Supporting Information

St. John et al. 10.1073/pnas.1323618111

SI Text

$$\frac{d\,p}{dt} = \frac{-p \cdot vdp}{kdp + p} + \frac{vtp}{knp + (C1n + C2n)^3}$$

$$\frac{d\,c1}{dt} = \frac{-c1 \cdot vdc1}{c1 + kdc1} + \frac{vtc1}{knc1 + (C1n + C2n)^3}$$

$$\frac{d\,c2}{dt} = \frac{-c2 \cdot vdc2}{c2 + kdc1} + \frac{vtc2}{knc1 + (C1n + C2n)^3}$$

$$\frac{d\,P}{dt} = -C1 \cdot P \cdot vaC1P + C1n \cdot vdC1P - C2 \cdot P \cdot vaC1P + C2n \cdot vdC1P - \frac{P \cdot vdP}{P + kdP} + ktxnp \cdot p$$

$$\frac{d\,C1}{dt} = -C1 \cdot P \cdot vaC1P - \frac{C1 \cdot vdC1}{C1 + kdC1} + C1n \cdot vdC1P + c1$$

$$\frac{d\,C2}{dt} = -C2 \cdot P \cdot vaC1P - \frac{C2 \cdot vdC2}{C2 + kdC1} + C2n \cdot vdC1P + c2$$

$$\frac{d\,C1n}{dt} = C1 \cdot P \cdot vaC1P - C1n \cdot vdC1P - \frac{C1n \cdot vdCn}{C1n + C2n + kdCn}$$

$$\frac{d\,C2n}{dt} = C2 \cdot P \cdot vaC1P - \frac{C2n \cdot MC2n \cdot vdCn}{C1n + C2n + kdCn} - C2n \cdot vdC1P$$

Model 1. Hirota et al. 2012 (1).

1. Hirota T, et al. (2012) Identification of small molecule activators of cryptochrome. *Science* 337(6098):1094–1097.

$$\frac{d\ CLKBM1}{dt} = BM1n \cdot kfCLKBM1 - CLKBM1 \cdot dCLKBM1 - CLKBM1 \cdot kdCLKBM1$$

$$\frac{d\ reverb}{dt} = \frac{V3max\left(g \cdot \frac{CLKBM1^v}{kt3} + 1\right)}{\frac{CLKBM1^v}{kt3}\left(\frac{PnCn + PnpCn}{ki3}\right)^w + \frac{CLKBM1^v}{kt3} + 1} - dreverb \cdot reverb$$

$$\frac{d\ ror}{dt} = \frac{V4max\left(h \cdot \frac{CLKBM1^p}{kt4} + 1\right)}{\frac{CLKBM1^p}{kt4} \cdot \left(\frac{PnCn + PnpCn}{ki4}\right)^q + \frac{CLKBM1^p}{kt4} + 1} - dror \cdot ror$$

$$\frac{d\ REVERBc}{dt} = -REVERBc \cdot dREVERBc - REVERBc \cdot kiREVERBc + kp3 \cdot reverb$$

$$\frac{d\ RORc}{dt} = -RORc \cdot dRORc - RORc \cdot kiRORc + kp4 \cdot ror$$

$$\frac{d\ REVERBn}{dt} = REVERBc \cdot kiREVERBc - REVERBn \cdot dREVERBn$$

$$\frac{d\ RORn}{dt} = RORc \cdot kiRORc - RORn \cdot dRORn$$

$$\frac{d\ bm1}{dt} = \frac{V5max\left(i \cdot \frac{RORn^n}{kt5} + 1\right)}{\frac{REVERBn^m}{ki5} + \frac{RORn^n}{kt5} + 1} - bm1 \cdot dbm1$$

$$\frac{d\ BM1c}{dt} = -BM1c \cdot dBM1c - BM1c \cdot kiBM1c + bm1 \cdot kp5$$

$$\frac{d\ BM1n}{dt} = BM1c \cdot kiBM1c - BM1n \cdot dBM1n - BM1n \cdot kfCLKBM1 + CLKBM1 \cdot kdCLKBM1$$

$$\frac{d\ per}{dt} = \frac{V1max\left(a \cdot \frac{CLKBM1^b}{kt1} + 1\right)}{\frac{CLKBM1^b}{kt1} \cdot \left(\frac{PnCn + PnpCn}{ki1}\right)^c + \frac{CLKBM1^b}{kt1} + 1} - dper \cdot per$$

$$\frac{d\ cry}{dt} = \frac{V2max\left(\frac{CLKBM1^3 \cdot d}{kt2^3} + 1\right)}{\left(\frac{REVERBn^{f1}}{ki21} + 1\right)\left(\frac{CLKBM1^3}{kt2^3} + \frac{CLKBM1^e}{kt2}\left(\frac{PnCn + PnpCn}{ki2}\right)^f + 1\right)} - cry \cdot dcry$$

$$\frac{d\ Cc}{dt} = -Cc \cdot Pc \cdot kfPcCc - Cc \cdot Pcp \cdot kfPcpCc - Cc \cdot dCc + PcCc \cdot kdPcCc + PcpCc \cdot kdPcpCc + cry \cdot kp2$$

$$\frac{d\ Pc}{dt} = -Cc \cdot Pc \cdot kfPcCc - Pc \cdot dPc - Pc \cdot kphPc + PcCc \cdot kdPcCc + Pcp \cdot kdphPcp + kp1 \cdot per$$

$$\frac{d\ Pcp}{dt} = -Cc \cdot Pcp \cdot kfPcpCc + Pc \cdot kphPc - Pcp \cdot dPcp - Pcp \cdot kdphPcp + PcpCc \cdot kdPcpCc$$

$$\frac{d\ PcpCc}{dt} = Cc \cdot Pcp \cdot kfPcpCc - PcpCc \cdot dPcpCc - PcpCc \cdot kdPcpCc - PcpCc \cdot kiPcpCc + PnpCn \cdot kePnpCn$$

$$\frac{d\ PcCc}{dt} = Cc \cdot Pc \cdot kfPcCc - PcCc \cdot dPcCc - PcCc \cdot kdPcCc - PcCc \cdot kiPcCc + PnCn \cdot kePnCn$$

$$\frac{d\ PnpCn}{dt} = PcpCc \cdot kiPcpCc - PnpCn \cdot dPnpCn - PnpCn \cdot kePnpCn$$

$$\frac{d\ PnCn}{dt} = PcCc \cdot kiPcCc - PnCn \cdot dPnCn - PnCn \cdot kePnCn$$

Model 2. Relógio et al. 2011 (1).

1. Relógio A, et al. (2011) Tuning the mammalian circadian clock: Robust synergy of two loops. *PLOS Comput Biol* 7(12):e1002309.

$$\frac{d\,MP}{dt} = -MP \cdot kdmp - \frac{MP \cdot vmP}{KmP + MP} + \frac{vsP \cdot BN^n}{BN^n + KAP^n}$$

$$\frac{d\,MC}{dt} = -MC \cdot kdmc - \frac{MC \cdot vmC}{KmC + MC} + \frac{vsC \cdot BN^n}{BN^n + KAC^n}$$

$$\frac{d\,MB}{dt} = -MB \cdot kdmb - \frac{MB \cdot vmB}{KmB + MB} + \frac{vsB \cdot KIB^m}{BN^m + KIB^m}$$

$$\frac{d\,PC}{dt} = -CC \cdot PC \cdot k3 + MP \cdot ksP - \frac{PC \cdot V1P}{Kp + PC} - PC \cdot kdn + PCC \cdot k4 + \frac{PCP \cdot V2P}{Kdp + PCP}$$

$$\frac{d\,CC}{dt} = -CC \cdot PC \cdot k3 - \frac{CC \cdot V1C}{CC + Kp} - CC \cdot kdnc + \frac{CCP \cdot V2C}{CCP + Kdp} + MC \cdot ksC + PCC \cdot k4$$

$$\frac{d\,PCP}{dt} = \frac{PC \cdot V1P}{Kp + PC} - \frac{PCP \cdot V2P}{Kdp + PCP} - PCP \cdot kdn - \frac{PCP \cdot vdPC}{Kdp + PCP}$$

$$\frac{d\,CCP}{dt} = \frac{CC \cdot V1C}{CC + Kp} - \frac{CCP \cdot V2C}{CCP + Kdp} - CCP \cdot kdn - \frac{CCP \cdot vdCC}{CCP + Kd}$$

$$\frac{d\,PCC}{dt} = CC \cdot PC \cdot k3 - \frac{PCC \cdot V1PC}{Kp + PCC} - PCC \cdot k1 - PCC \cdot k4 - PCC \cdot kdn + \frac{PCCP \cdot V2PC}{Kdp + PCCP} + PCN \cdot k2$$

$$\frac{d\,PCN}{dt} = -BN \cdot PCN \cdot k7 + IN \cdot k8 + PCC \cdot k1 - \frac{PCN \cdot V3PC}{Kp + PCN} - PCN \cdot k2 - PCN \cdot kdn + \frac{PCNP \cdot V4PC}{Kdp + PCNP}$$

$$\frac{d\,PCCP}{dt} = \frac{PCC \cdot V1PC}{Kp + PCC} - \frac{PCCP \cdot V2PC}{Kdp + PCCP} - PCCP \cdot kdn - \frac{PCCP \cdot vdPCC}{Kd + PCCP}$$

$$\frac{d\,PCNP}{dt} = \frac{PCN \cdot V3PC}{Kp + PCN} - \frac{PCNP \cdot V4PC}{Kdp + PCNP} - PCNP \cdot kdn - \frac{PCNP \cdot vdPCN}{Kd + PCNP}$$

$$\frac{d\,BC}{dt} = \frac{-BC \cdot V1B}{BC + Kp} - BC \cdot k5 - BC \cdot kdn + \frac{BCP \cdot V2B}{BCP + Kdp} + BN \cdot k6 + MB \cdot ksB$$

$$\frac{d\,BCP}{dt} = \frac{BC \cdot V1B}{BC + Kp} - \frac{BCP \cdot V2B}{BCP + Kdp} - BCP \cdot kdn - \frac{BCP \cdot vdBC}{BCP + Kd}$$

$$\frac{d\,BN}{dt} = BC \cdot k5 - BN \cdot PCN \cdot k7 - \frac{BN \cdot V3B}{BN + Kp} - BN \cdot k6 - BN \cdot kdn + \frac{BNP \cdot V4B}{BNP + Kdp} + IN \cdot k8$$

$$\frac{d\,BNP}{dt} = \frac{BN \cdot V3B}{BN + Kp} - \frac{BNP \cdot V4B}{BNP + Kdp} - BNP \cdot kdn - \frac{BNP \cdot vdBN}{BNP + Kd}$$

$$\frac{d\,IN}{dt} = BN \cdot PCN \cdot k7 - IN \cdot k8 - IN \cdot kdn - \frac{IN \cdot vdIN}{IN + Kd}$$

Model 3. Leloup and Goldbeter 2003 (1).

1. Leloup JC, Goldbeter A (2003) Toward a detailed computational model for the mammalian circadian clock. *Proc Natl Acad Sci USA* 100(12):7051–7056.

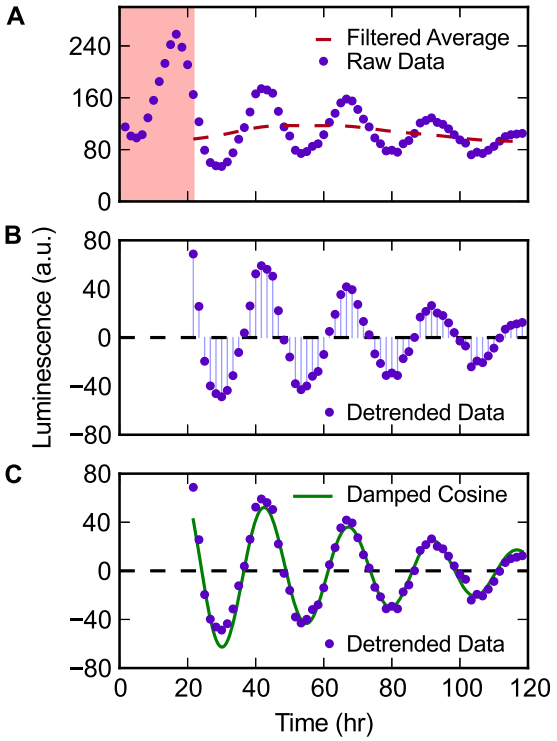

Fig. S1. Analysis of circadian reporter luminescence data. (*A*) Raw luminescence data are first cropped by removing the initial transient region (first 12 points). The moving baseline is estimated using a Hodrick–Prescott filter with smoothing parameter 1,600 (red dashed line). (*B*) Data are detrended by subtracting the moving baseline from the raw data. The detrended data are used to calculate the relative amplitude of the oscillations via SD. (*C*) Periods are estimated by fitting a damped cosine curve (green solid line) to the detrended data.

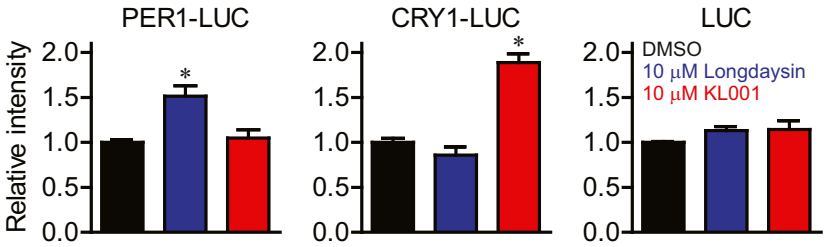

Fig. S2. Effects of longdaysin and KL001 on period 1 (PER1)-luciferase (LUC) and cryptochrome 1 (CRY1)-LUC abundance. HEK293 stable cell lines expressing PER1-LUC, CRY1-LUC, or LUC from a constitutive promoter were treated with DMSO, 10 μM longdaysin, or 10 μM KL001 for 24 h, and luminescence was measured. The luminescence intensity relative to DMSO control is shown as mean ± SEM ($n = 4–8$). *$P < 0.001$ compared with DMSO (one-way ANOVA with Dunnett's post hoc test).

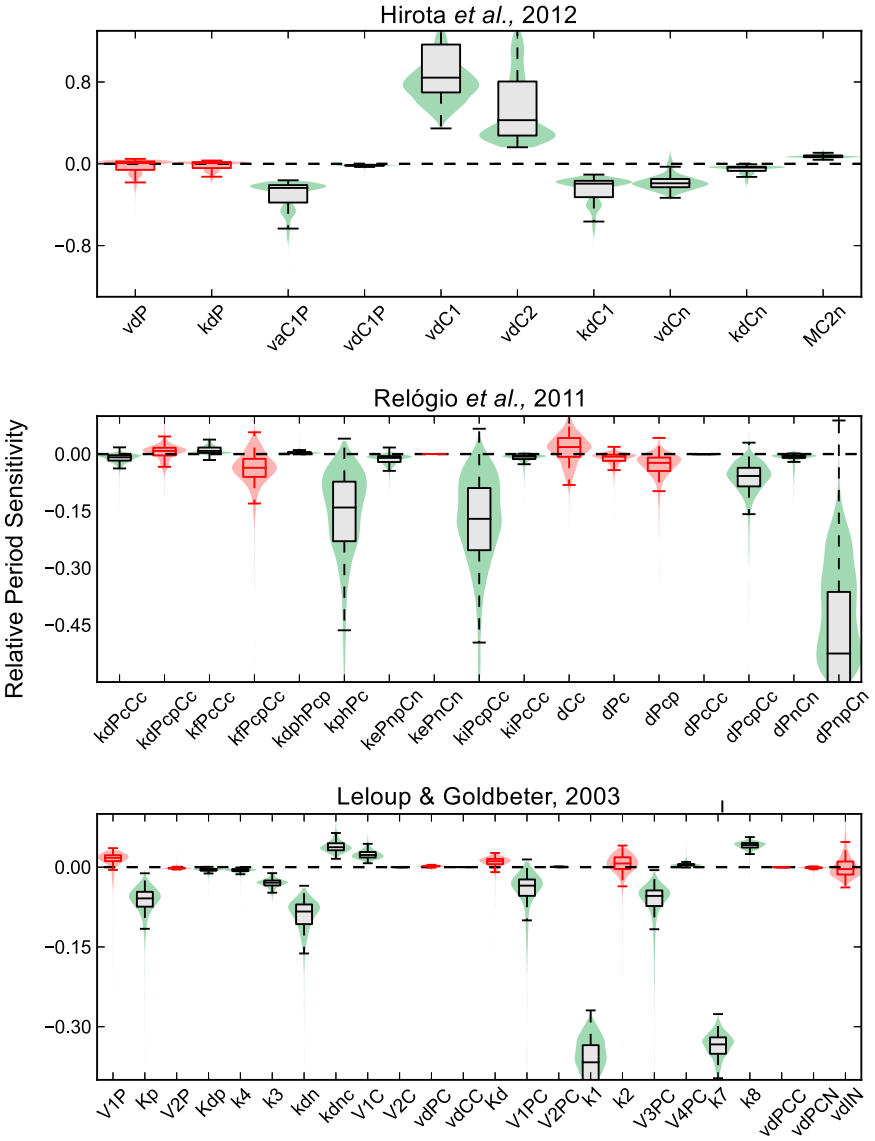

Fig. S3. Bootstrap confidence intervals in relative period sensitivities. Violin plots for distributions in relative period sensitivities for parameters associated with PER and CRY proteins. Whiskers extend to the most extreme data point within 1.5× the inner quartile range. Distributions in which the 5th and 95th percentile lie on opposite sides of the *x* axis are colored red and deemed nonidentifiable.

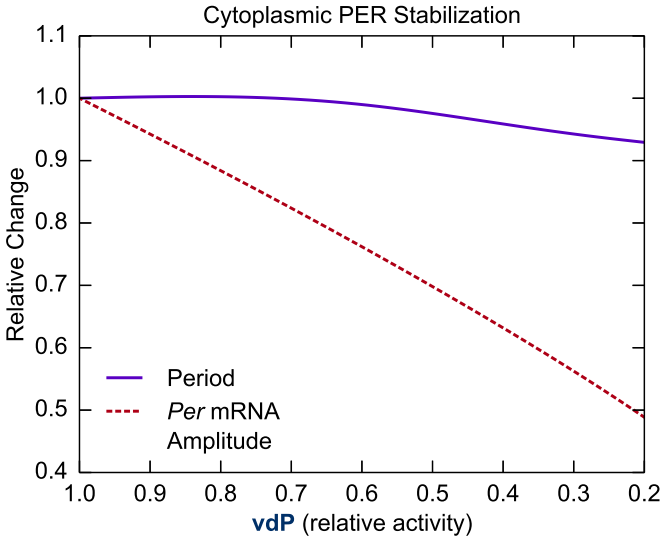

Fig. S4. Effect of cytoplasmic PER stabilization on period and E box transcription amplitude. Relative period and peak-to-trough amplitude change in *Per* mRNA resulting from a reduction in the vdP parameter (PER cytoplasmic degradation rate) in the model from ref. 1.

1. Hirota T, et al. (2012) Identification of small molecule activators of cryptochrome. *Science* 337(6098):1094–1097.

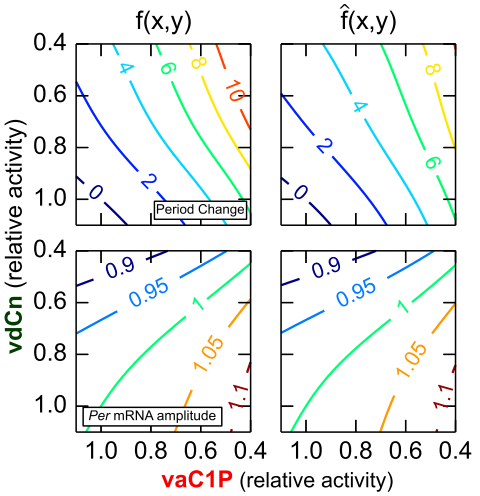

Fig. S5. Calculation of R^2 values for Fig. 5*B*. Contour plots show changes to period and mRNA amplitude from inhibition of nuclear CRY degradation and PER nuclear import. Calculated values after applying both perturbations, $f(x, y)$, are compared with the linear sum of both individual perturbations, $\hat{f}(x,y)$. The similar profiles in both pairs of plots indicate cooperative and competitive effects are largely absent. $R^2 = 0.924$ and 0.999 for period change and *Per* mRNA amplitude, respectively.