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Cite as: J. Chem. Phys. **119**, 11508 (2003); https://doi.org/10.1063/1.1624053
Submitted: 17 July 2003 . Accepted: 12 September 2003 . Published Online: 21 November 2003

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(Received 17 July 2003; accepted 12 September 2003)

We have studied the influence of internal noise on a circadian clock system using stochastic simulation methods and chemical Langevin equations. It is found that internal noise can induce circadian oscillations, when the corresponding deterministic system does not oscillate. The performance of the noise induced circadian oscillation undergoes a maximum with the variation of the internal noise level, showing the occurrence of internal noise stochastic resonance. Since the magnitude of the internal noise is changed via the variation of the system size, these phenomena also demonstrate a kind of system size resonance. © *2003 American Institute of Physics.*
[DOI: 10.1063/1.1624053]

I. INTRODUCTION

In the last two decades, the constructive roles of noise and disorder in nonlinear systems have been extensively studied.[1] Among them the most well known phenomenon is stochastic resonance (SR),[2] which demonstrates that noise can help a nonlinear system to detect and amplify weak external signals. The fingerprint of SR is that there exists an optimal noise level where the signal-to-noise ratio (SNR) of the output signal reaches a maximum. Since it was originally proposed by Benzi and collaborators in 1980's to account for the periodically recurrent ice ages,[3] SR has gained ever-growing attention in a variety of scientific fields. Although SR originally involves three components, say, the bistable system, external signal, and external white noise, it has been widely extended to various situations. For example, the system may be monostable, excitable, oscillatory, threshold-free, or nondynamical; the external signal can be aperiodic or even chaotic; and the external noise can be white or colored, etc.[4] In addition, the external signal may not be necessary if the system is tuned near a bifurcation point between a stable node and a limit cycle. In such cases, noise can induce coherent oscillation, the strength of which also undergoes a maximum when the noise intensity is changed, showing SR-like behavior known as coherent resonance[5] or internal signal stochastic resonance.[6] Very recently, more and more attention has been paid to SR-like phenomena in biological systems, from ion channel gating and neuron spiking, to life supporting system and human balance control systems.[7] As stated by Hänggi, it would indeed seem strange to us if nature would not have taken advantage of the benefits of ambient noises for nonlinear transmission and/or amplification of feeble information rather than ignoring it.

However, most of the studies so far only account for *external* noise. Usually, the system's dynamics is described by a deterministic differential equation and then a noise term is added to the equation directly, additively or multiplicatively. The properties of the external noise, such as its intensity or correlation time/length, depend only on the environment and have no relevance to the system's dynamic features or the system size. However, in chemical reaction systems there is another source of noise resulting from the random fluctuations of the stochastic chemical reaction events, the *internal* noise. Such internal noises depend on the reaction details as well as the system size. It is generally accepted that the magnitude of the internal noise scales inversely with the system size V. In the macroscopic limit when V is infinite, the internal noise can be ignored and the system's dynamics is described by a deterministic equation if no *ad hoc* external noise is present. However, for chemical reactions in small systems, such as those biochemical reactions taking place in living cells[8] or catalytic reactions happening on nanoscale crystal surfaces,[9] the number of reacting molecules could be low and the internal noise must be taken into account. Therefore, an intriguing question is how the system's dynamics is affected by the internal noise. Specifically, we are wondering whether or not the system's dynamics shows some SR-like behavior with the internal noise, which can be called internal noise stochastic resonance (INSR).

In the present paper, we have studied how the internal noise affects the dynamics of a circadian clock system. A wide range of living organisms uses circadian clocks to keep internal sense of daily time and keep their behavior accordingly.[10] Most of these clocks use intracellular genetic networks based on positive and negative regulatory elements, where the number of reactant molecules is often low.[11] Therefore, the question is how the circadian oscillations are influenced by the internal noise. Actually, many efforts have been paid to this issue, but most works so far assume that the internal noise is destructive and they mainly focus on the robustness or resistance of circadian oscillations to such internal noise. In Ref. 12, Gaspard performed a the-

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TABLE I. Parameter descriptions and values used in Eq. (1).

Parameter	Description	Value
ν_s	Transcription rate of the clock gene	Control parameter
k_l	Threshold beyond which the nuclear protein repress the transcription of its gene	0.2 nM
n	Hill coefficient characterizing the repression	4
ν_m	Maximum rate of mRNA degradation	0.3 nM h^{-1}
k_m	Michaelis constant related to mRNA degradation	0.2 nM
k_s	Translation rate of mRNA to protein	2.0 h^{-1}
ν_{sd}	Maximum rate of protein degradation	1.5 nM h^{-1}
k_d	Michaelis constant related to protein degradation	0.1 nM
k_1	Transport rate of protein into the nucleus	0.2 h^{-1}
k_2	Transport rate of protein out of the nucleus	0.2 h^{-1}

oretical study on the robustness of mesoscopic chemical clocks, and he found that a minimum number of molecules is required for the mesoscopic oscillations to remain correlated in time. Barkai and Leibler argued that the sensitivity to internal noise and the robustness to such uncertainties were probably decisive factors in the evolution of circadian clocks, and should be reflected in the underlying oscillation mechanism.[13–15] In our study, however, we find that internal noise can also play constructive roles: internal noise can induce circadian oscillations when the system parameters have values that would not sustain oscillations in the deterministic model. In addition, the noise-induced circadian oscillation (NICO) shows the best performance at an optimal noise level, demonstrating the occurrence of INSR in such a system. Since the magnitude of the internal noise is changed via the variation of the system size, the INSR also represents itself as a kind of *system size resonance*.

II. MODEL DESCRIPTION

The model used in the present paper incorporates the transcription of the gene involved in the biochemical clock and transport of the mRNA (M) into the cytosol where it is translated into clock proteins (P_C) and degraded. The protein can be degraded or transported into the nucleus (P_N) where it exerts a negative regulation on the expression of its gene. Such negative regulation forms the core mechanism of the oscillation behavior. If the internal noise is ignored, the time evolution of the three species is governed by the following deterministic kinetic equations:[16,17]

$$\frac{d[M]}{dt} = \nu_s \frac{k_1^n}{k_1^n + [P_N]^n} - \nu_m \frac{[M]}{k_m + [M]},$$

$$\frac{d[P_C]}{dt} = k_s[M] - \nu_d \frac{[P_C]}{k_d + [P_C]} - k_1[P_C] + k_2[P_N],$$

$$\frac{d[P_N]}{dt} = k_1[P_C] - k_2[P_N]. \quad (1)$$

In these equations, the variables $[M]$, $[P_C]$, and $[P_N]$ denote the concentrations of the clock gene mRNA and of the cytosolic and nuclear forms of the clock protein, respectively. The descriptions of the parameters and their values are listed in Table I. We choose the transcription rate ν_s as the control parameter.

To account for the internal noise, such a deterministic description is no longer valid. Basically, one can describe the reaction system as a birth-death stochastic process governed by a chemical master equation, which describes the time evolution of the probability of having a given number of molecules of the three species.[18] Generally, there is no procedure to solve this master equation analytically, but it provides the starting point for numerical simulations. A widely used simulation algorithm was introduced by Gillespie in 1977,[19] which stochastically determines what is the next reaction step and when it will happen according to the transition rate of each reaction process. This simulation method is *exact* because it exactly accounts for the stochastic nature of the reaction events. For the current model, the six reaction steps and corresponding transition rates are shown in Table II (note that the transition rates are proportional to the system size V).

Although the exact simulation method has been widely used to study the properties and effects of internal noise in a variety of systems, it is very time consuming and hardly applicable if the system size is large, which limits its use when a broad range of system size must be considered. To solve this problem, Gillespie developed recently a *τ-leap* method[20] that randomly determines how many steps will take place for each reaction channel in the next ''macroinfinitesimal'' time interval τ. It was proved that the τ-leap method is a rather good approximation of the exact one when the system size is large. Therefore, it is convenient for us to use the

TABLE II. Reaction steps and corresponding transition rates involved in the model.

Reaction step	Description	Transition rate
$G \rightarrow M + G$	Transcription of the clock gene	$W_1 = a_1 \cdot V = \frac{\nu_s k_l^n}{k_l^n + [P_N]^n} \cdot V$
$M \rightarrow$	mRNA degradation	$W_2 = a_2 \cdot V = \nu_m \frac{[M]}{k_m + [M]} \cdot V$
$M \rightarrow P_C + M$	Translation of mRNA into protein	$W_3 = a_3 \cdot V = k_s[M] \cdot V$
$P_C \rightarrow$	Degradation of cytosolic protein	$W_4 = a_4 \cdot V = \nu_d \frac{[P_C]}{k_d + [P_C]} \cdot V$
$P_C \rightarrow P_N$	Transport of protein into the nucleus	$W_5 = a_5 \cdot V = k_1[P_C] \cdot V$
$P_N \rightarrow P_C$	Transport of protein out of the necleus	$W_6 = a_6 \cdot V = k_2[P_N] \cdot V$

exact method for small systems and τ-leap method for large ones during our stochastic simulation if a large range of system size must be accounted for.

The exact method and the τ-leap method have provided a direct way to study the effect of internal noise, however, they are still not quite efficient. Furthermore, such direct stochastic simulation methods cannot afford us a clear perspective on the origin and magnitude of the internal noise in the system. Very recently, Gillespie found that if a macroinfinitesimal time scale exists in the system, its dynamics can be well approximated by a chemical Langevin equation (CLE).[21] Such a CLE clearly shows how the internal noise involved in the chemical reactions is related to the parameter values and the system size, as well as the state variables that evolve with time. Specifically, the CLE for the current model reads

$$\frac{d[M]}{dt}=(a_1-a_2)+\frac{1}{\sqrt{V}}[\sqrt{a_1}\xi_1(t)-\sqrt{a_2}\xi_2(t)],$$

$$\frac{d[P_C]}{dt}=(a_3-a_4-a_5+a_6)+\frac{1}{\sqrt{V}}[\sqrt{a_3}\xi_3(t)-\sqrt{a_4}\xi_4(t)-\sqrt{a_5}\xi_5(t)+\sqrt{a_6}\xi_6(t)],$$

$$\frac{d[P_N]}{dt}=(a_5-a_6)+\frac{1}{\sqrt{V}}[\sqrt{a_5}\xi_5(t)-\sqrt{a_6}\xi_6(t)]. \qquad (2)$$

Here $a_{i=1,\ldots,6}$ are the transition rates per volume shown in Table II, and $\xi_{i=1,\ldots,6}(t)$ are Gaussian white noises with $\langle\xi_i(t)=0\rangle$ and $\langle\xi_i(t)\xi_j(t')\rangle=\delta_{ij}\delta(t-t')$. In the absence of the second terms in the brackets at the right side, the earlier equations are the same as the deterministic ones (1). Therefore, these terms actually denote the internal noises. It is clear that the magnitude of the internal noises scales as $1/\sqrt{V}$, and they depend not only on the control parameters but also on the concentrations of $[M]$, $[P_C]$, and $[P_N]$.

To address the influence of internal noise on the system's dynamics, we need to scan the magnitude of the internal noise over a relatively wide range. In addition, we also need to keep the corresponding deterministic kinetics unchanged, so that what we obtain is purely the effect of internal noise. Although we may change the internal noise via the variation of a certain control parameter as shown in Eq. (2), this would also change the deterministic kinetics in Eq. (1). But the deterministic kinetics does not depend on the system size V. Therefore, in the present work, the magnitude of the internal noise will be changed via the change of V.

In the following parts, we will mainly use the CLE as our stochastic model for numerical simulation. The exact simulation method and the τ-leap method are also used to show consistency if necessary. The results of the stochastic models will also be compared with the deterministic ones to show the effects of internal noise.

III. RESULTS AND DISCUSSION

To investigate the effect of internal noise, it is useful to study the corresponding deterministic kinetics as comparison. To do this, we perform numerical calculation of Eq. (1)

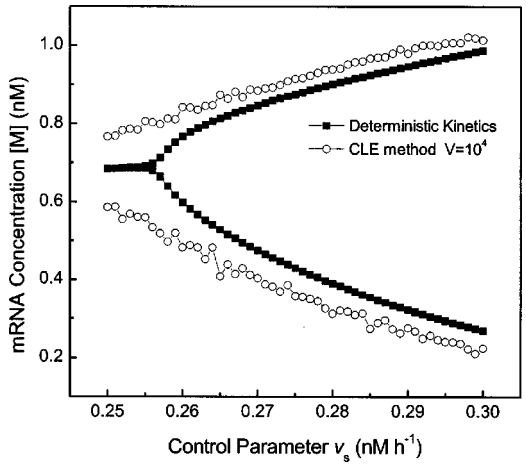

FIG. 1. Bifurcation diagram for the deterministic equation (squares). The Hopf bifurcation value is about 0.257. For comparison, the range of the stochastic oscillation for $V=10^4$ obtained from the chemical Langevin equation is also displayed (circles).

using explicit Eular method with time step 0.005. With the variation of the control parameter ν_s, the system undergoes a supercritical Hopf bifurcation (HB) at $\nu_s\approx 0.257$ from a stable steady state to a stable limit cycle. The period of the oscillation near the HB point is about 26 h, which decreases slowly when ν_s increases. The maximum and minimum values of $[M]$ are plotted in Fig. 1. The HB point divides the nearby parameter space into two regions: the steady state region (SS region) to the left side and the oscillation region (OSC region) to the right side.

In Ref. 16, the influence of internal noise deep inside the OSC region had been studied. The conclusion is that if the system size is too small, the oscillations will be no longer correlated in time. Therefore, internal noise always plays a destructive role in this region. However, as stated by the authors there, such a conclusion fails when the system is tuned near the Hopf bifurcation point. One should note that it is always near the critical points where noise can play constructive roles. Therefore, much more attention should be paid to the region close to the HB.

In the present work, we focus on the effect of internal noise when ν_s is tuned very close to the HB point but inside the SS region. When the system size is very large and the deterministic kinetics applies, the system would not sustain oscillation. However, if the system size is small, simulations via the exact method, the τ-leap method or the CLE method, all show ''stochastic'' oscillations. Such stochastic oscillation is distinct from random noise in that there is a clear peak in its power spectrum. Since these oscillations are induced by the internal noise, one may call them NICO. To compare with the deterministic kinetics, we have also plotted the range of the NICO of $[M]$ for $V=10^4$ in Fig. 1. Obviously, the HB point defined in the deterministic kinetics now disappears. In other words, when the system size is small, one cannot qualitatively distinguish the SS region from the OSC region from the time behavior only.

The phenomenon of NICO implies some kind of resonance effect. If the system size is very large and the internal noise is ignorable, there is no oscillation in the SS region.

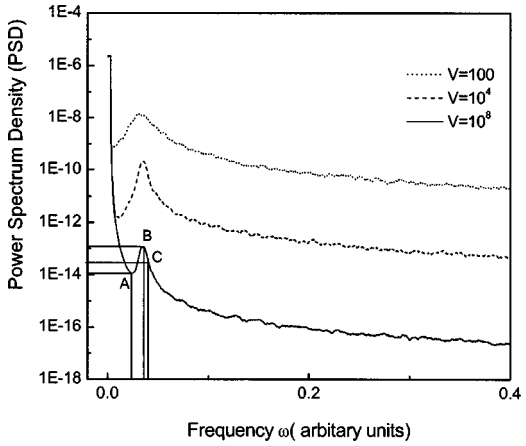

FIG. 2. Smoothed power spectrums for the stochastic oscillation of $[M]$ for three different system sizes $V=100$, 10^4, and 10^8, respectively. The control parameter is $\nu_s=0.25$. The curve for $V=100$ is obtained from the exact simulation method, while the other two are obtained by the τ-leap method. The points *A*, *B*, and *C* in the PSD curve for $V=10^8$ demonstrate how to calculate the effective SNR, i.e., $\beta=[P(B)/P(A)]\times\omega_B/(\omega_C-\omega_B)$, where point C is located by the condition $P(C)=P(B)/e$. Note that arbitrary unit is used for the PSD.

When the system size is too small, the internal noise is so large that the NICO will be overwhelmed. Hence, for some intermediate system size and internal noise level, NICO is the most pronounced. In Fig. 2, the power spectrums for the stochastic oscillations of $[M]$ are plotted for three different system sizes. The control parameter is $\nu_s=0.25$ which is slightly less than the HB value. The smoothed curves are obtained by nearest averaging over 50 points from the original ones. The time series used to calculate the power spectrum contains 16 384 data points with an average time interval 0.5. A Welch window function is used during the estimation of the power spectrum.[22] Clear peaks appear in the power spectrum, which implies that the time series contains periodic information. When the system size decreases from 10^8 to 100, both the signal level and noise background increase at the peak. For an intermediate system size $V=10^4$, the peak is the most pronounced among the three.

To measure the relative performance of the stochastic oscillations quantitatively, we define an effective SNR as $\beta=R/(\Delta\omega/\omega_p)$, where ω_p is the frequency at the peak, $\Delta\omega$ is the width between ω_p and the frequency ω_1 satisfying $\omega_1>\omega_p$ and $P(\omega_1)=P(\omega_p)/e$, here $P(\cdot)$ denotes the power spectrum density (PSD) for a given frequency; $R=P(\omega_p)/P(\omega_2)$, where $P(\omega_2)$ is the smallest PSD value between $P(0)$ and $P(\omega_p)$. See also the caption of Fig. 2 for more details. The dependence of β on system size for $\nu_s=0.25$ is plotted in Fig. 3(a). A clear maximum is present for system size $V\sim10^4$, which demonstrates the existence of a resonance region. Since this resonance effect is purely induced by the internal noise, we thus simply call it INSR.

In Fig. 3(a), good qualitative agreement among the CLE method, the exact simulation method and the τ-leap method is apparent. Specifically, the CLE method and the τ-leap method show excellent quantitative agreements for $V\geqslant10^4$. These agreements imply that it's convenient to use the CLE to study the qualitative effects of internal noise in a system-

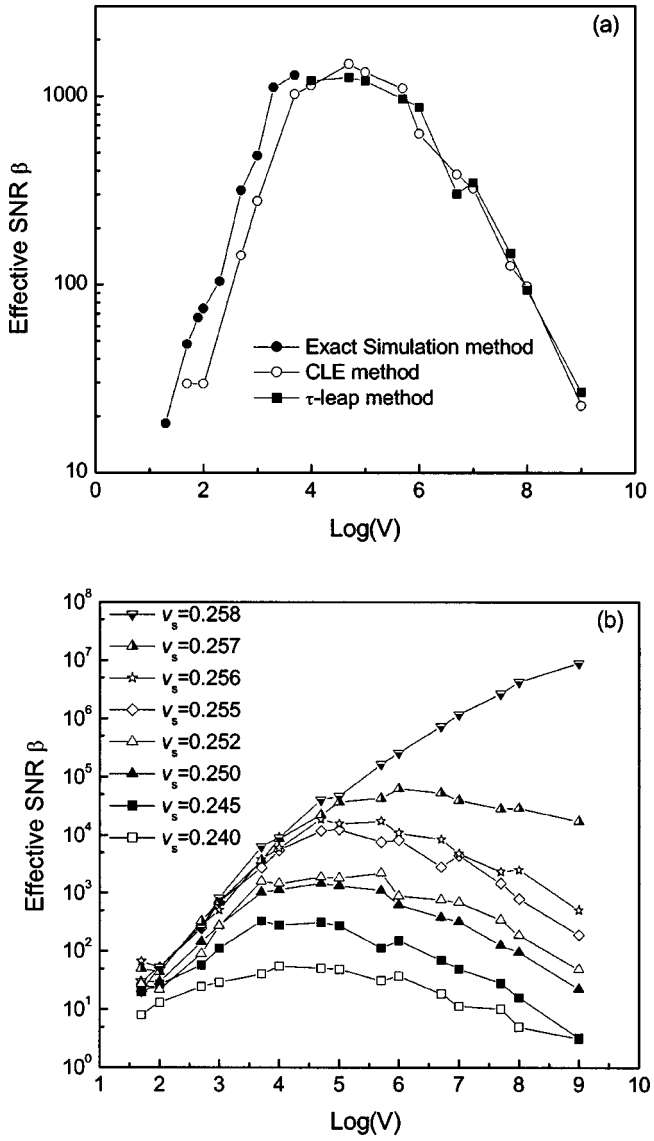

FIG. 3. (a) Dependence of the effective SNR on the system size for $\nu_s=0.25$. Solid circles: results from exact simulation method for $V<10^4$; solid squares: results from τ-leap approximation method for $V\geqslant10^4$; open circles: results obtained via chemical Langevin equation. All the data are averaged over 20 independent runs. (b) The dependence of SNR on system size for different choices of the control parameter. The results are obtained by the CLE method.

atic way. Using the CLE, we have also studied how the INSR behavior depends on the value of the control parameter. This is shown in Fig. 3(b). When the control parameter ν_s comes closer to the HB point, the ISNR curve becomes higher. For ν_s nearly identical to the HB value, there is a plateau in the curve. For ν_s slightly larger than the HB value, the peak disappears and the SNR monotonically increases with the increment of system size.

Such INSR phenomenon might be relevant to circadian oscillations in two ways: First, since the internal noises are unavoidable, circadian oscillations taking place in subcellular systems are intrinsically stochastic oscillations. Due to the occurrence of NICO, circadian oscillations can be quite robust to variation of control parameters. Second, instead of trying to resist the internal noise, circadian clock systems

may also exploit it to induce and enhance the oscillation performance via tuning of internal noise. It is also interesting to note that the spontaneous action potential in neurons shows the best time precision when the density of axon ion channels reaches an optimal level,[23] and the calcium signaling processes in many cells also show maximum sensitivity if the cluster size of the release channels is optimal.[24] Such behaviors imply that INSR might be a widely used mechanism for living organisms to adapt and function.

IV. CONCLUSION

In conclusion, we have studied the influence of internal noise on a circadian clock system using stochastic simulation methods and chemical Langevin equations. It is found that internal noise can induce circadian oscillations, when the corresponding deterministic system does not oscillate. The performance of the noise induced circadian oscillation undergoes a maximum with the variation of the internal noise level, which demonstrates the occurrence of internal noise stochastic resonance. Since the magnitude of the internal noise is changed via the change of system size, this phenomenon also represents itself as a kind of system size resonance. These findings may imply the ubiquitous importance of internal noise in the functioning processes of living organisms.

ACKNOWLEDGMENT

This work is supported by the National Science Foundation of China (20173052, 20203017).

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