A saturated reaction in repressor synthesis creates a daytime dead zone in circadian clocks

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S1 Text
Relation between phase shift and phase sensitivity

Here we first derive the equation for phase shift $\Delta \phi$ Eq. (6) in the main text by the phase reduction method following (1). Then, we describe the adjoint method to numerically compute phase sensitivity $Z$.

In general, dynamical system with state variables $x$ modeling the circadian clock can be described as

$$\frac{dx(t)}{dt} = F(x(t)), \quad (S1)$$

where $F(x)$ specifies the time evolution of $x$. In our case, $F(x)$ describes biochemical reactions in a negative feedback loop in the absence of light signals (i.e. constant dark condition). We assume that the dynamical system Eq. (S1) has a stable limit cycle $x_{LC}(t)$ in the state space. We then denote dynamics in the presence of perturbation $p(t, x)$ as

$$\frac{dx(t)}{dt} = F(x(t)) + p(t, x(t)). \quad (S2)$$

In the present study, $p$ represents the perturbation in biochemical reactions induced by light signals.

We define a phase $\varphi (0 \leq \varphi < 2\pi)$ based on the limit cycle of the unperturbed system Eq. (S1) such that $\varphi$ increases at a constant speed (1):

$$\frac{d\varphi(t)}{dt} = \omega, \quad (S3)$$

where $\omega = 2\pi/T_p$ and $T_p$ is the period of oscillation. We also denote the limit cycle $x_{LC}(t)$ as a function of $\varphi$, $x(\varphi) = x_{LC}(\varphi(t))$. Subsequently, we assign the phase to the state space.

If a trajectory $x(t; x_0)$ of Eq. (S1) which started at $x_0$, converges to a point on the limit cycle $x_{LC}(\varphi_0/\omega + t)$ for $t \to \infty$, we assign the phase $\varphi_0$ to $x_0$. With this definition, we may denote the phase of $x(t)$ as $\varphi(x(t))$.

Then, in the presence of weak perturbation ($|p| \ll 1$), the time evolution of phase can be described in the first order approximation (1):

$$\frac{d\varphi(t)}{dt} = \omega + \tilde{Z}(\varphi) \cdot G(t, \varphi), \quad (S4)$$
where \( \mathbf{Z}(\varphi) \equiv \partial \varphi(\chi(\varphi))/\partial \chi \) and \( G(t, \varphi) \equiv p(t, \chi(\varphi)) \).

After integrating Eq. (S4), the phase difference \( \Delta \phi \) measured in time between perturbed and unperturbed systems with \( \gamma(t) \) in Eq. (4) in the main text can be approximated as
\[
\Delta \phi \approx \varepsilon T_p / 2 \pi \int_{t_i}^{t_f} \mathbf{Z}(\varphi(t')) \cdot G(t', \varphi(t')) dt'.
\] (S5)

We obtain the phase sensitivity \( \mathbf{Z}(t) \equiv (T_p/2\pi) \mathbf{Z}(\varphi(t)) \) by numerically solving the following differential equation:
\[
\frac{d\mathbf{Z}(t)}{dt} = -L(x_{LC}(t))^T \mathbf{Z}(t),
\] (S6a)
with the normalization condition:
\[
\mathbf{Z}(t) \cdot F(x_{LC}(t)) = 1,
\] (S6b)
where \( L(x_{LC}(t)) \) is the Jacobian around the limit cycle \( x_{LC}(t) \) of Eq. (S1), \( L(x_{LC}(t)) = \partial F/\partial x \bigg|_{x=x_{LC}(t)} \) and \( T \) in Eq. (S6a) indicates transpose of a matrix. We used the Euler method to solve Eq. (S6). Note that Eq. (S6) should be solved backward to obtain \( \mathbf{Z} \), otherwise it diverges because \(-L\) has positive eigenvalues for a stable limit cycle.

**Dependence of the dead zone length and amplitude of phase sensitivity on reaction parameters in the degradation response**

Here, we describe the dependence of the dead zone length \( L_d \) and amplitude of phase sensitivity \( Z_d \) on each reaction parameter in Eqs. (1-3) for the degradation response (S4 Fig.). In general, the dead zone length \( L_d \) depends on a reaction parameter nonmonotonically. There is a peak value of \( L_d \) in the oscillatory parameter range between the upper and lower Hopf bifurcation points. The peak of \( L_d \) is located near the lower Hopf bifurcation point for the translation rate \( \gamma_1 \) and nuclear transport rate \( \gamma_2 \) (S4A, B Fig.), suggesting that smaller values of these parameters extend the dead zone length. In contrast, for the maximum degradation rate \( \gamma_3 \), the peak of \( L_d \) is located near the upper Hopf bifurcation point (S4C Fig.). This result suggests that the faster degradation of nuclear protein favors a longer dead zone. For the threshold for transcriptional repression \( K_1 \), \( L_d \) peaks near the lower Hopf bifurcation point (S4D Fig.). The condition for the dead
zone $z_{\text{min}}/K_1 \ll 1$ is more likely to be satisfied for a larger value of $K_1$. However, $z_{\text{min}}$ also increases for the larger $K_1$ (S4D Fig.) and it takes more time for $z(t)$ to return to its original value after light-induced degradation. This slow recovery of $z(t)$ tends to cause prolonged transcription and results in phase delay. Thus, a smaller value of $K_1$ is more favorable for a longer dead zone.

The amplitude of phase sensitivity $-Z_z$ becomes large near a Hopf bifurcation point (the fourth column of S4 Fig.). At the vicinity of a Hopf bifurcation point, the amplitudes of state variables $x$, $y$ and $z$ become smaller. It has been reported that the phase of circadian clocks with a smaller amplitude is more sensitive to perturbation, such as light and temperature pulses, than the clocks with a larger amplitude (2, 3). The observation that the magnitude of phase sensitivity is larger near a Hopf bifurcation point is thus consistent with these previous reports.

The time interval where light signals cause phase advances ($-Z_z > 0$) extends for larger values of translation rate $\gamma_1$ and/or smaller values of maximum degradation rate of nuclear protein $\gamma_3$ (S4A, C Fig.). This is because the decreasing phase of mRNA becomes longer due to higher levels of nuclear protein as $\gamma_1$ becomes larger and/or $\gamma_3$ becomes smaller. Light-induced degradation of nuclear protein at decreasing phase of mRNA relieves transcriptional repression earlier, resulting in phase advance.

**Dead zone formation for the degradation response in other oscillator models**

To show the generality of the proposed mechanism for dead zone formation for the degradation response, here we analyze another *Drosophila* circadian clock model and a synthetic oscillator model.

As an alternative model for the *Drosophila* clock, we use the one proposed by Ueda et al. 2001 (4). The model includes interlocked feedback loops of PER/TIM and CLOCK/CYCLE (Fig. 2 in (4)). The PER/TIM complex represses their transcription, whereas activates the transcription of *Clock*. The CLOCK/CYCLE complex induces the transcription of *Per* and *Tim*, whereas represses their own transcription. We introduce a light-induced degradation of cytoplasmic TIM protein, \( \text{Tim}_c \).
\[
\frac{dT_{im}}{dt} = S_4 T_{im} - V_1 P_{er} T_{mc} + V_2 P_{tc} - \left( D_4 + \gamma_1(t) \right) \frac{T_{mc}}{L_4 + T_{mc}} - D_0 T_{mc}, 
\]

where \( T_{im} \) is the levels of \( Tim \) mRNA, \( P_{er} \) is the levels of cytoplasmic PER protein, and \( P_{tc} \) is the levels of the cytoplasmic PER/TIM complex. The first term represents the translation of TIM. The second term represents the PER/TIM complex formation, whereas the third term is for dissociation of the complex. The fourth term represents the nonlinear degradation of TIM protein and the fifth term is its linear degradation. \( \gamma(t) \) represents the light induced degradation as defined by Eq. (4) in the main text. Dynamics of the other variables are described as in Ueda et al. 2001 (4). Also, we use the same parameter values as in Ueda et al. 2001.

We confirm that the saturation of TIM degradation lengthens the dead zone by decreasing the values of \( L_4 \) in Eq. (S7) (S5A, B Fig.). The minimum value of \( T_{mc} \) decreases as \( L_4 \) becomes smaller (S5A Fig.). To observe how light-induced degradation changes the transcription of \( Tim \), we compute the transcription rate determined by PER/TIM, \( 1/(1+(PT_n/R_2)^r) \) where \( PT_n \) is the levels of nuclear PER/TIM, \( R_2 \) and \( r \) are the threshold and Hill coefficient for repression, respectively, as in Ueda et al. 2001. A dead zone is generated when the transcription rate is saturated and a light signal does not further increase it (S5C, D Fig.). Thus, the results derived with the simpler model Eqs. (1-3) in the main text hold for the more complex model of the \textit{Drosophila} clock.

Next, we consider a repressilator model. Although the repressilator was originally proposed as a synthetic oscillator in bacteria (5), the relevance of its regulatory structure to the circadian clock was recently proposed (6). We consider three transcriptional regulators X, Y, and Z. X represses Y, Y represses Z and Z represses X. We denote mRNA levels of X and protein levels of X, Y, and Z as \( m_x, x, y, \) and \( z \), respectively. We describe the time evolution of these variables as:

\[
\frac{1}{\tau} \frac{dm_x(t)}{dt} = \frac{1}{1 + (z(t)/K_1)^n} - m_x(t),
\]

(S8a)

\[
\frac{1}{\tau} \frac{dx(t)}{dt} = \gamma_1 m_x(t) - \gamma_2 x(t),
\]

(S8b)

\[
\frac{1}{\tau} \frac{dy(t)}{dt} = \gamma_3 \frac{1}{1 + (x(t)/K_2)^n} - \gamma_4 y(t),
\]

(S8c)
\[
\frac{1}{\tau} \frac{dz(t)}{dt} = \gamma_5 \frac{1}{1 + \left(\frac{y(t)}{K_3}\right)^n} - \left(\gamma_6 + \gamma_l(t)\right) \frac{z(t)}{K_4 + z(t)}.
\]

(S8d)

Note that we consider the mRNA of \(x\) because we use the same model for the induction response later (see the section "Dead zone formation for the induction response in other oscillator models"). For simplicity, we assume linear degradation of \(x\) and \(y\), whereas a saturated degradation of \(z\). \(\gamma_l\) in Eq. (S8d) represents the degradation of \(z\) induced by external signals as in the degradation response for the circadian clock. \(\gamma_l\) is defined by Eq. (4) in the main text. We set parameter values as follows: \(\gamma_1 = 0.013, \gamma_2 = 0.059, \gamma_3 = 39.49, \gamma_4 = 3.88, \gamma_5 = 29.16, \gamma_6 = 0.282, K_1 = 0.08, K_2 = 0.05, K_3 = 0.034, K_4 = 0.017, n = 4\) and \(\tau = 0.354\).

The model Eq. (S8) generates a stable limit cycle (S5E Fig.) and a dead zone in a PRC when the levels of \(z\) are lower (S5F Fig.). When the dead zone is formed, the transcription rate of \(x\), \(1/(1+(z/K_1)^n)\) is saturated (S5G Fig.). In contrast, when a change in the transcription rate occurs, a phase shift is induced (S5H Fig.). Thus, the same conclusion holds for the repressilator model.

**Random parameter generation**

To check whether a model can create a dead zone in a PRC, we generate parameter sets randomly from uniform distributions and compute phase sensitivity \(Z\) for limit cycles of those parameter sets. Values of each parameter are chosen randomly from a uniform distribution between \(10^{-2}\) and \(10^2\). We use a logarithmic scale for choosing values from the uniform distribution. We generate \(10^6\) parameter sets and examine the linear stability of the steady state. If the Jacobian with a parameter set has complex eigenvalues with a positive real part, we consider that the parameter set can generate a limit cycle. We count the number of such oscillatory parameter sets and compute the fraction over the total \(10^6\) parameter sets. The fraction should represent how likely a system generates oscillations.

We then randomly select 2000 parameter sets with which the model generates a stable limit cycle. We numerically calculate phase sensitivity \(Z(t)\) of those 2000 limit cycles and check the length of a spanned time window within which \(|Z(t)| < \theta\) as defined in Eq. (7) in the main text. A phase sensitivity may have several time windows that satisfy this criterion. In such cases, we choose the longest one for statistical analysis shown in S14Fig.
Saturation of transport of repressor protein from the cytoplasm to the nucleus

We examine whether a saturation of repressor protein transport from the cytoplasm to the nucleus can create a dead zone in a PRC of the induction response. We introduce a saturation term of nuclear transport into Eqs. (9) and (10) in the main text as

\[ \frac{1}{\tau} \frac{dy(t)}{dt} = \gamma_1 x(t) - \gamma_2 \frac{y(t)}{\kappa_y + y(t)}, \]  
\[ \frac{1}{\tau} \frac{dz(t)}{dt} = \gamma_2 \frac{y(t)}{\kappa_y + y(t)} - \gamma_3 \frac{z(t)}{K_m + z(t)}. \]

\( \kappa \) much smaller than the peak value of \( y(t) \) can saturate the transport in Eq. (S9) (S7A Fig.). The dynamics of mRNA \( x \) is described by Eq. (8) in the main text.

The PRC and phase sensitivity of Eqs. (8, S9) shown in S7B, C Fig. do not include an extended dead zone. Figure S7D shows the time series of \( x, y \) and \( z \) in Eqs. (8, S9) with a light pulse at \( t_l/T_p = 0.15 \). The increase in mRNA \( x \) by the light pulse elevates the levels of cytoplasmic protein \( y \). As expected, the levels of nuclear protein \( z \) do not increase immediately after the light pulse due to the saturation of transport. However, the accumulated cytoplasmic protein eventually enters the nucleus, causing a higher peak value of \( z \). The excess amount of nuclear protein thus results in a phase delay.

To further confirm that the saturation of transport cannot create a dead zone, we examine the phase sensitivity of limit cycles of the model Eqs. (8, S9) for randomly generated parameter sets (section "Random parameter generation"). Linear stability analysis around the steady state indicates that 4732 out of \( 10^6 \) randomly generated parameter sets (0.47\%) can generate limit cycles. This number is \( \sim 3 \)-fold lower than that of the non-saturation model Eqs. (8-10) (1.5\%) and almost half as that for the translation saturation model Eqs. (8, 10, 11) (0.88\%), indicating that saturation of transport reduces parameter domains for oscillations more severely. Moreover, although we numerically compute phase sensitivity \( Z_x \) using 2000 parameter sets, their dead zone lengths \( L_{d} \) are less than 1/24. Thus, the saturation of transport is less likely to produce a dead zone. These results also confirm that the saturation of biochemical reactions that is unaccompanied by cancelation of the effect of light signals cannot create a dead zone in the PRC. It is not saturation itself but the unaltered time series of nuclear protein that causes a dead zone.

\[ \tau \frac{dy(t)}{dt} = \gamma_1 x(t) - \gamma_2 \frac{y(t)}{\kappa_y + y(t)}, \]
\[ \tau \frac{dz(t)}{dt} = \gamma_2 \frac{y(t)}{\kappa_y + y(t)} - \gamma_3 \frac{z(t)}{K_m + z(t)}. \]
Dead zone generated by the saturation of repressor mRNA degradation

To test whether the saturation of repressor mRNA degradation can create a dead zone in daytime in the induction response, we consider the following dimensionless equation:

\[
\frac{1}{\tau} \frac{dx(t)}{dt} = \frac{\gamma_1}{1 + \left(\frac{z(t)}{K_c}\right)^{x_0}} + \gamma_x(t) - \frac{\gamma_x}{K_x + x(t)}, \quad (S10a)
\]

\[
\frac{1}{\tau} \frac{dy(t)}{dt} = \gamma_x x(t) - y(t), \quad (S10b)
\]

\[
\frac{1}{\tau} \frac{dz(t)}{dt} = y(t) - \frac{\gamma_2}{K_m + z(t)}, \quad (S10c)
\]

where \( \gamma_x \) is the maximum degradation rate and \( K_c \) is the Michaelis constant of mRNA degradation. The degradation rate of mRNA can be approximated as \( \sim \frac{\gamma_x}{K_x} \) when \( x/K_x << 1 \). Thus, strong saturation \( (K_c << 1) \) increases the rate of mRNA degradation when the mRNA abundance is low. Note that because the unit of the degradation rate for the Michaelis-Menten function is different from the one in the linear degradation function, we apply nondimensionalization different from other equations \( (e.g., \text{Eqs. (8-10) in the main text}) \) to derive Eq. \( (S10) \). With the saturation of mRNA degradation, the wave form of mRNA \( x(t) \) becomes more pulse-like \( (S8A \text{ Fig.}) \).

In the presence of saturation of mRNA degradation, a dead zone appears when the levels of mRNA \( x \) are lower, \( x/K_c << 1 \) \( (S8B, C \text{ Fig.}) \). mRNAs induced by a light signal within this time window are quickly degraded due to the sharp increase of the Michaelis-Menten function. Hence, light pulses neither affect the levels of nuclear protein \( (S8D, G \text{ Fig.}) \) nor change the phase of oscillation. In contrast, light signals can cause phase shifts when the levels of mRNA are higher \( x/K_c >> 1 \) \( (S8B, C \text{ Fig.}) \). In this regime, the transient increase of mRNA does not affect the speed of degradation due to saturation. A light signal at the increasing phase of mRNA causes phase advance, because it decreases the forthcoming peak of both mRNA and nuclear protein, relieving repression earlier \( (S8E \text{ Fig.}) \). A light signal at the peak or decreasing phases of mRNA results in a phase delay \( (S8B, C \text{ Fig.}) \), as it increases the peak value of nuclear protein, prolonging transcriptional repression \( (S8F \text{ Fig.}) \). In summary, the saturation of repressor mRNA degradation creates a dead zone only when the levels of mRNA are lower.
Dead zone formation for the induction response in other oscillator models

To examine whether saturated translation creates a dead zone in other oscillator models, here we consider an interlocked feedback loop model for the mammalian circadian clock and the repressilator model Eq. (S8).

We first consider the interlocked feedbacks observed in the mammalian circadian clock. The model includes regulations among Per, Bmal1 and Rev-erb (7, 8). Free BMAL1 protein induces transcription of Per and Rev-erb through E-box in their promoter regions. Nuclear PER protein binds to free BMAL1. The BMAL1/PER complex becomes a repressor for Per and Rev-erb by excluding the binding of free BMAL1 protein to E-box. REV-ERB protein represses the transcription of Bmal1. We model the time evolution of mRNA $x_i$, cytoplasmic protein $y_i$ and nuclear protein $z_i (i \in \{p, b, r\})$. Subscript $p$ indicates that these variables are for Per, subscript $b$ for Bmal1 and $r$ for Rev-erb. The time evolution of the mRNA and protein levels is described by the following differential equations:

For Per:

$$\frac{1}{\tau} \frac{dx_p(t)}{dt} = \frac{(z_b(t)/K_1)^{n_p}}{1+(z_b(t)/K_1)^{n_p}+(z_b(t)z_p(t)/K_2)^{n_p}} + \gamma_1(t) - x_p(t), \quad (S11a)$$

$$\frac{1}{\tau} \frac{dy_p(t)}{dt} = \gamma_1 \frac{y_p(t)}{K_p+y_p(t)} - \gamma_2 y_p(t), \quad (S11b)$$

$$\frac{1}{\tau} \frac{dz_p(t)}{dt} = \gamma_2 y_p(t) - \gamma_3 \frac{z_p(t)}{K_p+z_p(t)}, \quad (S11c)$$

for Bmal1:

$$\frac{1}{\tau} \frac{dx_b(t)}{dt} = \frac{1}{1+(z_b(t)/K_3)^{n_b}} - x_b(t), \quad (S11d)$$

$$\frac{1}{\tau} \frac{dy_b(t)}{dt} = x_b(t) - y_b(t), \quad (S11e)$$

$$\frac{1}{\tau} \frac{dz_b(t)}{dt} = y_b(t) - z_b(t), \quad (S11f)$$

and for Rev-erb:
The model can generate a stable limit cycle (S12A Fig.). The levels of *Per* and *Rev-erb* RNAs peak at similar timing, whereas there is a significant phase difference at protein levels (S12A Fig.). Such phase relations were observed in experiment (9). We confirm that the interlocked feedback model can produce a dead zone when the levels of *Per* mRNA are higher (S12B Fig.).

Next, we consider the repressilator model with the induction response. We modify Eqs. (S8a), (S8b) and (S8d) to include induction by external signals and the saturation of translation as:

\[
\frac{1}{\tau} \frac{dx_t(t)}{dt} = \frac{1}{1 + (z_t(t)/K_a)^n} + \gamma_1 x_t(t) - m_x(t), \quad (S11g)
\]

\[
\frac{1}{\tau} \frac{dy_t(t)}{dt} = \gamma_2 y_t(t) - \gamma_3 y_t(t), \quad (S11h)
\]

\[
\frac{1}{\tau} \frac{dz_t(t)}{dt} = \gamma_3 y_t(t) - \gamma_6 K_r + z_t(t). \quad (S11i)
\]

\(\gamma_i\) in Eq. (S11a) represents the light-induced transcription of *Per*, defined by Eq. (4) in the main text. We introduce the saturation of PER protein translation as in Eq. (S11b). We simplify the dynamics of *Bmal1* by assuming linear translation and degradation of nuclear protein. In addition, we set most parameters in equations for *Bmal1* to unity for simplicity.

We use the following parameter values in simulations: \(\gamma_1 = 18.5, \gamma_2 = 0.031, \gamma_3 = 14.1, \gamma_4 = 33.0, \gamma_5 = 2.2, \gamma_6 = 16.1, K_1 = 0.579, K_2 = 1.83, K_t = 0.015, K_p = 0.025, K_3 = 9.82, K_4 = 0.709, K_5 = 2.0, K_r = 0.782, n_p = 4.0, n_b = 2, n_r = 4\) and \(\tau = 1.273\).

The equation for protein levels of Y is given by Eq. (S8c). We use the following parameter values in simulations: \(\gamma_1 = 0.312, \gamma_2 = 0.028, \gamma_3 = 34.48, \gamma_4 = 2.779, \gamma_5 = 0.629, \gamma_6 = 0.035, K_1 = 0.023, K_2 = 5.455, K_3 = 2.121, K_4 = 0.005, K_5 = 0.056, n = 4\) and \(\tau = 0.92\).

S10
The model can generate a stable limit cycle with the above parameter set (S12C Fig.).
With the saturation of translation, a dead zone is generated when the levels of $m_s$ are higher (S12D Fig.).

Thus, the saturation of repressor translation can generate a dead zone even in more complex models.

**Parameter domains for oscillation with the saturation of repressor translation**

Previous studies revealed that nonlinear reaction terms in a negative feedback loop change parameter domains for generating oscillations (10, 11). Saturation of translation tends to make the system less likely to oscillate (10). Indeed, smaller Michaelis constant of translation saturation $K_t$ in Eq. (11) in the main text may lead to $dy/dt \approx \pi(\gamma_1 - \gamma_2 y)$, breaking the feedback loop. To study to what extent saturation of translation in Eq. (11) in the main text reduces the parameter domains for oscillations, we randomly generate $10^6$ parameter sets from uniform distributions and examine the fraction of oscillatory parameter sets for both the translation saturation and non-saturation models (section "Random parameter generation"). To determine whether a parameter set can generate a limit cycle, we perform linear stability analysis of Eqs. (8, 10) and (11) in the main text around the steady state. We find that the fraction of oscillatory parameter sets detected in this way is 0.88%. This value is almost half as that for the non-saturation model Eq. (8-10) (1.5%). Thus, the saturation of repressor translation narrows the parameter domains for oscillations.

Then, to clarify how the saturation reduces parameter domains for oscillation, we draw two-dimensional phase diagrams with the amplitude of mRNA $x$ for Eqs. (8, 10) and (11) (S13Fig.). For better comparisons between smaller and larger values of $K_t$, we fix the ratio $\gamma_1/K_t = c$ in S13 Fig. With this parameterization, translation rate for $x/K_t \ll 1$ is same among different $K_t$ values, $\sim(\gamma_1/K_t)x = cx$. For $\gamma_2$ and $K_1$, the strong saturation of translation reduces parameter domains for oscillations by both increasing lower bounds and decreasing upper bounds (S13A, C Fig.). In contrast, for $\gamma_3$ and $K_m$, smaller values of $K_t$ mainly decrease the upper bounds of oscillatory domains (S13B, D Fig.), suggesting that slower degradation of nuclear protein and its stronger saturation are required for sustaining oscillation. Given that smaller values of $K_m$ also lengthen the dead zone (S11E...
Fig.), the saturation of protein degradation is key to both sustaining oscillation and dead zone formation.

**Night-time dead zone generated by the Hill function in translation**

We notice that the Hill function in translation Eq. (12) in the main text can create a dead zone when the levels of mRNA $x$ are lower (S14A Fig.). Such dead zone is more likely to be formed when the minimum levels of mRNA $x$ is much lower than the threshold $K_i$ in the Hill function of Eq. (12). A Hill function realizes a translational switch with a threshold $K_i$. If the levels of mRNA $x$ are lower than $K_i$ and light induction is weak, $x$ does not surpass $K_i$ and translation does not occur. Hence, when the levels of mRNA are low, the Hill function can cancel the influence of the mRNA induction by light signals (S14B, C Fig.). This result further indicates that the cancelation of the influence of mRNA induction by light signals generates a dead zone in the PRC.

Subsequently, we study the dead zone formation with randomly generated parameter sets. For this, we fix the Hill coefficient $h$ in Eq. (12) as $h = 4$. As before, we generate $10^6$ parameter sets randomly from uniform distributions and check the linear stability of the steady state (section "Random parameter generation"). This analysis finds that 36174 out of $10^6$ ($\sim 3.6\%$) parameter sets are oscillatory. In contrast, the fraction of oscillatory parameter sets for the linear translation model Eq. (8-10) in the main text is $\sim 1.5\%$. Thus, the Hill function in translation allows the system to be more oscillatory than the linear translation process Eq. (9). Furthermore, the dead zone length $L_d$ distributes more broadly for $h = 4$ than $h = 1$ (S14D, E Fig.). Out of 2000 parameter sets used for numerical computation of the phase sensitivity $Z_x$, 17.7% (354/2000) create dead zones of which length $L_d$ is longer than $1/24$. 30 parameter sets out of 354 generate dead zones when the levels of mRNA are higher than $K_i$ as shown in Fig. 7A. Remaining 324 form dead zones when the levels of mRNA are lower than $K_i$ as shown in S14A Fig. Our analysis on the Hill function indicates that the type of nonlinear functions in translation can determine at which phase of oscillation a dead zone is generated.

**SUPPLEMENTARY REFERENCES**


