Physica A 501 (2018) 170–177

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

A dual role of extrinsic noise in coupled synthetic clock cells due to a two-steps synchronization mechanism

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HIGHLIGHTS

- The synchronization dynamics under stochastic noise are explored.
- The effects of extrinsic noise original from signal molecule are studied by evaluating the order parameters.
- A theoretical analysis by using the small-noise approximation is presented.

ARTICLE INFO

Article history:
Received 30 September 2017
Received in revised form 22 December 2017
Available online 21 February 2018

Keywords:
Synchronization dynamics
Stochastic noise

ABSTRACT

Based on the model describing two coupled synthetic clock cells, the synchronization dynamics under stochastic noise are explored. As extrinsic noise from signal is the predominant form of noise for all gene promoters, we investigate the effects of extrinsic noise original from signal molecule by evaluating the order parameters. It is found that strong noise is beneficial for the synchronization of loose-coupling system, while it destroys the synchronization of tight-coupling system. The underlying mechanisms of these two opposite effects are clarified numerically and theoretically. Our research illustrates that (i) when the coupling strength is small, the noise mainly adjusts the period difference of two cells and the system becomes regular. Theoretical study reveals that the mean effect of noise is like to be influx while signal flow is efflux under such a situation. (ii) With the increment of coupling strength, the cells have the same frequency. It is obvious that the noise mainly changes the phase difference between the two cells and destroys the synchronization of the system. (iii) We also demonstrate that, under certain moderate noise intensities, the noise can induce the synchronization order to be the worst. This nonlinear behavior only can be observed in a very narrow region of coupling strength.
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1. Introduction

The analysis of complex systems from the viewpoint of networks has become an important interdisciplinary issue. It has been shown that physical and dynamical processes, such as cascading failures [1–3], epidemic spreadings [4,5], oscillation deaths [6], and network synchronization [7–11], are strongly influenced by the topology of the connections, the strength of the connections and fluctuations.

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https://doi.org/10.1016/j.physa.2018.02.134
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In biological networks, fluctuations original from environmental conditions or genetic variation are inherent in every molecular event that takes place in bio-systems [12–21]. Noise sources were thought to disturb the phase synchronization, and therefore have long been considered to exert a negative influence on the precise temporal relationship between oscillators [14]. Noises from circumstance were found to have a negative effect to the order of two different delay-coupled complex dynamical networks [15]. The synchronization robustness criterion was discussed by Chen et al. in a population of synthetic genetic oscillators [16]. They found that if the synchronization robustness is stronger than the sum of intrinsic robustness and extrinsic robustness, the stochastic coupled synthetic oscillators can be robustly synchronized in spite of intrinsic parameter fluctuation and extrinsic noise.

However, under some circumstances, noise can play a constructive role on the synchronization. Hauschildt and his cooperators investigated a network composed of two coupled neurons [17]. They found external noise-induced cooperative dynamics and discussed the control of the stochastic synchronization. Internal noise of bio-system is unavoidable. In two coupled calcium subsystems, internal noise could increase the oscillation region [18]. This study showed an optimal volume for the coupled subsystems to exhibit the best performance of the stochastic oscillation.

All of these findings indicate an important role of noise on the synchronization of interacting dynamical elements. It remains, however, unclear that under what conditions noise effect is constructive or destructive in a coupled system. In order to answer this question, we employ a correlated synthetic clock model proposed by Ojalvo et al. [22]. Since synchronization is determined both by the period difference and the phase difference, we choose the coupled system composed with only two cells to realize the calculations of those two main factors. A Gaussian white noise is introduced into the diffusion rate of the coupling signal element AI to simulate the extrinsic fluctuation from environment. We put our emphasis on the effects of noise through calculating the order parameters of the coupled system. Our goal is to reveal the potential effects of extrinsic noise on two coupled clocks and the possible dynamical mechanisms for different regulatory roles of extrinsic noise.

The paper is organized as follows. In Section 2, the stochastic model describing two coupled synthetic clocks subject to extrinsic fluctuation is given by the ordinary differential equations. In Section 3, for the deterministic model, we will discuss the effects of cell density on the order parameter and period difference between two cells. For the stochastic model, we will study the effects of extrinsic noise on synchronization and compare theoretically the mean effect of noise with signal. Furthermore, the underlying physical mechanisms for the observed phenomena are discussed. We end with discussion in Section 4.

2. Model

The model we considered is composed of two oscillators. Each one communicates with the environment that constructs the correlation between them (Fig. 1(a)). This model is based on a synthetic clocks, such a system can be composed of two cells coupling through quorum-sensing mechanism by signal element AI (autoinducer) [22]. Each cell has two parts shown in Fig. 1(b): one is a synthetical repressilator composed with three genes (*lacI*, *tetR*, and *lacI*), the products of which inhibit the transcription of each other in a cyclic away. The other part is the intercell signaling apparatus that makes use of AI (synthesized from LuxI) and protein LuxR. The complex LuxR–AI activates transcription of gene *LacI*. Since the gene that encodes LuxI is under the control of the repressilator protein LacI, this intercell signaling apparatus can be incorporated into the part one.

Under the above design, the mRNA dynamics is

$$\begin{aligned} \frac{da_i}{dt} &= -a_i + \frac{\alpha}{1+C_i^n}, \\ \frac{db_i}{dt} &= -b_i + \frac{\alpha}{1+A_i^n}, \\ \frac{dc_i}{dt} &= -c_i + \frac{\alpha}{1+B_i^n} + \frac{\kappa S_i}{1+S_i}. \end{aligned} \tag{1}$$

Here a_i, b_i, and c_i are the concentrations in cell i ($i = 1$ or 2) of mRNA transcribed from *tetR*, *cI*, and *lacI*, respectively, and the concentration of the corresponding proteins are presented by A_i, B_i, and C_i. The concentration of AI inside each cell is denoted to be S_i.

The protein dynamics is given by

$$\frac{dA_i}{dt} = \beta(a_i - A_i), \tag{2}$$

and is given similarly for B_i (with b_i) and C_i (with c_i).

The dynamical evolution of the intracellular AI concentration is affected by degradation, synthesis, and diffusion toward/from the intercellular medium:

$$\frac{dS_i}{dt} = -k_{s0}S_i + k_{s1}A_i - \eta(S_i - S_e). \tag{3}$$

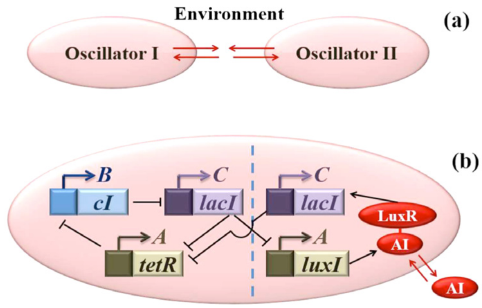

Fig. 1. Scheme of the repressilator network coupled to a quorum-sensing mechanism. (A) Two cells are coupled through the communication with environment. (B) The detail mechanism in *cell* 1 (*cell* 2 is the same). The original repressilator module is located on the left of the vertical dashed lined, and the new coupling module appears on the right.

There are three sensitive parameters (others can be found in [22]). One is β presenting the ratio between the mRNA and protein lifetimes. Considering the oscillator population may likely contain substantial differences from cell to cell [23], β is set as 0.974 for *cell* 1 and 1.023 for *cell* 2 (chosen from a random Gaussian distribution of mean $\bar{\beta} = 1$ and standard deviation $\delta\beta = 0.05$). Hence, the period difference of two cells is given. The second is S_e which denotes the extracellular concentration of AI. In the quasi-steady-state approximation, the extracellular AI concentration can be approximated by $S_e \equiv Q\bar{S}$ where Q is the quorum-sensing coupling strength and is linearly proportional to the cell density [22]. The third is η which measures the diffusion rate of AI across the cell membrane. Noise in gene transcription networks is inevitable. Since the cells in our model are the mean approximations of two clusters, fluctuations in cells can be ignored. The noise in the crosstalk of two cells is domain in our model. For simplicity, an extrinsic noise from signal molecule is introduced into η to simulate the environmental thermal fluctuations:

$$\eta = \eta(1 + \xi_i(t)), \tag{4}$$

where $\xi_i(t)$ is a Gaussian white noise with $\langle\xi_i(t)\rangle = 0$, $\langle\xi_i(t)\xi_i(t')\rangle = D\delta(t - t')$. Here $\delta(t - t')$ is Delta Function which is 1 only when $t = t'$ or 0 on other times. Since the stochastic fluctuations we considered are from the cross-talks between two cells, the sources of noise are independent for the independent of the inside processes of AI to different cells. So $\xi_i(t)$ is different to each cell. At the same time, this setting can avoid the determination of negative or positive role of noise from the definition. In the following section, we will discuss the effect of signal noise (i.e., extrinsic noise) on the order parameter of coupled synthetic clocks.

3. Result and discussion

A two-steps transition mechanism to synchronization in the deterministic system

In absence of noise, the transition to synchronization was found with the increment of coupling strength (due to an increase in cell density) [22]. However, the detailed steps during the construction of synchronization are still unknown. In order to characterize quantitatively this transition process, an order parameter R is introduced to the model:

$$R = \frac{\langle M^2\rangle - \langle M\rangle^2}{\overline{\langle b_i^2\rangle - \langle b_i\rangle^2}}, \tag{5}$$

where $M = \frac{1}{2}(b_1+b_2)$, $\langle\cdots\rangle$ denotes time average, and $\overline{\ldots}$ indicates average over two cells. In this way, in the unsynchronized regime, $R \approx 0$, whereas $R \approx 1$ in the synchronized case. When it comes to the system composed of only two cells, the period difference between two oscillators (defined as $\Delta T = [T_1] - [T_2]$, where $[T_i]$ denotes the mean period of cell i) can also be evaluated. We want to combine the results of R and ΔT to discuss the potential mechanism of synchronization. The results are depicted in Fig. 2.

In the case of diluted condition (e.g., $Q = 0.1$), the system consists of two weakly coupled limit-cycle oscillators with a period difference $\Delta T = -0.35$ h (point A). Our result show that the value of R is about 0.5 but not 0 when Q is 0. This is because that our system only has two little difference cells. As the cell density increases, the diffusion of extracellular AI molecules into the cells provides a mechanism of intercell coupling, which leads to frequency-locked while with different phases (point B). Furthermore, when the cell density is large enough, the full synchronization (i.e., phase-locked state) is observed (point C).

Our result shows that the coupled system achieves the synchronization step by step, i.e., a two-steps transition mechanism. Autoinducers will decrease the difference between the frequencies of two subsystems firstly and then influence

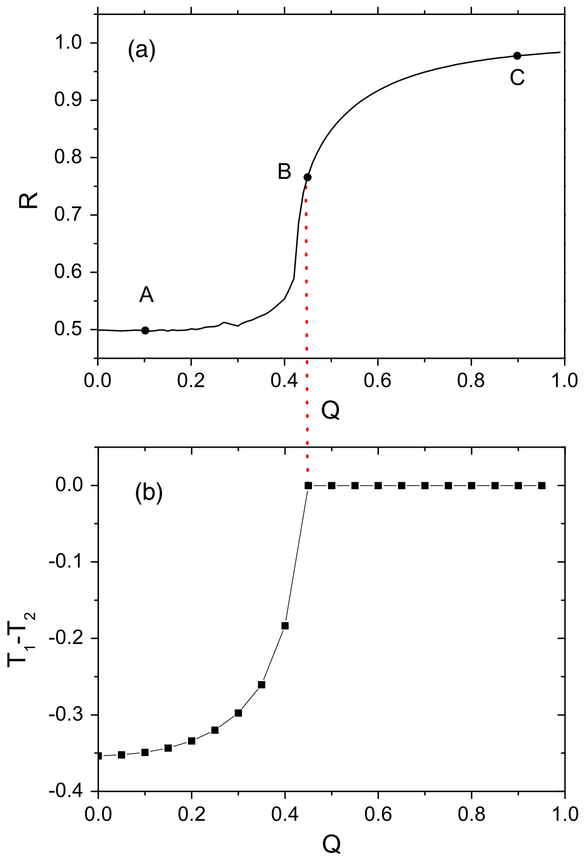

Fig. 2. (a) Synchronization transition and (b) period difference between two cells for increasing Q. $\alpha = 216$, $\kappa = 20$, $n = 2.0$, $k_{s0} = 1$, $\eta = 2.0$, and $k_{s1} = 0.01$. Point A: $Q = 0.1$; Point B: $Q = 0.45$; Point C: $Q = 0.9$.

their phase difference. The behavior shown in Fig. 2 is similar to that found in suprachiasmatic nucleus (SCN) system [24]. We also check our result by using other definition of order parameter and obtain the same result.

A dual role of extrinsic noise in the stochastic system under different cell density

Total noise in gene transcription networks is typically divided into two components: intrinsic and extrinsic. Extrinsic fluctuations might arise from environmental heterogeneity or from global cell-to-cell variations in metabolic or biosynthetic activities [25]. Raser and O'Shea found that extrinsic fluctuations are the predominant form of noise for all gene promoters measured through two-reporter method [26]. In this part, we will discussion the noise effect at point A, B and C in Fig. 2.

The dependences of order parameter R on noise intensity of $\xi_i(t)$ under different cell densities are shown in the left row of Fig. 3. At point A in Fig. 2, weak coupling causes the two cells oscillation with their own periods and the initial value of R is small. When fluctuations from the signal AI are considered, R increases monotonously with the increasing of noise intensity D as shown in Fig. 3(a). Noise plays a constructive role in such loosely coupled system. On the other hand, synchrony in the tightly coupled system can be destroyed by noise. In Fig. 3(c), it can be found that the initial value of R is approaching to 1 at beginning and then is decreasing with the increasing of D. When the system is at frequency-locking state (point B in Fig. 2), the effect of fluctuations is nonlinear that R decreases firstly and then increases with the change of D. A minimal value of the order exists under special noise intensity in Fig. 3(b). That is to say the noise can induce the order of the phase-locking system to be the worst under a special cell density. The variation of the order parameter caused by the noise is comparable in a–c (about 10^{-1} order of magnitude). This result shows that extrinsic noise exhibits remarkable diversity in coupled cells. In order to explain what is the critical factor that adjusts the order parameter, the effects of noise on the period difference and on the phase difference are studied.

Our previous results in Fig. 2 illustrate that the synchronization of the coupled system is realized step by step. There are two main factors acting on the synchronization: one is period difference, the other is phase difference. We want to find out which will play a dominant role under loosely/tightly coupled situation. Firstly, we study the change of ΔT with the increasing of noise strength D. The results are shown in Fig. 3(d)–(f). Fig. 3(d) shows when the coupling strength Q is small, noise decreases the difference between periods of two cells dramatically that leading to the increasing of R in Fig. 3(a). Under this situation, the change of period deference caused by noise is dominant. When the coupling is tight, it can be seen from

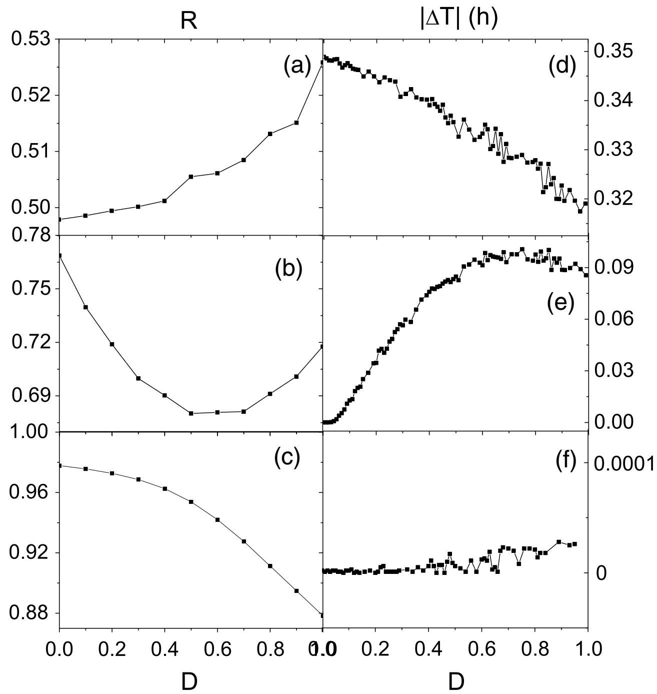

Fig. 3. The order parameter R and ΔT as a function of D. (a), (d) $Q = 0.1$; (b), (e) $Q = 0.45$; (c), (f) $Q = 0.9$. Other parameters are the same with Fig. 2. The stochastic equations are integrated with fourth order Runge–Kutta time stepping scheme. The size of the integration step Δ is equal to 0.0001. The multiplicative noise is treated with the Euler algorithm and is approximate to first order in Δ.

Fig. 3(f) that the change of ΔT is slightly. It has been mentioned above that the variation of R due to noise is comparable under different densities. However, the variation of $|\Delta T|$ in Fig. 3(f) is around 0. This may be explained through Fig. 2(b). In the noisy system, noise can drive ΔT to move along the line $\Delta T - Q$. When the system is at point C, $\Delta T(Q)$ is on a plateau. That is to say the noise pushes ΔT moving on this plateau and the change of ΔT is nearly 0. Under this situation, the change of phase difference caused by noise is dominant. The nonlinear phenomenon in Fig. 3(b) will be studied later.

Dynamical mechanism underlying the different regulation roles of extrinsic noise

Above, only a qualitative discussion is presented. There are still some questions. It is unknown why the noise drives the couple system orderly or disorderly which results in the decrease or increase of ΔT with changes of Q. In order to explain this, the effect of multiplicative noise $\xi(t)$ in this loosely correlated system is calculated theoretically. Our motivation is to analyze the systematic effect of signal noise on signaling dynamics and synchronization. Considering the average between cells, we can rewrite Eq. (3) as

$$\frac{d\langle S_i\rangle}{dt} = -k_{s0}\langle S_i\rangle + k_{s1}\langle A_i\rangle - \eta(\langle S_i\rangle - S_e) - \eta\langle\xi(S_i - S_e)\rangle. \tag{6}$$

Here, $\langle . \rangle$ means the average between cells.

Setting $\eta(S_i - S_e) = g(S_i)$, we can get

$$\eta\langle\xi(S_i - S_e)\rangle = \langle\xi g(S_i)\rangle. \tag{7}$$

Considering as a first order approximation in a small-noise expansions,

$$g(S_i(t)) = g(\langle S_i\rangle) + g'(\langle S_i\rangle)(S_i - \langle S_i\rangle). \tag{8}$$

So

$$\langle\xi g(S_i(t))\rangle = \langle\xi g(\langle S_i\rangle)\rangle + \langle\xi g'(\langle S_i\rangle)(S_i - \langle S_i\rangle)\rangle. \tag{9}$$

The first item on the right of equal sign is zero since ξ is Gaussian white noise. so

$$\langle\xi g(S_i(t))\rangle = \langle\xi g'(\langle S_i\rangle)(S_i - \langle S_i\rangle)\rangle. \tag{10}$$

S_i can also be expended with $\langle S_i\rangle$. The influence of noise can be expressed as

$$\langle\xi g(S_i(t))\rangle = 0.5g'(\langle S_i\rangle)g(\langle S_i\rangle)D. \tag{11}$$

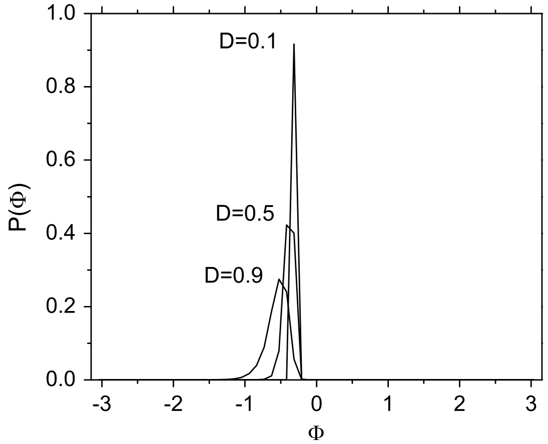

Fig. 4. The distribution of Φ under different noise intensity when $Q = 0.9$. $P(\Phi)$ is from narrow to wide and is far from $\Phi = 0$ gradually with the increasing of D.

Finally, the computation of this average value by means of standard techniques [26] leads to the following effective deterministic model, which can be considered as a first order approximation in a small-noise expansions:

$$\begin{aligned}\frac{d\langle S_i\rangle}{dt} &= -k_{s0}\langle S_i\rangle + k_{s1}\langle A_i\rangle - (1-0.5D\eta)g(\langle S_i\rangle)\\ &= -k_{s0}\langle S_i\rangle + k_{s1}\langle A_i\rangle - \eta(1-\frac{D}{2}\eta)(\langle S_i\rangle - S_e).\end{aligned} \quad (12)$$

In this way, D can be thought to be a modulation of η. If the couple is loose, $S_e \ll S_i$ and $S_i - S_e$ is mostly like to be positive and the signal elements are explored from the cells. Fluctuations under this condition would like to weaken the lose of signal element. Systematic effect of noise acts as influx signal which decreases ΔT as shown in Fig. 3(d) and increases R in Fig. 3(a). This theoretical can explain why the system is moving to right not left.

Another question is what destroys the synchrony even $|\Delta T| \approx 0$ (as shown in Fig. 3f) with increasing noise intensity. In order to address it, we study the different distribution of phase difference with changing D. Set $p(\Phi)$, where $\Phi = mod(\phi_1 - \phi_2, 2\pi)$ ($\phi_i(t) = 2\pi\frac{t-\tau_k^i}{\tau_{k+1}^i-\tau_k^i} + 2\pi k$, τ_k^i is the time of the kth spike of the ith cell), this distribution of Φ can be calculated between two tightly coupled cells numerically in Fig. 4 and the result gives some information about the main factor that influence the order parameter. The distribution of Φ is narrow and high when the noise is weak and the peak of $p(\Phi)$ is near 0. With increasing D, synchrony is destroyed by noise. So $p(\Phi)$ spreads and the peak is far from 0. The phase difference becomes large with the increment of noise, hence R is decreased.

Finally, let we get back to Fig. 3(b) where the change of R with increasing D is nonlinear. From Fig. 3(e), it can be observed that the change of $|\Delta T|$ is monotonous with the increment of D. That is to say the decreasing part of R curve is caused by the increasing of $|\Delta T|$ while the increasing part may be resulted from the change of $\Delta\phi$. We can explain this result from Fig. 2 where the coupled system is at point B without fluctuations. When the noise intensity is nonzero but small, it will push R dropping dramatically along the line shown in Fig. 2(b). When the noise intensity is strong enough, R will increase similar to the situation in Fig. 3(a). The region of nonlinear dependence of R on D is also checked. As seen in Fig. 5, it is illustrated that the nonlinear region is very narrow.

4. Conclusion

In conclusion, the role of noise in coupled system is important and exhibits remarkable diversity. As extrinsic noise from signal is the predominant form of noise for all gene promoters [26], here we have studied the effects of extrinsic signal noise on two coupled oscillators. The model we used is two correlated synthetic clocks. Such a system is originated from the negative autoregulation of gene expression, hence is an important example of correlated biochemical oscillators [27,28]. The simplicity of the model allows us to fully explore and understand the range of dynamical behavior it exhibits.

In absence of noise, the system experiences obviously two transitions (i.e., period-locked and phase-locked) and finally reaches a full synchronization. Therefore, a two-steps mechanism is observed in the deterministic model. This is the same with that in true clock cells [25]. Next, we put our emphasis on the stochastic system. It is found that (i) when the coupling is loose, increasing noise decreases the period difference between two cells hence increases the order parameter R. (ii) When the tight couple induces the periods of two cells to be equal, the noise mainly modulates the phase difference that decreases R. A dual role of signal noise is discovered. The main factor for such an opposite effect of noise is due to the different mode

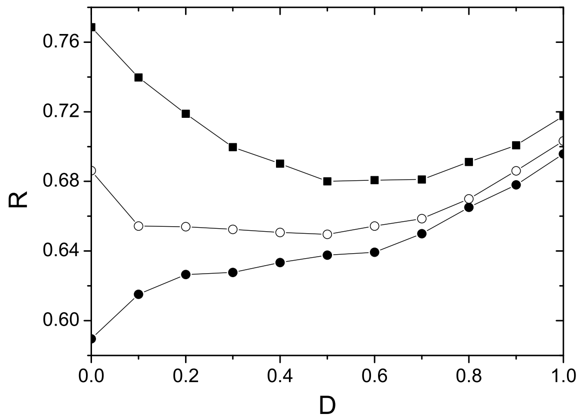

Fig. 5. The transition from monotonously increasing of R to monotonously decreasing. Filled square: $Q = 0.45$; Round: $Q = 0.43$; Filled round: $Q = 0.42$. Other parameters are the same with Fig. 2.

of coupling. The loose coupling can induce efflux of signal from cells ($S_i - S_e > 0$) and decreases the level of signal elements. Theoretical study shows that the mean effect of extrinsic noise from signal under such circumstance is mostly like to be influx which leads to the increase of R. On the other hand, the contribution of the tight coupling is to increase the level of signal elements AI. Since signal flow is most like to be influx, the effect of noise is to increase the lose of signal. The transition from (i) to (ii) is also observed around frequency-locking state where the order of the system is the worst under some noise intensities.

Our research provides a preliminary study about the dynamical quorum sensing and synchronization when stochastic noises are involved. Also, we attempt to present a theoretical analysis by using the small-noise approximation to clarify the opposite roles of external signal noise. These phenomena are believed to have important implications to the performance and functionality of some realistic systems. However, the further work is required. only two coupled synthetic clock cells are considered here. The intrinsic noise due to small cell size and small molecular number is neglected. Furthermore, the time delay also should be considered in the future.

Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities, China (Grants Nos. 2662015QC041 and 2662014BQ069), Huazhong Agricultural University Scientific Technological Self-innovation Foundation, China (Program No. 2015RC021), and the National Natural Science Foundation of China (Grants Nos. 11675060, 91730301, 11547244, 11474117).

References

[1] W. Wang, Y. Lai, D. Aembruster, Chaos 21 (2011) 033112.
[2] Q. Zhao, M. Yi, Y. Liu, Phys. Biol. 8 (2011) 055004.
[3] L.L. Lu, Y. Jia, W.H. Liu, et al., Complexity 2017 (2017) 7628537.
[4] G. Ren, X. Wang, Chaos 24 (2014) 023116.
[5] Q. Zhao, C.G. Yao, J. Tang, et al., Front. Phys. 11 (2016) 110501.
[6] W. Zou, D.V. Senthilkumar, Raphael Nagao, I.Z. Kiss, Y. Tang, A. Koseska, J. Duan, J. Kurths, Nature Commun. 6 (2015) 7709.
[7] T.K.DM. Peron, F.A. Rodrigues, Phys. Rev. E 86 (2012) 016102.
[8] W. Master, J. Hasty, L.S. Tsimring, Phys. Rev. Lett. 113 (2014) 128102.
[9] M.H. Matheny, M. Grau, L.G. Villanueva, R.B. Karabalin, M.C. Cross, M.L. Roukes, Phys. Rev. Lett. 112 (2014) 014101.
[10] S. Sunada, K. Arai, K. Yoshimura, M. Adachi, Phys. Rev. Lett. 112 (2014) 204101.
[11] Q. Zhao, C.G. Yao, M. Yi, Eur. Phys. J. B 84 (2011) 299.
[12] N. Locatelli, A. Accioly, R. Matsunoto, A. Fukushima, H. Kubota, S. Yuasa, V. Cros, L.G. Pereiral, D. Querlioz, J.V. Kim, J. Grollier, Phys. Rev. Appl. 2 (2014) 034009.
[13] M. Komarov, S. Gupta, A. Pikovsky, Europhys. Lett. 106 (2014) 40003.
[14] R.L. Stratonovich, Topics in the Theory of Random Noise, Vol. 2, Gordon and Breach, New York, 1967.
[15] Y. Sun, W. Li, J. Ruan, Commun. Nonlinear Sci. Numer. Simul. 18 (4) (2013) 989.
[16] B. Chen, C. Hsu, BMC Syst. Biol. 6 (27) (2012) 2904.
[17] B. Hauschildt, N.B. Janson, A. Balanov, E. Scńoll, Phys. Rev. E 74 (2006) 051906.
[18] Q. Liu, Y. Wang, Biophys. Chem. 129 (1) (2007) 23.
[19] D. McMillen, N. Kopell, J. Hasty, J.J. Collins, Proc. Natl. Acad. Sci. USA 99 (2002) 679.
[20] V.K. Vanag, et al., Nature 406 (2000) 389–391.
[21] Q. Liu, Y. Jia, Phys. Rev. E 70 (2004) 041907.
[22] J.G. Ojalvo, M.B. Elowitz, S.H. Strogatz, Proc. Natl. Acad. Sci. USA 101 (2004) 10955.

[23] A. Becskei, L. Serrano, Nature 405 (2000) 590.
[24] D. Gonze, S. Bernard, C. Waltermann, A. Kramer, Biophys. J. 104 (2005) 058388.
[25] J.M. Pedraza, A.V. Oudenaarden, Science 307 (2005) 1965.
[26] J.M. Raser, E.K. O'Shea, Science 309 (2005) 2010.
[27] S. Dann, C.S. Pittendrigh, J. Comp. Physiol. 106 (1976) 291.
[28] S. Yamazaki, R. Numano, M. Abe, A. Hida, R. Takahashi, M. Ueda, G.D. Block, Y. Sakaki, M. Menaker, H. Tei, Science 288 (2000) 682.