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

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Phase-transition-like behavior is found to occur in globally coupled systems consisting of finite numbers of elements, and a theoretical explanation of this behavior is given. The system studied is a population of globally pulse-coupled integrate-and-fire cells subject to a small additive noise. As the population size is changed, the system exhibits phase-transition-like behavior, that is, there exists a well-defined critical system size above which the system remains in a monostable state with high-frequency activity and below which a new phase characterized by the alternation of high- and low-frequency types of activity appears. The mean field motion obeys a stochastic process with a state-dependent noise, and the above described phenomenon can be interpreted as a noise-induced transition characteristic of such processes. The coexistence of high- and low-frequency activity observed in finite size systems was reported by Cohen, Soen and Braun[Physica A **249** (1998), 600] in experiments on cultivated heart cells. The present report gives the first qualitative interpretation of their experimental results.

§1. Introduction

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 areas to which their study has been applied include chemical reactions,[2] societies 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 in which the finiteness of the system size should be taken into account explicitly. Here we cite two existing theoretical studies on the collective dynamics of populations 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 demonstrated numerically the existence of phase-transition-like behavior existing only for finite systems. Apart from these theoretical studies, an interesting experiment was reported recently by Cohen et al.[1] They cultivated heart cells in various population sizes and found that these cells exhibit system-size-dependent behavior. Some more details of their reports are the following. Heart cells extracted from the ventricles of neonatal rats were cultivated, and time series of their spontaneous spiking activity were recorded. Initially, these heart cells were prevented from interacting by a chemical treatment, but after some time, they spontaneously assembled to form sub-

groups. These cell groups were cultivated, and the spontaneous spike activity of the individual cells was observed. One interesting feature of the experimental results is the following. An isolated cell exhibits random and slow spontaneous spike activity, in which the interspike intervals (ISI) are distributed sparsely, with an average ISI of 5–10 seconds. The series of spikes exhibited by the cells belonging to relatively small groups are composed of two components characterized by a distribution with double peaks. The first low-frequency component is nearly the same as that obtained from the spike series for isolated cells. The other component seems to come from a spike series which is more regular and whose ISI is shorter, approximately 1 second. These low- and high-frequency spikes are exhibited alternately in time. If the cell group is sufficiently large, the individual cells exhibit only high-frequency spike activity of good periodicity. The above summarized experimental results are remarkable in that the dynamics of the individual cells depend qualitatively on the population size, and still await theoretical interpretation. In particular, we would like to know the origin of the transition that occurs as the population size is changed and whether the mechanism involved is universal, beyond the particular class of systems of the cultivated heart cells. The goal of this paper is to provide an answer to these questions. This can be realized analytically by using a simple dynamical model exhibiting coexistence of high- and low-frequency activity under suitable conditions.

§2. Model and numerical results

We employ a globally coupled noisy integrate-and-fire model that is often used in studies of the neurodynamics of the brain. In this model, the dynamics of a single cell are given by

$$\dot{x}_i(t) = I + \xi_i(t), \quad x_i(t) \leq 1, \quad (i = 1, \cdots, N) \tag{2·1}$$

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 that 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 we have

$$x_i(t_i^{(n)}) = 1 \quad \rightarrow \quad x_i(t_i^{(n)} + dt) = f, \quad (n = 1, \cdots) \tag{2·2}$$

where $t_i^{(n)}$ is the timing of the spike, and the tag (n) indicates the numbering of the spiking events. When a cell fires, there immediately results a pulse-like stimulus on all the other cells in the population. A given cell will experience the sum of such stimuli coming from all the other cells. Assuming that the effect of each stimulus decays exponentially, one may conveniently introduce an order parameter $r(t)$ defined by

$$r(t) = \frac{1}{N} \sum_{i=1}^{N} \sum_{n; t^{(n)} < t} \exp(-\lambda(t - t_i^{(n)})), \tag{2·3}$$

whose effect is experienced uniformlly by all 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 a dependence of the resetting value of f on r like

$$f(r) = f_0(1 - e^{-\beta r}). \tag{2·4}$$

Note that an increase of r implies an increase of f, with the upper limit f_0.

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

$$P_{\rm ISI}(T) = \frac{1 - f(r)}{\sqrt{4\pi DT^3}} \exp\left(-\frac{(1 - f(r) - IT)^2}{4DT}\right). \tag{2·5}$$

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

$$\omega(r) = \frac{I}{1 - f(r)} = \frac{I}{(1 - f_0) + f_0 \cdot e^{-\beta r}}. \tag{2·6}$$

One can see that larger/smaller r corresponds to larger/smaller ω or higher/lower frequency activity. The above results are also consistent with the experimentally observed facts regarding heart cells that when the cells are isolated the spiking frequency is lowest and the distribution of the corresponding ISI is broadest.

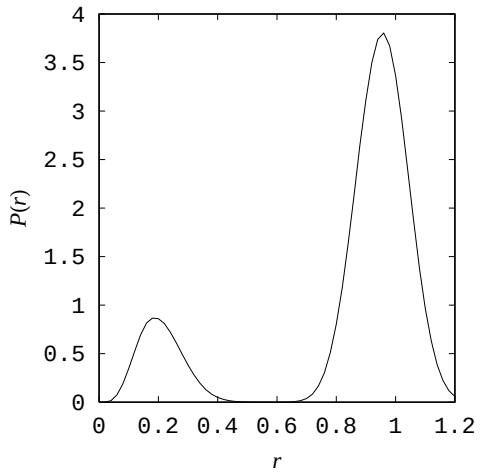

Fig. 1. Distribution function for the mean field r calculated numerically from Eqs. (2·1) – (2·4) with $N = 20$. The other parameter values are $I = 0.087, \lambda = 1.0, D = 10^{-2}, \beta = 5.0$ and $f_0 = 0.92$.

Two remarks should be given here concerning model. Firstly, we have taken into account the effect of the mean field on the resetting state by assuming f depends on r. However, our choice for the manner in which the mean field r affects single elements is rather arbitrary. What is important here is that the rate of spiking ω should be a nonlinear function of r. Under this condition, other choices, such as setting $f(r) = 0$ and replacing I by a function of r, $I(r)$, would give qualitatively the same results. Secondly, our main goal is to understand, analytically if possible, some general features of the collective dynamics shared by finite-size systems rather than reproducing precisely the experimental results for real heart cells, so that Eqs. (2·1) – (2·4), which may not be so realistic for heart cells, should still be useful enough as a working model.

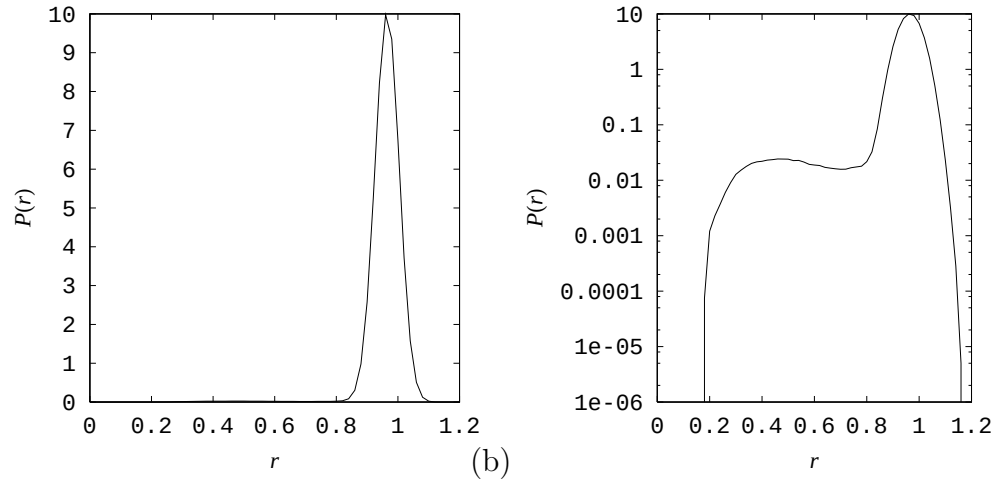

Fig. 2. Distribution function for the mean field r calculated numerically from Eqs. (2·1) – (2·4) with $N = 100$. The other parameter values are same as in Fig. 1. (b) is plotted on semilogarithmic scale.

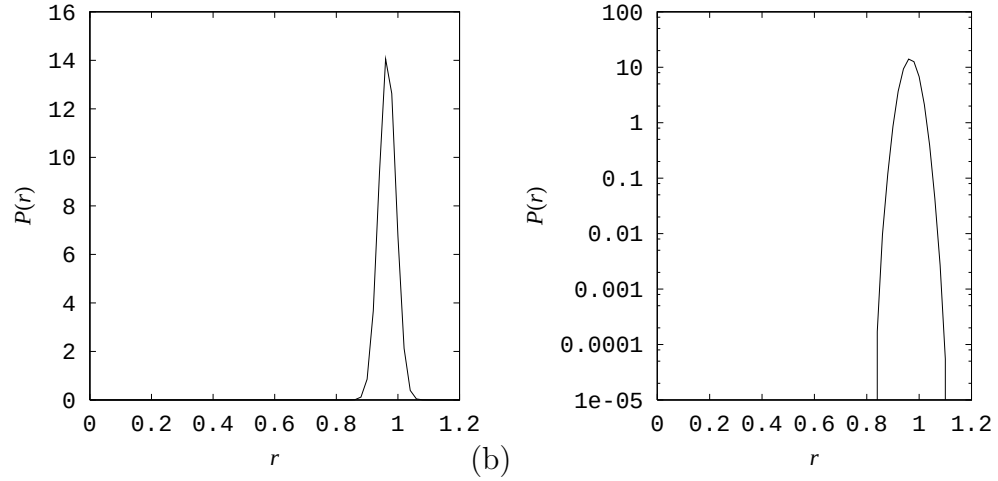

Fig. 3. Distribution function for the mean field r calculated numerically from Eqs. (2·1) – (2·4) with $N = 200$. The other parameter values are the same as in Fig. 1. In (b) the data are plotted on a semilogarithmic scale.

Equations (2·1) – (2·4) were solved numerically with various values of N, from which the distribution functions of r, denoted $P(r, t)$, are obtained. Figures 1 – 3 display $P(r, t)$ for the cases $N = 20$, 100 and 200, respectively. In order to make clear the difference between the cases $N = 100$ and 200, the data in Figs. 2(b) and 3(b) are plotted on semilogarithmic scales. For a sufficiently large system size, the distribution has a single sharp peak at about $r = 1.0$, corresponding to coherent high-frequency activity. It seems that the distribution undergoes 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 existence of the double peaks implies the coexistence of different steady states. Actually, the coexistence of high- and low-frequency states is a feature observed experimentally in real heart cells. Our model gives a fairly well-defined critical population size associated with a transition from a monostable state to a coexistence state.

§3. Adiabatic approximation

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 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

$$\frac{\partial P(r,t)}{\partial t} = \sum_{n=1}^{\infty} \left(-\frac{\partial}{\partial r}\right)^n D^{(n)}(r,t)P(r,t), \tag{3·1}$$

where $D^{(n)}$ is defined as

$$D^{(n)}(r,t) = \frac{1}{n!}\lim_{\tau\to 0}\frac{1}{\tau}\langle[r(t+\tau)-r(t)]^n\rangle|_{r(t)=r}. \tag{3·2}$$

To find explicit forms of $D^{(n)}$, we calculate $r(t+\tau)-r(t)$ from Eq. (2·3) for small τ under the condition that $r(t)=r$. We obtain

$$\begin{aligned} r(t+\tau)-r(t) &= (e^{-\lambda\tau}-1)r + \frac{1}{N}\sum_{i=1}^{N}\sum_{n;t<t^{(n)}<t+\tau} e^{-\lambda(t+\tau-t_i^{(n)})} \\ &= (e^{-\lambda\tau}-1)r + \frac{1}{N}\sum_{i=1}^{N} n_i(t,t+\tau), \end{aligned} \tag{3·3}$$

where $n_i(t,t+\tau)$ is the number of spikes of the i-th cell during a short interval t – $t+\tau$. To obtain the last expression in Eq. (3·3), we use the smallness of τ and replace $e^{-\lambda(t+\tau-t_i^{(n)})}$ with 1. Because $r(t)$ 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 spikes is represented 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

$$P_n(n) = \frac{e^{-\omega(r)\tau}\,(\omega(r)\tau)^n}{n!}. \tag{3·4}$$

Applying Eq. (3·4) to Eq. (3·3) and then to Eq. (3·2), we obtain

$$\begin{aligned} D^{(1)} &= -\lambda r + \lim_{\tau\to 0}\frac{1}{\tau}\langle n\rangle = -\lambda r + \omega(r), \\ D^{(2)} &= \frac{1}{2N}\lim_{\tau\to 0}\frac{1}{\tau}\langle(n-\langle n\rangle)^2\rangle = \frac{\omega(r)}{2N}. \end{aligned} \tag{3·5}$$

Noting that $D^{(n)} \sim O(N^{1-n})$, and ignoring terms smaller than $O(N^{-2})$, Eq. (3·5) then reduces to a Fokker-Plank equation,[21)]

$$\begin{aligned}\frac{\partial P(r,t)}{\partial t} &= -\frac{\partial}{\partial r} J(r,t) \\ &= -\frac{\partial}{\partial r}\left[(-\lambda r + \omega(r))P(r,t) - \frac{\partial}{\partial r}\frac{\omega(r)}{2N}P(r,t)\right]. \end{aligned} \tag{3·6}$$

This equation is equivalent to the Langevin equation

$$\dot{r}(t) = -\lambda r + \omega(r) + \sqrt{\frac{\omega(r)}{N}} \cdot \xi(t), \tag{3·7}$$

where the last term represents Gaussian noise with the properties $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$. It should be noted that the noise strength of the stochastic process Eq. (3·7) depends on r. Indeed, the fact that the mean field of a finite size coupled system obeys a stochastic process with state-dependent noise is one main conclusion of the present paper. While the strength D of the additive noise ξ_i does not appear explicitly in Eqs. (3·6) and (3·7), the additive noise plays an important role implicitly. Firstly, from this evolution equation (3·7) 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 necessary condition for the adiabatic approximation to hold may be expressed in terms of D as

$$\frac{D}{(1 - f(r))^2} \gg \left| \frac{-\lambda r + \omega(r)}{r} \right|. \tag{3·8}$$

Secondly, to calculate Eq. (3·5), we have assumed that N cells are independent of each other, which is insured by employing a ξ_i with sufficiently large D. It is also necessary to maintain the independence of the cells so that synchronization cannot occur.

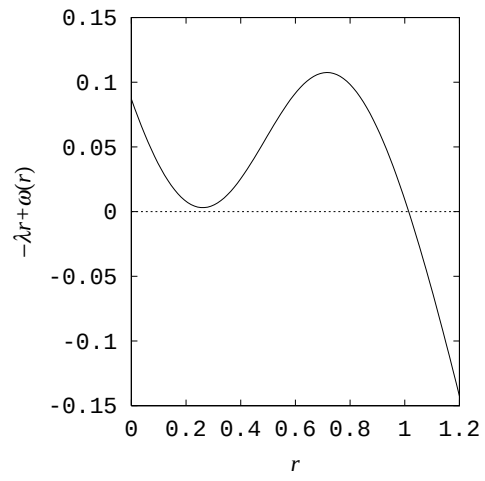

Fig. 4. The systematic part of Eq. (3·7) as a function of r.

As the second step, we study the behavior of the mean field r using Eqs. (3·6) and (3·7). The systematic part of Eq. (3·7), 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 $r = r_c$. A system with smaller N behaves differently, due to 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 corresponds to a bifurcation exhibited by the locus of the extrema of the distribution function. It can be shown that Eqs. (3·6) and (3·7) exhibit such a transition. The steady

distribution for r is obtained from Eq. (3·6), where we assume a vanishing probability current, i.e. $J = 0$. Thus,

$$P_{\text{steady}}(r) \propto \exp(-\Phi(r)) = \exp\left(-\left[2N\int^{r}\frac{-\lambda s+\omega(s)}{\omega(s)}ds - \ln\omega(r)\right]\right), \tag{3·9}$$

where Φ represents an effective potential. Figures 5(a) – (c) display $P_{\text{steady}}(r)$ obtained from Eq. (3·9) for $N = 20$, 100 and 200, respectively. Because the extrema of P are identical to the extrema of Φ, they can be found from

$$\frac{d\Phi}{dr} = 0 \tag{3·10}$$

or

$$N = \frac{\omega'(r)}{2(-\lambda r+\omega(r))}. \tag{3·11}$$

Equation (3·11) gives a bifurcation diagram for the extrema as depicted in Fig. 6, where the solid lines and dotted line represent 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 – 4. The location of the maximum corresponding to each vertical line thus obtained analytically is in good agreement with the numerical simulation, whose results are presented in Figs. 1 – 3. It is clear from Eq. (3·11) and Fig. 6 that there exists a phase transition when N is changed. There exists a well-defined critical population size N_c for this transition. For the general Langevin equation

$$\dot{r}(t) = f(r) + \sqrt{2g(r)}\cdot\xi(t), \tag{3·12}$$

extrema of the steady distribution are given as intersection points of $f(r)$ and $g'(r)$. Then, what is essential in order for there to be a finite size transition is that the evolution equation of mean field can be described in a closed form in which the system size N appears explicitly.

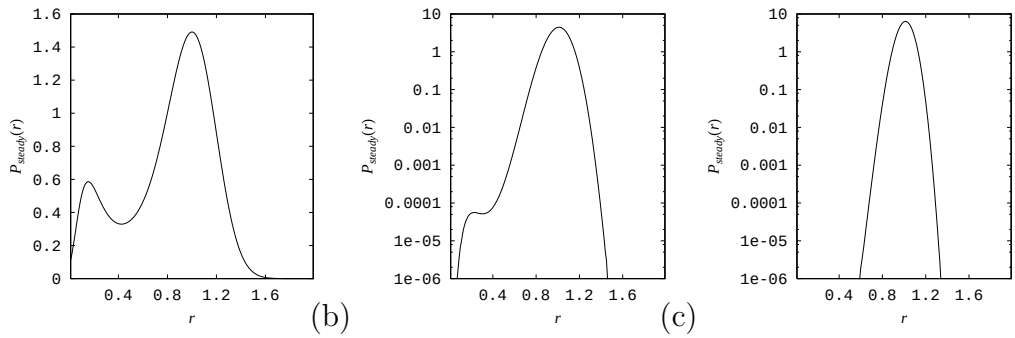

Fig. 5. Steady distribution function for the mean field r calculated analytically from Eq. (3·9) with (a)$N = 20$, (b)$N = 100$ and (c)$N = 200$, (b) and (c) are plotted with semilogarithmic scale.

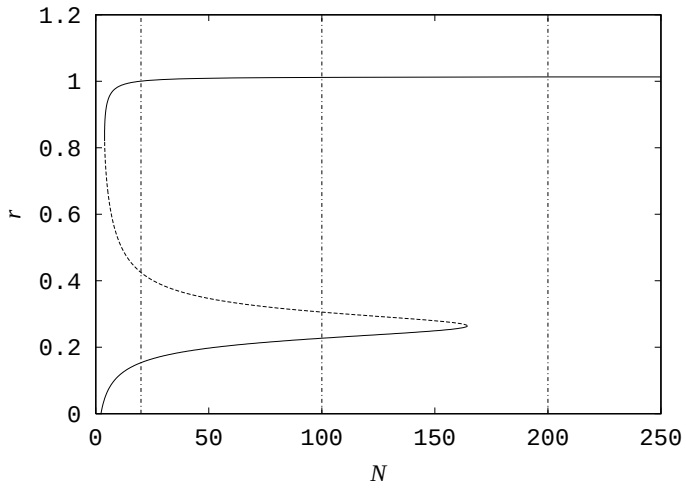

Fig. 6. Bifurcation diagram of extrema of the steady distribution function $P(r)$ obtained from Eq. (3·11). Solid and dotted curves indicate maxima and minima, respectively. Vertical lines indicate the values of N chosen in Figs. 1 – 3.

§4. Concluding remarks

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

Finally, a few comments should be given. It is not our intention in the present paper to reproduce experimental results (e.g., those of Cohen) quantitatively. Our main goal is 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 cells interact through electrical coupling or gap junctions, which is local, and this fact is completely ignored in the present analysis. Gap junctions are not described as pulse couplings employing our analysis but as direct mean field couplings $r = \sum_{i=1}^{N} x_i/N$. However, it is difficult to apply our theory to such direct couplings, because the time scales of the mean field r and the single elements x_i cannot be separated clearly. The first important theory on transitions induced by finiteness of the system size was developed by Pikovsky et al.[16] Some differences between their work 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 the collective dynamics there. Secondly, we succeeded in clarifying analytically the origin of the transition as a noise-induce transition.

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