omega_0 = 0.2\omega_0$ and 3:1 mode-locking for $\omega_0 = 0.1\omega_0$. In the opposite limit of very large drive amplitudes, the phase follows the drive without spiking. Note the different values of $\epsilon_c$ as given by the locations of the first discontinuous increase in $\langle \phi \rangle$. Finally, figure 10c: shows a plot of $\langle \phi \rangle$ versus the drive frequency. A staircase structure is evident, with the mean phase velocity $\langle \dot{\phi} \rangle$ quantized into integral multiples of the stimulus frequency $\omega_0$. For very low $\omega_0$ or very large $\omega_0$, the mean phase velocity is zero. The key result for the present is that in the absence of noise, weak stimuli do not produce an appreciable response.

Appendix B. Time-dependent transition rates

In this appendix, we apply the path-integral method for random processes to obtain an expression for the escape rate out of one of the metastable wells of the driven noisy Adler equation washboard potential, in the presence of a periodic drive with a low amplitude $e \ll F - \omega_0$ and a low frequency $\omega_\ell < \omega_0$. A similar calculation was done in [29]. We will focus on the case where the activation energy barrier $\Delta U$ is large compared with the thermal energy $D$. Thus, the particle spends most of its time in one of the local minima. We will also focus on the case where the washboard potential is sufficiently steep so that one can neglect the probability of the particle moving up a maximum ‘to the left’. The escape rate $\Gamma_\ell$ from a metastable state in the absence of any time dependence was obtained in earlier studies [32–34] (see equation (B.8)) and is proportional to $\exp(-\Delta U/D)$. An extensive literature has focused on calculating time-averaged transition rates $\Gamma$ for the case of time-dependent potentials [35–40]. Here, we will give a brief sketch.

For a given escape event, the dynamics of $\phi$ can be split into two regimes: motion up the potential towards a maximum, and motion down the potential towards the next local minimum. The dynamics of $\phi$ moving up the potential is driven by a statistically rare series of stochastic events, while the motion down the potential is largely a deterministic process that is fast compared with the uphill motion. If the potential is time dependent, then the time-dependent escape rate across the energy barrier is given by the diffusion current at the top of the energy barrier $I_{\phi}(t) = -\partial \langle \phi(t) \phi(t) \rangle / \partial \phi$, where $\phi(t)$ is the probability for the ‘phase particle’ to have a phase $\phi$ at time $t$. This probability is proportional to the path integral

$$P(\phi, t) \propto \int d\phi(0)=\phi D\phi(t)e^{-S(\phi(t))/D}. \quad (B.1)$$

The effective, time-dependent action of the path integral is

$$S(\phi(t)) = \int_0^t \left( \frac{1}{4} \frac{\partial \phi(t)}{\partial \phi} \right)^2 dt.$$
where
\[
\frac{\partial U(\phi, t)}{\partial \phi} = -\omega_0 + \frac{F}{2} \sin(\phi) + \epsilon \sin(\phi - \omega_0 t). \tag{B2}
\]

In the limit of small \(D\), the dominant contribution to the path integral comes from paths that are extrema of the action, which are solutions of \(\delta S(\delta \phi)/\delta \phi = 0\). The ‘most probable escape path’ (MPEP) for a barrier escape problem is the solution of \(\delta \phi(t) = \partial U(\phi, t)/\partial \phi\), with boundary conditions \(\phi(t = \infty) = \phi_s\) the stable minimum, and \(\phi(t = -\infty) = \phi_u\) the unstable maximum (figure 1) [35–40]. Note the inversion of the initial and final times of the MPEP compared to the physical process of uphill diffusion [41].

Let \(\phi_0(t)\) be the MPEP for the case when there is no applied stimulus (\(\epsilon = 0\), with a corresponding time-independent escape rate \(I_0\). Expanding the action perturbatively to the lowest order in \(\epsilon\) gives [35–40]
\[
S_\epsilon(\phi') = \Delta U - \epsilon w_1(\tau), \tag{B3}
\]
where
\[
w_1(\tau) = \int_{-\infty}^{\infty} \phi_0(t) \sin(\phi_0(t) - \omega_0 t + \tau) dt. \tag{B4}
\]

Here, \(\Delta U\) is the activation energy barrier and \(\epsilon w_1(\tau)\) is the work done by the drive during the barrier escape process of the MPEP. Finally, \(\tau\) represents the phase difference between the drive and the MPEP for \(\epsilon = 0\). The average escape rate \(\Gamma(\epsilon)\) can be approximated as an average over this phase difference [35–39, 42]
\[
\frac{\Gamma(\epsilon)}{I_0} \approx \frac{1}{2\pi} \int_{-\pi}^{\pi} e^{\epsilon w_1(\tau)/D} d\tau, \tag{B5}
\]
where we only include corrections of order \(\epsilon\) in the exponential.

Before continuing with the calculation of \(\Gamma(\epsilon)\) for our case, we start with two general results for a drive which is an odd function of time. Expanding \(\Gamma(\epsilon)\) in powers of \(\epsilon\), the first-order term
\[
\left. \frac{d\Gamma}{d\epsilon} \right|_{\epsilon = 0} = \frac{I_0}{D} \left( w_1(\tau) e^{\epsilon w_1(\tau)/D} \right)_{\epsilon = 0} = \frac{I_0}{2\pi D} \int_{-\pi}^{\pi} w_1(\tau) d\tau = 0 \tag{B6}
\]
vanishes. This results from the fact that \(w_1(\tau)\) is an odd function, \(w_1(\tau) = -w_1(-\tau)\). The second-order term is non-zero
\[
\left. \frac{1}{2} \frac{d^2\Gamma}{d\epsilon^2} \right|_{\epsilon = 0} = \frac{I_0}{2\pi D} \left( w_1(\tau)^2 \right)_{\epsilon = 0}, \tag{B7}
\]
We define \(\Delta I(\epsilon) = \Gamma(\epsilon) - I(0)\) to be the dynamical susceptibility. Taking for \(I_0\) the Kramers escape rate
\[
I_0 = \left( \frac{\lambda_\text{s}}{2\pi} \right)^{\frac{1}{2}} e^{-\Delta U/D}, \tag{B8}
\]
with \(\lambda_\text{s}\) the curvature of the potential at the minimum and \(\lambda_\text{s}\) the curvature at the maximum, yields, to lowest order in \(\epsilon\)
\[
\Delta I(\epsilon) \approx \frac{\lambda_\text{s}^2}{4\pi D^2} e^{-\Delta U/D} \left( w_1(\tau)^2 \right), \tag{B9}
\]
The stochastic resonance behaviour is now apparent. The noise dependence of \(\Delta I(\epsilon)\) is given explicitly, and it can be seen that the response vanishes for both \(D \rightarrow 0\) and \(D \rightarrow \infty\).

To arrive at an explicit expression, we start by approximating \(\phi(t)\) in the argument of the sin function in equation (B3) by the average phase \(\phi_0 = (\phi_0 - \phi_u)/2\). This approximation is justified by the fact that the phase particle moves very slowly at the top of the energy barrier as well as near the metastable minimum. Because \(\phi_u(0)\) is very small at these points, the main contribution to the integral in equation (B4) comes from \(\phi(0) \approx \phi_u(0)\) halfway between the two extrema. As \(\tau\) is an arbitrary phase, one can redefine it to eliminate \(\phi_u(0)\)
\[
w_1(\tau) \approx \int_{-\infty}^{\infty} \phi_0(t) \sin(\omega_0 t + \tau) dt. \tag{B10}
\]

The phase velocity of the MPEP is approximated as
\[
\phi_0(t) = \begin{cases} 
\lambda_\text{s} \phi_0 e^{-\lambda_\text{s} t} & \text{if } t \leq 0 \\
\lambda_\text{u} \phi_0 e^{-\lambda_\text{u} t} & \text{if } t > 0
\end{cases}, \tag{B11}
\]
where
\[
\lambda_\text{s} \phi_0 = \lambda_\text{u} \phi_0 = \sqrt{\frac{2\Delta U |\lambda_\text{s}| |\lambda_\text{u}|}{|\lambda_\text{s}| + |\lambda_\text{u}|}}. \tag{B12}
\]
This was obtained by approximating the potential as piecewise parabolic, with the two parabolas having curvatures \(\lambda_\text{s}\) and \(\lambda_\text{u}\). The parabolas are matched at \(\phi_0\). Note that the phase velocity goes to zero for \(t = -\infty\) and \(t = +\infty\), reaching its maximum value \(\lambda_\text{u} \phi_0 = \lambda_\text{s} \phi_0\) at \(t = 0\). Substituting equation (B11) into equation (B10), one obtains an expression for \(w_1(\tau)\). Using this result in equation (B5) and noting that \(-\lambda_\text{s} = \lambda_\text{u} = \lambda\) gives us the following expression for the average escape rate:
\[
\Gamma(\epsilon) = \frac{I_0}{\omega_0} \left( \frac{2\lambda^2 \epsilon}{D(\omega_0^2 + \lambda^2)} \sqrt{\frac{2\Delta U |\lambda_\text{s}| |\lambda_\text{u}|}{\lambda}} \right). \tag{B13}
\]
The activation energy \(\Delta U\) can be obtained from the original washboard potential
\[
\Delta U = 2 \sqrt{\omega_0^2 - \omega_0 \cos^{-1}\left(\frac{\omega_0}{F}\right)}, \tag{B14}
\]
where \(I_0\) is the modified Bessel function of the first kind, while \(\lambda = \sqrt{\omega_0^2 - \omega_0^2}\). Equation (2.3) is derived from equation (B13) by expanding the Bessel function to second order in its argument and ignoring higher-order terms. Finally, equation (2.4) for the phase dependence of the escape rate is obtained using the adiabatic approximation with equations (B8) and (B11).

**Appendix C. Synchronization**

Here, we show that a large array of driven noisy Adler equation oscillators responds linearly to the drive, unlike a single oscillator. Let \(\phi_0\) be the phase of the drive where spiking occurs, and let \(N_e\) be the number of spikes. The synchronization...
order parameter is defined as
\[
\psi = \frac{1}{N} \left| \sum_{k=1}^{N} e^{i \alpha_k} \right|.
\]
(C.1)

In figure 11, we plot the amplitude of the numerically computed order parameter as a function of \( \varepsilon \).

For small \( \varepsilon \), the order parameter indeed increases linearly with the drive amplitude.

References


