Entropically Enhanced Excitability in Small Systems

J. W. Shuai[1] and P. Jung[1,2]

[1]*Department of Physics and Astronomy and Quantitative Biology Institute, Ohio University, Athens, Ohio 45701, USA*
[2]*Center for Theoretical Biophysics, University of California San Diego, La Jolla, California 92093, USA*

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We consider the dynamics of *small* excitable systems, ubiquitous in physics, chemistry, and biology. Spontaneous excitation rates induced by system-size fluctuations exhibit sharp maxima at multiple, small system sizes at which also the system's response to external perturbations is strongly enhanced. This novel effect is traced back to algebraic features of small integers and thus generic.

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Excitable dynamics (for a recent review, see [1]) occurs in a variety of systems ranging from the electric behavior of neuronal membranes [2] over calcium-based excitability (for a recent review, see [3]) to chemical reactions [4]. Recently, the study of system-size fluctuations in excitable systems has led to the emergence of novel concepts such as system-size stochastic and coherence resonance [5–8], where system-size fluctuations are exploited to generate coherent signals or amplify small external signals. The mechanism for these effects is based on the relation between system size and strength of intrinsic noise that allows for the tuning of the intrinsic noise by changing the system size and thus exploiting stochastic and coherence resonance. These effects, however, are not characteristic to small systems and can occur on any scale.

In this Letter we report on novel phenomena that are robust and *genuine* to *small excitable systems* subject to system-size fluctuations. Examples of small excitable systems include small ion channel clusters [3], and chemical reactions in nanoscale reactors [9].

We find (1) that the excitation rate induced by system-size fluctuations exhibits sharp maxima at multiple small system sizes and (2) that at these *magic system sizes* the response to external perturbations is strongly enhanced. These novel effects are traced back to algebraic properties of the system's entropy density occurring only at small system sizes, but not in the macroscopic limit.

As a working model for an excitable system we choose a cluster of sodium ion channels embedded in a leaky neuronal membrane. Removing the potassium conductance from the original Hodgkin-Huxley model and increasing the leak conductance to account for the other voltage-independent channels, we arrive at the following set of equations

$$\begin{aligned} \dot{u} &= g_{\mathrm{Na}} m^3 h(u_{\mathrm{Na}} - u) + g_l(u_l - u) + I_{\mathrm{ext}}, \\ \dot{x} &= \alpha_x(1 - x) - \beta_x x, \end{aligned} \tag{1}$$

with the conductances $g_{\mathrm{Na}} = 120/\mathrm{ms}$, $g_l = 9.1/\mathrm{ms}$, and $x = m, h$. The current I_{ext} represents external perturbations. The voltage u is measured in mV, time t in ms, and the reversal potentials are given by $u_{\mathrm{Na}} = 115$ mV and $u_l = 10.6$ mV. The rates $\alpha_{m,h}$ and $\beta_{m,h}$ are given by

$$\begin{aligned} \alpha_m &= 0.1\,\frac{25.0 - u}{\exp[(25 - u)/10.0] - 1.0}, \\ \beta_m &= 4.0\exp(-u/18.0), \qquad \alpha_h = 0.07\exp(-u/20.0), \\ \beta_h &= (\exp[(30 - u)/10.0] + 1.0)^{-1}. \end{aligned} \tag{2}$$

Although there are no potassium channels present, the inactivation of the sodium channels renders this system excitable and action potentials are generated (see Fig. 4). Since the dynamics of m is much faster than that of h, we further reduce the model for now by replacing the variable m by its quasi-steady state value $m_\infty = \alpha_m/(\alpha_m + \beta_m)$. The resulting two-variable model

$$\begin{aligned} \dot{u} &= g_{\mathrm{Na}} m_\infty^3(u) h(u_{\mathrm{Na}} - u) + g_l(u_l - u) \equiv g_1(u, h), \\ \dot{h} &= \alpha_h(1 - h) - \beta_h h \equiv g_2(u, h) \end{aligned} \tag{3}$$

can be analyzed in terms of null-cline analysis (see Fig. 1). The nullclines intersect at a single point, which is a stable fixed point rendering the system excitable. In order to fire an action potential, the variable h has to exceed a thresh-

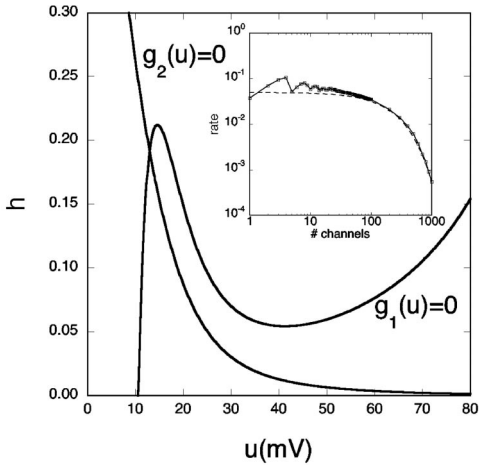

FIG. 1. Null clines of the reduced model of the sodium channel cluster [Eq. (3)]. The inset shows the excitation rate of the cluster as a function of the number of channels (i.e., system size).

old of about $h_{\min} = 0.24$ for the parameters used here at $I_{\text{ext}} = 0$. The action potentials have a maximum amplitude of about 80 mV and all have the same amplitude regardless of the perturbation that caused them. The above described model is meaningful when the conductance is facilitated by a large number of sodium channels where h is the fraction of activated sodium channels.

When we consider small excitable systems, i.e., a cluster of a few sodium channels only, where each sodium channel switches between the open and the closed states due to thermal noise, a stochastic description is necessary. To this end, we consider the stochastic version of the reduced model [Eqs. (3)] which is obtained by replacing the variable h with the discrete fraction of h-open channels, n/n_0, where n_0 is the total number of sodium channels in the cluster and n is the number of channels in the h-open state. We call the channel h open as we only model the inactivation process h stochastically at this point. The stochastic differential equation for the voltage then reads

$$\dot{u} = g_{\text{Na}} m_\infty^3 (n/n_0)(u_{\text{Na}} - u) + g_l(u_l - u). \qquad (4)$$

Each channel can be in two states, h open, the conducting state, and h closed. The switching of each channel is simulated by a Markov process (for a recent comparison of algorithms see [10]) with the opening rate α_h and closing rate β_h, respectively. The fraction of h-open channels n/n_0 is determined at each instant of time. The differential equation for the voltage [Eq. (4)] is integrated with an appropriately small time step using a first-order solver. As a result, stochastic trains of action potentials are generated and characterized by their spiking rate r. The amplitudes of the action potentials vary somewhat within a range of 80–100 mV.

In the limit of large system sizes (see inset of Fig. 1), i.e., for large numbers of sodium channels, the firing rate decreases to zero exponentially, i.e., $[r(n_0) \propto \exp(-kn_0)$ with $k = 0.002]$ (dashed line in inset) as to be expected for an activated process where the energy fluctuations decay inverse with the system size n_0.

Most interesting are the deviations from this asymptotic behavior as the system becomes small and peaks in the firing rate $r(n_0)$ emerge at certain cluster sizes (see Fig. 2). The peaks grow bigger as the sodium channel cluster decreases in size.

While a systematic theory for those peaks is presented below, we will present here a cartoon that better captures the underlying mechanism. The nullclines in Fig. 1 indicate that in order to fire an action potential at least a minimal fraction $h_{\min} \approx 0.24$ of the channels need to be h open at the resting voltage. If for instance the cluster is comprised of $n_0 = 3$ channels, the states of the cluster with $n = 1, 2$, or 3 h-open channels are states that can trigger an action potential because of $n/n_0 > h_{\min}$ for these 3 states. Thus 3 out of all 4 possible h-open states are associated with an action potential. Similarly, if the cluster comprises 4 channels, $4/5$ of all possible states are associated with an action potential since $1/4 > h_{\min}$. Since there are more states associated with the firing state (i.e., $4/5 > 3/4$), the probability of firing and thus the firing rate is increased as n_0 increased from 3 to 4, as can be seen in the upper panel of Fig. 2. If, however, the cluster comprises 5 channels only $4/6$ of all h-open states are associated with an action potential since now at least two channels need to be h activated $(2/5 > h_{\min})$. The fraction of the numbers of states of the channel cluster associated with an action potential, which we define as the *entropy density of the firing state*, drops as the cluster size is increased from 4 to 5. As a consequence, the firing rate drops to a lower level as n_0 increased from 4 to 5. This entropic effect is strong enough only *at small system sizes* to modulate the excitability.

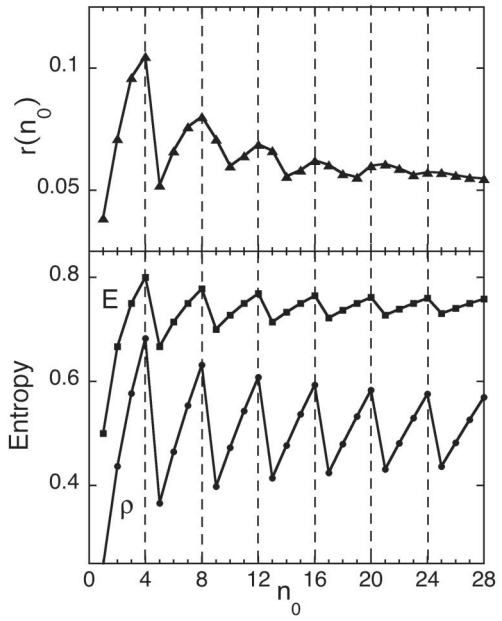

FIG. 2. The spontaneous firing rate r as a function of the cluster size n_0 (triangles in upper panel) is compared with the entropy density $E(n_0)$ [Eq. (5)] (squares) and the probability $\rho(n_0)$ (circle) at $h_{\min} = 0.24$ (lower panel).

This idea can be generalized for a cluster of n_0 sodium channels. The entropy density $E(n_0, h_{\min})$ of the firing state is given by the ratio of the number of states that can trigger an action potential, i.e., the entropy, and the number $n_0 + 1$ of all possible h-open states. Algebraically this boils down to calculating the fraction of all fractions $\frac{0}{n_0}, \frac{1}{n_0}, \frac{2}{n_0}, \ldots, \frac{n_0}{n_0}$ with values above the threshold $h_{\min}$, i.e.,

$$E(n_0, h_{\min}) = [n_0 - \text{integer}(n_0 h_{\min})]/(n_0 + 1). \qquad (5)$$

The entropy density $E(n_0, h_{\min})$ is plotted also in Fig. 2 and shows indeed maxima at exactly those system sizes where the rate exhibits maxima. Although the sequence of peaks is periodic with period 1 for the particular value of the threshold in this Letter, it can be of period $l(>1)$ for other values of the threshold (see Fig. 5).

Although the theory presented above captures the observed effect of multiple peaks quite well, it is not entirely accurate for our model since we treat the system as a *microcanonical* ensemble where all states have the same likelihood. This is obviously incorrect as it is less likely that all n_0 channels are open than just a few. In the following we sketch an accurate theory which generates an expression for the entropy density which exhibits the same peaks as the simple theory above.

The probability that n of the n_0 sodium channels are h open is approximately given by

$$P(n, n_0) = \binom{n_0}{n} p_o(u_0)^n p_c^{(n_0-n)}(u_0), \tag{6}$$

where $p_o = \alpha_h(u)/[\alpha_h(u) + \beta_h(u)]$ and $p_c = 1 - p_o$ denote the probabilities for a channel to be h open or closed at a membrane potential of u. Furthermore, u_0 denotes the membrane voltage in the resting state. The constant voltage is a good approximation as most of the (slow) inactivation changes occur prior to the action potential where the voltage changes are small. The probability ρ that the cluster elicits an action potential is obtained by adding the probabilities for all states that correspond to a fraction of h-open channels larger than or equal to $h_{\min}$. This sum has to be determined numerically and exhibits peaks at exactly the same values of the system size as we found with the phenomenological theory presented above (see Fig. 2). Although this theory is accurate, it does not generate the insight into the phenomenon as well as the phenomenological theory.

The response of the excitable system to perturbations can be probed by a periodic current $I_{\text{ext}} = -I_0 + I_0 \times \sin(2\pi\nu t)$ in Eq. (1). The modulation function is chosen such that at the maximum amplitude of the perturbation the excitation threshold is 0.24 (as above) and higher in between the maxima. In order to assess the response to the periodic signal we calculate the power spectrum of the stochastic spike train generated by the cluster, where the spikes are approximated by δ functions at the times t_n of their occurrence, i.e.,

$$S(\nu) = \frac{1}{T}\left|\sum_n \exp(-2i\pi\nu t_n)\right|^2, \tag{7}$$

where T is the length of the spike train. The power spectra exhibit sharp peaks at the frequency of the perturbation. The weights of these peaks are a measure of the system's response to the periodic signal [11] and are plotted in Fig. 3 as a function of the cluster size for three different perturbations. The response of the excitable system to the periodic perturbation exhibits maxima at exactly the same system sizes where the spontaneous excitation rate exhibits maxima. As can be seen in Fig. 3, the optimal system sizes are not sensitive to variations in the perturbation amplitude I_0 or frequency ν.

In the system we studied above, the action potentials were almost uniform in amplitude, although there were some fluctuations due to channel noise. If we do not do the adiabatic approximation in Eq. (1), i.e., replace the dynamic variable $m(t)$ by its steady state m_∞, we have to model also the fast activation $m(t)$ of each channel by a Markov process similar as we did with the inactivation $h(t)$ above. Each ion channel has three m gates and one h gate with opening and closing rates given in Eqs. (2). A channel is open if all the activation gates m and the inactivation gate h are open. The fraction of open states n/n_0, determined through simulations of Markov processes, enters in the differential equation for the membrane potential, i.e.,

$$\dot{u} = g_{\text{Na}}(n/n_0)(u_{\text{Na}} - u) + g_l(u_l - u), \tag{8}$$

which is integrated with a first-order solver. In Fig. 4 we show a short train of spikes with a variety of amplitudes. In comparison to the reduced model studied above, the action

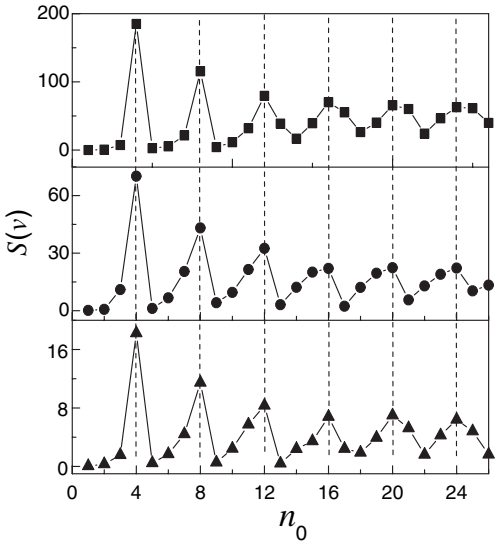

FIG. 3. Response amplitudes $S(\nu)$ [Eq. (7)] as a function of the cluster size, for $I_0 = 1.0$, $\nu = 0.8$ Hz (triangles), $I_0 = 2.0$, $\nu = 0.8$ Hz (circles), and $I_0 = 2.5$, $\nu = 0.4$ Hz (squares).

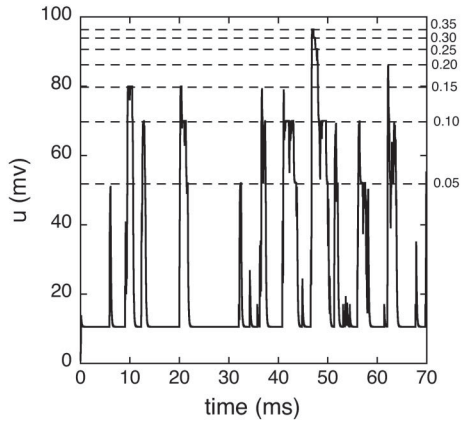

FIG. 4. A spike train is shown generated by the stochastic model Eq. (8) for a cluster of 20 sodium channels. Each amplitude of the action potentials is associated with a certain fraction of open channels annotated at the right end of the dashed lines.

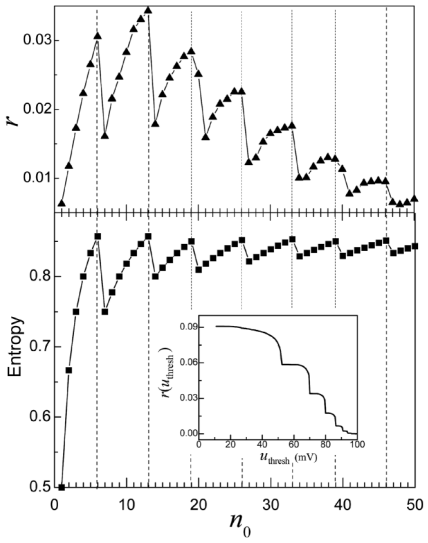

FIG. 5. The spontaneous firing rate of action potentials with amplitude larger than 79.8 mV (upper panel) is compared with the entropy density $E(n_0, 0.15)$. The inset shows the cumulative rate of action potentials as a function of the action potential amplitude for a cluster of 20 sodium channels.

potential amplitudes exhibit more variation. Each action potential amplitude is associated with a unique fraction of open sodium channels, the larger the amplitude the larger the fraction of open channels. The relation of action potential amplitude and fraction of open channels can be found by integrating Eq. (8) at a given number of open channels n_{open}. The horizontal, dashed lines in Fig. 4 are drawn at the voltages obtained from this calculation.

The consequence of the variability of amplitudes is that the spiking rate depends on the amplitude which is chosen as an indicator for an action potential (see inset in Fig. 5). We therefore calculate the rate of action potentials $r(n_0, u_{\text{thresh}})$ with an amplitude larger than u_{thresh}, as a function of the cluster size n_0 at various spike amplitudes u_{thresh}. Similar to the reduced model above, the spiking rate exhibits a series of peaks at multiple optimal system sizes (see Fig. 5). These optimal system sizes, however, now depend on the threshold amplitude u_{thresh} since the minimum fraction of open channels necessary to generate such a spike depend on u_{thresh}. An action potential amplitude of 79.8 mV, for example, requires a fraction of open channels of at least 0.15 (see Fig. 4). In Fig. 5 we compare the rate of action potentials of amplitudes of at least 79.8 mV and the entropy density of the clusters $E(n_0, h_{\min} = 0.15)$. Maxima in the firing rate coincide well with maxima in the entropy density $E(n_0, h_{\min} = 0.15)$. Similar good agreement is found for other action potential amplitudes.

In summary, we have reported on novel effects that occur in *small* excitable systems. At multiple small system sizes, the spontaneous excitation rate as well as the system's response to perturbations is enhanced. This effect has been traced back to oscillatory variations of the entropy density of the cluster states as function of the cluster size that only occur at small system sizes. Mathematically, the effect boils down to arithmetic features of inverse integers and is thus generic and independent of system details like channel conductance as long as the cluster remains homogeneous and excitable. System-size stochastic resonance [5,7] is based on exploiting stochastic resonance by tuning the size of the system such that the internal noise strength is at the resonant value. Such a resonance—in contrast to the results in this Letter—can be at small and large system sizes. It is not based on the algebraic properties of inverse integers. Stochastic multiresonance [12]—associated with an infinite number of peaks in the signal-to-noise ratio—is a property of specific Langevin equations that are invariant with respect to a stretching transformation in conjunction with rescaling of the noise strength. No such specific symmetries are required for the effect we are describing here. In fact, the Fokker-Planck approach obtained by truncating the master equation does not exhibit the small-size peaks.

The effect we report here could be applied for the design of small sensors by placing a precise number of ion channels onto a small patch of membrane or artificial lipid layer. As we describe in a upcoming full-length paper, the patch of membrane must be electrically insulated from its environment and have a size that is adjusted to the type of channel, and their conductances.

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