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Effects of internal noise for calcium signaling in a coupled cell system

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We have studied the collective behavior of calcium signaling in a linear array of coupled cells, taking into account the influence of internal noise. For a single cell, the performance of the stochastic calcium oscillations shows two maxima as a function of the cell size, indicating the occurrence of system size bi-resonance. When the cells are coupled together, we find that the increase of the coupling strength or the number of cells can considerably enhance the first peak, but decrease the second one. The occurrence of the bi-resonance and the distinct dependence on the coupling are shown to be relevant with regard to the system's deterministic bifurcation features.

1 Introduction

The constructive role of noise in nonlinear systems, especially stochastic resonance (SR), has drawn great research interest in the last two decades.[1,2] Recently, a new type of SR-like phenomenon, system size resonance (SSR), has gained growing attention.[3–12] So far, mainly two types of 'size resonance' behavior have been reported. On one hand, Pikovsky *et al.* reported that in an array of coupled noisy bistable systems subjected to an external periodic forcing, an optimal response is obtained when the system size, here is the number of elements in the system, has an optimal value.[3] In such a case, the system size plays a role in changing the external noise intensity subjected to the mean field. In the absence of an external signal, system-size coherent resonance (CR) can be found in a one-dimensional lattice of diffusively coupled excitable neurons.[4,5] On the other hand, it has been demonstrated that for chemical oscillation reactions taking place in small-scale systems, stochastic oscillations can be observed and there exists an optimal system size such that the stochastic oscillations show the best performances. For instance, ion channel clusters of optimal sizes can enhance the encoding of a sub-threshold stimulus,[6–8] and optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters.[9,10] Using a circadian clock model and the Brusselator model, our group have found that internal noise can lead to stochastic oscillations in the region close to the deterministic oscillatory dynamics, and an optimal system size exists for such stochastic oscillations.[11,12] One notes the first type is mainly a result of coupling and the noise is mainly external, while the second type is a result of the interplay between the internal noise and the systems' nonlinear dynamics.

It is well known that intracellular calcium (Ca^{2+}) is one of the most important second messengers in the cytosol of living cells. Cytosolic calcium oscillations play a vital role as a communication mechanism between distinct parts of the cell or between adjacent cells in the tissue. Many processes, such as intracellular and intercellular signaling processes, muscle contraction, cell fertilization, gene expression, and so on, are all controlled by the oscillatory regime of the cytosolic calcium concentration. There is a vast literature contributed to the mathematical modeling of calcium oscillations,[13] and most of these models are deterministic and do not account for any stochastic effects. However, the biochemical reactions involved in the calcium oscillation take place inside a single cell and the number of reactant molecules could be low, which will lead to considerable internal noise. Therefore, it is an important problem as to how the internal noise would influence calcium signaling in cell systems.

In fact, the role of internal noise for intracellular calcium signaling has gained much attention recently. For example, the groups of Jung and Hänggi reported that optimal channel noise can play rather constructive roles for intracellular calcium signaling.[6–10] In a recent study, using a model for intracellular calcium signaling in hepatocyte cells, we showed that internal noise can induce stochastic calcium oscillations in a parameter regime which is subthreshold to deterministic oscillatory dynamics, and the performance of the stochastic calcium oscillation can show two maxima with the variation of the cell size, indicating the occurrence of system size bi-resonance (SSBR).[14]

Here, in the present paper, we have studied how internal noise would influence calcium signaling in a one-dimensional chain of coupled cells. In real systems, cells are often coupled together to accomplish cellular functions.[13] Therefore, after knowing something about the behavior of a single cell, it is naturally the next step to study coupled cell systems. Specifically, for the purpose of the present work, we are wondering whether the SSBR behavior observed in a single cell also exists in coupled systems, and if so, how it is affected by the coupling strength and the number of cells. Consequently, we find that SSBR behavior also exists when the collective behavior of the system is considered, and with the increase of the coupling strength or the number of cells, the first maxima can be obviously enhanced, while the second one is suppressed. The relevance of such a phenomenon with the system's deterministic bifurcation features is discussed.

2 Model

The model used here is proposed by Höfer to account for the intracellular Ca^{2+} oscillation in hepatocyte cells.[15] In a single cell, the Ca^{2+} signaling dynamics involves the interplay of

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Ca^{2+} fluxes from and into the endoplasmic reticulum (ER) and across the plasma membrane. Denoting the population number of Ca^{2+} in the cytosol by X and that in the whole cell by Z, the reactions in the cell can be grouped into four elementary processes involving the change of X or Z by 1.[16] The processes and the corresponding reaction rates $a_{j=1,\ldots,4}(x,z)$ are given by:

$$X \to X+1,\ a_1(x,z) = V\rho\left(\nu_0 + \nu_c\frac{P}{k_0+P} + \frac{\alpha k_r(x,P)}{\beta}z\right) \quad (1a)$$

$$X \to X-1,\ a_2(x,z) = V\rho\left(\nu_4\frac{x^2}{k_4^2+x^2} + \frac{\alpha k_r(x,p)}{\beta}(1+\beta)x + \alpha\nu_3\frac{x^2}{k_3^2+x^2}\right) \quad (1b)$$

$$Z \to Z+1,\ a_3(x,z) = V\rho\left(\nu_0 + \nu_0\frac{P}{k_0+P}\right) \quad (1c)$$

$$Z \to Z-1,\ a_4(x,z) = V\rho\nu_4\frac{x^2}{k_4^2+x^2} \quad (1d)$$

where

$$k_r(x,P) = k_1\left[\frac{d_2(d_1+P)Px}{(d_p+P)(d_a+x)[d_2(d_1+P)+x(d_3+P)]}\right]^3 + k_2$$

Note that $a_{j=1,\ldots,4}(x,z)$ are simply written as $a_{j=1,\ldots,4}$ in the following eqns. (2) and (3), V is the volume of the cytosolic compartment of the cell which is proportional to the cell size, and $x = X/V$, $z = Z/V$ are the concentrations of X and Z, respectively. P is the concentration of inositol triphosphate (IP_3) in the cell, which denotes the level of the agonist simulation and is chosen to be the control parameter. See the caption of Fig. 1 for other parameter values. If the internal noise is ignored, the calcium dynamics inside a single cell can be described by the following deterministic equations,

$$\frac{dx}{dt} = (a_1 - a_2)/V,\ \frac{dz}{dt} = (a_3 - a_4)/V \quad (2)$$

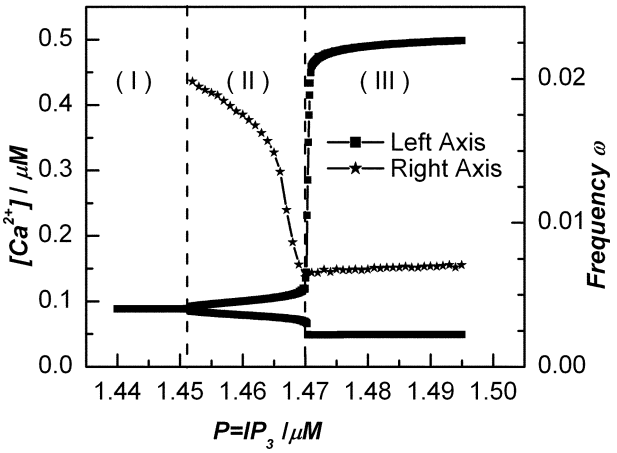

Fig. 1 Bifurcation diagram for the deterministic model (2). The solid squares denote the maximum and minimum of the deterministic oscillation range (left axis), and the stars correspond to the frequency (right axis). The parameter space is divided into three distinct regions: (I) Steady state region ($P < 1.45$ μM); (II) Small oscillation region ($1.45 < P < 1.47$ μM); (III) Relaxation oscillation region ($P > 1.47$ μM). The structural characteristics of a cell are $\alpha = 2.0$, $\rho = 0.02$ μm^{-1}, $\beta = 0.2$; $v_0 = 0.2$ is a background Ca^{2+} leakage, $v_c = 4.0$ is the max rate of IP_3 induced Ca^{2+} influx, $v_3 = 9.0$ the max rate of ER uptake of Ca^{2+}, $v_4 = 3.6$ the max rate of calcium efflux (units: μM s^{-1}); Other parameters are $k_0 = 4.0$, $k_3 = 0.12$, $k_4 = 0.12$, $d_1 = 0.3$, $d_2 = 0.4$, $d_3 = 0.2$, $d_p = 0.2$, $d_a = 0.4$ (units: μM); $k_1 = 40.0$ s^{-1}, $k_2 = 0.02$ s^{-1}. See refs. 15 and 16 for more details.

With the variation of the control parameter P, eqn. (2) undergoes a Hopf Bifurcation (HB) at $P \approx 1.45$ μM, above which Ca^{2+} oscillations appear and below which only stable steady state can be observed as shown in Fig. 1.

However, for a real living cell whose size is small, such a deterministic model is no longer strictly valid due to the existence of considerable internal noise. Instead, a mesoscopic stochastic model must be used. An applicable method is the chemical Langevin equation (CLE) proposed by Gillespie,[17] which is derived from the chemical master equation governing the time evolution of the probability of having given numbers of reacting species X and Z. The CLE gives us clear information about how the internal noise depends on the system size as well as the reaction dynamics. Specifically, the CLE for the current system inside a single cell reads:

$$\dot{\bar{x}} = \frac{1}{V}(a_1 - a_2 + \sqrt{a_1}\zeta_1(t) - \sqrt{a_2}\zeta_2(t)), \quad (3a)$$

$$\dot{\bar{z}} = \frac{1}{V}(a_3 - a_4 + \sqrt{a_3}\zeta_3(t) - \sqrt{a_4}\zeta_4(t)), \quad (3b)$$

where $\zeta_{i=1,\ldots,4}(t)$ are Gaussian white noises with $\langle\zeta_i(t)\zeta_i(t')\rangle = \delta_{ij}\delta(t-t')$ and $\langle\zeta_i(t)\rangle = 0$. Since all the reaction rates $a_{j=1,\ldots,4}$ are proportional to the system size V as illustrated in eqn. (1), the strength of the internal noise terms in the CLE (3) scales as $1/\sqrt{V}$. According to eqn. (3), in the assumed limit $V \to \infty$ corresponding to the macroscopic system, the internal noise can be ignored and one recovers the deterministic dynamics given by eqn. (2). For a typical cell for which the size V is small, however, the internal noise terms may become crucial. Keeping in mind that external noise often plays interesting roles near some kinds of critical points, we will also tune the system near the HB point. In order to study the pure effects of the internal noise, we will keep all other parameters fixed and change the size V only.

3 Results and discussion

For completeness, we will first outline the behavior of a single cell ($N = 1$). We tune the control parameter $P = 1.3$ μM, which is below but close to the HB point, such that the system stays in a steady state according to the deterministic eqn. (2). As stated above, however, the system's dynamical behavior must be described by eqn. (3) and thus depends strongly on the cell size V. In Fig. 2, we have plotted five typical time series of x for different cell sizes, $V = 100$, 1000, 10^5, 10^6 and 10^8 μm^3, respectively. If V is too small ($V \leq 100$), internal noise dominates and the temporal behavior is rather random although some spikes can be observed. If V is large enough ($V > 10^8$), the internal noise is too small to induce the Ca^{2+} oscillation, and the system only slightly fluctuates around the steady state defined by the deterministic equation. However, for some intermediate cell sizes, such as for $V = 1000$ and 10^6, stochastic oscillations can be observed apparently. One notes that oscillation is of relaxation type with large and nearly constant amplitude for $V \sim 1000$, and of small amplitude for $V \sim 10^6$.

To characterize the relative regularity of the stochastic calcium oscillations, we have calculated the power spectrum density (PSD) of the time series $x(t)$ to determine the effective signal-to-noise ratio (SNR). The SNR is defined as the peak height in the PSD divided by its relative width and has already been widely used in the literature. We have used a time series containing 16384 data points to calculate the PSD values. Please see refs. 11, 12 and 14 for more details of the definition and calculation of the SNR. The SNR shows two maxima as V is varied, as depicted in Fig. 3, indicating the occurrence of system size bi-resonance (SSBR). Accordingly, the frequencies of the stochastic oscillations are also shown. Note that the

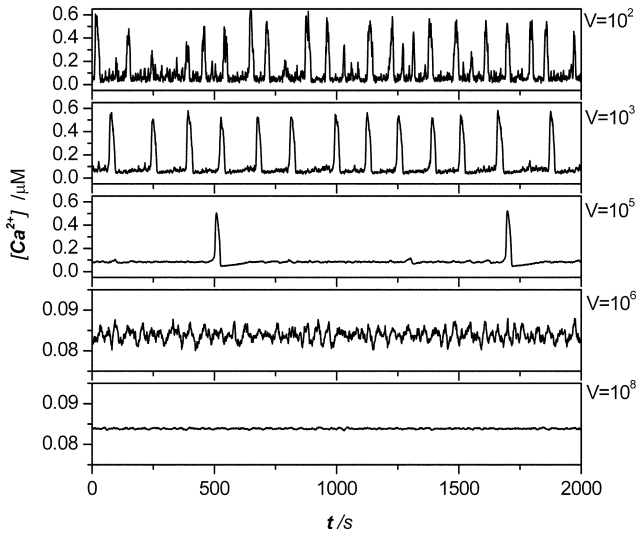

Fig. 2 Five typical time series of $x(t)$ with different cell sizes V for $N = 1$. From top to down, $V = 10^2$, 10^3, 10^5, 10^6 and 10^8 μm^3, respectively. For $V = 10^3$, the stochastic oscillation is of relaxation type with large amplitude, and for $V = 10^6$, the oscillation amplitude is very small.

SNR values are averaged over 20 independent runs here for $N = 1$ and in the following parts for the coupled system.

The occurrence of SSBR may be very relevant to the deterministic bifurcation features displayed in Fig. 1. With the variation of the control parameter P, the bifurcation diagram can be divided into three distinct regions. In region (I) ($P <$ HB $\equiv 1.45$ μM), there are no deterministic oscillations. In region (II) ($1.45 < P < 1.47$ μM), deterministic oscillations of small amplitude appear. In region (III) ($P >$ 1.47 μM), the oscillations are of relaxation type with large amplitude and small frequency. Therefore, when the system lies in region (I) as we have done in the present work, a small noise may 'drive' the system into region (II) and induce stochastic oscillations of small amplitude, while large noise can induce the stochastic relaxation oscillations of large amplitude like those in region (III). Both types of stochastic oscillations may show coherent resonances with the noise intensity, hence resulting in the bi-resonance in different noise ranges.

We now turn to a chain of N cells coupled through mass diffusion of calcium *via* gap-junctions.[15,16] The dynamics of the coupled system reads:

$$x_i = \frac{1}{V}[(a_1 - a_2) + (\sqrt{a_1}\zeta_1(t) - \sqrt{a_1}\zeta_1(t))] + C(x_{i+1} + x_{i-1} - 2x_i) \quad (4a)$$

$$z_i = \frac{1}{V}[(a_3 - a_4) + (\sqrt{a_3}\zeta_3(t) - \sqrt{a_4}\zeta_4(t))] + C(x_{i+1} + x_{i-1} - 2x_i) \quad (4b)$$

Here, $a_{j=1,\ldots,4}$ to the right side simply denote $a_{j=1,\ldots,4}(x_i,z_i)$, which are the rates in the ith cell. Note here the diffusion of calcium results in the identical changes in the number of X and Z,[15,16] and C denotes the coupling strength.

To describe the collective response of the coupled oscillators, we introduce the average cytosolic calcium concentration as

$$X(t) = \frac{1}{N}\sum_{i=1}^{N} x_i(t).$$

We numerically integrate eqn. (4) using the standard procedure for stochastic differential equations with the time step 0.01 s. For each parameter set, the power spectrum of $X(t)$ and the corresponding SNR are calculated. As noted above, the final SNR values are obtained *via* averaging over 20 independent runs.

First, we consider how the collective behavior of the system depends on the chain length N. The parameters are fixed at $P = 1.3$ μM and $C = 0.04$, and the internal noise intensity is adjusted *via* the change of V. The plots of SNR *vs.* V for different chain length N are given in Fig. 4(a). Interestingly, the two peaks observed in a single cell show rather different

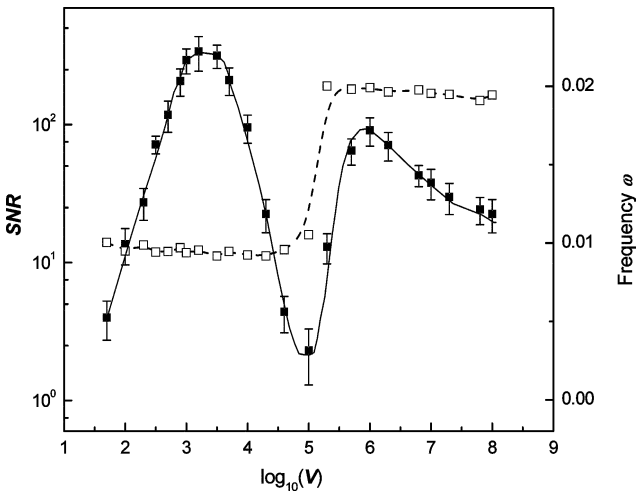

Fig. 3 The SNR (left axis) and the corresponding principal frequency (right axis) of the stochastic oscillations for $P = 1.3$ and $N = 1$, obtained by the CLE (eqn. (3)). The clear double peaks in the SNR curve indicate the occurrence of system size bi-resonance. Note that the stochastic oscillations regarding the two peaks have different natures according to the frequency values. The error bars for the SNR are also shown.

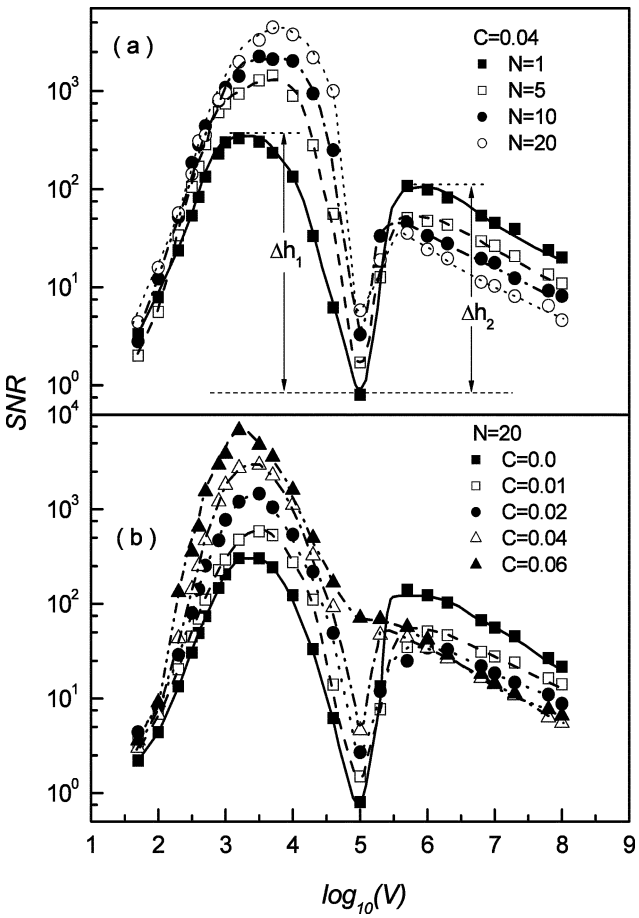

Fig. 4 (a) Plots of SNR *versus* the cell size V for different chain length $N = 1, 5, 10, 20$, respectively, for a fixed coupling strength $C = 0.04$; (b) The dependence of SNR on cell size V for different values of coupling strength $C = 0, 0.01, 0.02, 0.04, 0.06$, respectively, for a fixed chain length $N = 20$.

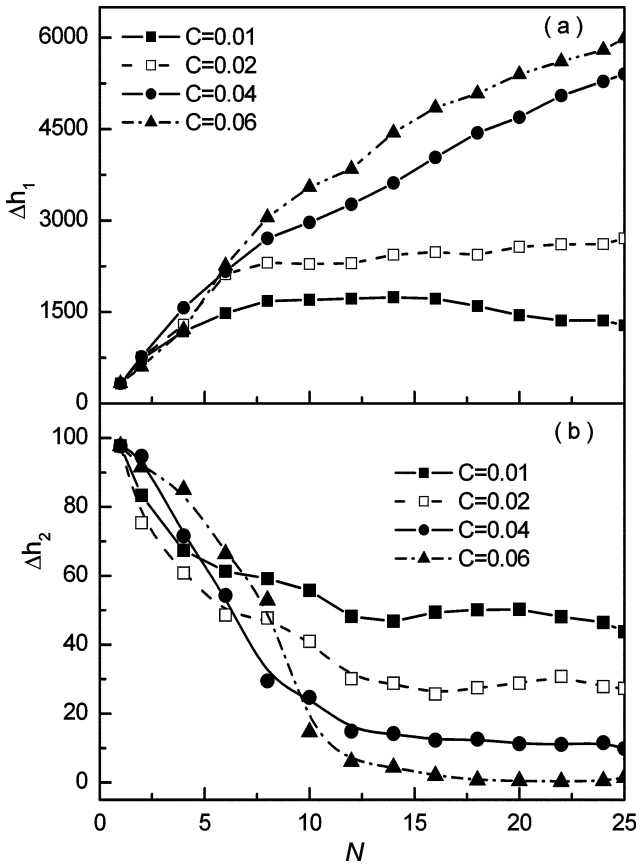

Fig. 5 The dependence of the peak heights (a) Δh_1 and (b) Δh_2 on the number of cells N for $C = 0.01$, 0.02, 0.04, 0.06, respectively. The definitions of Δh_1 and Δh_2 are shown in Fig. 4(a).

dependences on N. While the first peak is significantly enhanced by the coupling, the second one is obviously suppressed. We note that the enhancement of the first peak is consistent with the well-known phenomena of array-enhanced SR or CR,[18,19] but the suppression of the second peak is not reported before. Secondly, we fix the chain length $N = 20$ and study the effect of the coupling strength C. The results are shown in Fig. 4(b), where the first peak is again considerably enhanced with the increment of the C, and the second one is also suppressed. If C is large enough for $N = 20$, the second peak will completely vanish.

In order to get a global view, we have studied how the heights of the two peaks change with N and C. We introduce $\Delta h_{1,2} = h_{1,2} - h_0$, to describe the peak heights, where $h_{1,2}$ are the SNR values of the two peaks, and h_0 is the minimum SNR value between the two peaks (see Fig. 4(a)). For a fixed coupling strength, *e.g.*, $C = 0.04$, the height of the first peak increases monotonically with the increment of N (Fig. 5(a)), and the second peak decreases (Fig. 5(b)).

Why the two peaks have such different dependences on the coupling is an open question. Intuitively, we think that their distinct oscillation features, *i.e.*, large relaxation oscillations for the first peak and small amplitude oscillations for the second one, might be the very reason. But a thorough understanding of this phenomenon deserves more detailed calculations and finally possible analytical works.

How can the findings of the present paper have implications for living cellular functions is another interesting question. At the current stage, three points may be addressed. On one hand, the existence of stochastic oscillations indicates that intracellular calcium oscillations can sustain in a much greater parameter range than those predicted by the deterministic model, *i.e.*, it shows strong robustness to external stimulations which should be of benefit for their proper functions. On the other hand, due to the fact that the first resonance occurs at nearly constant cell size $V \sim 10^3$, and this size is of the same order as that of real living cells *in vivo*,[15,16] it seems that the kinetic coefficients of the mechanism have evolved to be optimal for the size of a cell. And finally, we find that the stochastic calcium oscillations show much stronger regularity when the cells are coupled together than separated alone, suggesting that intercellular communications should have played rather important roles in collective cellular functions.

4 Conclusion

In summary, we have studied the influence of internal noise on the calcium signaling in an array of coupled hepatocyte cells. For a single cell, internal noise can play rather constructive roles through the mechanism of system size bi-resonance, *i.e.*, internal noise can induce stochastic calcium oscillations in a region subthreshold to deterministic oscillatory dynamics, and the SNR of the stochastic oscillation bypass two maxima with the variation of the cell size. It is interesting to note that the first maximum matches the real cell size *in vivo*, suggesting that the cell system might work at an optimal size. Furthermore, we find that the two peaks show rather different behavior when the cells are coupled together, *i.e.*, while the first resonance peak can be considerably enhanced by the coupling, the second one is suppressed. We think that the distinct deterministic bifurcation features of the system should have some inherent relevance with such a phenomenon. We hope our findings could find some interesting applications for calcium signaling in real systems, and can also open more perspectives in the study of internal noise in biological systems.

Acknowledgements

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