Supporting Information

Effects of Stochastic Single-Molecule Reactions on Coherent Ensemble Oscillations in the KaiABC Circadian Clock

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Supporting Text

In this supporting text, we explain Eqs. 2, 3, 6 and 7 of the main text. In our model, the binding status of molecular complexes in the system is represented by a set of $3N$ variables $\{i_{1k}, i_{2k}, j_k\}$ with $k = 1, \cdots, N$, where $0 \leq i_{1k} \leq 6$ is the number of KaiB molecules bound on the CI domains of kth KaiC hexamer, $i_{2k} = 0$ or 1 is the number of KaiA dimer bound on the CII ring of the kth KaiC hexamer, and $0 \leq j_k \leq i_{1k}$ is the number of KaiA dimers bound on KaiB in the kth KaiCB complex. Thus, by writing the probability that a binding status $\{i_{1k}, i_{2k}, j_k\}$ is realized in the system at time t as $P(i_{11}, i_{21}, j_1, \cdots, i_{1k}, i_{2k}, j_k, \cdots, i_{1N}, i_{2N}, j_N, t)$, the stochastic binding/unbinding reactions are described by a master equation for this probability. We approximate this N-body probability by factorizing it into one-body probabilities as

$$P(i_{11}, i_{21}, j_1, \cdots, i_{1k}, i_{2k}, j_k, \cdots, i_{1N}, i_{2N}, j_N, t) = \prod_{k=1}^{N} P(i_{1k}, i_{2k}, j_k, t). \qquad \text{(S1)}$$

This Hartree-like approximation was used to describe the single-molecular stochastic reactions in the system of gene expression.[1] We can further write $P(i_{1k} = 0, i_{2k} = 1, j_k, t) = P_{\mathrm{C_6A_2}}(k, t)$, $P(i_{1k} = 0, i_{2k} = 0, j_k, t) = P_{\mathrm{C_6B_0}}(k, t)$, and $P(i_{1k} = i, i_{2k} = 0, j_k = j, t) = P_{\mathrm{C_6B_iA_{2j}}}(k, t)$ assuming $P(i_{1k} \neq 0, i_{2k} \neq 0, j_k, t) = 0$. Because reactions in the CI domains and those in the CII domains are related only indirectly through the allosteric communication $W(k)$, we can separately write the master equations for $P_{\mathrm{C_6A_2}}(k, t)$ and $P_{\mathrm{C_6B_iA_{2j}}}(k, t)$. The equation for $P_{\mathrm{C_6A_2}}(k, t)$ is

$\frac{d}{dt}P_{\mathrm{C_6A_2}}(k,t) = h_A x P_{\mathrm{C_6B_0}}(k,t) - f_A P_{\mathrm{C_6A_2}}(k,t),$ which leads to Eq. 2 under the quasi-equilibrium approximation of KaiA binding/unbinding. With the same quasi-equilibrium approximation, KaiB binding/unbinding reactions are described without considering whether KaiA is bound on KaiB or not. Therefore, the master equations for $P_{\mathrm{C_6B}_i\mathrm{A}_{2j}}(k,t)$ are summarized by writing $P_{\mathrm{C_6B}_i}(k,t) = \sum_{j=0}^{i} P_{\mathrm{C_6B}_i\mathrm{A}_{2j}}(k,t)$, which leads to Eq. 3. We should note that $P_{\mathrm{C_6B_0}}(k,t)$ appearing in Eqs. 2, 3, and 5 relates $P_{\mathrm{C_6B}_i}$ and $P_{\mathrm{C_6A_2}}$.

For simplicity, we assume that KaiA dimer binds to and unbinds from every KaiB molecule without showing cooperative interactions between different KaiA dimers or between neighboring KaiB monomers on KaiC. Then, the ratio of the KaiA-bound KaiB to the KaiA-unbound KaiB should be $g_{BA}x = h_{BA}x/f_{BA}$. Therefore, if the number of KaiB molecules on the KaiC is i, the expected number of KaiA dimers bound in that KaiCBA complex is $i\, g_{BA}x/(1 + g_{BA}x)$. Then, the expectation value of the total number of KaiA dimers bound in KaiCBA complexes in the system should be

$$\frac{g_{BA}x}{1 + g_{BA}x} \sum_{k=1}^{N} \sum_{i=1}^{6} i P_{\mathrm{C_6B}_i}(k,t), \qquad \text{(S2)}$$

where $P_{\mathrm{C_6B}_i}(k,t)$ is the probability that i molecules of KaiB are bound on kth KaiC at time t. By dividing this factor with volume, we have the last term in Eq. 6.

For discussing the structure change of the kth KaiC hexamer, we assume that free energy F_k is affected by the level of phosphorylation U_k, probability of KaiA binding on the CII ring of KaiC hexamer p_k^{CA}, probability that KaiB binds to the CI domains of jth subunit of KaiC hexamer p_{kj}^{CB}, and the effect of ATP hydrolysis q_k as

$$F_k = -\frac{1}{6}\sum_{j=1}^{6} w_j(k)\,(c_0 - c_1 U_k + c_2 p_k^{CA} - q_k)$$

$$+c_3 \sum_{j=1}^{6} w_j(k)\, p_{kj}^{CB} - J \sum_{j=1}^{5} w_j(k) w_{j+1}(k), \qquad \text{(S3)}$$

where $w_j(k)$ is the structure order parameter of jth subunit of kth KaiC hexamer with $W(k) = (1/6)\sum_{j=1}^{6} w_j(k)$. $J > 0$ in Eq. S3 represents the cooperativity of structural transitions in neighboring subunits. We may regard $w_j(k)$ as an Ising spin and U_k, p_k^{CA}, q_k, and p_{kj}^{CB} as external fields applied to spins. In our previous publication, the Monte Carlo-type simulation of this "spin" system was performed with Hamiltonian similar to Eq. S3 for analyzing the single-molecular KaiC oscillation.[2] In the large J limit, the cooperativity is strong enough to have $w_j(k) = W(k)$. Then, Eq. S3 is effectively represented by

$$H_k = -W(k)(c_0 - c_1 U_k + c_2 p_k^{CA} - q_k) + c_3 W(k) \sum_{j=1}^{6} p_{kj}^{CB}. \qquad \text{(S4)}$$

By writing $p_k^{CB} = \sum_{j=1}^{6} p_{kj}^{CB}$ and $C_k = c_0 - c_1 U_k + c_2 p_k^{CA} - c_3 p_k^{CB} - q_k$, we have $H_k = -W(k) C_k$. The expectation value of $W(k)$ at temperature T should be

$$\langle W(k) \rangle = \sum_{W=-1}^{1} W \exp\left(-\frac{H_k}{k_B T}\right) \Bigg/ \sum_{W=-1}^{1} \exp\left(-\frac{H_k}{k_B T}\right) = \tanh\left(\frac{C_k}{k_B T}\right). \qquad \text{(S4)}$$

If we regard the quasi-equilibrium value $\langle W(k) \rangle$ as $W(k, t)$ in the slow dynamics, then we have Eq. 7.

References

1. Sasai, M; Wolynes, P. G. Stochastic gene expression as a many-body problem. *Proc Natl Acad Sci USA* **2003**, *100*, 2374–2379.
2. Das, S.; Terada, T. P.; Sasai, M. Single-molecular and ensemble-level oscillations of cyanobacterial circadian clock. *Biophys Physicobiol* **2018,** *15*, 136-150.