Subharmonic stochastic synchronization and resonance in neuronal systems

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We study the response of a model neuron, driven simultaneously by noise and at least two weak periodic signals. We focus on signals with frequencies components $kf_0,(k+1)f_0,\ldots(k+n)f_0$ with $k>1$. The neuron's output is a sequence of pulses spaced at random interpulse intervals. We find an optimum input noise intensity for which the output pulses are spaced $\sim 1/f_0$, i.e., there is a stochastic resonance (SR) at a frequency missing in the input. Even higher noise intensities uncover additional, but weaker, resonances at frequencies present in the input. This is a different form of SR whereby the most robust resonance is the one enhancing a frequency, which is absent in the input, and which is not possible to recover via any linear processing. This can be important in understanding sensory systems including the neuronal mechanism for perception of complex tones.

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Excitable dynamics underlies the behavior of many biological systems, chemical reactions as well as cardiac and nerve cells [1]. In these systems, while a small input produces no response, a perturbation large enough elicits a transient large amplitude pulse or "firing." Over the last decades the dynamic of these systems in response to periodic deterministic forcing has been studied extensively [1–3]. The interplay of stochastic and deterministic forces was explored as well [4], including the case of stochastic resonance (SR) [5]. In the regime of SR some characteristics of the input signal (signal-to-noise ratio, degrees of coherence, etc.) at the output of the system are optimally enhanced at some optimal noise level. For the case of neurons SR manifest itself as maximum coherence between the period of the input signal and the intervals between "firings."

Works on neuronal SR have dealt with inputs composed either by a single harmonic component [6–9] or, in the other extreme by aperiodic signals [10–12] with no discrete spectral peaks. However, signals impinging on sensory neurons often have multiple discrete spectral lines, as for example in the cases of human speech and musical tones. It is then an important issue to understand how neurons respond to such inputs. In this paper we analyze the response of a model neuron driven by noise and by a weak signal composed of the sum of at least two periodic tones. Despite its oversimplification, it will be shown that this setting already produces a rich dynamics that we judge has relevant connections with various biological problems.

The system considered is a nondynamical threshold device already discussed in the literature [13]. Instead of the dynamical equation the system is reduced to the set of rules comparing $x(t)$ with U_{th} like $x(t)>U_{th}$ or $<U_{th}$. Whenever $x(t)$ crosses the fixed threshold (dotted line in Fig. 1) $U_{th}=1$, the system emits a "spike," i.e., a rectangular pulse of relatively short fixed duration, emulating in a very simplified

way the neuronal "firing." The only relevant quantity here is the timing of these spikes, as in most biological neurons [14].

The signals considered here are

$$x(t)=A(\sin f_1 2\pi t+\sin f_2 2\pi t+\cdots+\sin f_n 2\pi t)1/n+\xi(t),\tag{1}$$

where $f_1=kf_0,\ f_2=(k+1)f_0,\ldots,f_n=(k+n-1)f_0,$ and $k>1$. The term $\xi(t)$ is a zero mean Gaussian distributed white noise with variance σ.

Let us choose first a signal composed of two periodic terms with $f_1=2$ Hz and $f_2=3$ Hz. The amplitude of the deterministic term is set such that for zero noise there are no firings (see Fig. 1), which is the case usually considered in classical SR. It is important to note, from simple visual in-
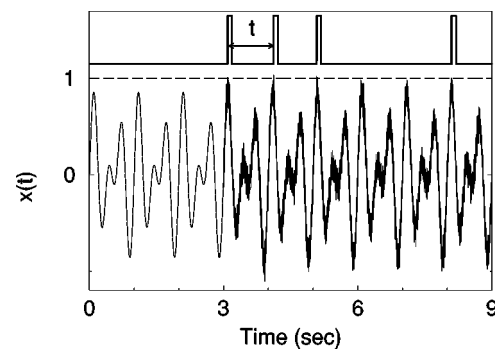

FIG. 1. Snapshot of $x(t)$ (lower trace) for a signal constructed by adding two sinusoidal terms of frequencies $f_1=2$ Hz and $f_2=3$ Hz. For illustration purposes, the noise amplitude is set to $\sigma=0$ during the initial 3 sec and $\sigma=0.075$ thereafter. Note that the signal is subthreshold in the noise-free condition. Each noise-induced threshold crossing produces a pulse (upper trace) which is the output of the neuron. The interpulses interval "t" is the quantity of interest.
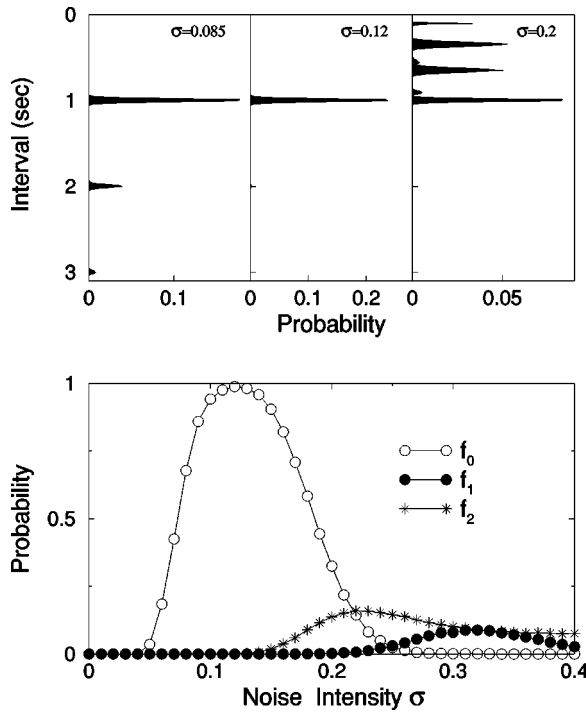
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FIG. 2. Top panels: Density distribution of interspike intervals t in the system Eq. (1) for three noise intensities. Bottom panel: Signal-to noise ratio computed as the probability of observing an interspike interval of a given $t(+/-\Delta t)$ as a function of noise variance σ estimated at the two input signals' time scales: f_1 (stars) and f_2 (filled circles) as well as for f_0 (empty circles). The largest resonance is for the f_0, i.e., a subharmonic which is not present in the input. ($A=0.9$, $f_0=1$ Hz, $f_1=2$ Hz, $f_2=3$ Hz, $\Delta t =0.051/f$ with $f=f_0$, f_1, or f_2.)

spection, that the signal reveals the very well known effect of linear superposition of waves: when two or more periodic waves come together, they will interfere with each other. Two waves will add wherever a peak from one matches a peak from the other, that is constructive interference. Wherever a peak from one wave matches a trough in another wave, they will partially cancel each other out, that is destructive interference. For the f_1 and f_2 values selected here the *highest* peaks of constructive interference repeats at $f_0 =1$ Hz. This is relevant to understand the dynamics because these peaks are the closest points to threshold implying that there will be some optimum noise intensity at which a large number of threshold crossings will be occurring at intervals $\sim 1/f_0$. It is important to keep in mind that the input energy at f_0 is zero, despite our immediate visual impression when analyzing Fig. 1.

We proceed to simulate numerically the system Eq. (1). The results are presented in Fig. 2. The top three panels correspond to the density distribution of firing intervals computed from simulations using relatively low, intermediate, and high noise intensities, respectively. Notice that for the intermediate noise variance, all firing intervals are spaced by ~ 1 sec, corresponding to the firings in phase with the successive peaks discussed above. For relatively low noise intensity (left panel) spikes also occur at the peaks of the deterministic signals but with random "skipping" of one or

more cycles, as described for conventional SR [6]. For even larger noise levels, shortest intervals are observed (right panel); the most frequent interspike intervals correspond either to 1 sec or to $t=1/f_2=1/3$ or its multiples. Thus, as a function of noise intensity neural firings become more or less coherent to different time scales. This is better shown by the plot in the bottom panel of Fig. 2. Each of the three curves represent the probability of observing an interspike interval equal or near to $1/f_0$, $1/f_1$, or $1/f_2$, respectively, computed as the ratio between the number of spikes with intervals within the time scale of interest and all other intervals. From the plot, it is immediately clear that the strongest resonance is the one that enhances f_0 (open circles), a time scale not present in the input. Further increase leads to a second but weaker resonance for the highest frequency (f_2) of the input pair. Finally the weakest resonance, occurring at even higher noise intensity, is for f_1.

We have verified that for signals composed of harmonic components, the frequency of the strongest resonance always corresponds to the difference $f_{n+1}-f_n$, (independently of the relative phases of the components). However, we are about to see that the resonance at the difference frequency is just a singular case of a more general phenomenon. Signals are often comprised of individual components (sometimes called "partials") that are not integer multiples of a unique fundamental. In this case the wave form is aperiodic. This type of complex signals are said to be "inharmonic." Let us construct such a signal by shifting all components of an originally harmonic complex by the same amount. We find that the frequency of the main resonance shifts linearly despite the fact that the frequency difference between successive partials remains constant. Specifically, the periodic terms are shifted multiples of f_0 (the absent fundamental) and partials are labeled: $f_1=kf_0+\Delta f$; $f_2=(k+1)f_0 +\Delta f, \ldots, f_n=(k+n-1)f_0+\Delta f$.

The results of simulating Eq. (1) with two periodic components for a wide range of f_1 frequencies (1.5 Hz to 7 Hz) are presented in Fig. 3. The noise amplitude is fixed at the optimum value for the strongest resonance shown in Fig. 2. For presentation purposes, the computed interspike intervals are plotted in two ways: in the top panel the data is plotted as instantaneous frequency of pulse firing f_p (i.e., $1/t$) while in the bottom panel as the input-firing frequency ratios (f_1/f_p). The probability of observing a spike with a given rate is represented using a gray scale. It can be seen that in response to the simultaneous frequency shift of both partials the neuron firing rate changes in a peculiar way. This is better visualized in the bottom panel where it is seen that the input-output ratios cluster around the nearest integer approximating f_1/f_0. It is clear that there is "locking" or stepwise synchronization (in a statistical sense) between the input frequency and the output frequency. A simple argument shows that these resonances are expected at a frequency

$$f_r=f_0+\frac{\Delta f}{k+1/2}. \tag{2}$$

Let us assume that the nonlinear stochastic thresholding simply detects the position of the *highest* peaks produced by
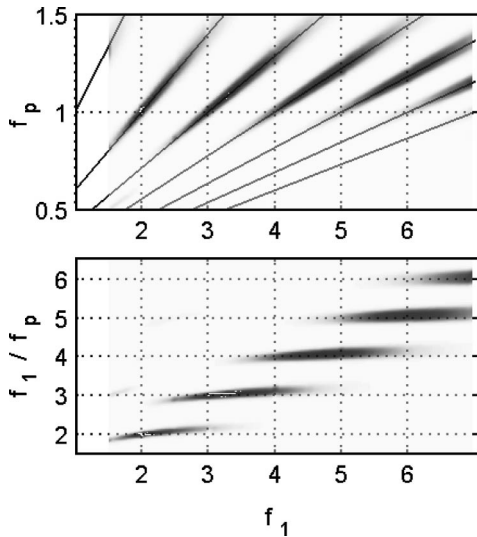
FIG. 3. Main resonances for two-frequencies signals. Top panel: The probability (as gray scale) of observing a spike with a given instantaneous firing frequency f_p (in the ordinate) as a function of the frequency f_1 of the lowest of two components of the input signal (abscissa). Family of lines is the theoretical expectation [Eq. (2)] for $k=1$–7. Bottom panel: The same data from the top panel are replotted as input-output frequency ratio vs input frequency f_1 ($A=0.9$, $\sigma=0.12$, $f_0=1$ Hz).
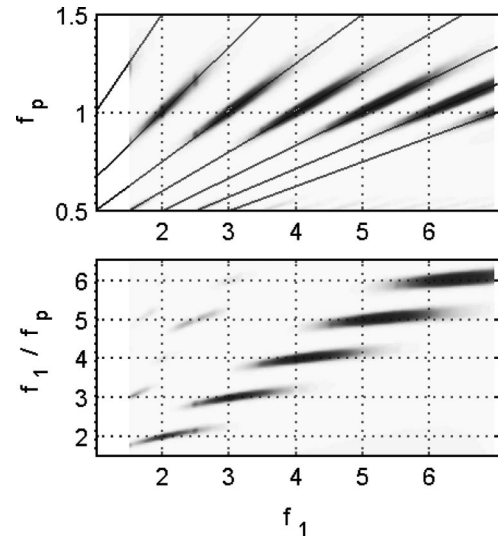

FIG. 4. Main resonances for three-frequencies signals. Top panel: The probability (as gray scale) of observing a spike with a given instantaneous firing frequency f_p as a function of the frequency f_1 of the lowest of the three components of the input signal. Family of lines is the theoretical expectation [i.e., Eq. (3) with $N=3$] for $k=1$–7. Bottom panel: The same data from the top panel are replotted as input/output frequency vs input frequency f_1 ($A=0.9$, $\sigma=0.12$, $f_0=1$ Hz).

constructive interference of the two sinusoidal signals of frequencies f_1 and f_2 and equal amplitudes. Note that $\sin(2\pi f_1 t)+\sin(2\pi f_2 t)=2\sin(2\pi(f^-/2)t)\cos(2\pi(f^+/2)t)$, i.e., the linear superposition is equivalent to modulate in amplitude a carrier of frequency $f^+/2=(f_2+f_1)/2$ with a sinusoid of frequency $f^-/2=(f_2-f_1)/2$, the well known beating phenomenon. A careful inspection shows that the interval between the two most prominent peaks is equal to the nearest integer number n, of half-periods of the carrier lying within a half-period of the modulating signal. For the case of a couple of harmonically related signals satisfying $f_1=kf_0$ and $f_2=(k+1)f_0$ we get $n=f^+/f^-=2k+1$ the corresponding interval is $n/f^+=1/f_0$, the period of the composed signal. On the other hand, for a shifted inharmonic complex, n will remain constant as long as the shift is small enough, and the most probable interval will be given by $nT^+=n/f^+=(2k+1)/((2k+1)f_0+2\Delta f)$ leading to Eq. (2). Figure 3 shows the agreement of this expression with the numerical data. In addition, notice the effects of the constant in the denominator of the expression: even though the data points are mostly clustered near the integers, there is a systematic deviation from zero slope, more notorious at the low k values.

A similar resonance phenomenon occurs in neurons responding to signals with more than two components. Figure 4 shows, (using the same format of Fig. 3) the results obtained from simulations using three sinusoidal terms spaced by $f_0=1$ Hz, and shifted in the same way as for the two components. The similarity with the results for two components is immediately apparent. The difference is in the slopes of the average shift of the output instantaneous firing rate. While in the two components case this goes $\sim 1/(k+1/2)$ in the three-frequencies case goes $\sim 1/(k+1)$.

In fact, a generalization of the argument above shows that for stimuli composed of N sinusoidal signals of frequencies $kf_0+\Delta f,(k+1)f_0+\Delta f\cdots(k+N-1)f_0+\Delta f$, resonances would occur at frequencies given by

$$f_r=f_0+\frac{\Delta f}{k+(N-1)/2}. \qquad (3)$$

We have verified numerically that the neuron model response accurately follows this prediction for N as large as 10; the numerical results are simple translations of Figs. 3 and 4, as expected from Eq. (3). Thus, the plots in Fig. 3 are representative (after proper ordinate translation) of the response to signals composed of even N partials and those in Fig. 4 of signals with odd N partials. Notice that the case $N=1$ accounts for the known case of a neuron responding with a subharmonic frequency when driven by just one subthreshold sinusoidal signal. For $N=2$ this formula is identical to the one obtained in [19] for the main three-frequency (deterministic) resonance of an oscillator subject to this kind of stimulation. For $N=3$ the formula accounts for the results displayed in Fig. 4. All results reported here were also replicated using the FitzHugh-Nagumo neuron model.

In summary, we have shown the existence of a form of SR whereby a frequency absent in the input is enhanced in the system response, a type of phenomenon not possible within the framework of linear signal processing. The phenomenon is eminently nonlinear and amounts also to the first reported manifestation of a SR of subharmonic character. We have provided a general expression predicting the strongest resonant response of the neuron model to an important range of possible wave forms. The scenario discussed in this letter resembles other problems including the analysis of intercep-

tion of two pulse trains investigated sporadically over the last 50 years by Richards [15], Miller [16] and more recently [17] in the context of radar warning receivers. It is also connected with the recent proposal of (deterministic) three-frequencies resonances [18] involved on the perception of sound pitch [19]. The pitch of a complex sound is the subjective place that we judge is on the musical scale. How perception of complex tones occurs is still an unsettled issue despite extensive experimental and theoretical work. Some of the results presented here resemble both the psychophysical data in the literature [20], as well as its analysis published recently [19], in particular our results in Fig. 3 agree very well with the scaling presented in [19]. The stochastic nonlinear detection described here can be the basis of the neuronal mechanism underlying detection of pitch of complex sounds in the auditory periphery. Cariani and Delgutte [21] experimental results provide many objective clues supporting this contention which can be further investigated.

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