Model 1: ODEs comprising the mechanistic model of the circadian negative feedback loop from Hirota *et al.*, 2012. Lower case letters (p: *Per*, c1: *Cry1*, c2: *Cry2*) are mRNA state variables. Uppercase letters (P: PER, C1: CRY1, C2: CRY2) are the cytosolic proteins. C1N: PER-CRY1 and C2N: PER-CRY2 are the nuclear transcription factors.

$$\frac{d\mathbf{p}}{dt} = \frac{v_{\text{txn,p}}}{k_{\text{txn,p}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{\text{deg,p}}\ \mathbf{p}}{k_{\text{deg,p}} + \mathbf{p}} \tag{1}$$

$$\frac{d\mathbf{c1}}{dt} = \frac{v_{\text{txn,c1}}}{k_{\text{txn,c}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{\text{deg,c1}}\ \mathbf{c1}}{k_{\text{deg,c}} + \mathbf{c1}} \tag{2}$$

$$\frac{d\mathbf{c2}}{dt} = \frac{v_{\text{txn,c2}}}{k_{\text{txn,c}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{\text{deg,c2}}\ \mathbf{c2}}{k_{\text{deg,c}} + \mathbf{c2}} \tag{3}$$

$$\begin{aligned}\frac{d\mathbf{P}}{dt} = {} & k_{\text{tln,p}}\ \mathbf{p} - \frac{v_{\text{deg,P}}\ \mathbf{P}}{k_{\text{deg,P}} + \mathbf{P}} - v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C1} + v_{\text{d,CP}}\ \mathbf{C1N} \\ & - v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C2} + v_{\text{d,CP}}\ \mathbf{C2N}\end{aligned} \tag{4}$$

$$\frac{d\mathbf{C1}}{dt} = \mathbf{c1} - \frac{v_{\text{deg,C1}}\ \mathbf{C1}}{k_{\text{deg,C}} + \mathbf{C1}} - v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C1} + v_{\text{d,CP}}\ \mathbf{C1N} \tag{5}$$

$$\frac{d\mathbf{C2}}{dt} = \mathbf{c2} - \frac{v_{\text{deg,C2}}\ \mathbf{C2}}{k_{\text{deg,C}} + \mathbf{C2}} - v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C2} + v_{\text{d,CP}}\ \mathbf{C2N} \tag{6}$$

$$\frac{d\mathbf{C1N}}{dt} = v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C1} - v_{\text{d,CP}}\ \mathbf{C1N} - \frac{(vdCn - u(t))\ \mathbf{C1N}}{k_{\text{deg,Cn}} + \mathbf{C1N} + \mathbf{C2N}} \tag{7}$$

$$\frac{d\mathbf{C2N}}{dt} = v_{\text{a,CP}}\ \mathbf{P}\ \mathbf{C2} - v_{\text{d,CP}}\ \mathbf{C2N} - \frac{((vdCn - u(t))\ m_{\mathbf{C2N}})\ \mathbf{C2N}}{k_{\text{deg,Cn}} + \mathbf{C2N} + \mathbf{C1N}} \tag{8}$$

Table 1: Parameter values for Model 1 from Hirota *et al.* 2012.. Parameter 16, $vdCn$, is modulated by KL001, and therefore is the control target.

	Parameter	Description	Value
1	$v_{\text{txn},\mathbf{p}}$	*Per* Transcription rate	0.195
2	$v_{\text{txn},\mathbf{c1}}$	*Cry1* Transcription rate	0.131
3	$v_{\text{txn},\mathbf{c2}}$	*Cry1* Transcription rate	0.114
4	$k_{\text{txn},\mathbf{p}}$	*Per* Repression constant	0.425
5	$k_{\text{txn},\mathbf{c}}$	*Cry1/2* Repression constant	0.259
6	$v_{\text{deg},\mathbf{p}}$	*Per* Max degradation rate	0.326
7	$v_{\text{deg},\mathbf{c1}}$	*Cry1* Max degradation rate	0.676
8	$v_{\text{deg},\mathbf{c2}}$	*Cry2* Max degradation rate	0.608
9	$k_{\text{deg},\mathbf{p}}$	*Per* Degradation constant	0.011
10	$k_{\text{deg},\mathbf{c}}$	*Cry1/2* Degradation constant	1.149
11	$v_{\text{deg},\mathbf{P}}$	Max PERc degradation rate	2.970
12	$k_{\text{deg},\mathbf{P}}$	PERc degradation constant	0.034
13	$v_{\text{deg},\mathbf{C1}}$	Max CRY1c degradation rate	1.523
14	$v_{\text{deg},\mathbf{C2}}$	Max CRY2c degradation rate	1.686
15	$k_{\text{deg},\mathbf{C}}$	CRYc degradation constant	2.017
16	$vdCn$	CRYn degradation rate	0.101
17	$m_{\mathbf{C2N}}$	CRY2n degradation multiplier	3.318
18	$k_{\text{deg},\mathbf{CP}}$	CRYn degradation constant	0.053
19	$v_{\text{a},\mathbf{CP}}$	CRYn association rate	0.041
20	$v_{\text{d},\mathbf{CP}}$	CRYn dissociation rate	0.002
21	$k_{\text{tln},\mathbf{p}}$	PER translation rate	3.000