Supporting Material for
Noise-induced Cooperative Behavior in a Multi-Cell System,

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APPENDIX A: MASTER EQUATION AND CUMULANTS WITH DELAYS

1. Master equation in a cell with coupling to the environment

Assume that there are n identical cells, which are coupled with a common extracellular environment. Consider a system containing n_0 chemical reactions with m molecular species or molecules in one cell. Let $X = (X_1, ..., X_m)$ be the state of the molecules at the time t, i.e., X_i is the number of the ith molecule at t in the cell. Let $Y = (Y_1, ..., Y_m)$ be environment variables coupled to the cell, which are assumed to be relatively steady in contrast to X and freely diffusible among cells, e.g., Y is the total numbers of the extracellular X for a multi-cell system.

Define $p(X;\, t)$ to be the probability function for the state $X(t)$ at t. Then, the dynamics of the system can generally be described by the master equation (Van Kampen, 1992) with an initial state $X(0)$ at $t = 0$:

$$\frac{\partial p(X;t)}{\partial t} = \sum_{k=1}^{n_0} \left[w_k(X - \theta_k) p(X - \theta_k;\, t) - w_k(X) p(X;\, t) \right], \tag{A1}$$

where $\theta_k = (\theta_{k,1},\, \theta_{k,2},\, \cdots,\, \theta_{k,m})$ is an integer-valued vector for the change of the state, i.e., θ_{kj} is a change in the number of the jth molecule by the kth reaction. $w_k(X)$ is a transition rate from state X to $X + \theta_k$ by the kth chemical reaction. In addition to the intracellular chemical reactions, the master equation (A1) includes linear diffusion reactions or the coupling reactions with the environment, which are approximately expressed by the following chemical reactions with feedback delays τ_i

$$X_i \underset{d_{ii}v/V}{\overset{d_{ii}}{\rightleftharpoons}} Y_i \tag{A2}$$

where d_{ii} is the diffusion rate of the ith molecule between the cell and the environment, and Y_i is the total number of the ith molecule in the environment. Moreover, the extracellular

noises associated with the diffusion process of X are also incorporated in eqn.(A1), which can be equivalently described in the form of the following chemical reaction

$$X_i \underset{\sigma_{ii}^2 v/(2Y_i)}{\overset{\sigma_{ii}^2 v/(2X_i)}{\rightleftharpoons}} Y_i, \tag{A3}$$

where σ_{ii}^2 is the extracellular noise intensity or the variance, which affects the cell dynamics through cellular signals X_i and Y_i. Notice that both p and w_k are functions of the environment variables Y, which are dropped in (A1) for the sake of simplicity. $d_{ii} = 0$ if the ith molecule is not a coupling variable between the cell and the environment.

Assume that the system is well mixed due to the free diffusion and transportation processes of signal molecules between the environment and each cell, which means that the signal molecules are randomly distributed in a uniform sense throughout the environment. When there are a sufficiently large number of cells, i.e., $n \to \infty$, the concentration of Y approaches the average or the mean field concentration of X, i.e., $Y/V = N(t-\tau) \equiv \langle X(t-\tau)/v \rangle$ which represents the time-delayed feedback effects. $v = \bar{v}A$ and $V = \bar{V}$ where $\bar{v}$ and $\bar{V}$ are the individual cell volume and the total environment volume respectively, and A is the Avogadro number. N is the mean value of the concentration X/v.

Next we derive the master equation for the synthetic gene network shown in Fig.1. Let AI_2 and $LuxR_2$ indicate AI and LuxR protein dimers, and AL and ALD represent $AI_2 - LuxR_2$ and $AI_2 - LuxR_2 - DNA$ complexes, respectively. For convenience, we define the following molecules: X_1, LuxI; X_2, LuxR; X_3, AL; X_4, ALD; X_5, AI_2; X_6, $LuxR_2$; X_7, $mRNA_{LuxI}$; X_8, $mRNA_{LuxR}$; X_9, AI; and Y, AI_2 in the environment. Define n_D as the total number of DNA, and n_{DNA} as the free DNA number. Then, by the conservation condition, we have $n_{DNA} + X_4 = n_D$. From eqns.(A1)-(A3), the transition rates and the states corresponding to reactions (6)-(16) are listed as Table 1, where the last two rows represent the diffusion process and the extracellular noise effect between each cell and the environment for AI according to eqns.(15)-(16). In Table 1, the volume factors v and V are multiplied to some w_k to convert the concentration to the number of the molecule because the reaction rates k_1-k_4 are second-order reactions and are defined not by the numbers but by the concentrations in the given data of this paper.

TABLE 1: Transition rates and states

k	X_1 $\theta_{k,1}$	X_2 $\theta_{k,2}$	X_3 $\theta_{k,3}$	X_4 $\theta_{k,4}$	X_5 $\theta_{k,5}$	X_6 $\theta_{k,6}$	X_7 $\theta_{k,7}$	X_8 $\theta_{k,8}$	X_9 $\theta_{k,9}$	w_k
1	0	0	0	0	0	0	0	0	1	$k_a X_1(t)$
2	0	0	0	0	1	0	0	0	-2	$k_1 X_9(t)(X_9(t)-1)/v$
3	0	0	0	0	-1	0	0	0	2	$k_{-1} X_5(t)$
4	0	-2	0	0	0	1	0	0	0	$k_2 X_2(t)(X_2(t)-1)/v$
5	0	2	0	0	0	-1	0	0	0	$k_{-2} X_6(t)$
6	0	0	1	0	-1	-1	0	0	0	$k_3 X_5(t) X_6(t)/v$
7	0	0	-1	0	1	1	0	0	0	$k_{-3} X_3(t)$
8	0	0	-1	1	0	0	0	0	0	$k_4 X_3(t)(n_D - X_4(t))/v$
9	0	0	1	-1	0	0	0	0	0	$k_{-4} X_4(t)$
10	0	0	0	0	0	0	1	1	0	$k_m(n_D - X_4(t))$
11	0	0	0	0	0	0	1	1	0	$\alpha k_m X_4(t)$
12	1	0	0	0	0	0	0	0	0	$k_{pi} X_7(t)$
13	0	1	0	0	0	0	0	0	0	$k_{pr} X_8(t)$
14	0	0	0	0	0	0	-1	0	0	$e_{mi} X_7(t)$
15	0	0	0	0	0	0	0	-1	0	$e_{mr} X_8(t)$
16	-1	0	0	0	0	0	0	0	0	$e_i X_1(t)$
17	0	-1	0	0	0	0	0	0	0	$e_r X_2(t)$
18	0	0	0	0	0	0	0	0	-1	$e_a X_9(t)$
19*	0	0	0	0	0	0	0	0	1	$dY_9(t)v/V + (\sigma)^2 v/2$
20	0	0	0	0	0	0	0	0	-1	$dX_9(t) + (\sigma)^2 v/2$

* If $n \to \infty$, then $Y_9(t) = \langle X_9(t-\tau) \rangle \frac{V}{v}$.

- The transition rate $w_k(X(t)) = 0$ if $w_k(X(t)) < 0$ or if $w_k(X(t))$ has a variable $X_i(t)$ satisfying $X_i(t) + \theta_{k,i} < 0$, due to nonnegative values of w_k and $X(t)$.
- $w_k(X(t)) = 0$ if $w_k(X(t))$ has a term $n_D - X_4(t)$ satisfying either $n_D - X_4(t) < 0$ or $n_D - (X_4(t) + \theta_{k,4}) < 0$, due to the conservation condition of the DNA number.

2. Langevin equations

By Taylor expansion of $w_k(X(t) - \theta_k)p(X(t) - \theta_k)$ to order two in eqn.(A1), we obtain the following Fokker-Plank equation (Van Kampen, 1992; Risken, 1989):

$$\frac{\partial p(X(t);t)}{\partial t} = \sum_{k=1}^{n_0} \left[-\sum_{i=1}^{m} \theta_{k,i} \frac{\partial}{\partial X_i} + \sum_{i,j=1}^{m} \frac{\theta_{k,i}\theta_{k,j}}{2} \frac{\partial^2}{\partial X_i \partial X_j} \right] w_k(X(t)) p(X(t);\, t). \tag{A4}$$

Let the first n_I reactions be the intracellular chemical reactions. Then the remaining $n_E = n_0 - n_I$ reactions are the reactions interacting with the environment. Define

$$\bar{K}_i(X(t)) = \sum_{k=1}^{n_I} \theta_{k,i} w_k(X(t))$$
$$\bar{K}_{ij}(X(t)) = \sum_{k=1}^{n_I} \theta_{k,i}\theta_{k,j} w_k(X(t))$$

for all i and j. Let the concentrations of $X(t)$ and $Y(t)$ be $x(t)$ and $y(t)$, respectively, i.e., $x(t) = X(t)/v$ and $y(t) = Y(t)/V$. By using the concentrations,

$$f_i(x(t)) \equiv \bar{K}_i(vx(t))/v; K_{ij}(x(t)) \equiv \bar{K}_{ij}(vx(t))/v, \tag{A5}$$

then from eqns.(A1)-(A3), the Langevin equations corresponding to eqn.(A4) are given as follows (Van Kampen, 1992; Risken, 1989):

$$\frac{dx_i(t)}{dt} = F_i + \xi_i(t) \equiv f_i(x(t)) + d_{ii}(y_i(t) - x_i(t)) + \xi_i(t), \tag{A6}$$

where $\xi_i(t)$ are Gaussian white noises that have zero means $\langle \xi_i(t) \rangle = 0$ and covariances $\langle \xi_i(t)\xi_j(t') \rangle = F_{ij} \equiv (K_{ij}(x(t)) + d_{ij}(y_i(t) + x_j(t)) + \sigma_{ij}^2)\delta(t - t')$. Notice that $d_{ij} = \sigma_{ij} = 0$ for $i \neq j$, $d_{ii} = 0$ if variable $x_i(t)$ is not a coupling variable with the environment. Moreover, $\sigma_{jj} = \sigma$, if $j = 4, 5$ or 9, otherwise, $\sigma_{jj} = 0$.

Assuming $n \to \infty$, in the system of Fig.1, the Langevin equations can be derived from Table 1 according to (A6).

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= -e_i x_1(t) + k_{pi} x_7(t) + \xi_1 \\
\frac{dx_2(t)}{dt} &= -2k_2 x_2(t)(x_2(t) - \tfrac{1}{v}) + 2k_{-2} x_6(t) + k_{pr} x_8(t) - e_r x_2(t) + \xi_2 \\
\frac{dx_3(t)}{dt} &= k_3 x_5(t) x_6(t) - x_3(t)(k_{-3} + k_4(\tfrac{n_D}{v} - x_4(t))) + k_{-4} x_4(t) + \xi_3 \\
\frac{dx_4(t)}{dt} &= k_4 x_3(t)(\tfrac{n_D}{v} - x_4(t)) - k_{-4} x_4(t) + \xi_4 \\
\frac{dx_5(t)}{dt} &= k_1 x_9(t)(x_9(t) - \tfrac{1}{v}) - k_{-1} x_5(t) - k_3 x_5(t) x_6(t) + k_{-3} x_3(t) + \xi_5 \\
\frac{dx_6(t)}{dt} &= k_2 x_2(t)(x_2(t) - \tfrac{1}{v}) - k_{-2} x_6(t) - k_3 x_5(t) x_6(t) + k_{-3} x_3(t) + \xi_6 \\
\frac{dx_7(t)}{dt} &= k_m(\tfrac{n_D}{v} - x_4(t)) + \alpha k_m x_4(t) - e_{mi} x_7(t) + \xi_7 \\
\frac{dx_8(t)}{dt} &= k_m(\tfrac{n_D}{v} - x_4(t)) + \alpha k_m x_4(t) - e_{mr} x_8(t) + \xi_8 \\
\frac{dx_9(t)}{dt} &= -2k_1 x_9(t)(x_9(t) - \tfrac{1}{v}) + 2k_{-1} x_5(t) + k_a x_1(t) - e_a x_9(t) + d(\langle x_9(t - \tau) \rangle - x_9(t)) + \xi_9,
\end{aligned} \tag{A7}$$

where

$$\langle \xi_i(t)\xi_j(t') \rangle = K_{ij}\delta(t - t') \text{ for } i \neq 9 \text{ and } j \neq 9 \text{ with } K_{ij} = K_{ji}$$

$$\langle \xi_9(t)\xi_9(t')\rangle = (K_{99} + d(\langle x_9(t-\tau)\rangle \frac{V}{v} + x_9(t)) + (\sigma V)^2)\delta(t-t')$$

and

$$\begin{aligned}
K_{11}(t) &= e_i x_1(t) + k_{pi} x_7 \\
K_{22}(t) &= 4k_2 x_2(t)(x_2(t) - \frac{1}{v}) + 4k_{-2} x_6(t) + k_{pr} x_8 + e_r x_2(t) \\
K_{33}(t) &= k_3 x_5(t) x_6(t) + x_3(t)(k_{-3} + k_4(\frac{n_D}{v} - x_4(t))) + k_{-4} x_4(t) \\
K_{44}(t) &= k_4 x_3(t)(\frac{n_D}{v} - x_4(t)) + k_{-4} x_4(t) + \sigma^2 \\
K_{55}(t) &= k_1 x_9(t)(x_9(t) - \frac{1}{v}) + k_{-1} x_5(t) + k_3 x_5(t) x_6(t) + k_{-3} x_3(t) + \sigma^2 \\
K_{66}(t) &= k_2 x_2(t)(x_2(t) - \frac{1}{v}) + k_{-2} x_6(t) + k_3 x_5(t) x_6(t) + k_{-3} x_3(t) \\
K_{77}(t) &= k_m(\frac{n_D}{v} - x_4(t)) + \alpha k_m x_4(t) + e_{mi} x_7(t) \\
K_{88}(t) &= k_m(\frac{n_D}{v} - x_4(t)) + \alpha k_m x_4(t) + e_{mr} x_8(t) \\
K_{99}(t) &= 4k_1 x_9(t)(x_9(t) - \frac{1}{v}) + 4k_{-1} x_5(t)) + k_a x_1(t) + d(\langle x_9(t-\tau)\rangle - x_9(t)) + e_a x_9(t) + \sigma^2 \\
K_{26}(t) &= -2k_2 x_2(t)(x_2(t) - \frac{1}{v}) - 2k_{-2} x_6(t) \\
K_{34}(t) &= -k_4 x_3(t)(\frac{n_D}{v} - x_4(t)) - k_{-4} x_4(t) \\
K_{35}(t) &= -k_3 x_5(t) x_6(t) - k_{-3} x_3(t) \\
K_{36}(t) &= -k_3 x_5(t) x_6(t) - k_{-3} x_3(t) \\
K_{56}(t) &= k_3 x_5(t) x_6(t) + k_{-3} x_3(t) \\
K_{59}(t) &= -2k_1 x_9(t)(x_9(t) - \frac{1}{v}) - 2k_{-1} x_5(t)\,,
\end{aligned}$$

and other $K_{ij} = 0$. Notice that if a term in f_i and K_{ij} is negative, then the corresponding term is zero, due to the constraints of w_k in the master equation.

In this paper, the intracellular noises ξ_i are directly derived from the master equation by the second order approximation of $\theta_{k,i}$, and they are additive and white with an identical and independent distribution for each cell. Theoretically, when the individual jumps or the changes $|\theta_{k,i}|$ of the number $X_i(t)$ are small, such an approximation approaches an accurate result (Van Kampen, 1992); i.e., the additive and white noises are an adequate representation of the fluctuations in a cell. Otherwise, the Ω expansion technique or other approximation methods should be adopted to approximate the master equation in a more accurate manner. In the numerical examples, the jumps $|\theta_{k,i}|$ are all 1 or 2, which are small compared with $X_i(t)$ but they may still have introduced errors in the simulation.

3. Cumulant equations

The first and second cumulants for any two random variables x_i and x_j are actually their means and covariances, i.e., $\langle x_i\rangle$, $\langle x_j\rangle$, and $\langle x_i x_j\rangle - \langle x_i\rangle\langle x_j\rangle$. Let $g(x(t),\, s) = \prod_{i=1}^{m} x_i^{s_i}(t)$, then, for each integer-valued vector $s = (s_1,\, s_2,\, \cdots,\, s_m)$, the moment evolution equations of (A6) are given as follows (Kawai *et al.*, 2004; Wojtkiewicz *et al.*, 1996):

$$\frac{d\langle g(x(t),\, s)\rangle}{dt} = \left\langle \sum_{i=1}^{m} F_i \frac{\partial g}{\partial x_i} \right\rangle + \frac{1}{2}\sum_{i=1}^{m}\sum_{j=1}^{m} \left\langle F_{ij}\frac{\partial^2 g}{\partial x_i \partial x_j} \right\rangle, \tag{A8}$$

which can be used straightforward to derive cumulant evolution equations.

For the Gaussian approximation, all odd central moments vanish, and any even central moment can be expressed as products of the second central moments. For instance, $\langle x_i x_j x_k x_l\rangle_c = \langle x_i x_j\rangle_c\langle x_k x_l\rangle_c + \langle x_i x_k\rangle_c\langle x_j x_l\rangle_c + \langle x_i x_l\rangle_c\langle x_j x_k\rangle_c$, and $\langle x_i x_i x_i x_j x_j x_k\rangle_c = 6\langle x_i x_i\rangle_c\langle x_i x_j\rangle_c\langle x_j x_k\rangle_c + 6\langle x_i x_j\rangle_c^2\langle x_i x_k\rangle_c + 3\langle x_i x_i\rangle_c\langle x_i x_k\rangle_c\langle x_j x_j\rangle_c$, where all moments are central moments, i.e., $\langle x\rangle_c = \langle x - \langle x\rangle\rangle$. Notice that cumulants are identical to central moments for the first, second and third orders, and any differentiable function can be expanded around $\langle x\rangle$ by central moments, i.e., for the Gaussian distributions, by letting all odd central moments zero,

$$\langle f(x)\rangle = f(\langle x\rangle) + \frac{1}{2!}\frac{\partial^2 f(\langle x\rangle)}{\partial x^2}\langle xx\rangle_c + \frac{1}{4!}\frac{\partial^4 f(\langle x\rangle)}{\partial x^4}\langle xxxx\rangle_c + \cdots. \tag{A9}$$

Thus, we derive eqn.(4) by eqn.(A8), which can be further simplified by eqn.(A9) with the assumption of the Gaussian distributions. Next we derive the cumulant evolution equations for the synthetic gene network shown in Fig.1.

Define N_i to be the first cumulant or the mean value of x_i in the cell, and M_{ij} to be the second cumulant or the covariance of x_i and x_j. Then, according to eqn.(4), we have evolution equations

for the first and second cumulants or the means and the covariances:

$$
\begin{aligned}
\frac{dN_1}{dt} &= -e_i N_1 + k_{pi} N_7 \\
\frac{dN_2}{dt} &= -2k_2\left(N_2^2 + M_{22}\right) + 2k_{-2}N_6 + k_{pr}N_8 + (\frac{2k_2}{v} - e_r)N_2 \\
\frac{dN_3}{dt} &= k_3\left(N_5N_6 + M_{56}\right) - N_3(t)\left(k_{-3} + \frac{k_4 n_D}{v} - k_4 N_4\right) + k_4 M_{34} + k_{-4}N_4 \\
\frac{dN_4}{dt} &= k_4 N_3\left(\frac{n_D}{v} - N_4\right) - k_{-4}N_4 - k_4 M_{34} \\
\frac{dN_5}{dt} &= k_1\left(N_9^2 + M_{99}\right) - k_{-1}N_5 - k_3\left(N_5N_6 + M_{56}\right) + k_{-3}N_3 - \frac{k_1}{v}N_9 \\
\frac{dN_6}{dt} &= k_2\left(N_2^2 + M_{22}\right) - k_{-2}N_6 - k_3\left(N_5N_6 + M_{56}\right) + k_{-3}N_3 - \frac{k_2}{v}N_2 \\
\frac{dN_7}{dt} &= k_m(\frac{n_D}{v} - N_4) + \alpha k_m N_4 - e_{mi}N_7 \\
\frac{dN_8}{dt} &= k_m(\frac{n_D}{v} - N_4) + \alpha k_m N_4 - e_{mr}N_8 \\
\frac{dN_9}{dt} &= -2k_1\left(N_9^2 + M_{99}\right) + 2k_{-1}N_5 - e_a N_9 + k_a N_1 + \frac{2k_1}{v}N_9 + d(N_9(t-\tau) - N_9(t))
\end{aligned}
\tag{A10}
$$

$$
\begin{aligned}
\frac{1}{2}\frac{dM_{11}}{dt} &= \frac{1}{2}\left(e_i N_1 + k_{pi} N_7\right) - e_i M_{11} \\
\frac{1}{2}\frac{dM_{22}}{dt} &= 2k_2\left(N_2^2 + M_{22}\right) + 2k_{-2} N_6 + \frac{1}{2}k_{pr} N_8 + (\frac{1}{2}e_r - \frac{2k_2}{v})N_2 \\
&- \left(4k_2 N_2 + e_r\right) M_{22} + 2k_{-2} M_{26} + \frac{2k_2}{v} M_{22} \\
\frac{1}{2}\frac{dM_{33}}{dt} &= \frac{1}{2}\left(k_3\left(N_5 N_6 + M_{56}\right) + N_3\left(k_{-3} + \frac{k_4 n_D}{v} - k_4 N_4\right) - k_4 M_{34} + k_{-4} N_4\right) \\
&+ k_3 N_6 M_{35} + k_3 N_5 M_{36} - \left(-k_4 N_4 + k_{-3} + \frac{k_4 n_D}{v}\right) M_3 + \left(k_4 N_3 + k_{-4}\right) M_{34} \\
\frac{1}{2}\frac{dM_{44}}{dt} &= \frac{1}{2}\left(k_4 N_3\left(\frac{n_D}{v} - N_4\right) + k_{-4} N_4 - k_4 M_{34}\right) + k_4\left(\frac{n_D}{v} - N_4\right) M_{34} - \left(k_{-4} + k_4 N_3\right) M_{44} + \frac{1}{2}\sigma^2 \\
\frac{1}{2}\frac{dM_{55}}{dt} &= \frac{1}{2}\left(k_1\left(N_9^2 + M_{99}\right) + k_{-1} N_5 + k_3\left(N_5 N_6 + M_{56}\right) + k_{-3} N_3 - \frac{k_1}{v} N_9\right) \\
&- \left(k_{-1} + k_3 N_6\right) M_{55} + k_{-3} M_{35} - k_3 N_5 M_{56} + 2k_1 N_9 M_{59} - d M_{55} - \frac{k_1}{v} M_{59} + \frac{1}{2}\sigma^2 \\
\frac{1}{2}\frac{dM_{66}}{dt} &= \frac{1}{2}\left(k_2\left(N_2^2 + M_{22}\right) + k_{-2} N_6 + k_3\left(N_5 N_6 + M_{56}\right) + k_{-3} N_3 - \frac{k_2}{v} N_2\right) \\
&- \left(k_{-2} + k_3 N_5\right) M_{66} + 2k_2 N_2 M_{26} + k_{-3} M_{36} - k_3 N_6 M_{56} - \frac{k_2}{v} M_{26} \\
\frac{1}{2}\frac{dM_{77}}{dt} &= \frac{1}{2}\left(k_m(\frac{n_D}{v} - N_4) + \alpha k_m N_4 + e_{mi} N_7\right) - e_{mi} M_{77} \\
\frac{1}{2}\frac{dM_{88}}{dt} &= \frac{1}{2}\left(k_m(\frac{n_D}{v} - N_4) + \alpha k_m N_4 + e_{mr} N_8\right) - e_{mi} M_{88} \\
\frac{1}{2}\frac{dM_{99}}{dt} &= \frac{1}{2}\left(4k_1\left(N_9^2 + M_{99}\right) + 4k_{-1} N_5 + e_a N_9 + k_a N_1 - \frac{4k_1}{v} N_9 + d(N_5(t-\tau) - N_5)\right) \\
&- \left(e_a + 4k_1 N_9\right) M_{99} + k_a M_{19} + 2k_{-1} M_{59} + \frac{2k_1}{v} M_{99} + \frac{1}{2}\sigma^2 \\
\frac{dM_{26}}{dt} &= -2k_2(N_2^2 + M_{22}) - 2k_{-2} N_6 + \frac{2k_2}{v} N_2 \\
&+ 2k_2 N_2 M_{22} + 2k_{-2} M_{66} - \left(k_{-2} + e_r + 4k_2 N_2 + k_3 N_5\right) M_{26} - \frac{k_2}{v} M_{22} + \frac{2k_2}{v} M_{26} \\
\frac{dM_{34}}{dt} &= -\frac{k_4 n_D}{v} N_3 + k_4(N_3 N_4 + M_{34}) - k_{-4} N_4 \\
&+ k_4\left(\frac{n_D}{v} - N_4\right) M_{33} + \left(k_4 N_3 + k_{-4}\right) M_4 - \left(-k_4 N_4 + k_4 N_3 + k_{-3} + k_{-4} + \frac{k_4 n_D}{v}\right) M_{34} \\
\frac{dM_{35}}{dt} &= -k_3(N_5 N_6 + M_{56}) - k_{-3} N_3 \\
&+ k_{-3} M_{33} + k_3 N_6 M_{55} - \left(k_4(-N_4 + \frac{n_D}{v}) + k_{-1} + k_{-3} + k_3 N_6\right) M_{35} + k_3 N_5\left(M_{56} - M_{36}\right) \\
\frac{dM_{36}}{dt} &= -k_3(N_5 N_6 + M_{56}) - k_{-3} N_3 \\
&+ k_{-3} M_{33} + k_3 N_5 M_{66} - k_3 N_6 M_{35} - \left(k_{-2} + k_{-3} + k_4\frac{n_D}{v} + k_3 N_5 - k_4 N_4\right) M_{36} + k_3 N_6 M_{56} \\
\frac{dM_{56}}{dt} &= k_3(N_5 N_6 + M_{56}) + k_{-3} N_3 \\
&- k_3 N_6 M_{55} - k_3 N_5 M_{66} + k_{-3}\left(M_{35} + M_{36}\right) - \left(k_{-1} + k_{-2} + k_3 N_6 + k_3 N_5\right) M_{56} \\
\frac{dM_{59}}{dt} &= -2k_1(N_9^2 + M_{99}) - 2k_{-1} N_5 + \frac{2k_1}{v} N_9 \\
&+ 2k_{-1} M_{55} + 2k_1 N_9 M_{99} - \left(d + k_{-1} + e_a + k_3 N_6 + 4k_1 X_9\right) M_{59} - \frac{k_1}{v} M_{99} + \frac{2k_1}{v} M_{59}. \quad \text{(A11)}
\end{aligned}
$$

APPENDIX B: GILLESPIE ALGORITHM WITH TIME DELAYS AND MEAN FIELD VARIABLES

Based on the Direct Gillespie method (Gillespie, 1976, 2001), we give a detailed algorithm for the simulation of the master equation (A1), where $Y(t) \equiv \langle X(t-\tau)\rangle V/v$ with time delays. Let the superscript j of the algorithm indicate the jth cell, and assume there is one time delay τ although multiple delays can be incorporated in the algorithm in a similar manner.

1. Initialization: input the cell number n, the stop time t_{stop} and the initial states $X^j(0) = (X_1^j, ..., X_m^j)$ of the jth cell for $j = 1, ..., n$. Let $\langle X(r)\rangle = \sum_{j=1}^n X^j(0)/n$ for all $-\tau \le r \le 0$, and the time evolution $t^j = 0$.

2. Parallel computation for each cell: if $t^{MX} - t^{mx} \le \tau$, proceed with the parallel computation for each cell, i.e., $j = 1, ..., n$. Otherwise, choose only the mx-th cell, i.e., $j = mx$ to proceed with the following computation, where MX and mx are the cells with the maximal and the minimal current evolution times among $\{t^1, ..., t^n\}$ respectively.

   (a) Mean field variables: compute $\langle X(t^j - \tau)\rangle = \sum_{j=1}^n X^j(t^j - \tau)/n$, where $X^j(t^j - \tau)$ is the latest value of X^j at $t^j - \tau$. That is, if $t^j - \tau > 0$, then $X^j(t^j - \tau) = X^j(t_1^j)$ for two consecutive updating times t_1^j and t_2^j of the jth cell with $t_1^j \le t - \tau < t_2^j$; otherwise $X^j(t^j - \tau) = X^j(0)$.

   (b) Propensities: compute $w_i(X^j(t^j))$ for $i = 1, ..., n_0$ according to the state $X^j(t^j)$ and $\langle X(t^j - \tau)\rangle$.

   (c) Uniform random numbers: draw two uniform random numbers r_1^j and $r_2^j \in [0, 1)$.

   (d) Time interval $\Delta\tau^j$: compute $\Delta\tau^j = -(\ln r_1^j)/\sum_{i=1}^{n_0} w_i$ until the next reaction.

   (e) Next reaction μ^j: find the next reaction μ^j by taking μ^j to be the integer satisfying

   $$\sum_{i=1}^{\mu^j - 1} w_i < r_2^j (\sum_{i=1}^{n_0} w_i) \le \sum_{i=1}^{\mu^j} w_i. \tag{B1}$$

   (f) Update the time $t^j \to t^j + \Delta\tau^j$, and the state $X^j \to X^j + \theta_{\mu^j}$ according to the μ^jth reaction.

3. Termination check: if $\min\{t^1, ..., t^n\} > t_{stop}$, then terminate the computation; otherwise, go to step 2.

The Gellespie algorithm is considered as the standard one for stochastic simulation of biochemical systems. In particular, the algorithm entails the generation of an ensemble of sample trajectories of the system with correct statistics for a set of biochemical reactions, which ensure to asymptotically converge to the solution of the corresponding master equation. Clearly, the algorithm requires to store the sampling time and state in the time interval $[t^j - \tau, t^j]$ due to the time delays.

APPENDIX C: HOPF BIFURCATION OF THE EVOLUTION EQUATIONS

We give general conditions for Hopf bifurcation, under which the system (4) with time delays will converge to a nontrivial periodic solution.

Let $(\bar{N}, \bar{M})$ be an equilibrium of eqn.(4). The number of the nonzero elements in the covariance vector M is p. Denote functions $F_i(N(t), M(t))$, $G_{ij}(N(t), M(t)) - (d_{ii} + d_{jj})M_{ij}(t)$, and $d_{ij}(N_i(t - \tau_i) + N_j(t))$ by a $m \times 1$ vector function $F(N(t), M(t))$, a $p \times 1$ vector function $G(N(t), M(t))$ and a $p \times 1$ vector function $U(N(t - \tau), N(t))$, respectively. Define

$$A(\lambda) = \begin{pmatrix} \frac{\partial F}{\partial N} + P & \frac{\partial F}{\partial M} \\ \frac{\partial G}{\partial N} + Q & \frac{\partial G}{\partial M} \end{pmatrix}, \tag{C1}$$

where $P = \mathrm{diag}(d_{11}(e^{-\lambda\tau_1} - 1), \cdots, d_{mm}(e^{-\lambda\tau_m} - 1))$ is a $m \times m$ diagonal matrix. $Q = e^{-\lambda t}(U_{N_1}, \cdots, U_{N_m})$ is a $p \times m$ matrix, where U_{N_i} denotes the $p \times 1$ vector function $U(N(t - \tau), N(t))$, in which $N_j(t - \tau_j)$ and $N_j(t)$ for $j = 1, ..., m$ are replaced by zeros if $j \neq i$, and replaced by $e^{\lambda(t-\tau_i)}$ and $e^{\lambda t}$ if $j = i$, respectively. Then the characteristic equation of eqn.(4) evaluated at the equilibrium $(\bar{N}, \bar{M})$ is

$$\det(\lambda I - A(\lambda)) = 0, \tag{C2}$$

where I is the $(m + p) \times (m + p)$ identity matrix. Notice that A also includes the noise deviation σ due to G. For any parameter α in eqn.(4), such as coupling coefficients, time delays or noise deviations, we have the following theorem:

Theorem C.1 *Suppose that functions F, G and U, are sufficiently smoothly depending on the parameter α, and there is α_0 such that for $\alpha < \alpha_0$ all roots λ_k, $k = 1, 2, \cdots, m + p$, of the characteristic equation belong to the open left halfplane, whereas for $\alpha = \alpha_0$,*

1. $\lambda_{1,2}|_{\alpha=\alpha_0} = \pm i\omega_0$, $\omega_0 > 0$;
2. $\frac{dRe\lambda_{1,2}(\alpha)}{d\alpha}|_{\alpha=\alpha_0} > 0$, $Re\lambda_j|_{\alpha=\alpha_0} < 0$ $(j > 2)$,

then a periodic solution of system (4) arises near the solution $(N, M) = (\bar{N}, \bar{M})$ *and this solution is stable if it arises for* $\alpha > \alpha_0$ *and unstable in the opposite case.*

Under these conditions, if α increases and passes through the value α_0, then the stable equilibrium becomes unstable, i.e., $\alpha = \alpha_0$ is a critical value of the bifurcation. When α passes through α_0 in one of two directions, a periodic solution bifurcates from the equilibrium. Such a solution is stable if it arises for $\alpha > \alpha_0$ and unstable in the opposite case.

APPENDIX D: A SUFFICIENT CONDITION FOR SYNCHRONIZATION

When the number of cells, n is sufficiently large, we assume that the system can be expressed by a deterministic eqn.(4) by the Gaussian approximation. To directly consider the interconnection of cells, we replace $N_i(t-\tau)$ of eqn.(4) by $\sum_{k=1}^{n} N_i^k(t-\tau)/n$ due to y of eqn.(2). For such a case, the existence of periodic solutions in the system (4) implies that the original n cells show bulk synchronization. However, partial oscillations among cells are generally expected. For the consideration of generality, we divide the n cells into $\bar{n}$ ($\bar{n} \leq n$) different sets or groups, each set or group containing a fraction W_k, $k = 1, 2, \cdots, \bar{n}$, of n oscillators with

$$\sum_{k=1}^{\bar{n}} W^k = 1 \tag{D1}$$

where W^k is a non-negative scalar and $W^k n$ is an integer representing the number of cells in the k-th group. Since all the cells in each set are equivalent, we further use $R_i(t-\tau) \equiv \sum_{k=1}^{n} W^k N_i^k(t-\tau)$ to replace $\sum_{k=1}^{n} N_i^k(t-\tau)/n$. Thus, eqn.(4) is rewritten by the following system:

$$\begin{cases} \frac{dN_i^k(t)}{dt} = F_i(N^k(t), M^k(t)) + d_{ii}(R_i(t-\tau) - N_i^k(t)) \\ \frac{dM_{ij}^k(t)}{dt} = G_{ij}(N^k(t), M^k(t)) - (d_{ii} + d_{jj})M_{ij}^k(t) + d_{ij}(R_i(t-\tau) + N_j^k(t)), \end{cases} \tag{D2}$$

where $1 \leq k \leq \bar{n}$, $d_{ij} = 0$ if $i \neq j$, $M_{ij}^k(t) = M_{ji}^k(t)$. Note that bulk oscillation or in-phase synchronization of these $\bar{n}$ groups correspond to $\bar{n} = 1$. This implies that the bulk oscillation is a special case of solutions of eqn.(D2). However, phase-locked oscillations among cells are generally expected.

For clarity, (D2) is rewritten as

$$\begin{cases} \frac{dN_i^k(t)}{dt} = F_i(N^k(t), M^k(t)) + d_{ii}(R_i(t-\tau) - N_i^k(t)) \\ \frac{dM_{ii}^k(t)}{dt} = G_{ii}(N^k(t), M^k(t)) - 2d_{ii}M_{ii}^k(t) + 2d_{ii}(-M_{ii}^k(t) + N_i^k(t)) + d_{ii}[R_i(t-\tau) - N_i^k(t)] \\ \frac{dM_{ij}^k(t)}{dt} = G_{ij}(N^k(t), M^k(t)) - (d_{ii} + d_{jj})M_{ij}^k(t), \;\; i \neq j. \end{cases} \tag{D3}$$

By introducing a vector-valued variable Z labelling variables N and M, (D3) is further rewritten as the following compacted form:

$$\frac{d}{dt}\begin{pmatrix} z_1^k(t) \\ z_2^k(t) \\ z_3^k(t) \end{pmatrix} = H(Z^k(t);\,\mu) + \begin{pmatrix} D\sum_{k=1}^{\bar{n}} W^k z_1^k(t-\tau) - Dz_1^k(t) \\ D\sum_{k=1}^{\bar{n}} W^k z_1^k(t-\tau) - Dz_1^k(t) \\ O \end{pmatrix}, \tag{D4}$$

where $D = \begin{pmatrix} d_{11} & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & d_{mm} \end{pmatrix}$, $Z^k(t) = \begin{pmatrix} z_1^k(t) \\ z_2^k(t) \\ z_3^k(t) \end{pmatrix}$ with $z_1^k(t) \in \mathbf{R}^m$, $z_2^k(t) \in \mathbf{R}^m$ and $z_3^k(t) \in \mathbf{R}^{m(m-1)/2}$, and μ is a parameter (see below).

Eqn.(D4) may be regarded as a system of $\bar{n}$ identical groups coupled in a linear way with the time delays. Each group will be considered as a system with $m(m+3)/2$ distinct deterministic variables, which are governed by the dynamical equation in the following vector form:

$$\frac{dZ}{dt} = H(Z;\,\mu). \tag{D5}$$

Suppose that its steady state satisfies $H(\bar{Z};\,\mu) = 0$. Then, a steady state of the coupled system (D4) is

$$\bar{U} = \left(\bar{Z};\,\bar{Z};\,\cdots;\,\bar{Z}\right). \tag{D6}$$

We now study synchronization solutions of Eqn.(D4), i.e., phase-locked solutions with the nonzero phase difference. The mathematical analysis of mutual synchronization is a challenging problem. The pioneering work in this area is due to Winfree (1967, 1980, 1987), who simplified the problem by assuming that the oscillators are strongly attracted to their limit cycles, so that the amplitude variations can be neglected and only phase variations are needed to be considered. Winfree discovered that mutual synchronization is a cooperative phenomenon, by a temporal analogue of the phase transitions encountered in statistical physics.

Now, suppose that the system (D4) has a periodic solution of the form

$$Z^j(t) = P(t-\alpha_j T) = \begin{pmatrix} P_1(t-\alpha_j T) \\ P_2(t-\alpha_j T) \\ P_3(t-\alpha_j T) \end{pmatrix},\ 1 \le j \le \bar{n}, \tag{D7}$$

where $P(t)$ is a nontrivial vector-valued function with the least period $T > 0$, and $\alpha_1 = 0$. Such a solution is called a phase-locked solution of Eqn.(D4). Essentially, the oscillation in each cell is described by functions $P(t)$. Other cells, however, may be out of phase with the phase difference, $T\beta_j \equiv T\left(\alpha_{j+1} - \alpha_j\right)$. Here and henceforth we shall index the cells by j mod $\bar{n}$.

When eqn.(D7) is a solution of eqn.(D4), certain compatibility conditions must hold. To derive those conditions, consider the behavior of the j^{th} and the $(j+1)^{th}$ variables at times t and $t+\beta_j T$, respectively. From eqns.(D7) and (D4), for $2 \le j \le \bar{n}$,

$$\frac{dP_1(t-\alpha_j T)}{dt} = D\left[\sum_{k=1}^{\bar{n}} W^k P_1(t-\tau-(\alpha_k+\alpha_j)T) - P_1(t-\alpha_j T)\right] + H(P(t-\alpha_j T);\,\mu)$$

and

$$\frac{dP_1(t-\alpha_j T)}{dt} = D\left[\sum_{k=1}^{\bar{n}} W^k P_1(t-\tau-\alpha_k T) - P_1(t-\alpha_j T)\right] + H(P(t-\alpha_j T);\,\mu).$$

Subtracting the two equations, we have

$$D\sum_{l=1}^{\bar{n}} W^l \left[P_1(t-\tau-(\alpha_l+\alpha_j)T) - P_1(t-\alpha_l T)\right] = 0. \tag{D8}$$

Let

$$P_1(t) = \sum_{k=-\infty}^{\infty} \gamma_k e^{2\pi i k t/T} \tag{D9}$$

be the Fourier expansion of $P_1(t)$, where $i=\sqrt{-1}$. Then $\gamma_k = \bar{\gamma}_k$, and $\gamma_k = \frac{1}{T}\int_0^T P_1(t)e^{-2\pi i k t/T}dt$. Substituting eqn.(D9) into eqn.(D8) and using orthogonality, we find that basic compatibility conditions are

$$\det\left[\left(D\sum_{l=1}^{\bar{n}} W^l e^{-2\pi i k\alpha_l}\right)\left(e^{-2\pi i k\alpha_j}-1\right)\right] = 0 \tag{D10}$$

for all k for which $\gamma_k \neq 0$ and $2 \le j \le \bar{n}$, where $\det[\cdot]$ means the determinant.

Note that eqn.(D10) has the following trivial solution for all D and arbitrary W^k:

$$\alpha_j = 0,\ \ 1 \le j \le \bar{n},$$

which corresponds to the in-phase solution of eqn.(D4). We are more interested in nontrivial solution cases. For this, Assume

$$\det(D) = \prod_{l=1}^{\bar{n}} d_{ll} \neq 0. \tag{D11}$$

Then,

$$\sum_{l=1}^{\bar{n}} W^l e^{-2\pi i k\alpha_l} = 0. \tag{D12}$$

One solution of (D12) is

$$\alpha_j = \frac{j-1}{\bar{n}}, \quad 1 \le j \le \bar{n}, \tag{D13}$$

when

$$W^j = \frac{1}{\bar{n}}, \quad 1 \le j \le \bar{n}. \tag{D14}$$

Clearly, the solution corresponding to such a phase has the uniform phase difference.

An interesting phenomenon is in the case that n identical cells are coupled in a ring in which each cell is connected to its nearest neighbors as depicted in (Alexander and Auchmuty, 1986). In such a case, we have $\bar{n} \equiv n$.

Next, we give the existence conditions of such a periodic solution with period T for eqn.(D4), which are used to describe synchronization mechanism through cell-cell communication. We show that the conditions required are straightforward and are easy to verify for any particular example. These conditions strongly depend on coupling, time delay, variances of the noises and the kinetics.

For the system (D4), consider a problem to find a phase-locked solution of the form (D7). By eqns.(D7) and (D4), we see that

$$\frac{d}{dt}\begin{pmatrix} P_1(t) \\ P_2(t) \\ P_3(t) \end{pmatrix} = \begin{pmatrix} D\sum_{l=1}^{\bar{n}} W^l P_1(t-\tau-\alpha_l T) - DP_1(t) \\ D\sum_{l=1}^{\bar{n}} W^l P_1(t-\tau-\alpha_l T) - DP_1(t) \\ O \end{pmatrix} + H(P(t);\,\mu) \tag{D15}$$

and the oscillation in the j^{th} $(2 \le j \le \bar{n})$ group is given by

$$Z^j(t) = P(t - \alpha_j T). \tag{D16}$$

Thus, the existence of a synchronous solution of eqn.(D4) is converted to finding a periodic solution of system (D15). By Global Hopf Bifurcation Theorem (Alexander and Auchmuty, 1986), we only need to examine some algebraic conditions. To be specific, let $t' = \omega_0 t$ (where $\omega_0 = 2\pi/T$). Then, eqn.(D16) can be rewritten as

$$\omega_0 \frac{d}{dt}\begin{pmatrix} P_1(t') \\ P_2(t') \\ P_3(t') \end{pmatrix} = \begin{pmatrix} D\sum_{l=1}^{\bar{n}} W^l P_1(t'-2\pi\tau/T-2\pi\alpha_l) - DP_1(t') \\ D\sum_{l=1}^{\bar{n}} W^l P_1(t'-2\pi\tau/T-2\pi\alpha_l) - DP_1(t') \\ O \end{pmatrix} + H(P(t');\,\mu). \tag{D17}$$

Considering the linearization equation of (D17) evaluated at $\bar{U}$, we then have

$$\omega_0 \frac{d}{dt}\begin{pmatrix} P_1(t) \\ P_2(t) \\ P_3(t) \end{pmatrix} = \begin{pmatrix} D\sum_{l=1}^{\bar{n}} W^l P_1(t-2\pi\tau/T-2\pi\alpha_l) - DP_1(t) \\ D\sum_{l=1}^{\bar{n}} W^l P_1(t-2\pi\tau/T-2\pi\alpha_l) - DP_1(t) \\ O \end{pmatrix} + \mathcal{A}\cdot P(t), \tag{D18}$$

where $\mathcal{A} = \partial_P H(\bar{U});\, \mu)$. Let

$$\mathcal{B}_k(\mu) = \begin{pmatrix} D\left(\sum_{l=1}^{\bar{n}} W^l e^{-2\pi i k(\tau/T+\alpha_l)} - 1\right) & O & O \\ D\left(\sum_{l=1}^{\bar{n}} W^l e^{-2\pi i k(\tau/T+\alpha_l)} - 1\right) & O & O \\ O & O & O \end{pmatrix} + \mathcal{A} \tag{D19}$$

for $k = 0, \pm 1, \pm 2, \cdots$. In addition, because our main interest is in the effects of noises on synchronization oscillation, we take a parameter $\mu = \sigma$. Then, finally we reach the following theorem to conclude the existence conditions of phase-locked solutions (Alexander and Auchmuty, 1986).

Theorem D.1 *Suppose that function H is differentiable with respect to its arguments, and that $W^k = 1/\bar{n}$ for $1 \leq k \leq \bar{n}$. If for some $\mu = \mu_0$ and $\alpha_j = (j-1)/\bar{n}$ $(mod\ 1)$, the following conditions are satisfied:*

1. *$\mathcal{B}_0(\mu_0)$ of eqn.(D19) is non-singular;*
2. *$\mathcal{B}_1(\mu_0)$ of eqn.(D19) has a simple purely complex eigenvalue $i\omega_0$ with the corresponding left and right eigenvectors V_L and V_R respectively;*
3. *$ik\omega_0$ is not an eigenvalue of $\mathcal{B}_k(\mu_0)$ for $k \geq 2$;*
4. *$\Re\left(V_L \frac{d\mathcal{A}(\mu_0)}{d\mu} V_R\right) \neq 0$ where $\Re$ is an operator taking the real part of a complex number,*

then there is a global branch of 2π-periodic solutions of eqn.(D18) bifurcating from $(\bar{U},\, \mu_0,\, \omega_0)$, or equivalently, the original coupled system (D4) has a phase-locked solution with a uniform phase difference.

If these conditions in Theorem D.1 are satisfied, then the system (D4) definitely has a synchronous solution, and the corresponding synchronization mechanism is based on "global Hopf bifurcation". Such conditions are easy to use and enable us to predict, for a given set of parameter values, whether or not the intercell coupling and the noises synchronize the dynamical behaviors of cells.