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Optimal Implementations for Reliable Circadian Clocks

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Abstract

Circadian clocks are acquired through evolution to better adapt to the environment. One key goal in chronobiology is to identify the primary selective pressure which demands the circadian oscillatory system. We demonstrate that maximization of two fundamental measures, *regularity* and *entrainability*, entails the species-independent features of the clock. Our manuscript starts with a simple mathematical model with the definition of regularity for keeping time and entrainability to adapt synchronization. When these theoretical properties are optimized mathe-matically, we could observe two well-known phenomena. First, we found emergence of a dead zone, a time during which light pulses neither advance nor delay the clock. The dead zone ap-peared only when the input is solar-radiation like, and not under the sine or similar oscillation. Second, we found the role-sharing of two clock inputs, one for advance and the other for delay. This phenomenon is well observed in mammals, and is recently identified in higher plants too. Our model can also provide reasonable explanation of earlier experiments. When we reproduced the hamster experiment [PNAS, vol.108, 17219, 2011] in our model, corresponding to the gene expression patterns of two light-sensitive genes *Per*1 and *Per*2, the best phase difference and functional roles matched with experimental observations. All these clues indicate that circadian systems are optimally designed under sunlight through evolution.

Our findings provide an essential foundation for understanding the circadian system. Our approach can find unknown light-sensitive biomolecules (or genes) by comparing entrainability and regularity within the candidates. Furthermore, our approach can estimate quantities (or expressions), which are difficult to observe in experiments, from the viewpoint of optimality. Indeed, our optimization can estimate the phase-response curve of *Per*1 and *Per*2, which helps to understand their behavior under different light conditions. Our results indicate that a simple mathematical model can illuminate many complex phenomena observed in nature.