Resonant forcing of a silent Hodgkin-Huxley neuron

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Dynamical behavior of a silent Hodgkin-Huxley neuron subjected to external periodic perturbations is investigated. Induced dynamics for this forced system, exhibit nonlinear resonance with respect to the forcing frequency. Within the *U*-shaped resonance curve, both regular (phase locked) and irregular spike sequences are invoked. For appropriate tuning frequencies, this simple system generates spike trains recordings similar to ones observed in actual experiments.

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It is largely believed that the underlying excitability of neurons seems crucial in efforts to understand the information processing of an individual neuron or neural networks [1–5]. It is commonly believed that the observed neuronal spike trains reflect the strengths of inputs that trigger the action potential of excitable neurons [6,7]. Therefore, the spike sequences invoked vary in response to the applied stimuli (inputs). In the presence of a constant stimulus, emergence of an irregular firing sequence with a constant mean frequency has been reported [1,2]. These experiments, when repeated, yielded unrelated spike sequences. However, the mean firing frequency was essentially conserved. This led to the conjecture that the relevant part of the information is encoded in the mean frequency of neuronal firing [8], thus implying that interspike timing (activity) is largely irrelevant.

Many numerical studies involving generation and encoding of firing/spike sequences for neurons use the standard integrate and fire (IF) model [9–11]. This discrete IF system is largely accepted as a simple dynamical model for neural spiking. The IF neuron is considered ''silent'' if it exhibits fixed point dynamics. If the amplitude of the external stimulus exceeds a certain critical value, the IF neuron can exhibit self-excited oscillations. The intrinsic frequency of these oscillations is intimately related to the strength of the external stimulus. It was subsequently realized [9] that the IF model system has a possible disadvantage as it allows for an artificial reset of the action potential. Moreover, there is a complete absence of a refractory period for the provoked excitation. These potential drawbacks in the IF model led some researchers to consider an alternate model system for studying neuronal spiking. Hodgkin-Huxley (HH) neurons [12] are based on the well known HH system of equations [12] that include nonlinear conductances of Na (sodium) and K (potassium) ion channels. This model system (HH) is considered realistic as it adequately describes both the spiking behavior and refractory properties of real neurons. Similar to the IF neuron, the HH neuron can exhibit self-excited oscillations in the presence of external stimulus.

In this paper, we study the provoked dynamics of a silent HH neuron (autonomous system exhibits fixed point dynamics) under the influence of sinusoidal perturbations. Spike sequences induced by external forcing are studied as a function of the parameters of a forcing signal (amplitude and frequency). The invoked spike trains exhibit both phase-locked (periodic) dynamics and irregular spiking behavior. The provoked irregular dynamics are subsequently analyzed using return maps of interspike intervals (ISIs) and histograms. The ISIs involve plotting periods of time between two successive spike maxima neglecting the basal state (small) oscillations. A comparison between forced dynamics of the silent HH neuron and experimental results involving neuronal spiking is made.

The HH neuron can be simulated by the following set of coupled nonlinear ordinary differential equations:

$$C_M\frac{dV}{dt}=I-g_K n^4(V-V_K)-g_{Na}m^3h(V-V_{Na})-g_l(V-V_l), \tag{1}$$

$$dn/dt=\alpha_n(1-n)-\beta_n n, \tag{2}$$

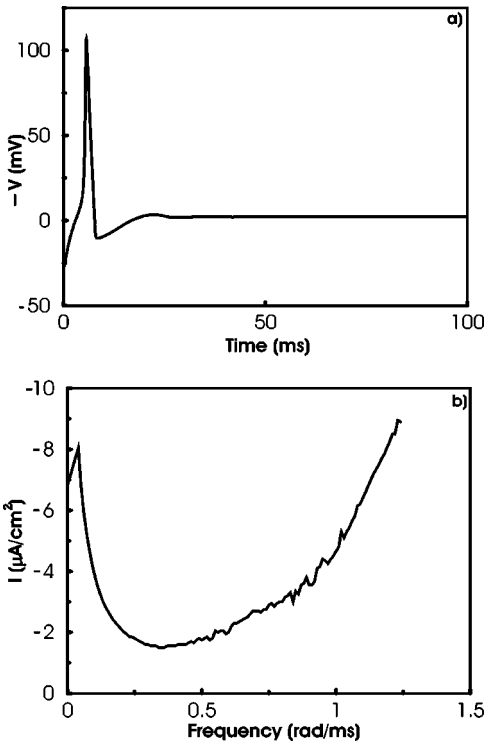

FIG. 1. (a) Time series of the silent HH neuron. The model parameters are specified in the text. The control parameter I_0 $(>I_c)=-2.85$ μA/cm^2, such that the model system exhibits fixed point dynamics. (b) The *U*-shaped curve encapsulates the region in parameter space (amplitude-frequency domain) where periodic modulations of I trigger spike trains in the model system.

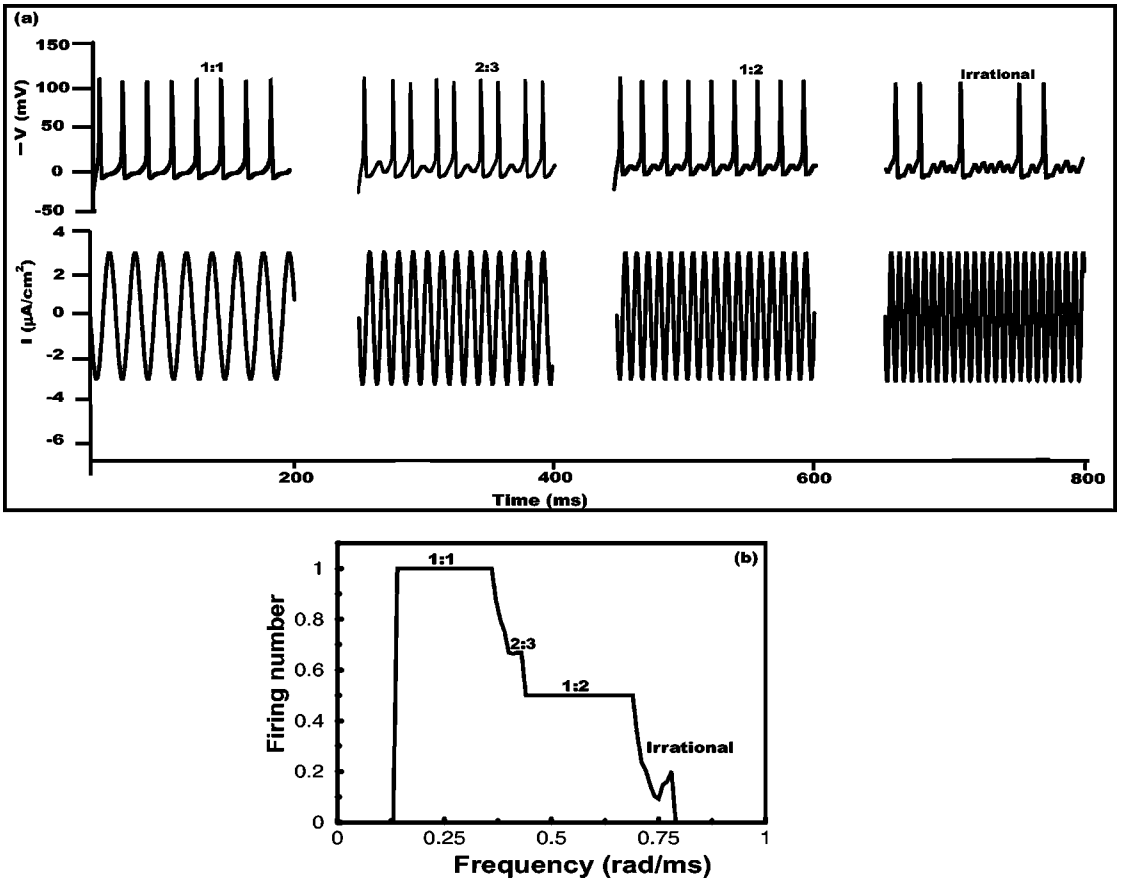

FIG. 2. Details within the *U*-shaped curve reveal different types of phase locked and irregular dynamics consistent with the existence of a nonlinear resonance between the frequency of the external forcing and that of the damped oscillations around the stable focus. (a) Time series for the different firing patterns invoked. Also shown are the corresponding periodic modulations responsible for their inception. (b) Devil's-staircase-like structure encapsulated by the *U*-shaped region for $I_0=-3\ \mu\mathrm{A/cm}^2$. It indicates the inception of both rational and irrational firing numbers under the influence of continuous periodic modulations.

$$dm/dt=\alpha_m(1-m)-\beta_m m, \tag{3}$$

$$dh/dt=\alpha_h(1-h)-\beta_h h. \tag{4}$$

The first equation represents the total ionic current (I) which is a sum of capacity current, current carried by potassium ions, current carried by sodium ions, and the leak current. C_M is the membrane capacity, while g_K, g_{Na}, and g_l are the conductances of the respective channels. V is the membrane potential, while V_K, V_{Na}, and V_l are proportional to the equilibrium potential of the different channels. Gating variables for the sodium and potassium channels are represented by m, h, and n. The α's and β's in the above equations are defined as,

$$\alpha_m=0.1(V+25)/\{\exp[(V+25)/10]-1\},$$

$$\beta_n=0.125\exp(V/80); \tag{5}$$

$$\alpha_m=0.1(V+25)/\{[\exp(V+25)/10]-1\},$$

$$\beta_m=4\exp(V/18); \tag{6}$$

$$\alpha_h=0.07\exp(V/20), \quad \beta_h=1/\{\exp[(V+30)/10]+1\}. \tag{7}$$

The model system is integrated using a fourth-order Runge-Kutta algorithm with a constant step size of 0.05. The following set of initial conditions $(V,n,m,h)=(-30\ \mathrm{mV},0,0,0)$ was used and system parameters were fixed at $(C_M,g_K,g_{Na},g_l,V_K,V_{Na},V_l)=(1\ \mu\mathrm{F/cm}^2,\ 36\ \mathrm{m}\Omega^{-1}/\mathrm{cm}^2,\ 120\ \mathrm{m}\Omega^{-1}/\mathrm{cm}^2,\ 0.3\ \mathrm{m}\Omega^{-1}/\mathrm{cm}^2,\ 12\ \mathrm{mV},\ -115\ \mathrm{mV},\ -10.613\ \mathrm{mV})$, respectively. The robustness of numerical results was verified by adding small amounts of additive noise to the model equations. The control (bifurcation) parameter I, when varied, results in the transformation of fixed point dynamics to self-exciting oscillations. Moreover, there is a parameter domain of bistability where stable focus and the limit cycle solution coexist. Choosing $I>I_c$, where $I_c=-6.7\ \mu\mathrm{A/cm}^2$ ensures that the parameter regions for oscillatory dynamics and bistability are precluded. Consequently for $I>I_c$, independent of initial conditions, the HH neuron is silent exhibiting fixed point dynamics. For the forcing of this silent HH neuron the control parameter I is varied sinusoidally,

$$I=I_0\sin(\omega t), \tag{8}$$

ensuring that $I_0>I_c$.

Figure 1(a) shows the steady state dynamics of the silent HH neuron (autonomous system). The frequency of the dis-

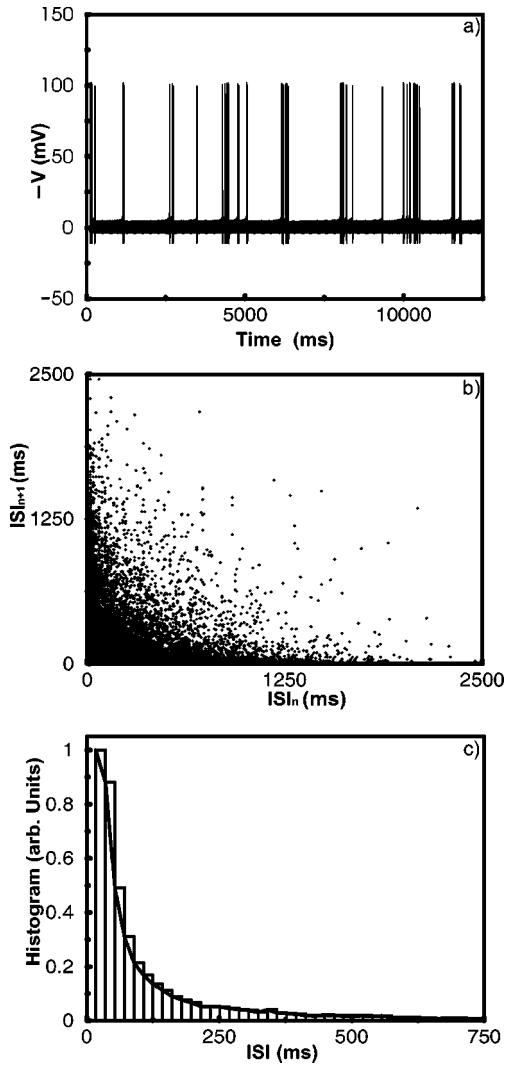

FIG. 3. (a) Irregular time series provoked by the forcing function with the following characteristic ($I_0 = -2.47\ \mu\mathrm{A/cm}^2, \omega = 0.67$ rad/ms). The other parameters are the same as mentioned in the text. (b) Return map with 34 159 interspike intervals (ISIs) of large spikes for the time series of (a). Only maxima greater than 90 mV were considered. (c) Histograms for the ISIs of (b). The solid curve is obtained by joining the successive maxima of the nearest-neighbor spacing distribution.

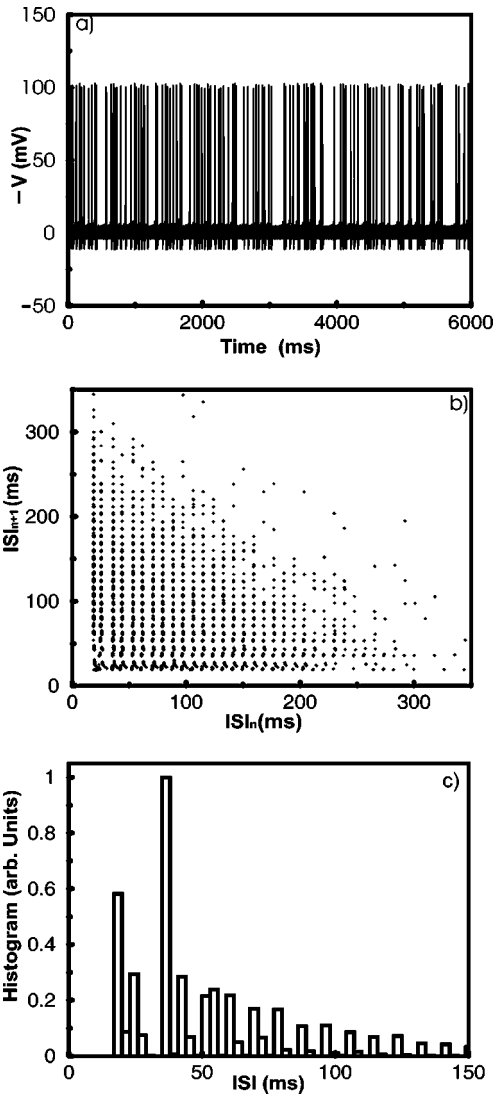

FIG. 4. (a) Irregular time series provoked by a forcing function with the following characteristic ($I_0 = -2.85\ \mu\mathrm{A/cm}^2, \omega = 0.71$ rad/ms). The other parameters are the same as mentioned in the text. (b) Return map with 36 467 interspike intervals (ISIs) of large spikes in the system of (a). Only maxima larger than 90 mV were considered. (c) Histograms for the ISIs of (b). It shows the existence of preferred frequency for the induced spiking.

sipative dynamics in the vicinity of the stable focus is about 0.425 rad/s. To reiterate, the periodic forcing of this neuron is achieved by sinusoidally varying the control parameter I under the condition $I_0 > I_c$. A frequency and amplitude scan in the vicinity of the Hopf bifurcation reveals the domain where nonlinear resonance lowers the parameter threshold for the forced system resulting in inception of the spiking behavior. The *U*-shaped curve of Fig. 1(b) represents the new dynamical threshold (function of the frequency of superimposed sinusoidal perturbations) for the forced system. The minima of this curve corresponds to the optimum frequency for which spiking can be generated with minimum effort [smallest amplitude (absolute) of external perturbations]. This frequency is comparable to that of the dissipative dynamics in the vicinity of the stable focus. This is related to the fact that the excitable system [Eqs. (1)–(4)] has a resonance at a frequency close to the imaginary part of the eigenvalues of the flow dynamics linearized around its fixed point [13]. In Ref. [13], the authors compute a similar *U*-shaped curve for an excitable chemical system.

Detailed investigation of invoked dynamics within the *U*-shaped curve reveals behavior consistent with two-frequency nonlinear resonance. To reiterate, the two interacting frequencies are, (a) frequency of the sinusoidal perturbation and (b) frequency of dissipative dynamics around the stable fixed point of the autonomous system. Figure 2(a) shows four induced spike profiles and the corresponding forcing functions. The provoked dynamics within the *U*-shaped curve can be classified into two categories: (a) a composite of basal state oscillations and spikes, (b) continuous spiking behavior only. Firing number (number of excitations/number of perturbations) was calculated for the

parameter domain encapsulated within the *U*-shaped curve. It reveals a devil's-staircase-like structure as shown in Fig. 2(b). This existence of devil's-staircase-like structure with clearly demarcated phase-locked domains is typical of the forced oscillatory/excitatory dynamics. Our simulations mimick the experimental recordings for the normal squid axons [14]. The membrane potential responses in squid axons under periodic stimulations included (a) phase-locked modes of response and (b) devil's-staircase-like structure in the firing number of the forced system.

It is interesting to observe that apart from the invoked periodic dynamics, there is a region of parameter space (within the *U*-shaped curve) where appropriate forcing frequencies provoke irregular spiking behavior. This too is consistent with the experimental findings for the normal squid axons [14]. In these experiments, for certain parameters of the superimposed periodic stimulation, irregular spike profiles were evoked for the forced squid axon [14]. This irregularity was attributed to the random switching between periodic subthreshold oscillation (nonfiring phase) and the firing phase (spike). This parameter region (numerical) for irregular firing was examined in further detail. Figure 3(a) shows an irregular spike sequence invoked for the forced system within the *U*-shaped region. The perturbation parameters are provided in the corresponding figure caption. Between two successive spikes, the trajectory is confined in the vicinity of a weakly unstable period-1 solution. However, eventually the dynamics diverge and enter a region of state-space domain from where a spike is initiated. This process is repeated (after every spike) but not replicated rendering the invoked time series chaotic. Figure 3(b) shows the return map of the ISIs for the irregular time series of Fig. 3(a). ISIs are the periods of time between two successive spike maxima disregarding the small oscillations in between. The calculated histogram distribution is shown in Fig. 3(c). Our analysis indicates that although the provoked process is not Poisson, there does seem to be an exponential-type decay in the probability distribution [as seen in Fig. 3(c)] for longer firing periods.

Figure 4(a) shows another irregular spiking sequence generated within the *U*-shaped region. The parameters of the forcing function are provided in the corresponding figure caption. Figure 4(b) shows the return map of the ISIs for this irregular time series. This plot shows a significant reduction of the ISI distribution compared to that of Fig. 3(b). There exists a sharp border for small ISI values and in addition, a pattern of orthogonal lines is discernible. Figure 4(c) shows the histogram distribution for the spiking sequence of Fig. 4(a). The distribution now is accumulated around the mean firing period of 36.5 ms. This implies that, the forced HH neuron possesses a preferred (mean) frequency of spiking activity.

Our results, within the resonance curve, indicate that both regular and irregular spike profiles can be provoked via a small amplitude forcing of the silent HH neuron. Furthermore, two different types of irregular spike sequences are invoked. Firstly there are irregular spike sequences whose corresponding ISIs are scattered [Fig. 3(b)]. Second, in close proximity, there are parameter domains where an increased spiking frequency is observed in the invoked irregular time series. For these time series, clearly demarcated patterns appear in the ISI return map [Fig. 4(b)]. Moreover, histogram distribution of Fig. 4(c) has a dominant peak implying a preferred spiking frequency.

In this paper, effects of external modulations on steady state (fixed point) neuronal dynamics were studied. Induced spike trains in the presence of external stimuli are considered pertinent to information processing in neurons and neural networks. In real systems, these external modulations could be caused by various neurotransmitters and/or by synaptic inputs. We find that for a range of forcing frequencies the threshold of firing for the silent HH neuron can be lowered via a nonlinear resonance. Moreover, spiking behavior invoked via continuous perturbation of a silent HH neuron system, can generate spike recordings similar to ones observed in actual experiments [14]. Apart from these experiments, the emergence of phase locking to superimposed perturbing frequencies has been observed in the auditory system of barn owl [15] and squid giant axons [16]. The work of Kaplan *et al.* [16] shows different types of phase locked and chaotic dynamics. However, we were unable to find the deterministic subthreshold chaos reported by them. In our simulations, successive spikes are separated by dynamics in the vicinity of a weakly unstable periodic orbit. Our numerical spike sequences are provoked by small amplitude perturbations with appropriate tuning frequencies, which might not be the case in the experiments mentioned earlier. Consequently, the system parameters in these experiments are not necessarily within the *U*-shaped nonlinear resonance curve obtained for the HH model.

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