

Double-System-Size Resonance for Spiking Activity of Coupled Hodgkin–Huxley Neurons

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The study of noise-induced constructive effects in nonlinear dynamic systems, especially stochastic resonance (SR)-like phenomena, has attracted great research interest.^[1,2] Very recently, the frontier of this interest has shifted to a new and quite interesting SR-like phenomenon, *system size resonance*.^[3–13] On the one hand, it was demonstrated that the collective behavior of an array of coupled noisy dynamic elements may be the most ordered when the system size—here the number of elements is N —has an optimal value.^[3–5] In such a case, the noise is *external*, and the system size N plays a role in changing the effective noise strength that is subjected to the mean field. For example, system-size stochastic resonance was found in an ensemble of coupled noisy bistable elements subjected to a small periodic force,^[3] and system-size coherent resonance was demonstrated in a one-dimensional lattice of diffusively cou-

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pled excitable neurons in the absence of an external signal.^[4] On the other hand, for oscillating chemical reactions taking place in small-scale systems, stochastic oscillations can be observed and there is an optimal system size at which such stochastic oscillations show the best performance.^[6–12] In such small systems, the numbers of the reactant molecules are often low and the *internal* noise resulting from the stochastic reaction events must be considered. It was reported that ion-channel clusters of optimal sizes can enhance the encoding of a subthreshold stimulus,^[6–7] and optimal intracellular calcium signaling appears at a certain size or distribution of the ion-channel clusters.^[8–10] In recent studies, by using a circadian-clock model and the Brusselator model, we have shown that the internal noise can induce stochastic oscillations in the region close to the deterministic oscillatory dynamics, and an optimal system size V exists for such stochastic oscillations, which are characterized by a clear maximum in the signal-to-noise ratio (SNR).^[11,12] Similar results were also obtained for intracellular calcium signaling processes, where a stochastic, internal system-size resonance of calcium oscillations was found for a noise strength that matches the cell size of a real living cell.^[13] To outline, a chain of N coupled noisy dynamic elements may show system-size N resonance, and a mesoscopic chemical oscillator of size V can show system-size V resonance. Note that the first one only accounts for external noise so far, and the second one results from the internal noise.

An interesting question arises: For coupled small-scale dynamic systems, can two such kinds of “size resonance” coexist? To answer this, we have studied the collective dynamical behavior of an array of N coupled Hodgkin–Huxley (HH) neurons,^[14] with each neuron a membrane patch size S . We not only consider the effects of internal channel noise (hence the patch size), but also those of the number of elements. Interestingly, we find that for a given number of neurons, N , there is an optimal patch size, S , where the collective behavior has a maximum order, and for a given patch size S , there is also an optimal value of N at which the collective behavior shows the best performance. Therefore, for the coupled HH neurons considered here, there is a kind of *double-system-size resonance*.

According to the well-known HH neuron model, the ion current across the biological membrane is carried mainly by the motion of sodium (Na^+) and potassium (K^+) ions through selective and voltage-gated ion channels embedded across the membrane. In addition, there is a leakage current present that is associated with other ions. Consequently, in the presence of an external stimulus, $I(t)$, the temporal evolution of the transmembrane potential $V(t)$ for a single neuron is governed by the differential Equation (1),

$$C \frac{dV}{dt} = -g_{\text{Na}} m^3 h (V - V_{\text{Na}}) - g_{\text{K}} n^4 (V - V_{\text{K}}) - g_{\text{L}} (V - V_{\text{L}}) + I(t) \quad (1)$$

where $g_{\text{Na}} = 120$, $g_{\text{K}} = 36$, and $g_{\text{L}} = 0.3 \text{ mS cm}^{-2}$ denote, respectively, the maximal conductance of the sodium, potassium, and other remaining ion channels per unit area, $C = 1 \text{ } \mu\text{F cm}^{-2}$ is the membrane capacitance per unit area, and $V_{\text{Na}} = 50$, $V_{\text{K}} =$

-77 , and $V_{\text{L}} = -54.4 \text{ mV}$ are the reversal potentials associated with sodium, potassium, and leakage conductance, respectively.

According to Hodgkin and Huxley, the conductance of a potassium channel is gated by four independent and identical gates, of which the probability of opening is denoted by n . Therefore, the term n^4 in Equation (1) denotes the probability for a potassium channel to remain open. Similarly, sodium channels are assumed to be gated by three identical gates with an opening probability m and one additional different gate with an opening probability h , such that the probability for a sodium channel to remain open is $m^3 h$. To take into account the internal channel noise, the stochastic gating variables m , h , and n obey the following Langevin equations [Eqs. (2a–c)]:^[15]

$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m + \xi_m(t) \quad (2a)$$

$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h + \xi_h(t) \quad (2b)$$

$$\dot{n} = \alpha_n(V)(1-n) - \beta_n(V)n + \xi_n(t) \quad (2c)$$

where $\xi_{i=m,n,h}(t)$ are Gaussian white noise with $\langle \xi_i(t) \rangle = 0$, $\langle \xi_i(t) \xi_j(t') \rangle_{i \neq j} = 0$, and $\langle \xi_i(t) \xi_i(t') \rangle = D_i \delta(t-t')$. $D_{i=m,n,h}$ denote the effective intensity of the internal channel noises, which are inversely proportional to the total number of sodium or potassium channels in the membrane patch as follows [Eqs. (3a–c)],

$$D_m = \frac{2}{N_{\text{Na}}} \frac{\alpha_m \beta_m}{\alpha_m + \beta_m} \quad (3a)$$

$$D_h = \frac{2}{N_{\text{Na}}} \frac{\alpha_h \beta_h}{\alpha_h + \beta_h} \quad (3b)$$

$$D_n = \frac{2}{N_{\text{K}}} \frac{\alpha_n \beta_n}{\alpha_n + \beta_n} \quad (3c)$$

Here the experimentally determined voltage transition rates are given explicitly by the expressions Equations (4a–f):^[10]

$$\alpha_m(V) = \frac{0.1(V+40)}{1 - e^{\frac{-(V+40)}{10}}} \quad (4a)$$

$$\beta_m(V) = 4e^{\frac{-(V+65)}{18}} \quad (4b)$$

$$\alpha_h(V) = 0.07e^{\frac{-(V+65)}{20}} \quad (4c)$$

$$\beta_h(V) = \{1 + e^{\frac{-(V+35)}{10}}\}^{-1} \quad (4d)$$

$$\alpha_n(V) = \frac{0.01(V+55)}{1 - e^{\frac{-(V+55)}{10}}} \quad (4e)$$

$$\beta_n(V) = 0.125e^{\frac{-(V+65)}{60}} \quad (4f)$$

N_{Na} and N_{K} are the total numbers of sodium and potassium

channels present in a given patch of membrane, respectively. By assuming that the density of ion channels on the membrane patch is homogeneous, N_{Na} and N_{K} are determined by using the membrane patch area S via $N_{\text{Na}} = \rho_{\text{Na}} S$ and $N_{\text{K}} = \rho_{\text{K}} S$, where $\rho_{\text{Na}} = 60$ and $\rho_{\text{K}} = 18 \mu\text{m}^{-2}$ are the corresponding ion-channel densities. Note that the intensity of the internal noises denoted by Equations (3) is inversely proportional to the membrane patch size S , which will be used as the parameter for system size in the following parts.

Now the dynamics of an array of coupled HH neurons can be described by Equations (5a) and (5b),

$$C \frac{dV_i}{dt} = -g_{\text{Na}} m_i^3 h_i (V_i - V_{\text{Na}}) - g_{\text{K}} n_i^4 (V_i - V_{\text{K}}) - g_{\text{L}} (V_i - V_{\text{L}}) + I + \varepsilon (V_{i-1} + V_{i+1} - 2V_i) \quad (5a)$$

where

$$\dot{x}_i = \alpha_{x_i} (V_i) (1 - x_i) - \beta_{x_i} (V_i) x_i + \xi_{x_i}(t) \quad (5b)$$

where $x = m, n, h$ and $1 \leq i \leq N$. Here N is the number of neurons and ε is the coupling strength. Numerical integration of Equation (5) is carried out by an explicit Euler method with a time step of 0.001 ms. Periodic boundary conditions are used and the parameter values for all the neurons are identical except for the noise terms $\xi_{x_i}(t)$. We take a periodic stimulus of the form $I = \sin(0.3t)$. The collective behavior of the array is defined as the average membrane potential $V_{\text{out}}(t) = \frac{1}{N} \sum_{i=1}^N V_i(t)$.

We first considered the dynamics of a single neuron ($N=1$). Actually, the influence of channel noise on a single neuron has been widely studied, and the main conclusion is that the internal channel noise can be functionally important for neuron dynamics.^[6,7,16-18] Specifically, Hänggi's group demonstrated the occurrence of internal noise stochastic resonance as well as coherent resonance in a single neuron, such that the spiking activity for a neuron was optimized when the membrane patch had an optimal size.^[7] Similar results have also been obtained in our present work, and we outline the main points here for consistency. If the membrane patch size S is too large, the internal noise is weak, so that the membrane potential only shows small-amplitude oscillations with very few occasional firing spikes, as displayed in Figure 1a. If S is too small, although the spike firing becomes more frequently, the internal noise is large and smears the regularity of the spike train (Figure 1c). Consequently, for an intermediate membrane patch size, the spike train is the most regular (Figure 1b). Therefore, there is an optimal patch size at which the neuron shows the best spiking activity. To quantitatively characterize the regularity of the spike train, we have calculated the coefficient of variance, which is defined as the mean square root of the spike interval T normalized to its mean value, namely, $R = \sqrt{\langle T^2 \rangle - \langle T \rangle^2} / \langle T \rangle$. Note that a spike occurs when the state variable $V_{\text{out}}(t)$ crosses a certain threshold value from below, and it turns out that the threshold value can vary in a wide range without altering the resulting spiking dynamics. The dependence of R on the patch size S is plotted in Figure 2 (left panel, circles), which shows a clear minimum around

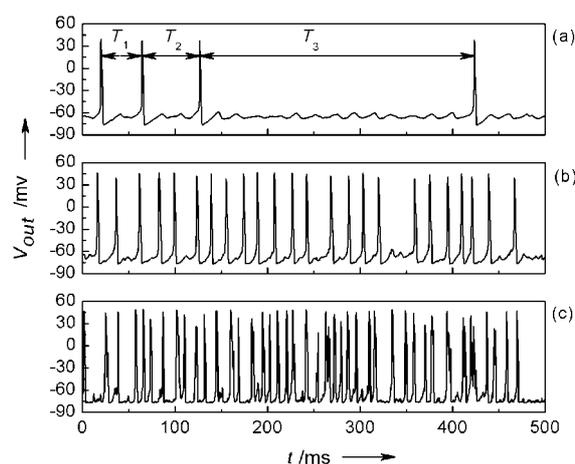


Figure 1. The membrane potential $V_{\text{out}}(t)$ for a single neuron ($N=1$) with different patch size S . a) $\log(S)=2.1$, b) $\log(S)=0.3$, c) $\log(S)=-1.25$ (the unit of S is μm^2). A regular spike train is observed for the intermediate patch size. T_1 , T_2 , and T_3 in (a) give examples of the spike interval.

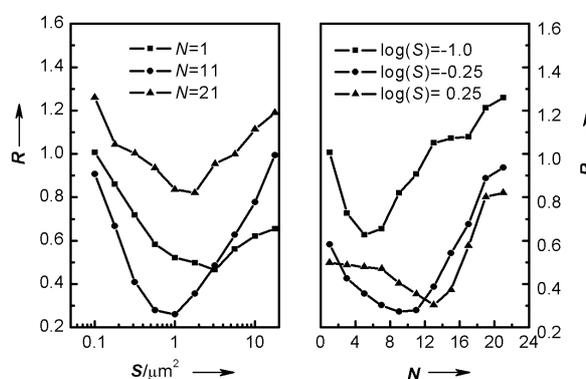


Figure 2. The dependence of R on the patch sizes S for given array size N (left), and on N for given S (right). The coupling strength is $\varepsilon=2.5$. Two types of "size resonance" are observed.

$S=1.0 \mu\text{m}^2$. The measure R could be of biological significance because it is related to the time precision of information processing and a smaller value of R means more closeness of the spike train to a periodic one, where R is obviously zero.

We now turn to the collective behavior of $N(>1)$ -coupled neurons. The coupling strength was $\varepsilon=2.5$ if not otherwise specified. Again we measured the regularity of the array's dynamics by use of the factor R . On the one hand, for given number of elements, we find that R always undergoes a minimum with the variation of the patch size S . For example, the $R \sim S$ curves for $N=11$ and 21 are also shown in Figure 2 (left). Therefore, the collective behavior of the ensemble shows resonance with the size of each element. On the other hand, for a given patch size S , R also goes through a minimum when the array size N changes, as depicted in Figure 2 (right). Therefore, the system's dynamics also show resonance with the network size. We can say that the system shows "double-system-size resonance".

To obtain a global view, we have performed detailed numerical simulations with N and S , scanning a wide range of differ-

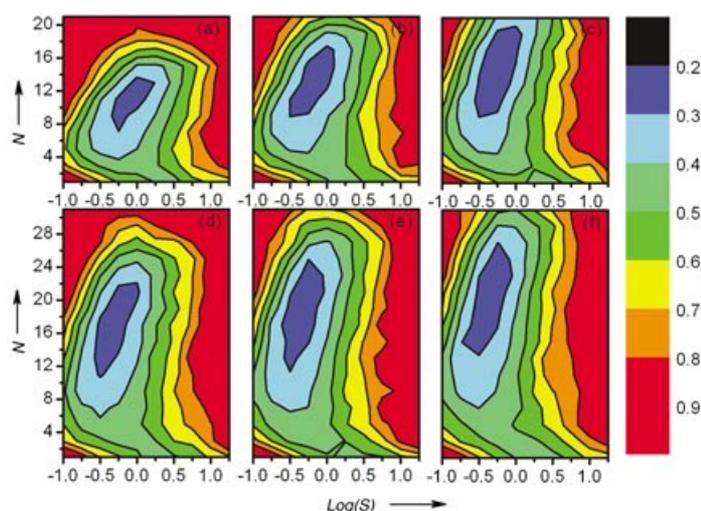


Figure 3. The contour plot of R as a function of N and S for different coupling strengths: $\varepsilon = 2.5, 3.75, 5.0, 6.25, 7.5,$ and 8.75 . Note that the maximum values of N are different in these pictures: $N_{\max} = 21$ in the upper row and $N_{\max} = 31$ in the lower row.

ent values. Consequently, we find a clear “optimal island” inside the $N \sim V$ parameter plane where the value of R reaches the bottom of a valley, as displayed in Figure 3a for $\varepsilon = 2.5$. An optimal number of coupled neurons with an optimal membrane patch size shows the best collective spiking activity.

In real systems, the coupling strength is also an important parameter, and the collective behavior of the coupled system may strongly depend on the coupling strength. In Figure 3, the influences of the coupling strength on the double-system-size resonance are shown. Evidently, the qualitative behavior is robust to the change of the coupling strength, although the position of the optimal island shifts toward the direction of larger values of N when ε increases.

Such a double-system-size-resonance phenomenon may have interesting implications for neuron dynamics in vivo. On the one hand, internal channel noise must be taken into account for neuron dynamics since the membrane patch size is small and the biochemical reactions associated with the channel gating processes are of a stochastic nature. A variety of important effects of channel noise in the dynamics of an isolated neuron have been reported, including stochastic resonance,^[2] enhanced synchronization,^[16] etc. On the other hand, it is found that in the central nervous system of higher animals, single neurons rarely matter and information is most likely to be processed using populations of cells.^[19] Therefore one should study the collective behavior of coupled neurons rather than a single neuron. In our present work, we find that for such a coupled system, to reach the best collective behavior (here the spiking activity), both the size of the element and the network should have an optimal value. At the current stage, we are not able to find examples of such observations in the literature; however, we hope our work might open up further perspectives in the study of such an issue.

In conclusion, we have studied the collective dynamics of an array of coupled identical HH neurons, taking into account the internal channel noise resulting from the stochastic gating

processes in the small membrane patch size. The effects of the patch size (hence internal noise) and the array size (the number of neurons) on the spiking activity of the averaged membrane potential are numerically studied. It is found that two system-size resonances occur, namely, the spiking behavior is the most regular when each neuron has an optimal patch size or the array size has an optimal value. Consequently, if both the patch size and array size have optimal values, the spiking will be at its highest regularity. We show that such a phenomenon of double-system-size resonance is robust to the variation of coupling strength. Our findings might find interesting and important applications for information processing in real neural systems.

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