System-Size Effects on the Collective Dynamics of Cell Populations with Global Coupling

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Phase-transitionlike behavior is found to occur in globally coupled systems of finite number of elements, and its theoretical explanation is provided. The system studied is a population of globally pulse-coupled integrate-and-fire cells subject to small additive noise. As the population size is changed, the system shows a phase-transitionlike behavior. That is, there exits a well-defined critical system size above which the system stays in a monostable state with high-frequency activity while below which a new phase characterized by alternation of high- and low frequency activities appears. The mean field motion obeys a stochastic process with state-dependent noise, and the above phenomenon can be interpreted as a noise-induced transition characteristic to such processes.

Collective dynamics of coupled dynamical elements represents a central issue of nonlinear dynamics, and has served as a subject of extensive study over the last few decades. The relevant branches include chemical reactions [2], society of living organisms [3–5], lasers [6,7], semiconductors [8,9], neural networks [10–12] and cardiac systems [3,13,14]. In most theoretical studies, however, the system size is assumed infinite. While this idealization could be valid for such systems like spatially extended chemical reactions, there seem to be important practical cases where the finiteness of the system size should explicitly be taken into account. Two existing theoretical studies on collective dynamics of populations are mentioned here in which the finiteness of the system size plays a crucial role. Firstly, Daido [15] investigated the collective behavior of an inhomogeneous system of oscillators focusing on the statistics of fluctuations close to the onset of collective motion. Secondly, Pikovsky et.al [16] studied coupled bistable elements and showed numerically a phase-transitionlike behavior existing only for finite systems. Apart from these theoretical studies, an interesting experiment was reported recently by N. Cohen et.al [1]. They cultivated heart cells in various population sizes and found that the cells exhibit system-size-dependent behavior. Some more details of their reports are the following. The heart cells extracted from ventricles of neonatal rats were cultivated, and time series of spontaneous spiking activities of these cells were recorded. Initially, the heart cells were made free of mutual contact by a chemical treatment, but after some time they spontaneously assemble to form subgroups. These cell groups were cultivated, and the spontaneous spike activity of the individual cells was observed. One interesting feature of the experimental results may be stated as follows. An isolated cell shows random and slow spontaneous spike activity where the interspike intervals (ISI) distribute sparsely with the average ISI of about 1 second. These low- and high frequency spikes are visited alternately in time. If the cell group is sufficiently large, the individual cells exhibit only high-frequency spike activities of good periodicity. The above experimental results are remarkable in that the dynamics of the individual cells depends qualitatively on the population size, and still await theoretical interpretation. In particular, we would like to know the origin of the transition which occurs as the population size is changed and whether the mechanism involved is universal beyond the particular class of systems of cultivated heart cells. The goal of this paper is to provide an answer to these questions. This can be achieved analytically by using a simple dynamical model showing coexistence of high- and low frequency activities under suitable conditions. Specifically, we employ globally coupled noisy integrated-and-fire model which is often used in the studies of neurodynamics of the brain. The dynamics of a single cell is given by

\[ \dot{x}_i(t) = I + \xi_i(t), \quad x_i(t) \leq 1, \quad (i = 1, \cdots, N), \]  

where \( \xi_i(t) \) is white Gaussian noise with the properties \( \langle \xi_i(t) \rangle = 0 \) and \( \langle \xi_i(t) \xi_j(t') \rangle = 2D \cdot \delta_{ij} \delta(t - t') \), and \( N \) is the system size which represents the principal control parameter. At the instant when \( x_i \) reaches the threshold \( x_i = 1 \), a spiking or firing event is assumed to occur for this cell in such a way that \( x_i \) is immediately reset to a certain value \( f \). Thus,

\[ x_i(t_i^{(n)}) = 1 \quad \rightarrow \quad x_i(t_i^{(n)} + dt) = f, \quad (n = 1, \cdots, N), \]
where \( t_i^{(n)} \) is the timing of the spike, the tag \((n)\) indicates the numbering of the spiking events. When a cell fires, this will immediately cause a pulsatile stimulus on all the other cells in the population. A given cell will receive a sum of such stimuli coming from various cells. Assuming that the effect of each stimuli decays exponentially, one may conveniently introduce an order parameter \( r(t) \) by

\[
r(t) = \frac{1}{N} \sum_{i=1}^{N} \sum_{n, t^{(n)}_i < t} \exp(-\lambda(t - t^{(n)}_i)),
\]

whose effect is experienced commonly over the cells. Since the primary effect of the order parameter should be to lower the effective threshold for each cell to fire, it would not be unreasonable to assume the dependence of the resetting value of \( f \) on \( r \) like

\[
f(r) = f_0(1 - e^{-\beta r}).
\]

Note that increasing \( r \) implies increasing \( f \) with the upper limit \( f_0 \).

Before discussing collective behavior, we show how a single cell behaves under fixed \( r \). Equations (1), (2) and (4) determine how the cells behave under a given value of \( r \). To characterize statistically the sequence of spikes generated, we derive a density distribution function of ISI. Because ISIs are given by the first passage time [17,18] of the stochastic process given by Eq.(1), their distribution can be obtained with the standard method and takes the form

\[
P_{ISI}(T) = \frac{1 - f(r)}{\sqrt{4\pi DT^3}} \exp\left(-\frac{(1 - f(r) - IT)^2}{4DT}\right).
\]

From this distribution, spike frequency \( \omega \) which is defined as the inverse of mean ISI, i.e., \( 1/\langle T \rangle \), becomes

\[
\omega(r) = \frac{I}{1 - f(r)} = \frac{I}{(1 - f_0) + f_0 \cdot e^{-\beta r}}.
\]

One can see that larger/smaller \( r \) corresponds to larger/smaller \( \omega \) or higher/lower frequency activity. The above results are also consistent with the experimental facts for the heart cells that when the cells are isolated the spiking frequency is the lowest and the distribution of the corresponding ISIs is the broadest.

Two remarks should be given on our model. Firstly, we have taken into account the effect of mean field on the resetting state by assuming \( f \) to depend on \( r \). However, our choice of the specific form of \( f(r) \) is rather arbitrary. What is important here is that the rate of spiking \( \omega \) should be an increasing function of \( r \). Under this condition, other choices of \( f(r) \) would give qualitatively the same results. Secondly, our main goal is to understand, analytically if possible, some general features of the collective dynamics shared commonly over the cells. Since the primary effect of the order parameter should be to lower the effective threshold for each cell to fire, it would not be unreasonable to assume the dependence of the resetting value of \( f \) on \( r \) like

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Equations (1) to (4) are calculated numerically with some values of \( N \), from which the distribution functions for \( r \), denoted as \( P(r,t) \), are obtained. Figures 1, 2 and 3 show \( P(r,t) \) for the cases of \( N = 20, 100 \) and 200, respectively. In order to make clear the difference between the cases of \( N = 100 \) and 200, the data in Figs.2b and 3b are plotted in semilogarithmic scales. For sufficiently large system size, the distribution has a single sharp peak about \( r = 1.0 \) corresponding to coherent high-frequency activity. It seems that the distribution shows no qualitative change as \( N \) becomes even larger. In contrast, a remarkable change occurs for smaller \( N \). Figures 1 and 2 show the appearance of a new peak at smaller \( r \) corresponding to low-frequency activity. The double peaks implies coexistence of the different steady states. Actually, the coexistence of high- and low-frequency states is the feature observed experimentally in real heart cells. Our model gives a fairly well-defined critical population size associated with a transition from monostable state to coexistence state.

In what follows, our analysis proceeds in two steps. We first derive an evolution equation for the mean field \( r(t) \). This can be achieved by assuming that the mean field \( r \) evolves much more slowly than the evolution of the individual \( x_i \) so that the adiabatic approximation is applicable. This assumption implies that the random variable \( r \) obeys a Markov process so that the equation for \( P(r,t) \) can be written in the form of a Kramers-Moyal expansion [19] [20] as,

\[
\frac{\partial P(r,t)}{\partial t} = \sum_{n=1}^{\infty} \left(-\frac{\partial}{\partial r}\right)^n D^{(n)}(r,t) P(r,t),
\]

where \( D^{(n)} \) is defined as
\[ D^{(n)}(r,t) = \frac{1}{n!} \lim_{\tau \to 0} \frac{1}{\tau} \langle [f(t+\tau) - f(t)]^n \rangle |_{r(t)=r}. \] (8)

To find explicit forms of \( D^{(n)} \), we calculate \( f(t+\tau) - f(t) \) from Eq.(3) for small \( \tau \) under the condition that \( f(t) = r \). We obtain

\[
\begin{align*}
    f(t+\tau) - f(t) &= (e^{-\lambda \tau} - 1)r + \frac{1}{N} \sum_{i=1}^{N} \sum_{n_i : t < t^{(n)} < t+\tau} e^{-\lambda (t+\tau - t^{(n)})} \\
    &= (e^{-\lambda \tau} - 1)r + \frac{1}{N} \sum_{i=1}^{N} n_i(t, t+\tau),
\end{align*}
\] (9)

where \( n_i(t, t+\tau) \) is the number of spikes of the \( i \)-th cell during a short interval \( t \sim t + \tau \). To obtain the last expression in Eq (9), we use smallness of \( \tau \) and replace \( e^{-\lambda (t+\tau - t^{(n)})} \) with 1. Since \( r(t) \) is a slow variable by assumption, no information on the dynamics of the individual \( x_i \) is relevant except for the timing of their spiking. The sequence of the spikes is expressed by a Poisson process of the mean spike rate \( \omega(r) \), so that the distribution for \( n_i(t, t+\tau) \), denoted by \( P_n(n) \), becomes

\[
P_n(n) = \frac{e^{-\omega(r)\tau} (\omega(r)\tau)^n}{n!}. \] (10)

Applying Eq.(10) to Eq.(9) and then to Eq.(8), we obtain

\[
\begin{align*}
    D^{(1)} &= -\lambda r + \lim_{\tau \to 0} \frac{1}{\tau} \langle n \rangle = -\lambda r + \omega(r), \\
    D^{(2)} &= \frac{1}{2N} \lim_{\tau \to 0} \frac{1}{\tau} \langle (n - \langle n \rangle)^2 \rangle = \frac{\omega(r)^2}{2N}.
\end{align*}
\] (11)

Noting that \( D^{(n)} \sim O(N^{1-n}) \), and neglecting the terms less than \( O(N^{-2}) \), Eq.(11) then reduces to a Fokker-Plank equation [21]

\[
\begin{align*}
    \frac{\partial P(r,t)}{\partial t} &= -\frac{\partial}{\partial r} J(r,t) \\
    &= -\frac{\partial}{\partial r} \left[ (\lambda r - \omega(r)) P(r,t) - \frac{\partial}{\partial r} \frac{\omega(r)}{2N} P(r,t) \right].
\end{align*}
\] (12)

The above equation is equivalent with the Langevin equation

\[
\dot{r}(t) = -\lambda r + \omega(r) + \sqrt{\frac{\omega(r)}{N}} \cdot \xi(t), \] (13)

where the last term represents noise which is gaussian with the properties \( \langle \xi(t) \rangle = 0 \) and \( \langle \xi(t)\xi(t') \rangle = \delta(t-t') \). From this evolution equation (13) and the characteristic time scale of \( x_i \), i.e., \( T_x = (1 - f(r))^2/D \), in which \( x_i \) can diffuse over the interval \([f(r), 1]\), the condition for the adiabatic approximation to hold may be expressed as

\[
\frac{D}{(1 - f(r))^2} \gg |\frac{-\lambda r + \omega(r)}{r}|.
\] (14)

It should be noted that the noise strength of the stochastic process Eq.(13) depend on \( r \). Indeed, the fact that the mean field of a finite size coupled system obeys a stochastic process with state dependent noise is a main conclusion of the present paper.

As the second step, we study the behavior of the mean field \( r \) using Eqs.(12) and (13). The systematic part of Eq.(13), i.e., \( -\lambda r + \omega(r) \), admits a single stable steady state \( r = r_c \) as shown in Fig.4. Thus, for \( N = \infty \) the distribution has a single delta peak at \( r = r_c \). The system with smaller \( N \) behaves differently, which comes from the state-dependence of the noise strength. It is well known that stochastic processes with such noise exhibit phase-transition-like behavior called noise-induced transition [22], which means a bifurcation exhibited by the locus of the extrema of the distribution function. It can be shown that Eqs.(12) and (13) exhibit such a transition. The steady distribution for \( r \) is obtained from Eq.(12) where we assume vanishing probability current, i.e., \( J = 0 \). Thus,
\[ P_{\text{steady}}(r) \propto \exp(-\Phi(r)) = \exp\left(-2N \int \frac{-\lambda s + \omega(s)}{\omega(s)} ds - \ln \omega(r) \right), \] (15)

where \( \Phi \) represents an effective potential. Because the extrema of \( P \) are identical with the extrema of \( \Phi \), they can be found from

\[ \frac{d\Phi}{dr} = 0 \] (16)

or

\[ N = \frac{\omega'(r)}{2(-\lambda r + \omega(r))}. \] (17)

Equation (17) gives a bifurcation diagram for the extrema as depicted in Fig.5, where the solid lines and dotted line show the loci of maxima and minima of \( P_{\text{steady}}(r) \), respectively; the three vertical lines indicate the particular system sizes corresponding to Figs.2, 3, and 4. The location of the maxima corresponding to each vertical lines thus obtained analytically is in good agreement with the numerical simulation whose results are shown in Figs.1 ~ 3. It is clear from Eq.(17) and Fig.5 that there exists a phase transition when \( N \) is changed. There exists a well-defined critical population size \( N_c \) for the transition.

In conclusion, the collective dynamics of integrate-and-fire cells is studied, from which the occurrence of a transition at a finite system size similar to cultivated heart cells is confirmed. In order to understand the origin of the transition, a stochastic differential equation for the mean field is first derived. The transition may be regarded as a noise-induced transition peculiar to systems with finite size. Such results do not seem confined to a specific model adopted, but could be observable in wide variety of noisy finite-size populations.

Finally, a few more comments should be given. It is not intended in the present paper to reproduce experimental results (e.g. those by Cohen) quantitatively. Our main goal was to make clear, with the aid of a relatively simple model, a certain qualitative feature of the collective dynamics exhibited by finite-size populations with noise. In more realistic models, the coupling should be local rather than global. In fact, real heart cell interact through electrical coupling or gap junctions which is local, and this fact is completely ignored in the present analysis. The first important theory on the transitions induced by finiteness of the system size was developed by Pikovsky et al. [16]. Some differences between their works and ours are the following. Firstly, they assume bistability from the outset for the individual elements, while no such assumption is introduced in our model; bistability appears naturally as a result of collective dynamics there. Secondly, we succeeded in clarifying analytically the origin of the transition as a noise-induce transition.

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FIG. 1. Distribution function for the mean field $r$ calculated numerically from Eq.(1)~(4) with $N=20$; other parameters are $I = 0.087, \lambda = 1.0, D = 10^{-2}, \beta = 5.0$ and $f_0 = 0.92$. 
FIG. 2. Distribution function for the mean field $r$ calculated numerically from Eq.(1)~(4) with $N=100$, other parameters are same to Fig.1, (b) is plotted with semilogarithmic scale.
FIG. 3. Distribution function for the mean field $r$ calculated numerically from Eq.(1)~(4) with $N=200$, other parameters are same as in Fig.1; in (b) the data are plotted in semilogarithmic scale.
FIG. 4. Systematic part of Eq.(13) as a function of $r$.

FIG. 5. Bifurcation diagram of extrema of the steady distribution function $P(r)$ obtained from Eq.(17). Solid and dotted curves indicate maxima and minima, respectively. Vertical lines indicate the values of $N$ chosen in Fig.1 ~ 3.