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Modelling of intercellular synchronization in the *Drosophila* circadian clock*

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In circadian rhythm generation, intercellular signaling factors are shown to play a crucial role in both sustaining intrinsic cellular rhythmicity and acquiring collective behaviours across a population of circadian neurons. However, the physical mechanism behind their role remains to be fully understood. In this paper, we propose an indirectly coupled multicellular model for the synchronization of *Drosophila* circadian oscillators combining both intracellular and intercellular dynamics. By simulating different experimental conditions, we find that such an indirect coupling way can synchronize both heterogeneous self-sustained circadian neurons and heterogeneous mutational damped circadian neurons. Moreover, they can also be entrained to ambient light–dark (LD) cycles depending on intercellular signaling.

Keywords: *Drosophila*, biological clock, circadian oscillation, synchronization
PACC: 8710, 8730E

1. Introduction

As an autonomous internal daily-timekeeping mechanism the circadian clock is responsible for the robust regulation of a variety of physiological and behavioural processes in a diverse range of organisms, including *Neurospora, Arabidopsis, Drosophila*, mouse, and humans.[1−6] As one of the most intensively researched model organisms, *Drosophila* is commonly used to study rhythm phenomena due to the relative ease of experimentation and the similarity to the mammalian circadian clock (reviewed in Refs.[7, 8]). In *Drosophila*, a group of genes encoding activator and repressor transcription regulatory factors, namely *period* (*per*), *timeless* (*tim*), *clock* (*clk*), *cycle* (*cyc*), *vrille* (*vri*), and *par domain protein* 1 (*pdp* 1), have been identified, which are necessary for circadian clock functions. These genes and their products are organized into two interconnecting transcription–translation feedback loops: a PER/TIM loop and a VRI/PDP1 loop.[9,10] In the adult *Drosophila* brain, the clock-gene-expressing neurons include three sets of lateral neurons (LNs) designated s-LN_v, l-LN_v, and LN_d, and three sets of dorsal neurons (DNs), DN1–3.[11] Recent studies have focused principally on one of these groups, with the small ventral LNs (s-LN_vs) taken as the best 'core pacemakers' regulating daily locomotor rhythms. The s-LN_v expresses the neuropeptide pigment dispersing factor (PDF)[12,13] that is closely related to crustacean pigment dispersing hormone (PDH). Loss of PDF expression produces abnormal locomotor rhythms, and the ablation of the PDF neurons generates a very similar phenotype.[14] These results confirm that s-LN_vs are the principal circadian pacemaker neurons in *Drosophila*[15] and support the hypothesis that the *pdf* encodes the principal circadian transmitter. The output pathways from the *Drosophila* clocks have not yet been delineated, but the brain neuroendocrine system is probably one target, with brain neurons controlling locomotor activity being another.[16,17] Evidence is available that the PDF is the main output factor of the LN_v clock neurons, necessary for maintaining the circadian locomotor activity and eclosion rhythm under the conditions corresponding to constant darkness (DD)[15] and for synchronizing pacemaker activity.[18,19] Following the recent identification of the *Drosophila* PDF receptor,[20,21] neurons that are targets of PDF signaling have been identified. These findings support the notion that the PDF is important for the synchro-

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nization of clock neurons. Furthermore, the experimental evidence also strongly suggests that robustness in timekeeping precision emerges in the collective behaviour and not at the single-cell level.[22] However, the intercellular mechanisms that allow large populations of coupled pacemaker cells to synchronize and coordinate their rhythms are not well understood.

Some conceptual models constructed from simple differential equation models of a single oscillating neuron and phenomenological descriptions of intercellular coupling have been proposed for studying circadian rhythm generation.[23−27] Although they are conceptually appealing and computationally efficient, such population models cannot be directly related to specific molecular events. Encouragingly, multicellular models based on more mechanistic descriptions of circadian gene regulation have also been presented for *Drosophila*,[28] the cockroach *Leucophaea maderae*[29] and mammals.[30,31] To understand the orchestration of timekeeping in the suprachiasmatic nucleus (SCN), Bernard *et al*[30] recently proposed a model for synchronizing circadian oscillators, which combines intracellular and intercellular dynamics at the single-cell level. The model is a heterogeneous network of circadian neural oscillators where individual oscillators are damped rather than self-sustained. Their results predict a dual role for the coupling factors within the SCN, both in maintaining the rhythmicity and in promoting the synchronization between the circadian oscillators. A multicellular model with a detailed molecular description of both a single circadian neuron and its intercellular signaling in the mammalian circadian clock has been developed by To *et al*.[31] In order to address how multiple cells produce coherent rhythms in the presence of internal noise without referring to external time cues, Ueda *et al* [28] extended a single cellular deterministic model on *Drosophila* circadian rhythms[32] to a three-dimensional 100-cellular stochastic model and suggested a mechanism which facilitated the constancy of the circadian rhythm with possible functional redundancy among different synchronizing factors.

It should be noted that a common characteristic of the previous models is that single self-sustained circadian neurons are directly coupled. To our knowledge, a multicellular model with an indirect intercellular coupling mechanism is not currently available for any organism. Here we develop a multicellular model of *Drosophila* circadian oscillators with the mechanism of signaling pathways. We simulate different experimental conditions and find that such an indirect coupling structure relying on a signal transduction cascade can efficiently synchronize not only heterogeneous self-sustained circadian neurons, but also heterogeneous damped circadian neurons. Moreover, they can also be entrained to ambient light-dark (LD) cycles depending on intercellular signaling. From these results in agreement with experimental observations, we can conclude that the proposed indirect coupling represents a possible mechanism for intercellular communication of mediating collective rhythms of *Drosophila* circadian oscillators.

2. Structure of the multicellular model

To simulate the synchronization of *Drosophila* circadian systems, a conceptual model is presented in this paper (Fig.1). It implements a core oscillator from

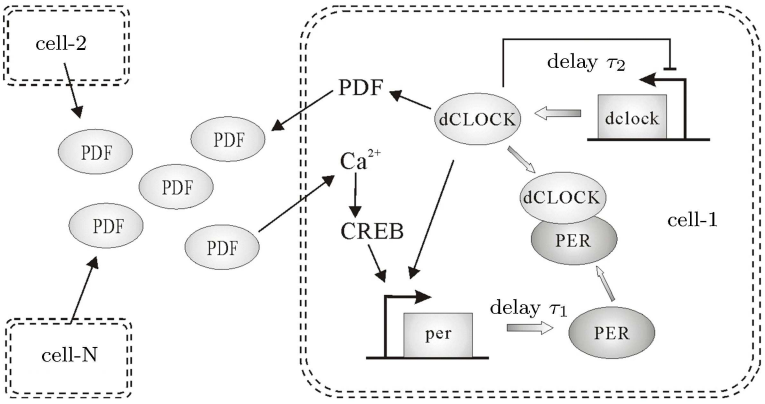


Fig.1. Schematic diagram of single-cell *Drosophila* circadian oscillators,[33] including the coupling mechanism. One hypothesized output of this clockwork is the circadian regulation of PDF release. We assume that the release of the neurotransmitter PDF in the intracellular medium is activated by dCLOCK. In turn, extracellular PDF binds to the G-protein coupled receptor PDFR to trigger a signaling cascade that activates *per* expression.

a previously published gene regulation model[33] with modifications by allowing the incorporation of communication between cells. In the original model of Ref.[33], each cell was described by two ordinary differential equations and circadian rhythms were generated by the action of two interacting feedback loops. Using a set of parameters, that model can generate autonomous sustained oscillations under some conditions corresponding to DD or be entrained by LD cycles. Here, we assume that the release of the neuropeptide PDF is induced by the protein dCLOCK. We modelled a two-step signal transduction cascade in which the neuropeptide PDF binds to its receptor to increase intracellular calcium and activate the cAMP response-element binding protein (CREB), which induces *per* transcription to modulate the oscillator phase.[34,35] With the neurotransmitter and the two-step signal transduction cascade, the complete dynamics of the ith cell is described by

$$\begin{aligned}
\frac{\mathrm{d}x_i}{\mathrm{d}t} &= \alpha_1 \frac{y_i^{\mathrm{free}}(t-\tau_1)}{\eta_1 + y_i^{\mathrm{free}}(t-\tau_1)} - \beta_1 x_i + \theta v_i, \\
\frac{\mathrm{d}y_i}{\mathrm{d}t} &= \alpha_2 \frac{\eta_2}{\eta_2 + y_i^{\mathrm{free}}(t-\tau_2)} - \beta_2 y_i, \\
\frac{\mathrm{d}s_i}{\mathrm{d}t} &= \alpha_3 y_i - \beta_3 s_i - d_{\mathrm{e}} s_i, \\
\frac{\mathrm{d}u_i}{\mathrm{d}t} &= \alpha_4 s_{\mathrm{e}} - \beta_4 u_i, \\
\frac{\mathrm{d}v_i}{\mathrm{d}t} &= \alpha_5 u_i - \beta_5 v_i
\end{aligned} \tag{1}$$

with $y_i^{\mathrm{free}} = y_i - x_i$ or zero, whichever is greater. The dynamical variables represent the following species: x, protein PER; y, protein dCLOCK; s, neurotransmitter PDF; u, Ca^{2+}; v, CREB. d_{e} is the diffusion rate from each cell to the common extracellular medium.

The interplay between individual neurons is not described by direct coupling but by diffusion and interchanging integration of neuropeptide s_i among all cells through the extracellular common PDF (s_{e}):

$$\frac{\mathrm{d}s_{\mathrm{e}}}{\mathrm{d}t} = K \sum_{i=1}^{N} s_i - d_{\mathrm{e}} s_{\mathrm{e}}. \tag{2}$$

On model, here we point out that our population model is different from that of so-called star-type coupling, and also from that of neural network. The main differences lie in the description of interaction among cells, e.g. any two cells are not directly coupled but indirectly interacted through the neurotransmitter PDF in the extracellular common medium, which is shared by all cells to trigger a signaling transduction cascade. Such a coupling is biologically plausible and has been used by many researchers.[36−40] Our numerical results in the present paper will verify that this indirect coupling approach is an effective way of achieving synchronization across a population of *Drosophila* circadian oscillators. Throughout this paper parameter values are fixed as follows: $\alpha_1 = 0.5\,\mathrm{nMh^{-1}}$, $\eta_1 = 0.3\,\mathrm{nM}$, $\tau_1 = 11\mathrm{h}$, $\alpha_2 = 0.25\,\mathrm{nMh^{-1}}$, $\eta_2 = 0.1\,\mathrm{nM}$, $\tau_2 = 10\,\mathrm{h}$, $\beta_2 = 0.5\,\mathrm{h^{-1}}$, $\alpha_3 = 0.3\,\mathrm{h^{-1}}$, $\beta_3 = 0.3\,\mathrm{h^{-1}}$, $\alpha_4 = 0.4\,\mathrm{h^{-1}}$, $\beta_4 = 0.45\,\mathrm{h^{-1}}$, $\alpha_5 = 0.3\,\mathrm{h^{-1}}$, $\beta_5 = 0.4\,\mathrm{h^{-1}}$, $d_{\mathrm{e}} = 0.3\,\mathrm{h^{-1}}$ and $\theta = 0.3\,\mathrm{h^{-1}}$. A set of parameter values for the single cell model, i.e. α_1, η_1, τ_1, α_2, η_2, τ_2 and β_2, has been minimally adapted from those of the original model[33] and a set of parameter values for the coupled system, i.e. α_3, β_3, α_4, β_4, α_5, β_5, d_{e} and θ, is chosen for the requirement of the network synchronization with nearly a circadian period. We point out that the latter set of parameters may be taken as somewhat arbitrary values because of lacking available experimental data. In fact, we numerically find that several other values of the latter set of parameters also yield a circadian period of oscillation.

3. Results

3.1. Indirect coupling can synchronize heterogeneous self-sustained circadian neurons

In *Drosophila*, circadian clocks have been identified in a diverse range of cell types throughout the head and the body.[19,41] The circadian oscillator population is likely to be substantially different from cell to cell, giving rise to a relatively broad distribution in the period of the individual clocks at any given time. In fact, the clocks in different cells have been considered to be nonidentical.[19,41,42] Accordingly, to mimic these cellular heterogeneities, random perturbations are introduced into the individual neuron models via kinetic parameter β_1 of Eq.(1) of the core oscillator. By setting the standard deviation in β_1 to 5% from their mean values, we simulate a population of oscillators in which the neurotransmitter is only perceived by the cells that release it (autocrine activation). Under the DD condition, we find that the isolated cells with autocrine activation could also become self-sustained oscillators or damped oscillators.[43] In addition, the free-running periods of the intrinsic oscillators are tightly distributed around 24h. The temporal evolutions of dCLOCK protein concentration of

150 circadian neurons are plotted in Figs.2(a) and 3(a), showing how the global operation of the system is completely disorganized such that no collective rhythm can exist under these conditions.

Now, we first test how well the coupled self-sustained oscillators are synchronized with each other under normal condition that mimics wild-type adult

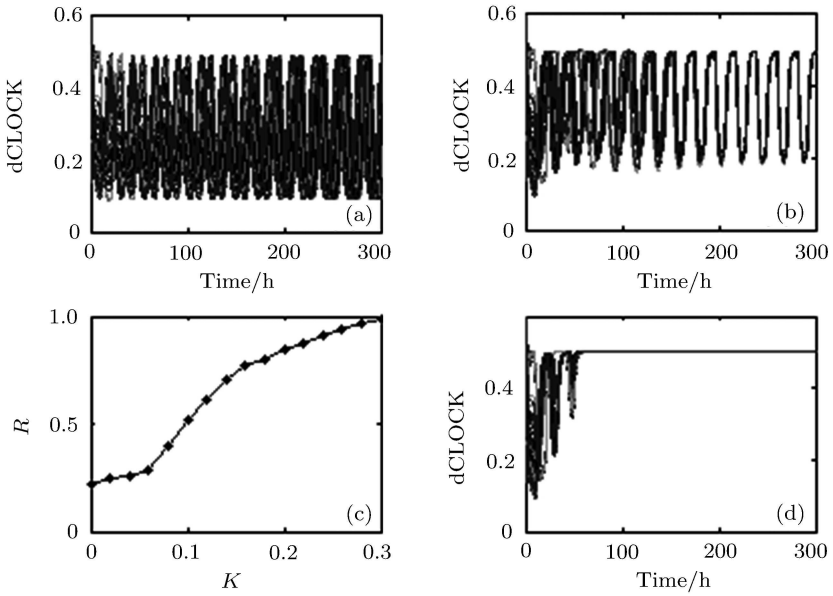


Fig.2. Synchronization of 150 self-sustained circadian neurons under DD condition, where panel (a) is for time evolution of dCLOCK concentration for $K = 0$, panel (b) for time evolution of dCLOCK concentration for $K = 0.3$, panel (c) for order parameter R versus coupling strength K, and panel (d) for time evolution of dCLOCK concentration for $K = 0.4$, with concentration being in nM.

Drosophila brain. Thus we set mean value of parameter $\beta_1 = 2.5$ to produce an ensemble of 150 self-sustained oscillators, as shown in Fig.2(a). To describe the strength of the synchronization signal, we introduce the parameter $K \geq 0$ that controls the overall coupling strength (see Eq.(2)). With the coupling intensity $K = 0.3$, the population is well synchronized, and the overall period is 21.3 h (Fig.2(b)), indicating that the PDF indirect coupling leads to a moderate decrease of the period. We could compensate deviations from the 24-h period by changing, e.g. degradation rates. However, because of the lack of *in vivo* data for compensation, we have avoided this extension in model.

Because not all of the oscillators have the same individual period due to cellular heterogeneity, a perfect synchronization cannot be achieved and a difference in phase between some oscillators still persists. To quantify how good the synchrony is, we calculate an order parameter which is, according to Ref.[37], defined as

$$R = \frac{< M^2 > - < M >^2}{\overline{< x_i^2 > - < x_i >^2}}, \tag{3}$$

where $M(t) = \dfrac{1}{N}\sum_{i=1}^{N} x_i(t)$ with N being the number of cells, $< \cdot >$ denotes the averaging over time, and $\overline{< \cdots >}$ indicates averaging over all cells. This parameter measures the distribution of phases of oscillators, and is in between 0 (no synchronous) and 1 (perfect synchronization with all oscillators in phase). The dependence of the order parameter R on coupling strength K is shown in Fig.2(c). From this figure, it can be observed that the coupled population model exhibits notable synchronized oscillations ($R \geq 0.84$) when $K \geq 0.2$, referring to Fig.2(b) for $K = 0.3$. When the coupling is very weak (e.g., $K = 0.05$), the multicellular system behaves as if it is composed of isolated cells, exhibiting incomplete synchronization (the numerical results are not shown). More interestingly, for a larger coupling strength (e.g., $K = 0.4$), the ensemble loses rhythmicity rapidly in a synchronous manner (see Fig.2(d)). In other words, the *Drosophila* has evolved into an adaptive mechanism only allowing moderate coupling strength to produce robust collective behaviour.

3.2. Indirect coupling can synchronize heterogeneous damped circadian neurons

Based on bioluminescence imaging to monitor *per 2* gene expression, in tissue explants and dissociated cells from clock mutant mice, Liu *et al*[44] found that the suprachiasmatic nucleus (SCN) intercellular coupling was able not only to synchronize rhythmic cells but also to stabilize and synchronize the transient rhythms in intrinsically compromised circadian neurons such as those in *per* $1^{-/-}$ or *cyc* $1^{-/-}$ SCN. Here we test whether the proposed indirect coupling scheme can restore the circadian rhythmicity among coupled damped *Drosophila* circadian neurons.

To mimic an ensemble of individual damped circadian neurons, the mean value of parameter β_1 was fixed at 3.5, i.e. $\beta_1 = 3.5$ (see Fig.3(a)). With the help of indirect coupling, isolated damped oscillators are driven into rhythmic circadian oscillations and operate in a synchronous manner as shown in Fig.3(b). Moreover, both the amplitude and the period in coupled damped circadian neurons are similar to those of coupled self-sustained circadian neurons as compared with those in Fig.2(b). From the dependence of order parameter R on coupling strength K shown in Fig.3(c) for coupled damped circadian neurons, we can see that when the coupling strength K is about 0.3, i.e. $K \approx 0.3$, the synchronization of such an ensemble is achieved. Also for a very large coupling intensity (e.g. $K \approx 0.5$), the coupled heterogeneous damped oscillators lose rhythmicity simultaneously (Fig.3(d)). These results indicate that for a *Drosophila* circadian system, intercellular communication not only can synchronize self-sustained rhythmic oscillators to regulate various physiological and behavioural processes, but also can stabilize and synchronize mutant damped circadian neurons to resist genetic perturbations.

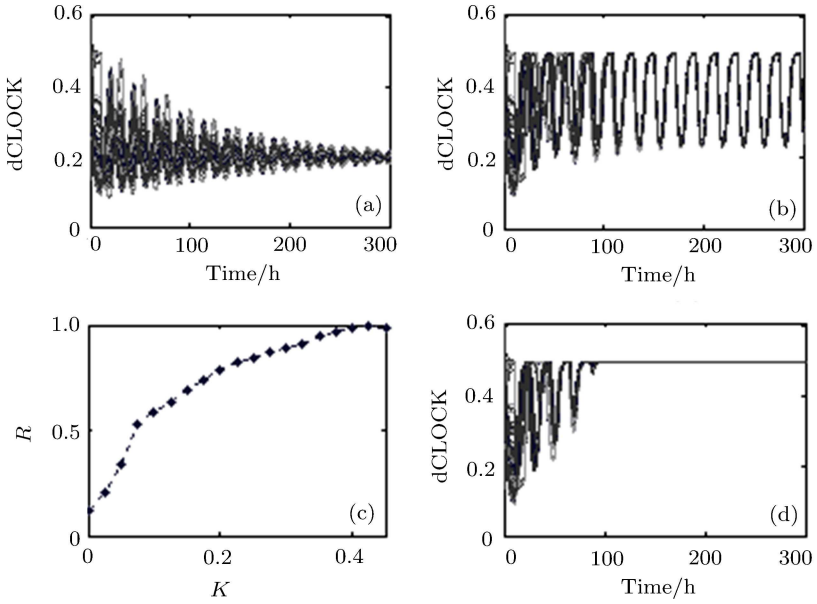


Fig.3. Curves for synchronization of 150 damped circadian neurons under DD condition, where panel (a) shows time evolution of dCLOCK concentration for $K = 0$, panel (b) indicates time evolution of dCLOCK concentration for $K = 0.45$, panel (c) exhibits order parameter R versus coupling strength K, and panel (d) gives time evolution of dCLOCK concentration for $K = 0.5$, with concentration being in nM.

4. Entrainment to LD cycles

A fundamental characteristic of circadian clocks is that they are entrained (phase-adjusted) by Zeitgeber, such as ambient light and temperature. In *Drosophila* it has been shown experimentally that the light enhances the degradation of TIM[45] and the changing of the TIM degradation rate has been used to model the light response and entrainment to LD cycles in the previous models. On the other hand, experimental findings have shown that nuclear phosphorylation of PER is strongly enhanced when TIM is removed from PER/TIM complexes[46] and multiple phosphorylations of PER precede its degradation.[47] These observations suggest that light, by accelerating TIM degradation, also accelerates the PER phosphoryla-

tion and the succeeding degradation of PER.[33] Because Eq.(1) describes only the evolutions of PER and dCLOCK concentrations, we simulate light exposure by enhancing PER degradation. To test whether our model is able to entrain to LD cycles, we simulate a 12h–12h LD cycle by imposing a periodic forcing on the degradation rate of protein PER (β_1 in Eq.(1)), i.e. we set $\beta_1 \to \beta_1 + L(t)$, where $L(t)$ is a square wave, given as

$$L(t) = \begin{cases} L_1, & \text{if } t \mod (t_{\text{light}} + t_{\text{dark}}) \leq t_{\text{light}}, \\ L_2, & \text{otherwise}, \end{cases} \quad (4)$$

where $t_{\text{light}} = 12$, $t_{\text{dark}} = 12$, $L(t) = L_1$ during the light phase and $L(t) = L_2$ during the dark phase.

In constant darkness conditions, the proposed indirect coupling with a weak strength ($K = 0.05$) cannot synchronize heterogeneous self-sustained population ($R \approx 0.25$) (see Fig.2(c)). Compared with the above, an LD cycle (with $L_1 = 5$ and $L_2 = 0.5$) can compensate such a coupling inefficiency and generate a well-coherent overall rhythm as shown in Fig.4(a).

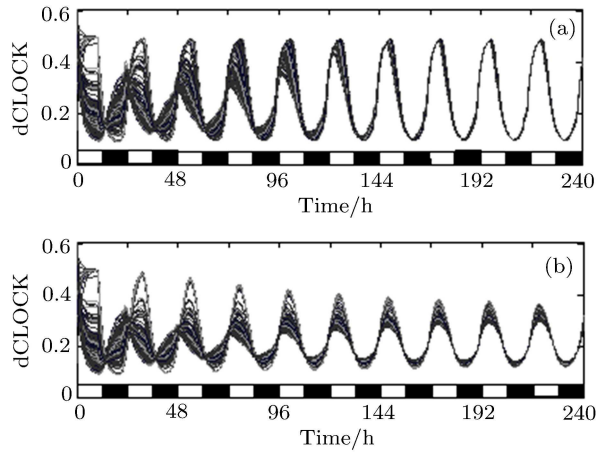


Fig.4. Entrainment by a 12:12 LD cycle in coupled heterogeneous self-sustained *Drosophila* circadian neurons (a) and coupled heterogeneous damped *Drosophila* circadian neurons (b).

However, for individual mutant damped neurons, the intercellular communication in an indirect manner not only can reestablish rhythmic oscillations, but also can synchronize intrinsically compromised cellular oscillators as shown in Fig.4(b). The dCLOCK concentration in Figs.4(a) and 4(b) peaks during the light with a period of 24 h, indicating that the rhythm has been entrained as seen *in vivo*. Our results demonstrate that similar to strong intercellular communication, the LD cycles provide another mechanism among heterogeneous *Drosophila* circadian neurons for compensating the coupling inefficiency and stabilizing the arrhythmic cells.

5. Conclusions and discussion

The fly *Drosophila* is an outstanding model organism for studying many areas of biology, including circadian rhythms. There is a vast and still growing store of knowledge on *Drosophila* genetics, development, anatomy, physiology, and behaviour. The analysis of circadian circuits in *Drosophila* aims to bridge the gap between cells and behaviour, and shed light on fundamental biology of behaviour. We have verified that our model can reproduce well-known behaviours of adult *Drosophila* brain, indicating that the proposed indirect coupling scheme may be a possible mechanism mediating synchronous behaviour among heterogeneous *Drosophila* circadian neurons.

Our proposed model clearly oversimplifies the known architecture of the adult *Drosophila* brain in several aspects. For example, (1) the single-cell model include neither phosphorylation of PER and TIM, nor the separate nuclear and cytoplasmic compartments; (2) Four of the s-LN$_v$s and all the l-LN$_v$s (not all circadian neurons) express the neuropeptide PDF;[20,21] (3) PDF receptor (PDFR) activation is not known to act via a two-step cascade to activate transcription of only the *per* gene as assumed in our model. Because the model successfully captures many features of circadian rhythmicity in the brain of *Drosophila* (e.g. synchronization of circadian neurons, entrainment to LD cycles), these simplifications may point to underlying rules and would be therefore reasonable. Finally, we point out that realistic circadian systems in *Drosophila* and mammal are intrinsically difficult to understand because the single-cell models are high dimensional, the network connectivity is highly complicated, and the wiring changes over time. Our investigation is a significant try for further understanding the basic mechanism of orchestration of timekeeping in realistic yet complex circadian systems.

Although the indirect coupling structure is employed to study the *Drosophila* circadian rhythm generation in the present paper, it is also plausible and applicable to the mammalian circadian clocks in the SCN. As the adult *Drosophila* brain[48] consists of six clusters of approximately 150 clock neurons and not all circadian neurons express the neuropeptide PDF, we need a sophisticated model to consider the spatial

structures of the adult *Drosophila* brain. In addition, various noises could influence the collective behaviour among circadian neurons. Thus extending our present multicellular model to the consideration of the destructive or constructive roles of noises is also our future work.

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