Electronic Supplementary Material

Discrete Stochastic Mammalian Model

This model is the discrete stochastic version of the model in [1], which, in turn, is constructed from Leloup and Goldbeter's [2] 16-state mammalian model. In Tables 1 and 2, we list the reactions involved in a single cell. To convert molar concentrations in the deterministic model to populations (number of each chemical species) requires converting the concentration to units of molecules per liter then multiplying by a cell volume V. The scaling constant Ω is given by

$$\Omega = N_A \text{ [molecules/liter]} \times V \text{ [liters]} \tag{1}$$

where Avogadro's number $N_A = 6.022 \times 10^{23}$. For $\Omega = 600$ used in this model

$$1 \text{ nM} \times \Omega = 1 \text{ nM} \times \frac{1 \text{ M}}{10^9 \text{ nM}} \times 6.022 \times 10^{23} \frac{molecules}{liter} \times V \text{ liters.} \tag{2}$$

Solving for V gives a volume of $V = 1.7e^{-15}$ liters.

Due to the small grid size currently feasible in a reasonable simulation run time, the coupling topology was changed from the 1/r distance weighting used in [1], to a mean-field coupling. This eliminates grid boundary effects that may skew results if the 1/r coupling were used in such a small grid. The VIP coupling (see Fig. 1 in [1]) is given in the algebraic equations 3 - 9. See [1] for the values of the constants used in this model.

$$\rho_i(t) = a\Omega \frac{M_{P,i}(t)}{M_{P,i}(t) + b\Omega} \tag{3}$$

VIP produced by cell

$$\gamma_i(t) = \frac{1}{N} \sum_{j=1}^{N} \rho_j(t) \tag{4}$$

γ_i is the VIP observed by cell i due to cell j and α_{ij} is the reciprocal of the distance between cells i and j.

$$\beta = \frac{\gamma}{K_D\Omega + \gamma} \tag{5}$$

receptor density

$$k\Omega Ca^{2+}_{Cytosol} = \nu_0\Omega + \nu_1\Omega\beta \tag{6}$$

cytosolic calcium balance

$$\nu_K = V_{MK}\Omega \frac{Ca^{2+}_{Cytosol}}{K_a + Ca^{2+}_{Cytosol}} \tag{7}$$

maximum kinase rate

$$\lambda = \frac{CB_T\Omega CB^*}{K_C\Omega + CB^*} \tag{8}$$

extent of CREB activation

$$\nu_{sP} = \nu_{sP0}\Omega + \lambda \tag{9}$$

maxiumum per transcription rate

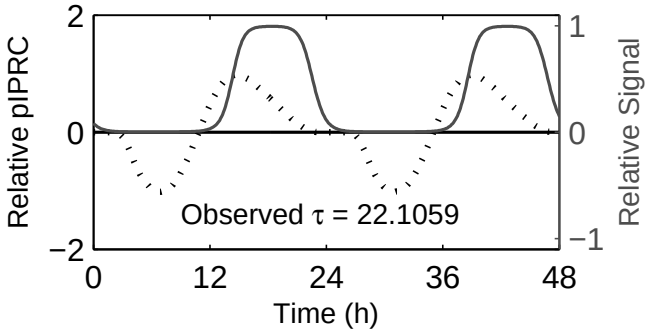
Table 1: Reactions 1 – 27 in 17 state model based on 16 state Leloup & Goldbeter model with added CREB equation

	Reaction	Probability of reaction	Transitions
0	$G \rightarrow G + M_P$	$w_0 = (\nu_{sP}\Omega)\frac{B_N^n}{(K_{AP}\Omega)^n + B_N^n}$	$M_P \rightarrow M_P + 1$
1	$M_P \rightarrow$	$w_1 = (\nu_{mP}\Omega)\frac{M_P}{(K_{mP}\Omega) + M_P}$	$M_P \rightarrow M_P - 1$
2	$M_P \rightarrow$	$w_2 = k_{dmp}M_P$	$M_P \rightarrow M_P - 1$
3	$G \rightarrow G + M_C$	$w_3 = (\nu_{sC}\Omega)\frac{B_N^n}{(K_{AC}\Omega)^n + B_N^n}$	$M_C \rightarrow M_C + 1$
4	$M_C \rightarrow$	$w_4 = (\nu_{mC}\Omega)\frac{M_C}{(K_{mC}\Omega) + M_C}$	$M_C \rightarrow M_C - 1$
5	$M_C \rightarrow$	$w_5 = k_{dmc}M_C$	$M_C \rightarrow M_C - 1$
6	$G \rightarrow G + M_B$	$w_6 = (\nu_{sB}\Omega)\frac{(K_{IB}\Omega)^m}{(K_{IB}\Omega)^m + B_N^m}$	$M_B \rightarrow M_B + 1$
7	$M_B \rightarrow$	$w_7 = (\nu_{mb}\Omega)\frac{M_B}{(K_{mB}\Omega) + M_B}$	$M_B \rightarrow M_B - 1$
8	$M_B \rightarrow$	$w_8 = k_{dmb}M_B$	$M_B \rightarrow M_B - 1$
9	$M_P \rightarrow P_C$	$w_9 = k_{sp}M_P$	$P_C \rightarrow P_C + 1$
10	$P_C \rightarrow P_{CP}$	$w_{10} = (V_{1P}\Omega)\frac{P_C}{(K_p\Omega) + P_C}$	$P_C \rightarrow P_C - 1, P_{CP} \rightarrow P_{CP} + 1$
11	$P_{CP} \rightarrow P_C$	$w_{11} = (V_{2P}\Omega)\frac{P_{CP}}{(K_{dp}\Omega) + P_{CP}}$	$P_C \rightarrow P_C + 1, P_{CP} \rightarrow P_{CP} - 1$
12	$PC_C \rightarrow P_C + C_C$	$w_{12} = k_4 PC_C$	$P_C \rightarrow P_C + 1, C_C \rightarrow C_C + 1$ $PC_C \rightarrow PC_C - 1$
13	$P_C + C_C \rightarrow PC_C$	$w_{13} = (\frac{k_3}{\Omega})P_C C_C$	$P_C \rightarrow P_C - 1, C_C \rightarrow C_C - 1$ $PC_C \rightarrow PC_C + 1$
14	$P_C \rightarrow$	$w_{14} = k_{dn}P_C$	$P_C \rightarrow P_C - 1$
15	$M_C \rightarrow C_C$	$w_{15} = k_{sC}M_C$	$C_C \rightarrow C_C + 1$
16	$C_C \rightarrow C_{CP}$	$w_{16} = (V_{1C}\Omega)\frac{C_C}{(K_p\Omega) + C_C}$	$C_C \rightarrow C_C - 1, C_{CP} \rightarrow C_{CP} + 1$
17	$C_{CP} \rightarrow C_C$	$w_{17} = (V_{2C}\Omega)\frac{C_{CP}}{(K_{dp}\Omega) + C_{CP}}$	$C_C \rightarrow C_C + 1, C_{CP} \rightarrow C_{CP} - 1$
18	$C_C \rightarrow$	$w_{18} = k_{dnc}C_C$	$C_C \rightarrow C_C - 1$
19	$P_{CP} \rightarrow$	$w_{19} = (\nu_{dPC}\Omega)\frac{P_{CP}}{(K_d\Omega) + P_{CP}}$	$P_{CP} \rightarrow P_{CP} - 1$
20	$P_{CP} \rightarrow$	$w_{20} = k_{dn}P_{CP}$	$P_{CP} \rightarrow P_{CP} - 1$
21	$C_{CP} \rightarrow$	$w_{21} = (\nu_{dCC}\Omega)\frac{C_{CP}}{(K_d\Omega) + C_{CP}}$	$C_{CP} \rightarrow C_{CP} - 1$
22	$C_{CP} \rightarrow$	$w_{22} = k_{dn}C_{CP}$	$C_{CP} \rightarrow C_{CP} - 1$
23	$PC_C \rightarrow PC_{CP}$	$w_{23} = (V_{1PC}\Omega)\frac{PC_C}{(K_p\Omega) + PC_C}$	$PC_C \rightarrow PC_C - 1, PC_{CP} \rightarrow PC_{CP} + 1$
24	$PC_{CP} \rightarrow PC_C$	$w_{24} = (V_{2PC}\Omega)\frac{PC_{CP}}{(K_{dp}\Omega) + PC_{CP}}$	$PC_C \rightarrow PC_C + 1, PC_{CP} \rightarrow PC_{CP} - 1$
25	$PC_N \rightarrow PC_C$	$w_{25} = k_2 PC_N$	$PC_C \rightarrow PC_C + 1, PC_N \rightarrow PC_N - 1$
26	$PC_C \rightarrow PC_N$	$w_{26} = k_1 PC_C$	$PC_C \rightarrow PC_C - 1, PC_N \rightarrow PC_N + 1$
27	$PC_C \rightarrow$	$w_{27} = k_{dn}PC_C$	$PC_C \rightarrow PC_C - 1$

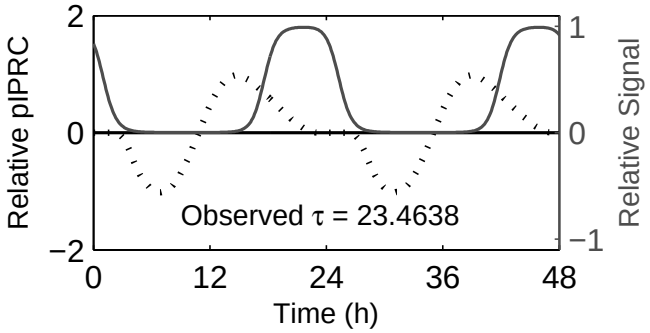
Table 2: Reactions 28 – 53 in 17 state model based on 16 state Leloup & Goldbeter model with added CREB equation

	Reaction	Probability of reaction	Transition
$PCn\frac{dPC_N}{dt}$			
28	$PC_N \rightarrow PC_{NP}$	$w_{28} = (V_{3PC}\Omega)\frac{PC_N}{(K_p\Omega)+PC_N}$	$PC_N \rightarrow PC_N - 1, PC_{NP} \rightarrow PC_{NP} + 1$
29	$PC_{NP} \rightarrow PC_N$	$w_{29} = (V_{4PC}\Omega)\frac{PC_{NP}}{(K_{dp}\Omega)+PC_{NP}}$	$PC_N \rightarrow PC_N + 1, PC_{NP} \rightarrow PC_{NP} - 1$
30	$PC_N + B_N \rightarrow I_N$	$w_{30} = (\frac{k_7}{\Omega})PC_N B_N$	$PC_N \rightarrow PC_N - 1, B_N \rightarrow B_N - 1$ $I_N \rightarrow I_N + 1$
31	$I_N \rightarrow PC_N + B_N$	$w_{31} = k_8 I_N$	$PC_N \rightarrow PC_N + 1, B_N \rightarrow B_N + 1$ $I_N \rightarrow I_N - 1$
32	$PC_N \rightarrow$	$w_{32} = k_{dn} PC_N$	$PC_N \rightarrow PC_N - 1$
33	$PC_{CP} \rightarrow$	$w_{33} = (V_{dPCC}\Omega)\frac{PC_{CP}}{(K_d\Omega)+PC_{CP}}$	$PC_{CP} \rightarrow PC_{CP} - 1$
34	$PC_{CP} \rightarrow$	$w_{34} = k_{dn} PC_{CP}$	$PC_{CP} \rightarrow PC_{CP} - 1$
35	$PC_{NP} \rightarrow$	$w_{35} = (V_{dPCN}\Omega)\frac{PC_{NP}}{(K_d\Omega)+PC_{NP}}$	$PC_{NP} \rightarrow PC_{NP} - 1$
36	$PC_{NP} \rightarrow$	$w_{36} = k_{dn} PC_{NP}$	$PC_{NP} \rightarrow PC_{NP} - 1$
37	$M_B \rightarrow B_C$	$w_{37} = k_{sB} M_B$	$B_C \rightarrow B_C + 1$
38	$B_C \rightarrow B_{CP}$	$w_{38} = (V_{1B}\Omega)\frac{B_C}{(K_p\Omega)+B_C}$	$B_C \rightarrow B_C - 1, B_{CP} \rightarrow B_{CP} + 1$
39	$B_{CP} \rightarrow B_C$	$w_{39} = (V_{2B}\Omega)\frac{B_{CP}}{(K_{dp}\Omega)+B_{CP}}$	$B_C \rightarrow B_C + 1, B_{CP} \rightarrow B_{CP} - 1$
40	$B_C \rightarrow B_N$	$w_{40} = k_5 B_C$	$B_C \rightarrow B_C - 1, B_N \rightarrow B_N + 1$
41	$B_N \rightarrow B_C$	$w_{41} = k_6 B_N$	$B_C \rightarrow B_C + 1, B_N \rightarrow B_N - 1$
42	$B_C \rightarrow$	$w_{42} = k_{dn} B_C$	$B_C \rightarrow B_C - 1$
43	$B_{CP} \rightarrow$	$w_{43} = (V_{dBC}\Omega)\frac{B_{CP}}{(K_d\Omega)+B_{CP}}$	$B_{CP} \rightarrow B_{CP} - 1$
44	$B_{CP} \rightarrow$	$w_{44} = k_{dn} B_{CP}$	$B_{CP} \rightarrow B_{CP} - 1$
45	$B_N \rightarrow B_{NP}$	$w_{45} = (V_{3B}\Omega)\frac{B_N}{(K_p\Omega)+B_N}$	$B_N \rightarrow B_N - 1, B_{NP} \rightarrow B_{NP} + 1$
46	$B_{NP} \rightarrow B_N$	$w_{46} = (V_{4B}\Omega)\frac{B_{NP}}{(K_{dp}\Omega)+B_{NP}}$	$B_N \rightarrow B_N + 1\, B_{NP} \rightarrow B_{NP} - 1$
47	$B_N \rightarrow$	$w_{47} = k_{dn} B_N$	$B_N \rightarrow B_N - 1$
48	$B_{NP} \rightarrow$	$w_{48} = (V_{dBN}\Omega)\frac{B_{NP}}{(K_d\Omega)+B_{NP}}$	$B_{NP} \rightarrow B_{NP} - 1$
49	$B_{NP} \rightarrow$	$w_{49} = k_{dn} B_{NP}$	$B_{NP} \rightarrow B_{NP} - 1$
50	$I_N \rightarrow$	$w_{50} = (V_{dIN}\Omega)\frac{I_N}{(K_d\Omega)+I_N}$	$I_N \rightarrow I_N - 1$
51	$I_N \rightarrow$	$w_{51} = k_{dn} I_N$	$I_N \rightarrow I_N - 1$
52	$CB^* \rightarrow$	$w_{52} = \Omega\big(\frac{\nu_P}{CB_T}\big)\big[(\frac{\nu_K}{\nu_P})\frac{\Omega - CB^*}{K_1+(\Omega-CB^*)}\big]$	$CB^* \rightarrow CB^* + 1$
53	$CB^* \rightarrow$	$w_{53} = \Omega\big(\frac{\nu_P}{CB_T}\big)\frac{CB^*}{K_2+CB^*}$	$CB^* \rightarrow CB^* - 1$

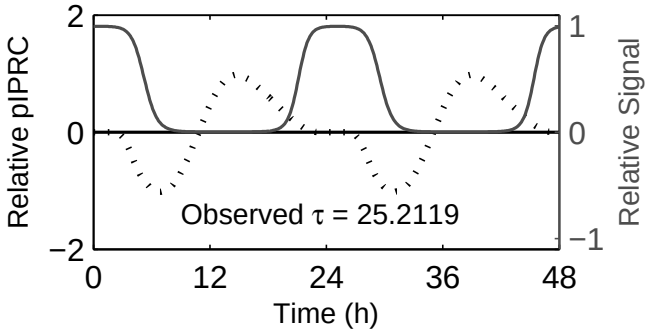
Additional Drosophila Model Coupling Mechanisms



(a) Coupling Mechanism: *tim* mRNA



(b) Coupling Mechanism: Cytoplasmic PER:TIM



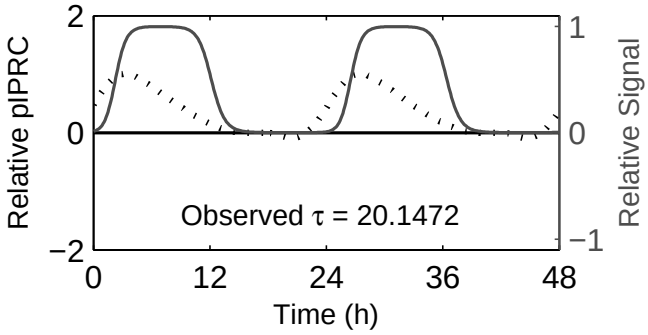
(c) Coupling Mechanism: Nuclear PER:TIM

Figure 1: The pIPRC (black dotted line) and signal trace (gray solid line) for coupling mechanisms which up-regulate *tim* mRNA degradation. The synchronizing factor is up-regulated by (a) *tim* mRNA, (b) cytoplasmic PER:TIM, and (c) nuclear PER:TIM. All curves are relative to the nominal maximal rate of *tim* mRNA degradation.

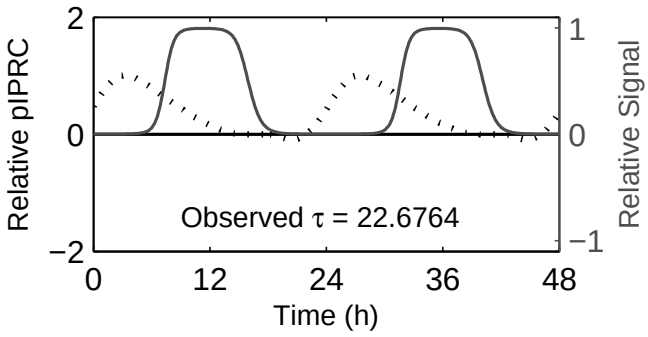
References

[1] T.-L. To, M. Henson, E. Herzog, and F. Doyle III, "A molecular model for intercellular synchronization in the mammalian circadian clock," *Biophys. J.*, vol. 92, pp. 3792–3803, Mar 2007.

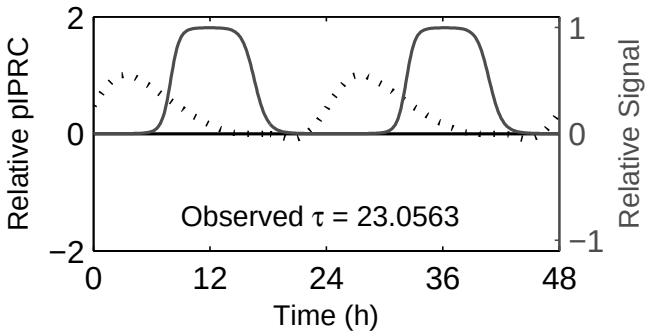
[2] J.-C. Leloup and A. Goldbeter, "Toward a detailed computational model for the mammalian circadian clock," *Proc. Natl. Acad. Sci. USA*, vol. 100, no. 12, pp. 7051–7056, Jun 2003.



(a) Coupling Mechanism: Cytoplasmic PER



(b) Coupling Mechanism: Cytoplasmic dCLK



(c) Coupling Mechanism: Cytoplasmic dCLK-CYC

Figure 2: The pIPRC (black dotted line) and signal trace (gray solid line) for coupling mechanisms that up-regulate *dClk* mRNA degradation. The synchronizing factor is up-regulated by cytoplasmic (a) PER, (b) dCLK, and (c) dCLK:CYC. All curves are relative to the nominal maximal rate of *dClk* mRNA degradation.