Frequency Enhancement in Coupled Noisy Excitable Elements

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(Received 20 January 2011; published 23 June 2011)

Oscillatory dynamics of coupled excitable FitzHugh-Nagumo elements in the presence of noise is investigated as a function of the coupling strength g. For two such coupled elements, their frequencies are enhanced and will synchronize at a frequency higher than the uncoupled frequencies of each element. As g increases, there is an unexpected peak in the frequency enhancement before reaching synchronization. The results can be understood with an analytic model based on the excitation across a potential barrier whose height is controlled by g. Simulation results of a coupled square lattice can quantitatively reproduce the unexpected peak in the variation of the beating rates observed in cultured cardiac cells experiments.

DOI: 10.1103/PhysRevLett.106.254102 PACS numbers: 05.45.Xt, 87.19.Hh, 87.19.ln

Periodic rhythm generations are important for biological systems. Two well-known examples are the sino-atrial (SA) node [1] for the generation of heart beats in our heart and the suprachiasmatic nucleus [2] in our brain to provide circadian rhythm for our body. Interestingly, these two important rhythms are not generated from a single oscillatory cell but rather from a network of more or less similar oscillatory cells. The periodic rhythm is then the result of the synchronization [3] of the elements in the network. Obviously, an advantage of such a network design is its robustness; that is: the failure of a few elements will not lead to the malfunction of the clock. However, for such a network design, there is a major unsolved issue of how the synchronized common frequency (Ω_0) of the network can be controlled. Presumably, this issue is related to the intrinsic dynamics of the elements in the network and the coupling between them. This issue would become trivial if the intrinsic properties of the individual cell (element) in the network can be controlled at will. Unfortunately, the intrinsic properties of the cells are more or less fixed by physiological conditions. It is the coupling between cells, such as synapses [4,5] between neurons or mechanical sensitive fibroblast [6] between cardiac myocytes, which can be tuned. Furthermore, experiments also indicated that gap-junction couplings between cells increases during cardiac cultures growth [7–9]. The beating rate of cardiac systems will be slower if the intercellular coupling is impaired, for example, by blocking the gap junction to mimic ischemia [10] or at low temperatures [11]. Therefore, it is proposed [12,13] that Ω_0 of the network can be controlled by changing the coupling strength between its elements. In fact, this view has been supported by experiments of neuronal [4,5] and cardiac [14,15] cultures. It has been observed experimentally that there is a significant variation in Ω_0 with culture time in the cardiac myocytes and fibroblasts culture as the system becoming synchronized [15]. Surprisingly, Ω_0 increased with cultured time and reached a maximum (from 1.4 to 2.3 Hz, enhanced by $\sim$65%) before it became completely synchronized [see Fig. 4(a)] at an enhanced frequency of $\sim$36% ($\sim$ 1.9 Hz) [15]. It is believed [15] that the coupling does not only produce the synchronization but can also change Ω_0 at the same time. It is not clear how a monotonic increase in coupling strength will lead to a nonmonotonic change in Ω_0.

However, an assembly of coupled limit-cycle oscillators cannot reproduce the experimental observations of the variation of Ω_0 with the coupling strength, as the system synchronized. This is due to the fact that the dynamic range of Ω_0 will usually lie between the maximum and the minimum of the intrinsic frequencies of the elements, i.e. Ω_0 is more or less bound to lie within the ‘‘compromised’’ frequency of its constituency. For example, in the mean-field Kuramoto phase-coupled oscillator network, the system synchronized at the mean of the intrinsic frequency distribution of the constituents [16]. To resolve this problem, we propose here that the limit-cycle oscillators can be replaced by coupled noisy excitable elements [17] in a phenomenon known as coherent resonance [18]. Since it is known [19] that the oscillatory behavior of excitable elements, when coupled to other excitable elements or passive elements, can be tuned by the coupling g, it is highly likely that these noisy elements can provide the needed response of Ω_0 with coupling as observed in experiments.

Employing the idea above, we have investigated the Ω_0 produced by these coupled noisy excitable elements under different g. We find that not only can Ω_0 be controlled by g, it can even be faster than the fastest individual uncoupled element under the same noise level. For a large ensemble of coupled elements in a network, our simulations show that Ω_0 can be enhanced up to $\sim$60% in some noise and coupling regimes. This enhancement effect can be understood analytically in a system with two elements.

Interestingly, this mean frequency is not monotonic in g. This last finding is consistent with experimental observations in cardiac culture if the growth of g in the culture is linear in time.

Consider a system of N coupled FitzHugh-Nagumo (FHN) noisy excitable elements [20], given by

$$\begin{aligned} \epsilon_i \dot{x}_i &= x_i - x_i^3/3 - y_i + \sum_j{}' g(x_j - x_i), \\ \dot{y}_i &= x_i + a_i + D_i \xi_i(t), \qquad i = 1, 2, \ldots, N, \end{aligned} \tag{1}$$

where g is the coupling strength, $\sum'$ denote summation over connected neighbors, the D_i's are the intensities (taken to be the same for simplicity) of uncorrelated noises with $\langle \xi_i(t) \xi_j(t') \rangle = \delta(t - t') \delta_{ij}$. Here, a_i is the parameter governing the excitability of the ith element. For $|a| > 1$, the element is excitable and would be harder to be excited if $|a|$ is larger. As usual, $\epsilon_i \ll 1$ implying x and y are the fast and slow variables, respectively. Spikes can be generated when the noise intensity is high enough to overcome the threshold [18], but otherwise the system is quiescent.

The frequency enhancement effect is already revealed in the simple case of two coupled noisy elements with different excitabilities as shown in Fig. 1. The firing frequency of the more excitable element ($a_1 = 1.05$) is higher than the less excitable one ($a_2 = 1.12$). Figure 1 shows the frequencies of both the fast and slow elements increase initially as g increases, attain maxima, decrease slowly, and then synchronize for stronger couplings. The noise strength in Fig. 1 is chosen such that the noisy excitable elements will result in more or less regular periodic oscillations, and we have verified that within a reasonable range of noise strengths, the results are qualitatively similar. The degree of synchronization of a collection of oscillators can be quantified by the mean square deviation (σ^2_{syn}) of the distribution of the phase differences between pairs of oscillators relative to a uniform one [21,22]. $\sigma^2_{\text{syn}} = 1$ and 0 denotes asynchrony and perfect global phase synchronization, respectively. σ^2_{syn} in Fig. 1 indicates that perfect synchronization is achieved at higher couplings. Note that as the coupling is increased, the system synchronized at a frequency that is slightly faster than either of the intrinsic uncoupled frequencies.

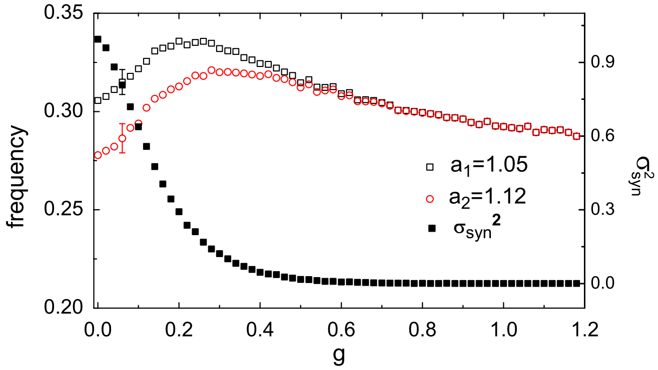
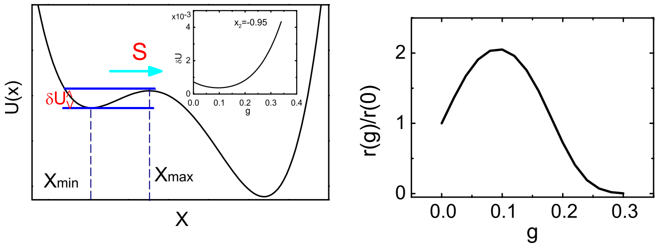


FIG. 1 (color online). Frequencies and degree of synchronization of two coupled noisy excitable FHN elements ($D = 0.65$, $a_1 = 1.05$, $a_2 = 1.12$, $\epsilon_1 = \epsilon_2 = 0.01$), under the same noise intensity. Upper two curves: frequencies. Lower curve: σ^2_{syn}.

In order to gain deeper insights for the physical mechanism of frequency enhancement, we analyze the two-element system in Eq. (1) using the fast-slow approach. The dynamics of a FHN element (say x_1) can be approximately viewed as the motion inside a double-well potential given by $U(x_1) = -\frac{x_1^2}{2} + \frac{x_1^4}{12} + y_1 x_1 + g x_1 (\frac{x_1}{2} - x_2)$. The slow variable y_1 is treated as a constant parameter (with value at the fixed point). The choice of x_2 is slightly above its fixed point value since even though it is at rest for most of the time, it can be excited by coupling and noise. Figure 2(a) shows schematically the double-well potential, and the barrier height δU depends on the coupling strength g. For an excitable cell, x_1 stays at the resting state (left hand side well) for most of the time and has to overcome δU to be activated to the excited state (right-hand side well). The activation can be resulted from noise or coupling from other cells. δU can be readily calculated as shown in the inset of Fig. 2(a), it decreases with g for small coupling but then increases for large coupling. The fact that δU has a minima for some coupling strength already revealed that there is an optimal coupling that x_1 can be excited and hence can fire more frequently. One can proceed further to compute the firing rate analytically using the Kramer's rate theory. The FHN noisy dynamics can be modeled by a Langevin equation for the dynamics of the fast variable as,

$$\begin{aligned} \epsilon_1 \dot{x}_1 &= x_1 - x_1^3/3 - y_1 + g(x_2 - x_1) + \mathcal{D} \xi_1(t) \\ &\equiv h(x_1(t)) + \mathcal{D} \xi_1, \end{aligned} \tag{2}$$

where $\mathcal{D}$ is some effective noise strength and ξ_1 is the Gaussian white noise. This Langevin equation can be reformulated to a Fokker-Planck equation [23] in terms of the space-time dependent probability density [$W(x, t)$] as



(a)

(b)

FIG. 2 (color online). (a) The schematic double-well potential of the FHN model as given in Eq. (2). The inset is the energy barrier δU as a function of g showing the existence of a minimal δU. (b) The normalized escaped rate calculated from Kramer's theory as a function of g. The parameters $x_2 = -0.95$ and $y_1 = -0.66$ were used in the approximation for the potential.

$$\frac{\partial W(x_1, t)}{\partial t} = \left[-\frac{\partial h[x_1(t)]}{\partial x_1} + \frac{\mathcal{D}^2}{2} \frac{\partial^2}{\partial x_1^2} \right] W(x_1, t). \quad (3)$$

Since the probability of hopping from the resting state to the excited state is determined by δU, the firing (hopping) rate can be estimated analytically [23]. One can obtain the escape rate from the resting to the excited states as the ratio of the probability flow $[S(x_1, t)]$ to the probability of finding the particle within the well around the resting state (P). The probability density and probability flow satisfy the continuity equation, and the escape rate r can be calculated [23] under steady state condition to give

$$r \equiv \frac{S}{P} = \frac{1}{2\pi} \sqrt{\frac{U''(x_{\min})}{U''(x_{\max})}} \exp\left(-\frac{2(U(x_{\max}) - U(x_{\min}))}{\mathcal{D}^2} \right), \quad (4)$$

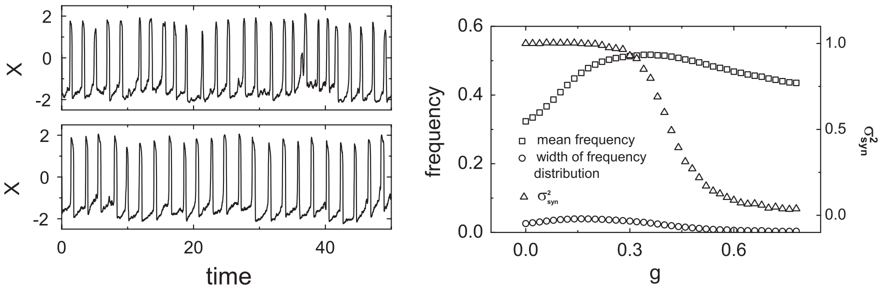
where $x_{\min}$ and $x_{\max}$ are the minimum and maximum of $U(x)$ as depicted in Fig. 2(a). Figure 2(b) displays the normalized escape rate as a function of the coupling g calculated from Eq. (4), showing a peak at some optimal coupling. Thus the frequency enhancement can be described by the enhanced escaping through the barrier at some coupling regime. It should be noted that the calculated escape rate will differ but still show qualitatively similar behavior with a somewhat different (but reasonable) choice of the values of y_1 and x_2 in the approximation.

Motivated by the experimental observations that the coupling between cells in a cardiac culture increases with time [7–9], similar idea can be used to understand the observations of cardiac cell culture experiments [15] quantitatively. Our rationale is based on the observation that the structure of a cardiac culture is similar to that of an SA node which is consisted of oscillating clusters [1] and the SA node is intrinsically noisy [11]. Hence, we apply the idea of noise-induced oscillation in excitable elements to mimic the oscillatory behavior of the clusters. We have performed simulations of coupled noisy FHN elements on a two-dimensional lattice. Each FHN element is identical and coupled to its nearest neighbors in a square lattice with identical coupling g, but each element is subjected to independent uncorrelated noises. In the simulation, the beating frequency distribution of these elements are recorded for different values of coupling strengths g. The time series of an oscillator in the network at two coupling characteristic strengths is displayed in Fig. 3(a) showing that the noisy oscillator is undergoing rather regular oscillations. Figure 3(b) shows the mean and width of the frequency distribution as a function of g. Note that the width of the frequency distribution also displays a peak as g increases towards synchronization due to the coupling between the elements.

The mean beating rate initially increases with low values of coupling strengths, attains a maximum as the elements become synchronized. There is a peak enhancement of about 60% and an enhancement of about 35% when the system is almost fully synchronized, which agrees quantitatively well with the experimental data in [15].

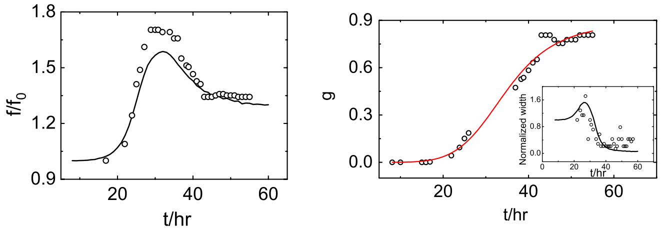
To make a further connection with the cardiac experiments, experimental data of mean beating rates as a function of time are made to match with the results of simulations on a square lattice by adjusting the values of g as a function of time. Figure 4(a) shows the normalized beating rate taken from Ref. [15] together with the adjusted simulation results. Figure 4(b) shows the variation of g as a function of time obtained with this procedure. It can be seen that there is a regime in which the coupling grows linearly with time as the system becomes fully synchronized, and then the growth stops. This last finding suggests that the coupling in the system undergoes a period of linear growth ($t \simeq 20$–40 hr) as the system is in the process to synchronize. During this linear growth period, the mean frequency of the system also shows a maximal frequency span. Presumably, such a large frequency span would be desirable for the system to search for the optimal beating rate for its biological functions. As a further check, using the obtained coupling variation with time in Fig. 4(b), one gets consistent results for the variation of the width of frequency distribution in simulations and experiment as shown in the inset of Fig. 4(b).

In the oscillatory behavior of coupled noisy excitable networks, usually a stronger noise would result in a larger



(a) (b)

FIG. 3. Simulation of coupled identical excitable elements ($a = 1.05$) on a square lattice (55×55), under independent noises of the same intensity ($D = 0.65$). (a) The time-series data of an element at coupling strengths $g = 0.36$ (upper panel) and 0.6 (lower panel). (b) The average frequency and width of frequency distribution. The degree of synchronization, $\sigma^2_{\rm syn}$ is also shown.



(a) (b)

FIG. 4 (color online). Comparison of the simulation results on a square lattice ($a_i = 1.05$, $D = 0.65$) with the cardiac synchronization data in [15]. (a) Solid curve: normalized average frequency of the square network. Open circles: experimental data. (b) Time dependence of the coupling strength deduced by matching with the experimental data. The curve is a guide to the eyes. Inset: Solid curve: simulation results of the normalized width of the frequency distribution of the square network. Open circles: experimental data.

frequency enhancement. For reasonable choices of noise strengths, the above frequency variation phenomenon still holds, for example, at $D = 0.45$, one obtains a maximal enhancement of about 50% for the square network. On the other hand, too strong a noise will make the oscillations too irregular, and the question is how should one choose a suitable noise strength to model the system. At a suitable noise strength, the oscillatory behavior should be rather coherent. For example in our square network with $D = 0.65$, Fig. 3(a) shows the time-series of an arbitrary element at some characteristic coupling regime as the system synchronized (σ^2_{syn} begins to vary strongly at $g = 0.36$ and become synchronized at $\simeq 0.6$), showing that the element is performing rather coherent oscillations at the noise strength $D = 0.65$. The regularity of the oscillations of the system at this noise strength can be described by the mean to width ratio of the frequency distributions, and for $g = 0.4$, the mean to width ratio is $\sim$20. This is comparable to the experimental observation in [15] of a mean to width ratio of about 10–30 as the system synchronized (at time 25–35 hr).

It is clear that the presence of noise in a network of excitable elements can produce nontrivial effects. Instead of staying at the usual compromised frequency, the frequencies of these coupled noisy elements are tuned by g. If the network of noisy oscillators in the SA nodes can also be modeled by our system, then the unusual abundance of fibroblast [24] in the SA node can be explained. Since only the number of fibroblasts can be changed in the SA node, it is plausible that the SA node uses the number of fibroblasts to tune its oscillation frequency through the effective coupling. Such a frequency enhancement effect appears to be rather generic in noisy excitable systems. We have verified that similar phenomenon can also be produced with a Hodgkin-Huxley model. Intuitively, this enhancement can be rationalized for excitable systems because the excitation of an element in an excitable network can induce the excitations of its neighbors through coupling and vice versa.

This work was supported by National Science Council of Taiwan under grant nos. 98-2112-M-008-023-MY3, 97-2112-M-001-003, and NCTS of Taiwan.

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[22] The phase dynamics of each cell is $\phi_i = 2\pi \frac{t-\tau^i_k}{\tau^i_{k+1}-\tau^i_k} + 2\pi k$, for $\tau^i_k \leq t < \tau^i_{k+1}$ where τ^i_k is the time of kth firing of the ith cell. The relative phase between two pair of elements is $\Phi_{ij} = (\phi_i - \phi_j)\mathrm{mod}2\pi$ and its variance relative to a uniform distribution is denoted by σ_{ij}. The mean variance between average over the whole network of N oscillators is given by $\sigma^2_{\text{syn}} = \frac{2}{N(N-1)}\sum_{1\leq i<j\leq N}\sigma^2_{ij}$.
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