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Firing and signal transduction associated with an intrinsic oscillation in neuronal systems

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We study the nonlinear firing and signal transduction of a neuron subject to both a constant stimulus and a weak periodic signal, each of which is too small to, separately, fire spikes for the neuron. The subthreshold constant stimulus, regarded as the total input to the neuron from other neurons and from the external world, is found to give rise to only an intrinsic subthreshold oscillation. This oscillation can lead to the transduction of the weak periodic signal via a mechanism similar to stochastic resonance. This may enable us to understand reported experimental results of oscillation associated signal transduction and of finite signal-to-noise ratio in the absence of external noise. In addition, the most sensitive frequency range for signal transduction is also found. [S1063-651X(98)50903-8]

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The phenomenon of stochastic resonance (SR) has been demonstrated in a variety of physical, biological, and other systems (see [1,2] and references therein). Such systems feature a threshold, such as a bistable potential or an excitable sensory neuron. The responses of these systems to a weak periodic signal are enhanced by the presence of noise. That is, SR can optimize the signal-to-noise ratio (SNR); the SNR first increases to a maximum and then decreases as the intensity of external noise increases [1,2]. A number of experiments on neural systems have been reported which show such nonlinear phenomena [3–9]. These include studies of the single mechanoreceptive sensory neurons from crayfish [3], rat skin [8], single interneurons from cricket abdominal ganglia [5], and the network of neurons from the mammalian brain [9]. The occurrence of SR has been argued as the ability to detect and transduce/encode information. More interestingly, it is also found in several experiments that the SNR is nonzero when the external noise is switched to zero [3,5,9]. This result was guessed to stem from the existence of internal noise in the neuronal system, but it still remains an important open question [3,10]. On the other hand, experiments have shown that there exists a frequency range below 100 Hz which is most sensitive for the signal transduction [5]. Whether this most sensitive range of signal frequency relates to the intrinsic nonlinear features of the neuronal system has not been clarified. In addition, it was reported in Ref. [11] that, under steady thermal stimulation the neuron showed some firing characteristics similar to SR behavior. It is argued that this sensory transduction may be due to the intrinsic oscillation of the neuron. But, how this oscillation arises and what role it plays have not yet been addressed.

Theoretically, although there have been some studies of SR in neural systems based on different models [12], there is little discussion of the aforementioned three aspects of the nonlinear firing of neurons. To interpret these very interesting and important experimental findings and to elucidate the physical origin of these complex phenomena, we report here a study of signal transduction for a weak periodic signal in the absence of external noise in a neuronal model. The neuron is assumed to be subject to a subthreshold constant stimulus which gives rise to a source of the intrinsic oscillation and evokes the neuron to encode the input periodic signal into a sequence of spikes. The encoding mode is found to be similar to that of SR and the signal transduction occurs within a frequency range below 100 Hz. The nonzero SNR we find in the absence of external noise appears to be relevant to the experimental findings. Furthermore, by arguing that thermal stimulation could be modeled by a constant stimulus plus a weak periodic signal, we are able to account for the experimental results reported in Ref. [11], which are not clearly understood in terms of the usual noise induced SR mechanism.

Let us start with the well-established Hindmarsh-Rose (HR) neuronal model [13,10,14,15] (a modified Fitzhugh's neuronal model [16])

$$\frac{dX}{dt}=Y-aX^3+bX^2-Z+I_0+I_1\sin(2\pi f_s t), \qquad (1)$$

$$\frac{dY}{dt}=c-dX^2-Y, \qquad (2)$$

$$\frac{dZ}{dt}=r[s(X-X_0)-Z], \qquad (3)$$

where $a=1.0$, $b=3.0$, $c=1.0$, $d=5.0$, $s=4.0$, $r=0.006$, and $X_0=-1.6$. Each neuron is characterized by three time-dependent variables: the membrane potential X, the recovery variable Y, and a slow adaptation current Z. Here I_0 is a constant stimulus and $I_1\sin(2\pi f_s t)$ is a weak periodic signal with I_1 and f_s being the amplitude and frequency of the signal, respectively.

The HR neuron is a self-excitable system. For a constant stimulus I_0, whether the neuron behaves as a damped subthreshold oscillation or as a limit cycle oscillation (suprathreshold) depends on the value of I_0. It is found that the minimal value of I_0 to fire spikes is $I_0=I_c=1.32$ [14]. When $I_0<I_c$, the stimulus induces only a damping oscillation on the quiescent state $X=X^*$ and of course there is no firing of spikes [see Fig. 1(a)]. This oscillation is considered to be intrinsic and its frequency is $f_{in}\simeq 30$ Hz (the period T_{in}

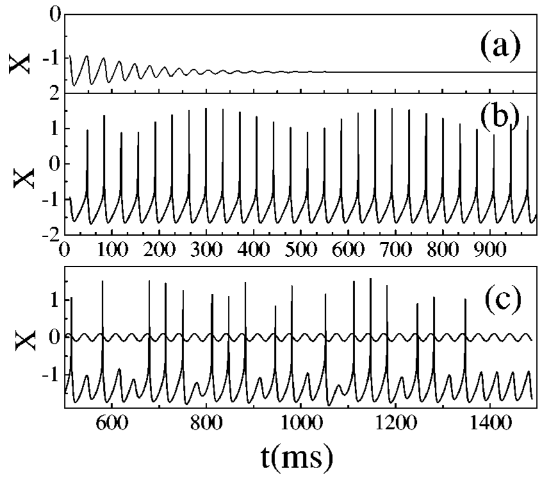

FIG. 1. The potential $X(t)$ of a neuron varying with time for (a) $I_0=1.31$ (no spikes firing); (b) $I_0=1.32$ (with spikes); (c) $I_0=0.96$ and a weak periodic signal $I_1\sin(2\pi f_s t)$ with $I_1=0.1$ and $f_s=30$Hz [also shown in (c)].

$\sim$33 ms). The duration of this oscillation increases as I_0 increases. When $I_0=I_c$ the oscillation leads to the firing of spikes with a frequency f_{in} [see Fig. 1(b)]. For $I_0>I_c$ the firing of spikes exhibits a period-adding behavior, or period-doubling of the potential $X(t)$, as studied in Refs. [14,17] previously.

Now let us see how the input evokes the firing of spikes for a subthreshold stimulus $I_0<I_c$ and whether the intrinsic oscillation is associated with the encoding of a weak periodic signal in some cases. Here, we consider I_0 as the total effect of ''input'' from the external world and from other neurons in the neural network, etc.. This input varies with time very slowly and is assumed to be small such that $I_0<I_c$ (e.g., $I_0=0.96$). Obviously, such a stimulus evokes no firing of spikes by itself, but supplies an intrinsic oscillation and drives the neuron from the quiescent state to a state sensitive to signal transduction. Actually, in a realistic case, the neuron always receives synaptic input from the network or the external surroundings, etc. All these can be modeled as a subthreshold input I_0. Once a small signal is added, certain responses or firing of spikes exist in the system. Indeed, by adding a very small periodic signal, say $I_1=0.1$ [18], we find numerically that there is a firing of spikes (or signal encoding) [see Fig. 1(c)]. The combination of both the intrinsic oscillation and the weak periodic signal causes the neuron to show a coherent firing similar to the phenomenon of SR. The spikes are triggered basically in every period of the signal T_s, but are occasionally interrupted with two, three, or more periods; the firing of spikes exhibits a random behavior [see Fig. 1(c)]. This can be understood from the signal encoding/transduction of a neuron through the firing of spikes evoked by its intrinsic oscillation. But more interestingly, this irregular firing dynamics is deterministic, with the firing mode related to the SR-like behavior (see Fig. 2), unlike the period-adding feature [14]. In addition, the firing also depends on the frequency of the periodic signal.

The coherent characteristics of the firing is clearly shown in Fig. 2. From the interspike interval (ISI) histogram, the peaks of the ISI's are located at integer multiples of the signal period nT_s up to $n=6$ with an approximately expo-

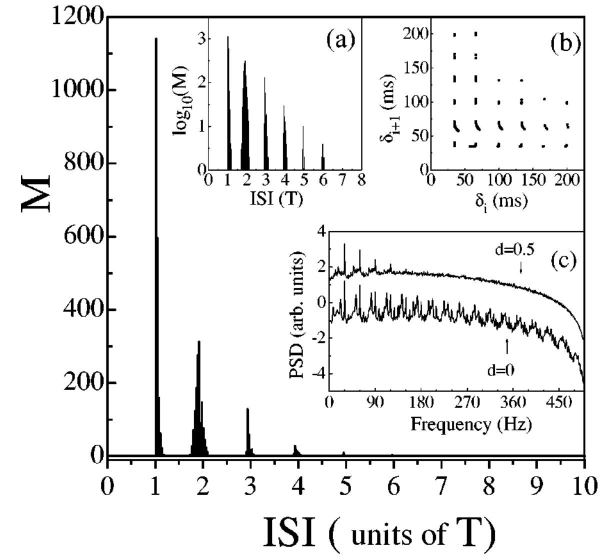

FIG. 2. The coherent characteristics of firing for a neuron with $I_0=0.96$ and a weak periodic signal $I_1\sin(2\pi f_s t)$ with $I_1=0.1$ and $f_s=30$ Hz. The main panel shows the interspike interval ISI (with units of the period of the signal $T_s=1/f_s=33.3$ ms) versus the number of spikes per bin M. Inset: (a) the logarithm of M against ISI; (b) the return map of the interspike interval δ_i against δ_{i+1}; (c) the power spectrum density of the firing of spikes without noise ($d=0$) and with Gaussian white noise ($d=0.5$). Here d is the noise intensity.

nential decay of the heights of the peaks as can be seen in inset (a) in Fig. 2. The firing of the neuron is modulated by the periodic signal, but is basically located at the first period ($n=1$); the number of firing events in this peak accounts for 60% of the total. Actually, this dominant peak relates to the maximum of the SNR. This indicates that the firing of the neuron is almost in synchrony with the signal. The return map, defined as the subsequent intervals of spikes $\delta_i=t_i-t_{i-1}$ (t_i is the firing time of the ith spike), is also shown in inset (b). One can see that the dots form a lattice with intersections at integer multiples of the period T_s. In Fig. 2, we show also the power spectrum density [see inset (c)]. It is clearly seen that there are several peaks at the frequency f_s of the signal and its harmonics, and that the first peak is about two orders of magnitude above the background. Due to the deterministic features of the chaotic firing, there are several small peaks at $f=f_s/n$ (with $n=2,3,4$), which represent the spikes with intervals of $T=nT_s$. For comparison, we consider also the case when Gaussian white noise is added to the neuron. From inset (c) in Fig. 2, we see that the firing is ''purified'' by the noise in encoding the signal and the peaks with subharmonics are restrained.

All these results imply that the SNR is finite although there is neither an external nor internal noise input to cause the neuron to exhibit SR behavior [10,12]. This may enable us to interpret the experimental results in Refs. [3,5,9] where there is still a finite SNR for a weak periodic signal when the external noise is switched off. (Of course, when both the external noise and the periodic signal are switched off, there are no responses from the neuron, except for some rare spontaneous firing in some cases.) Interestingly, the firing mechanism here is similar to SR since the stimulus I_0 evokes the neuron to exhibit a ''noiselike firing feature,'' i.e., chaotic

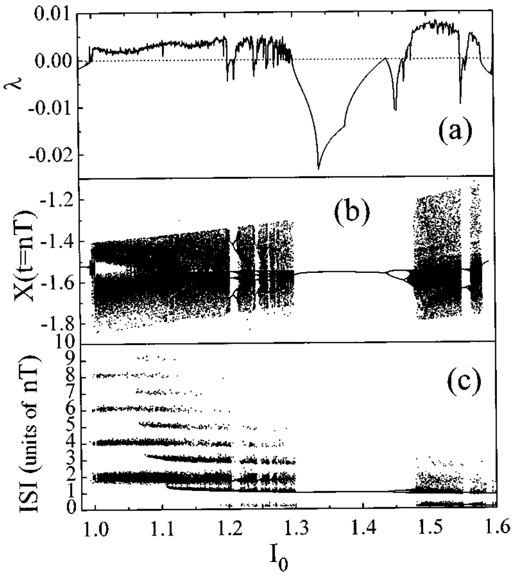

FIG. 3. The dynamical characteristics of a neuron as a function of I_0 [a weak periodic signal $I_1\sin(2\pi f_s t)$ with $I_1=0.1$ and $f_s=40$ Hz has been used]. (a) The maximum Lyapunov exponent λ; (b) the projection of potential $X(t)$ at time $t=nT_s=n2\pi/f_s$; (c) the interspike interval ISI (with units of the period T_s of the signal).

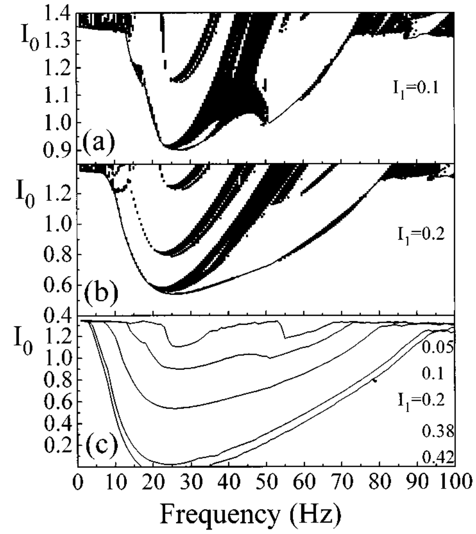

FIG. 4. The phase diagram of different dynamical behaviors in constant stimulus I_0 against the signal frequency f_s for different amplitudes I_1 of the signal. (a) and (b), the points represent the Lyapunov exponent $\lambda>0$, a chaotic firing of spikes. The blank regions represent periodic firing with $\lambda<0$ (above the enveloped line) or nonfiring (below the enveloped line); (c) different enveloped lines for different values of the amplitude I_1.

firing, although it is not itself noiselike . This feature results from the fact that the total effect of the stimulus I_0 and the periodic signal just places the neuron in a chaotic firing regime. Such a chaotic firing plays an effective role of ''noise'' and causes the neuron to fire near a preferred phase of the periodic signal. Physically, since there is a resonance of the signal with the deterministic chaotic firing background in the system, there should exist a distinct multimode in the histogram and a peak in the power spectrum density at the frequency of the signal. Notice that, due to the chaotic feature, the encoding of the signal has random components and the firing is interrupted occasionally.

From the maximum Lyapunov exponent and the projection of the potential $X(t=nT_s)$ shown in Figs. 3(a) and (b), we can see that the dynamical behavior of firing is different as I_0 changes. First, the periodic behaviors for both subthreshold oscillation and the suprathreshold firing are well specified by the Lyapunov exponent. When I_0 approaches 1.0, there is a saddle point bifurcation from the subthreshold oscillation ($\lambda<0$) of the potential $X(t)$ to a chaotic firing ($\lambda>0$) of spikes. But this chaotic firing belongs to a special firing mode. The firing interval $\delta_i=t_{i+1}-t_i$ is a multiple of the period of the signal, i.e., $\delta_i=nT_s$ with $n=2,4,6,8,10$ [see Fig. 3(c)]. As I_0 increses, this firing mode further changes into one of $\delta_i=nT$ with $n=1,2,3,4,5,\ldots$, i.e., the multimode with both odd and even periods of the signal. Then this firing mode is switched to the mode-locking state with the 1:1 firing of the period of the signal. Finally, the system enters into another chaotic region from a period-doubling state and the usual chaotic firing of the spikes occurs [14].

The phase diagram of different dynamical behavior of the system is shown in Fig. 4, where the dots correspond to the region of chaotic firing of spikes (with the positive maximum Lyapunov exponent $\lambda>0$) and the enveloped curves show the boundary between the firing and nonfiring regions. We can see that there is a threshold for each frequency, $I_c=I_c(f)$, which separates the diagram into the nonfiring region and the firing region. When $I_0<I_c(f)$ there is no firing of spikes, while for $I_0>I_c(f)$ the system shows a complex dynamical behavior of the firing, including periodic firings with $\lambda<0$ (or mode-locking state) and chaotic firings. For the periodic firings the neuron may fire one spike and two or more spikes in a burst, resembling the results obtained previously [14]. Nevertheless, the chaotic firing shows regular interspike intervals including random components like that shown in Fig. 2. This phase diagram is different in detail for different I_1 as shown in Fig. 4(c), but they all have similar features. We note that there exists a most sensitive range 5–70 Hz, where one needs less evoking stimulus I_0. As a matter of fact, this sensitive range results from a kind of ''resonance'' or ''modulation'' between the intrinsic oscillation of the neuron and the weak periodic signal; the input periodic signal will transfer energy to the neuron to evoke the firing of spikes when both frequencies are matchable. This nonlinear stimulus-frequency relation holds only in the low frequency range due to the intrinsic oscillation of the excitable features of the neuron [19]. Remarkably, the existence of such a region was indeed reported experimentally [5]. It is also worth noting that the detecting ability of the neurons will be significantly improved even in the presence of a small level of noise as long as the frequency of the signal falls in the sensitive region.

Finally, we note that the results presented in this work appear also to be relevant to the experimental findings in Ref. [11] where a similar firing feature of a sensory afferent neuron was reported, although only a steady thermal stimulation with noise is applied. Physically, as discussed before, the neuron receives a total effective stimulus which can be modeled as an input with fluctuations $\tilde{I}(t)$ around a mean value I_0, i.e., $I_{eff}(t)=I_0+\tilde{I}(t)$. Generally, the fluctuations have various components with different frequencies $\tilde{I}(t)=\Sigma_{i=1}^{N}I_i\sin(2\pi f_i t)$. Due to the intrinsic oscillatory feature of the neuron, there is a dominant component with a specific frequency related to the resonance characteristic. In the experiment, it is found that the neuron responds to a thermal stimulus with such a specific frequency, say f_s. Thus, the experimental situation may be modeled by $I_{eff}(t)=I_0+I_1\sin(2\pi f_s t)$, where the fluctuation is represented by the dominant component, that is, the effective stimulus is simplified as a sinusoidal form with a constant bias. This effective stimulus makes the neuron fire with a multimodal feature as illustrated in Refs. [11,20] Under certain thermal stimulation the bias (or I_0) and the frequency f_s of the effective stimulus in the experiment may fall in the nonlinear region shown in Fig. 4, so that the firing behavior of the neuron observed in Ref. [11] could be naturally expected from the present simulation.

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[20] A similar multimode has also been discussed by Longtin *et al.* [Neural Comput. **8**, 215 (1996)] based on a constant stimulus plus noise; but some temperature-related parameters must be built into the model.