PHYSICAL REVIEW E **80**, 011907 (2009)

Noise effect on persistence of memory in a positive-feedback gene regulatory circuit

Jun Tang,[1,*] Xianqing Yang,[1] Jun Ma,[2] and Ya Jia[3]
[1]*College of Science, China University of Mining and Technology, Xuzhou 221008, China*
[2]*Department of Physics, Lanzhou University of Technology, Lanzhou 730050, China*
[3]*Department of Physics and Institute of Biophysics, Huazhong Normal University, Wuhan 430079, China*

(Received 20 April 2009; published 9 July 2009)

Feedback circuits are important building blocks of gene regulatory network. Recent studies with simplified models found the advantage of coupled fast and slow feedback loops in creating bistable switch, and interlinked dual-time feedback loops can enhance robustness to stochasticity and persistence of memory. Based on the same feedback structure and mathematical model, the effect of noise on persistence of memory is investigated. It is found that (1) an intermediate amount of single-parameter noise plays a constructive role in persisting memory through noise-induced changing from monostable to bistable region, while larger single-parameter noise destroys the memory ability of the system through noise-induced transition between two stable states. (2) Different from the single-parameter noise, arbitrary amount of the internal noise destroys the memory ability of the system. (3) For the same feedback structure with less nonlinear feedback which is not enough to render the system bistability, the single-parameter noise can play similar constructive role through rendering the system bistability.

DOI: 10.1103/PhysRevE.80.011907 PACS number(s): 87.18.Tt, 05.40.Ca, 05.70.Fh

I. INTRODUCTION

Biological memory, which means biological systems exhibit prolonged or permanent responses to transient stimuli, is a ubiquitous phenomenon [1]. Complex gene networks store memory through creating two or many discrete, stable states of network activity [2–4]. In synthetic gene circuits, the bistability is generated by simple feedback loops. For example, the synthetic toggle switch is composed of two proteins (LacI and λcI), and each protein negatively regulates the synthesis of the other [5,6]. There are two possible steady states for this system. Because LacI production is repressed by λcI protein, an initial high concentration of λcI would be self-sustaining and lead to a state with high λcI and low LacI concentrations. Conversely, because λcI production is repressed by LacI, if LacI is initially present in high concentrations, a second stable state would entail high LacI and low λcI concentrations. In naturally occurring networks, the systems possess more complex organization of multiple nested feedback loops. For example, in the yeast *Saccharomyces cerevisiae*, the galactose signaling pathway involves more than four proteins, and they regulate the synthesis of each other negatively or positively [7]. Intuitively, the construction of gene networks influences the persistence of memory intensively. Recently, Smolen *et al.* [8] found that interlinked dual-time feedback loops can enhance persistence of memory.

Noise can be introduced into the gene regulatory network by diverse sources. The external noise originates from the random variations in one or more of the externally set control parameters, such as the rate constants associated with a given set of reactions. While the internal noise comes from discrete nature of biochemical events such as transcription, translation, multimerization, and protein/mRNA decay processes. The external and internal noises often exist in biological system simultaneously, and the effect of noise on biological system has been extensively studied from both theoretical and experimental points of view [7,9–15]. They can be controlled experimentally [14], and the total effects of noises can be decomposed into internal and external components [15]. Both noise sources can enhance or reduce the coherence in biological system, and external noise coherence resonance can be suppressed by internal noise, while internal noise coherence resonance can be enhanced by the modulation of external noise strength [13]. Noise is often perceived as being undesirable and unpredictable, however, more and more advantages of noises are found in recent decades. For instance, our previous work has proven that noise can play the constructive role to enhance coherence in the bistable neurons through noise-induced changing from bistable to oscillatory regime [16]. Based on a Ca^{2+} model presented by Li and Rinzel [17], Shuai *et al.* [9] found that internal noise play an important role in inducing subthreshold or superthreshold oscillation. In Ref. [7], Acar *et al.* enhanced the cellular memory by reducing the stochastic transition between stable states, obviously, noise plays a destructive role to memory in Ref. [7]. Now questions to be raised are as follows: can noise play some constructive role in persistence of memory in gene regulatory networks? If it can, what is the mechanism?

Motivated by the above consideration and based on the similar models used in Refs. [8,18,19], we explore the effects of two different noise sources on persisting memory. One is the noise originated from single-parameter control, which is named as "single-parameter noise" to differ from the global internal noise in the circuit. The other one is the internal noise due to molecule number fluctuations. The dual-time feedback structures in Refs. [8,18,19] can enhance the resistance of bistability to noise. This resistance ensures the transitions between two states, which destroy the memory of the system, may not be induced by little or intermediate amount of noise. This is important when the noise effect on memory

---

[*] Corresponding author; tjuns1979@yahoo.com.cn

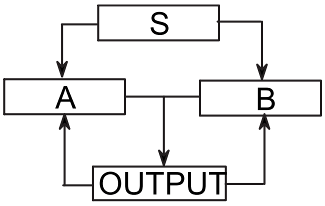

FIG. 1. Schematic of the feedback network, where arrows represent positive regulation.

is studied. The advantage of single-parameter noise in persistence of memory is numerically identified, and we explain the numerical results analytically by using small noise approximation. This paper is organized as follows. In Sec. II, an interlinked dual-time feedback circuit and corresponding mathematical model are introduced. In Sec. III, the effect of the single-parameter noise on the persistence of memory is studied numerically, and the results are explained by an approximate approach in the frame of a small-noise expansion. In Sec. IV, the effect of internal noise is discussed by simulation with the Gillespie algorithm. In Sec. V, we decrease the nonlinear feedback in the model to destroy the bistability of the system, and then the effect of single-parameter noise on persistence of memory is discussed similarly. We end with conclusions in Sec. VI.

II. MODEL

The model, which is schematized in Fig. 1, can be extracted from many realistic biological circuits [19]. Productions of both A and B are catalyzed by an external stimulus S. A and B add together to increase the production of the output element C, and C feeds back to increase the production of both A and B. Obviously, two coupled positive-feedback loops are formed in the circuit. The equations of the model are as follows [8,18]:

$$\tau_a \frac{da}{dt} = f(a,c) = \left(k_1 s + k_2 \frac{c^4}{c^4 + K^4}\right)(1-a) - \lambda a + k_m, \quad (1)$$

$$\tau_b \frac{db}{dt} = f(b,c) = \left(k_1 s + k_2 \frac{c^4}{c^4 + K^4}\right)(1-b) - \lambda b + k_m, \quad (2)$$

$$\frac{dc}{dt} = k_{on}(a+b)(1-c) - k_{off} c + k_{mo}, \quad (3)$$

where a, b, and c represent the concentration of A, B, and C, correspondingly, and s denotes the stimulus strength. τ_a, τ_b are the two time constants of feedback loops. The parameter values are $k_1=0.1$, $k_2=0.3$, $K=0.5$ μM, $k_m=0.01$, $k_{on}=1.0$ μM^{-1} s^{-1}, $k_{off}=0.3$ s^{-1}, $k_{mo}=0.003$ μ M s^{-1}, $\tau_a=2.0$ s, $\tau_b=200.0$ s, and $\lambda=1.12$. Compared to Ref. [18], λ is a parameter we introduce into the model to represent the effective decay constant, which may involve the degeneration of protein and dilution due to cell growth.

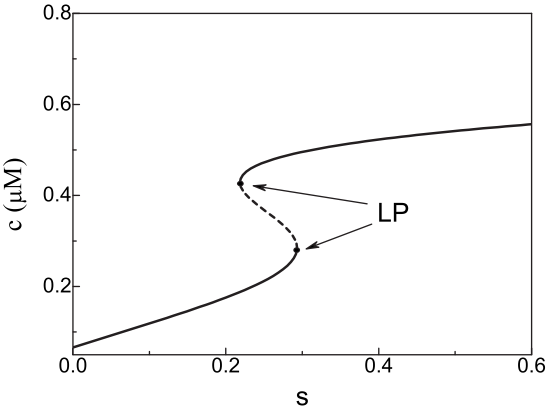

FIG. 2. Bifurcation diagram of output as a function of stimulus strength. LP denotes a limit point at which a steady state vanishes. The solid line indicates stable states, while the dashed line indicates the unstable states.

Bistable response of the system to external stimulus is due to high nonlinearity in the feedback from C to A and B. Figure 2 exhibits the response of the system to different stimulus strength. The two limit points (LPs) enclose a bistable region; for any s within this region, the model possesses two stable solutions and one unstable solution; for s out of this region, the model possesses only one stable solution. Stable solutions are separated into two branches by the unstable solution, the upper branch corresponds to bistable switch-on state, while the lower one corresponds to switch-off state. It is well known that an enough large amount of transient stimulus can drive the system from switch-off state to switch-on state, and if the system is bistable, it can maintain on the switch-on state after the stimulus is removed, this is the phenomenon of biological memory, otherwise, the system will draw back to switch-off state.

III. EFFECT OF SINGLE-PARAMETER NOISE FOR THE BISTABLE MODEL

In this section, the effect of noise originated from single-parameter fluctuation is discussed. In biological system, single-parameter control is ubiquitous. For example, the binding of extracellular agonists to specific receptor in the cell membrane increases the intracellular concentration of IP$_3$ [20]. In synthetic gene networks, the effective protein degradation rates are increased by using SsrA tags [21]. The control of specific parameters often bring along additional fluctuations which are larger than other noise source. So considering noise originated from single-parameter fluctuation is biological meaningful. It is assumed that the effective decay constant λ is subjected to additive random fluctuation, i.e., $\lambda \to \lambda + \xi(t)$. The additive fluctuation gives rise to two multiplicative noise terms in Eqs. (1) and (2), and the stochastic version of Eqs. (1) and (2) is given by

$$\tau_a \frac{da}{dt} = f(a,c) - a\xi(t), \quad (4)$$

$$\tau_b \frac{db}{dt} = f(b,c) - b\xi(t), \quad (5)$$

where the multiplicative noises are interpreted in Stratonovich sense, $\xi(t)$ is the Gaussian white noise. The statistical properties are given by

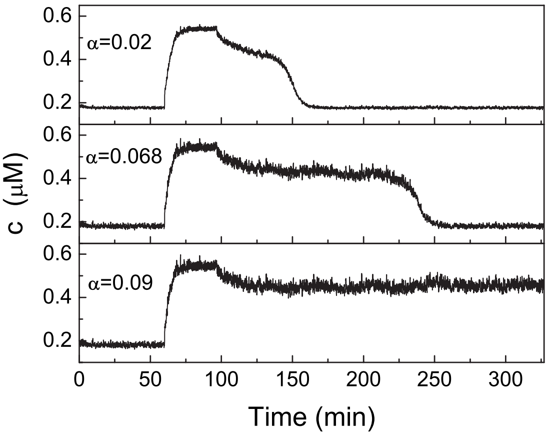

FIG. 3. Top to bottom: time series of the output for different noise intensities. The stimulus strength s is changed from 0.2 to 0.5 at time $t=60$ min and return to 0.2 at $t=97$ min.

$$\langle \xi(t) \rangle = 0, \langle \xi(t)\xi(t') \rangle = 2\alpha\delta(t-t'), \tag{6}$$

where α is the corresponding noise intensity and δ is the Kronecker symbol. We use a forward Euler integration scheme with a time step 10^{-3} s. Simulations verify further time step reduction does not significantly improve accuracy. The numerical algorithm presented by Sancho *et al.* [22] will be used to simulate the noise.

The basal stimulus strength is set 0.2, with this value the system is monostable and close to the bistable region (see Fig. 2). No phenomenon of persistence of memory can be found for the noise-free system. Otherwise, in Fig. 3, it is illustrated noise enhances the persistence of memory. In all simulations, the stimulus strength s is changed from the basal value to 0.5 at time $t=60$ min and return to basal value at $t=97$ min. It seems that the noise produces a new stable state, and the stability of the state increases with the intensity of the noise. To quantify the persistence of memory, we define the memory time t_m indicating the period between the time at which the stimulus is removed ($t=97$ min) and the output c is back to the switch-off state. For very low noise intensity, the memory time is short, and for intermediate α, the memory time increases, which corresponds to the prolonged memory. For large enough α, the system exhibits the phenomenon of permanent memory.

The average t_m for any values of α are calculated over 100 simulations. The results are exhibited in Fig. 4, it shows that for low noise intensity, t_m remains short, after α increases to about 0.06, t_m increases exponentially to infinity.

As mentioned in Sec. I, gene networks store memory through creating multistability of network activity, intuitively, the noise enhancing persistence of memory is due to the noise-induced change from monostable to bistable region. To analytically explain this change, an approximate approach is used. In order to establish the effect of the multiplicative noise term, we note that it has a nonzero mean equal to

$$\left\langle -\frac{x}{\tau_x}\xi(t) \right\rangle = \frac{\alpha}{\tau_x^2}\langle x \rangle, \tag{7}$$

where $x=a$ and b for Eqs. (4) and (5), correspondingly. The angular brackets denote averaging over the probability distribution of the multiplicative noise. According to Eq. (7), the noise term gives rise to a systematic nonzero contribution to the average dynamics of the system. This systematic contribution can be incorporated explicitly into Eqs. (4) and (5) as the first-order term of a small-noise expansion [23,24]. The effective equation for Eqs. (4) and (5) can be written as

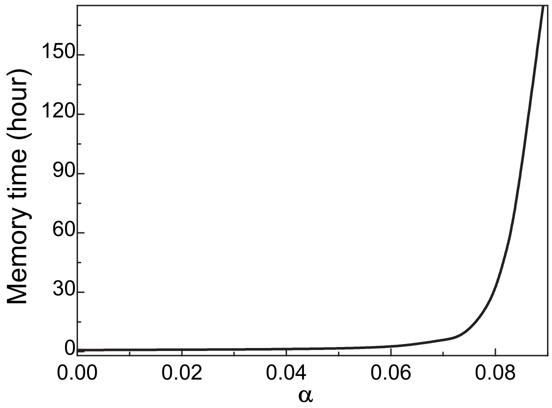

FIG. 4. Memory time t_m vs noise intensity α. The memory time is averaged over 100 simulations.

$$\tau_a\frac{da}{dt} = \left(k_1 s + k_2\frac{c^4}{c^4+K^4}\right)(1-a) - \left(\lambda - \frac{\alpha}{\tau_a}\right)a + k_m,$$

$$\tau_b\frac{db}{dt} = \left(k_1 s + k_2\frac{c^4}{c^4+K^4}\right)(1-b) - \left(\lambda - \frac{\alpha}{\tau_b}\right)b + k_m. \tag{8}$$

To understand the behavior of the effective model [Eqs. (3) and (8)], the stable states are calculated as a function of noise intensity α in Fig. 5. For α in the region (0.058, 0.576), the effective system is bistable, i.e., the noise induces the change from monostable to bistable region. The α value of the left "LP" approximately accords with the point at which the memory time starts to exponentially increase in Fig. 4.

It must be pointed out that the memory is destroyed by the noise larger than that one in Fig. 4 although the system is driven to bistable region because larger noise can induce spontaneous transition to switch-on state without increasing stimulus strength (see top of Fig. 6). For every larger noise

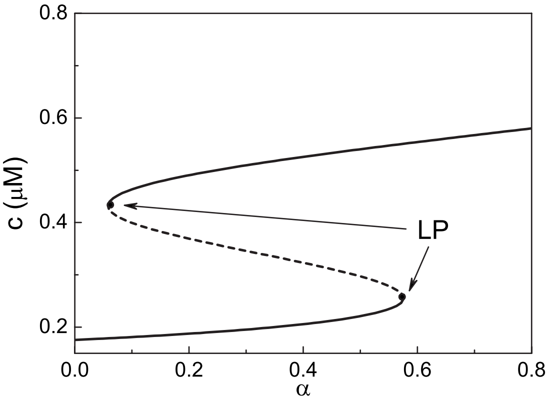

FIG. 5. Bifurcation diagram of output as a function of noise intensity α is plotted based on the effective model.

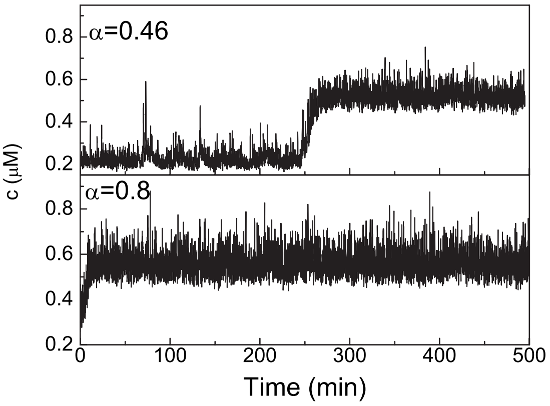

FIG. 6. Time series of the output for the large noise intensities. The stimulus strength s is fixed at the basal value 0.2.

intensity, we perform 100 simulations without increasing of s. In Fig. 7, the fraction of the simulations in which the spontaneous transition occurs within 500 min is displayed as a function of noise intensity. It shows that for noise intensity less than 0.4, almost no spontaneous transition occurs; for $0.4<\alpha<0.5$, the fraction steeply increases to 100%. Furthermore, for noise larger than about 0.57, the system spontaneously transits to the switch-on state at time close to $t=0$ min (see bottom of Fig. 6). It is because the noise intensity larger than the right LP in Fig. 5 drives the system to the region with only one switch-on state.

IV. EFFECT OF INTERNAL NOISE

Comparing to the single-parameter noise, this section will focus on the overall internal noise due to molecule number fluctuations. The fluctuations in the copy number of a, b, and c will be simulated with the Gillespie algorithm [25]. Relative to the rate equation with noise term [see Eqs. (4) and (5)], this algorithm is impressively complete and yields a detailed picture of the behavior of the system modeled. However, such completeness comes at a high computational cost and sacrifices any immediate prospect of analytical treatment, such as the small-noise approximation. The Gillespie algorithm takes variable time steps, and only one reaction occurs during each time step. Which reaction occur is determined randomly, with the probability of each reaction proportional to its deterministic rate. In Eqs. (1)–(3), each term on the right-hand side corresponds to a reaction rate. A volume factor Ω is introduced to implicitly represent the volume, i.e., increasing Ω corresponds to increasing volume while keeping average copy numbers per unit volume the same. See Ref. [8] for more simulation details. Obviously, larger Ω means the system is subjected to less copy number fluctuation (internal noise).

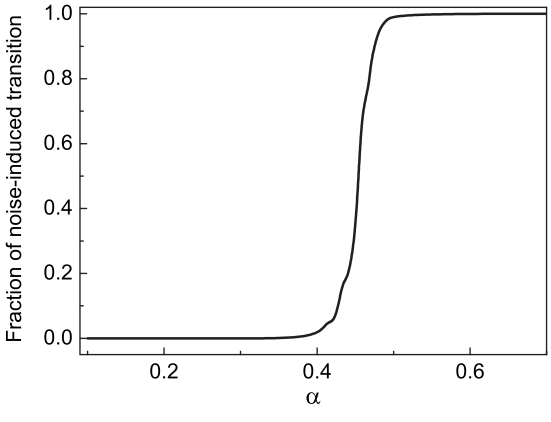

FIG. 7. The fraction of the simulations in which the spontaneous transition occurs within 500 min is plotted as a function of noise intensity.

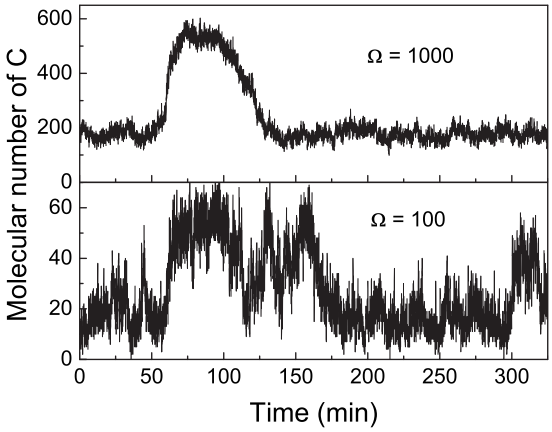

FIG. 8. Time series of the output for different effective volume factors. The stimulus strength s is changed from 0.2 to 0.5 at time $t=60$ min and return to 0.2 at $t=97$ min.

Similar to single-parameter noise, the stimulus strength s is changed from the basal value to 0.5 at time $t=60$ min and return to basal value at $t=97$ min. Many simulations with different Ω are performed, and no explicitly increase in memory time t_m is found (see top of Fig. 8). For enough little Ω, i.e., the system subjected to enough large amount of noise, the system transits spontaneously between the two stable states (see bottom of Fig. 8), memory ability of the system is totally destroyed.

In Fig. 9 the memory time t_m is averaged over 100 simulations for different Ω. It shows that the memory time decreases with the decrease in Ω or the increase in noise

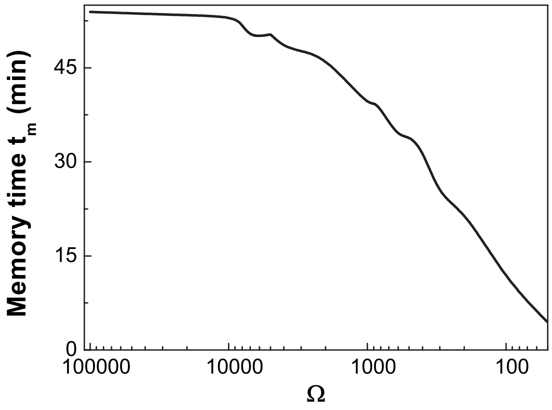

FIG. 9. Memory time t_m vs effective volume factors Ω. The memory time is averaged over 100 simulations.

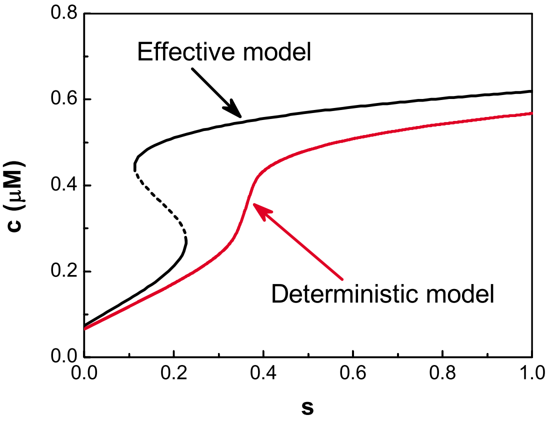

FIG. 10. (Color online) The steady states of the systems as a function of stimulus strength $s(k_2=0.28)$.

amount. Otherwise, comparing to the value of t_m in Fig. 4, t_m in Fig. 9 is too short to persist poor biological memory.

In some circumstance, the internal noise is modeled by simple Langevin equations, i.e., the additive noise terms are added to the deterministic equations. To compare with the Gillespie algorithm, here we also test the internal noise by Langevin method, no significant difference is obtained (results not show). In fact, the internal noise corresponds to overall fluctuations in biological system. We believe the overall fluctuations due to other sources, such as thermal fluctuations, influences the persistence of memory similarly to molecule number fluctuations. Comparing to the internal noise, the single-parameter noise corresponds to amplification of local fluctuation under the overall "background" noise. It is the local amplification that systematically changes the dynamics of the system and render it bistability.

V. EFFECT OF SINGLE-PARAMETER NOISE FOR THE MONOSTABLE MODEL

In Sec. III, the system is easily driven to bistable region by increasing stimulus strength although the basal stimulus strength is set 0.2, for which the system possesses only one stable states (see Fig. 2). Comparing to the deterministic dynamics, it seems that the single-parameter noise plays an accessorial role in driving the system to bistable region. The bistability is due to the nonlinear feedback from C to A and B. In this section, we decrease the nonlinear feedback through decreasing k_2 to 0.28, for which the system is not bistable for any stimulus strength (see Fig. 10). How does the single-parameter noise influence the persistence of memory in this nonbistable system?

As Sec. III does, the stimulus strength s is changed from the basal value to 0.5 at time $t=60$ min and return to basal value at $t=97$ min. Figure 11 shows that the same phenomenon of enhancing persistence of memory is found in the nonbistable system. The small-noise approximation is adapted to explain the enhancement. As an example, the stable states of the effective model are calculated as a function of s for $k_2=0.28$ and $\alpha=0.5$ (see Fig. 10). It seems that the noise renders the system bistability although the nonlinear feedback is not large enough to do so, i.e., the noise plays a role in rendering the system bistability as the nonlinear feedback does in Sec. III.

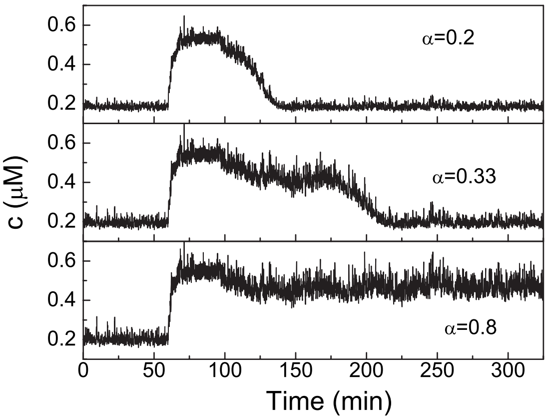

FIG. 11. Top to bottom: time series of the output for different noise intensities. The stimulus strength s is changed from 0.2 to 0.5 at time $t=60$ min and return to 0.2 at $t=97$ min$(k_2=0.28)$.

To compare the effect of the noise and the nonlinear feedback in rendering the system bistability, the bistable region of the effective model are plotted against the parameters k_2 and α in Fig. 12. It shows that with k_2 decreases from 0.3, more and more amount of noise are needed to render the system bistability, and the bistable region is narrowed. It can be easily understood in Figs. 3 and 11. In Fig. 3, noise intensity of less than 0.1 may persist permanent memory, while, in Fig. 11, noise intensity of 0.8 is needed. In one word, with decreased nonlinear feedback, the noise is less efficient in persisting memory. On the other hand, with the increase in α, the bistable region of the system are also narrowed. So we can come to the conclusion that the single-parameter noise is same as the nonlinear feedback in rendering the system bistability.

It must be pointed out that the analytical method used in this paper is valid for small noise. In the right part of Figs. 5 and 12, the analytical results may be inaccurate. However, we prefer to the accordance of analytical results and simulations for lower noise intensity. For high noise intensity, it is

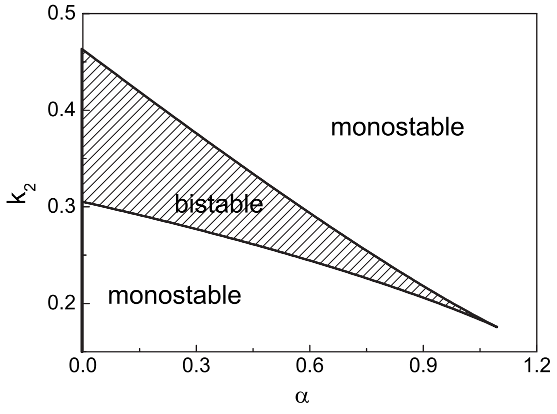

FIG. 12. Phase diagram showing the dynamics of the system. In the shadowed region, the effective model is bistable, elsewhere the model is monostable.

obvious that the large fluctuation or transiting between the states makes the persistence of memory impossible.

VI. CONCLUSION

In summary, we have studied the effect of noise on persistence of memory in an interlinked dual-time feedback loops, which is extracted from many realistic gene regulatory networks. It is found that the single-parameter noise due to single-parameter control plays a constructive role in maintaining prolonged even permanent memory while the internal noise cannot. A effective model is derived by using small-noise approximation to analytically explain the effect of single-parameter noise, and the constructive role of single-parameter noise is due to the noise-induced change from monostable to bistable region. Further comparing shows the single-parameter noise can solely render the system bistability while the increasing of stimulus cannot change it from monostable to bistable region.

The single-parameter noise in this paper is originated from parameter λ. We believe the noises that originated from the other parameters can also give rise to some systematic contribution to the dynamics of the system, which may link to some constructive biological function of noise, and this is a motivation of our future work.

ACKNOWLEDGMENTS

We thank Dr. Lijian Yang for her help. This work was supported by the National Natural Science Foundation of China under Grant Nos. 10875049 (Y.J.) and 10747005 (J.M.).

---

[1] Z. Han, T. M. Vondriska, L. Yang, W. R. MacLellan, J. N. Weiss, and Z. Qu, J. Theor. Biol. **246**, 755 (2007).
[2] W. Xiong and J. E. Ferrell, Nature (London) **426**, 460 (2003).
[3] B. M. Shykind *et al.*, Cell **117**, 801 (2004).
[4] N. I. Markevich, J. B. Hoek, and B. N. Kholodenko, J. Cell Biol. **164**, 353 (2004).
[5] H. K. Kobayashi, M. Kærn, M. Araki, K. Chung, T. S. Gardner, C. R. Cantor, and J. J. Collins, Proc. Natl. Acad. Sci. U.S.A. **101**, 8414 (2004).
[6] T. Tian and K. Burrage, Proc. Natl. Acad. Sci. U.S.A. **103**, 8372 (2006).
[7] M. Acar, A. Becskei, and A. V. Oudenaarden, Nature (London) **435**, 228 (2005).
[8] P. Smolen, D. A. Baxter, and J. H. Byrne, Phys. Rev. E **79**, 031902 (2009).
[9] J. W. Shuai and P. Jung, Phys. Rev. Lett. **88**, 068102 (2002).
[10] Z. H. Hou and H. W. Xin, Phys. Rev. E **60**, 6329 (1999); Z. H. Hou, L. F. Yang, and H. W. Xin, J. Chem. Phys. **111**, 1592 (1999); Z. W. Wang, Z. H. Hou, and H. W. Xin, Chem. Phys. Lett. **362**, 51 (2002).
[11] J. M. Raser and E. K. O'Shea, Science **309**, 2010 (2005).
[12] M. Thattai and A. V. Oudenaarden, Proc. Natl. Acad. Sci. U.S.A. **98**, 8614 (2001).
[13] M. Yi, Y. Jia, Q. Liu, J. Li, and C. Zhu, Phys. Rev. E **73**, 041923 (2006).
[14] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, Science **297**, 1183 (2002).
[15] P. S. Swain, M. B. Elowitz, and E. D. Siggia, Proc. Natl. Acad. Sci. U.S.A. **99**, 12795 (2002).
[16] J. Tang, Y. Jia, M. Yi, J. Ma, and J. Li, Phys. Rev. E **77**, 061905 (2008).
[17] Y. Li and J. Rinzel, J. Theor. Biol. **166**, 461 (1994).
[18] X. P. Zhang, Z. Cheng, F. Liu, and W. Wang, Phys. Rev. E **76**, 031924 (2007).
[19] O. Brandman, J. E. Ferrell, R. Li, and T. Meyer, Science **310**, 496 (2005).
[20] X. P. Sun, N. Callamaras, J. S. Marchant, and I. Parker, J. Physiol. **509**, 67 (1998).
[21] J. Hasty, D. McMillen, F. Isaacs, and J. J. Collins, Nat. Rev. Genet. **2**, 268 (2001).
[22] J. M. Sancho, M. San Miguel, S. L. Katz, and J. D. Gunton, Phys. Rev. A **26**, 1589 (1982).
[23] A. Zaikin, J. García-Ojalvo, R. Báscones, E. Ullner, and J. Kurths, Phys. Rev. Lett. **90**, 030601 (2003).
[24] J. García-Ojalvo and J. M. Sancho, *Noise in Spatially Extended Systems* (Springer, New York, 1999).
[25] D. Gillespie, J. Phys. Chem. **81**, 2340 (1977).