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Velocity response curves demonstrate the complexity of modeling entrainable clocks

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HIGHLIGHTS

- Four clock models with similar structure have different responses to light input.
- Biochemical mechanisms, rather than parameter values, determine phase sensitivity.
- Relative peak times of model components do not indicate phase sensitivity.

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ABSTRACT

Circadian clocks are biological oscillators that regulate daily behaviors in organisms across the kingdoms of life. Their rhythms are generated by complex systems, generally involving interlocked regulatory feedback loops. These rhythms are entrained by the daily light/dark cycle, ensuring that the internal clock time is coordinated with the environment. Mathematical models play an important role in understanding how the components work together to function as a clock which can be entrained by light. For a clock to entrain, it must be possible for it to be sped up or slowed down at appropriate times. To understand how biophysical processes affect the speed of the clock, one can compute velocity response curves (VRCs). Here, in a case study involving the fruit fly clock, we demonstrate that VRC analysis provides insight into a clock's response to light. We also show that biochemical mechanisms and parameters together determine a model's ability to respond realistically to light. The implication is that, if one is developing a model and its current form has an unrealistic response to light, then one must reexamine one's model structure, because searching for better parameter values is unlikely to lead to a realistic response to light.

1. Introduction

Nature abounds with rhythmic processes, many of which are controlled by biological oscillators. One such oscillator is a circadian clock, which is responsible for coordinating daily behavioral patterns in organisms across the kingdoms of life. A circadian clock runs in constant conditions (e.g. constant darkness) with a period of approximately 24 h and entrains its rhythms to those of the daily light/dark cycle so that its period becomes exactly 24 h. In the fruit fly *Drosophila melanogaster*, the mechanisms underlying both the free-running oscillations and the response to input have been studied extensively, but are still only partially understood (Peschel and Helfrich-Förster, 2011). At the core of the fly clockworks is a set of interlocked transcription–translation negative and positive feedback loops (Hardin, 2005). The clock depends on a complex, dynamic set of processes, making it difficult to discern the roles of individual components. In this paper, we address the relative contributions of clock components to its behaviors, including the peak times of its components and its response to light.

An increasingly popular approach to understanding a clock's biochemical mechanisms is to use mathematical models in concert with biological experimentation. A common modeling paradigm for clocks is to develop a system of ordinary differential equations that captures processes such as transcription, translation, and activation and to find a set of rate constants (parameters) for which the model exhibits limit cycle oscillations (Leloup, 2009). Such models have dynamics that evolve to a stable, periodic orbit (see Fig. 1A). One major advantage of limit cycle oscillators is that it is possible to map each parameter to its effects on the timing of the clock; we compute a sensitivity measure called a velocity response curve (VRC) (Taylor et al., 2008b, 2010; Rand et al., 2004), which predicts the effects of parametric perturbation on the clock's phase velocity. In other words, it predicts whether a clock will be temporarily sped up, slowed down, or unaffected by the

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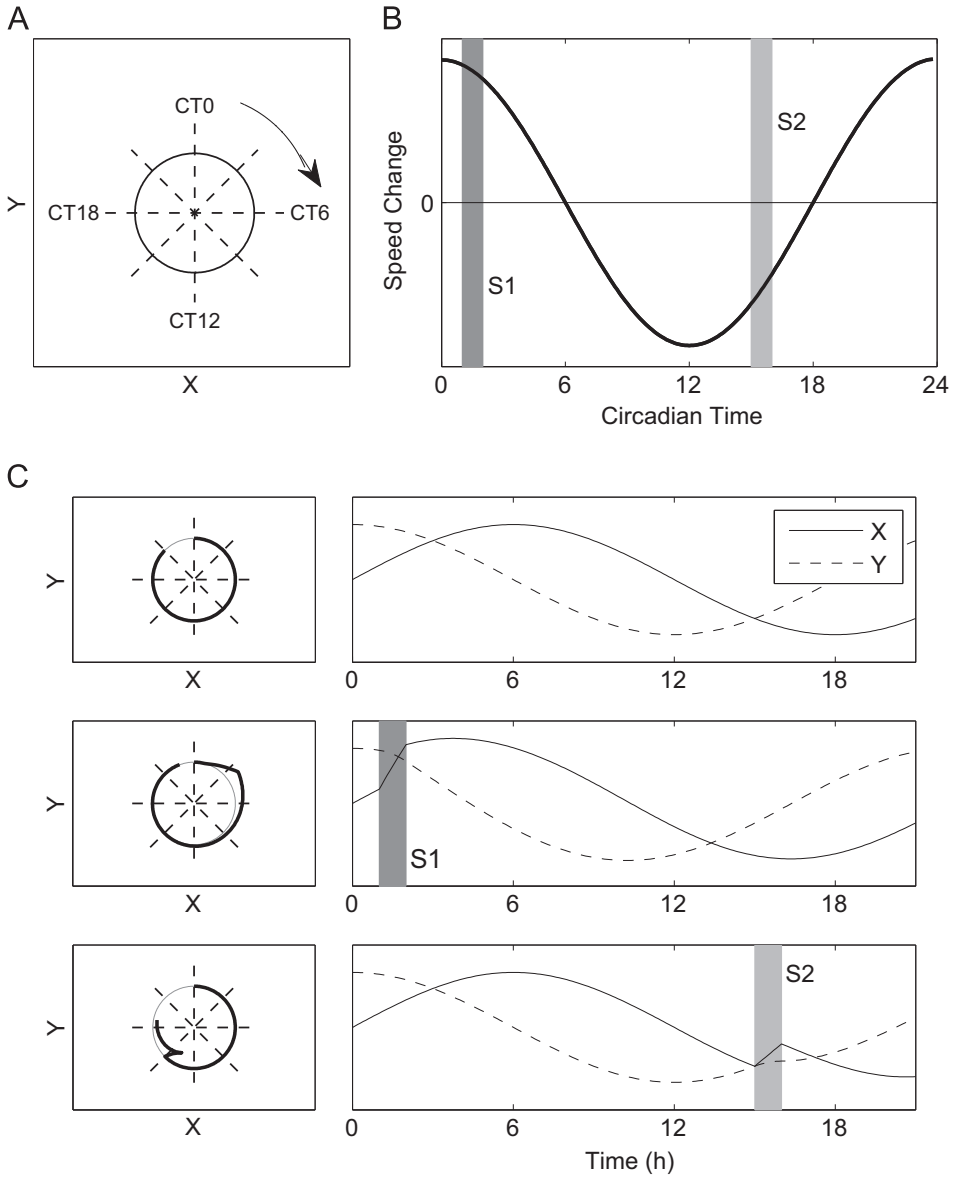

Fig. 1. A VRC indicates whether signals will speed up or slow down the clock. (A) We plot the limit cycle of a clock with two components (*X* and *Y*). Isochrons (dashed lines) indicate the phase of the clock. The phase is measured in circadian time, meaning the cycle is divided up into 24 circadian hours, each of which corresponds to an approximate time of day. Four isochrons are labeled: CT0 (dawn), CT6 (noon), CT12 (dusk), and CT18 (midnight). (B) We plot the VRC associated with a parameter that affects the dynamics of the clock's *X*-component by increasing its rate of accumulation. Positive values indicate when the clock will be sped up by a signal that increases the parameter's value. Negative values indicate when the clock will be slowed down by the same signal. We will illustrate the effect of two signals – one that arrives in the early morning (S1, dark gray bar) and one that arrives in the early nighttime (S2, light gray bar). (C) We draw the clock in the phase plane and as a time-series to demonstrate how signals affect its speed. For all panels, we compute the clock's trajectory, beginning at CT0, ending after 21 h (gray lines). In the unperturbed, 24-hour clock (top panel), the simulation ends at the CT21 isochron (the thick black line begins at CT0, travels clockwise, and ends at CT21). On the right, we show the *X* and *Y* trajectories as functions of time. In the middle panel, we show the clock receiving a signal from 1 to 2 h after CT0 (signal S1, labeled with the dark gray bar in both the trajectory and the VRC). The effect is to speed up the clock. Thus, after 21 h of simulation, the clock has passed the CT21 isochron. In the bottom panel, we show the clock receiving a signal from 15 to 16 h after CT0 (signal S2, light gray bar). The effect is to slow down the clock. Thus, the simulation ends before reaching the CT21 isochron.

change in parameter value. A perturbation to one parameter will have different effects at different phases of the clock's cycle (see Fig. 1B and 1C which uses the linear oscillator of Granada and Herzel, 2009). What conclusions can we draw from a VRC-based analysis? In particular, does the VRC to light indicate that the clock can both speed up and slow down the model to allow it to entrain to a 24-hour light/dark signal?

Mathematical models are constructed to answer specific questions about clock function. For example, the basic mechanism underlying the clock oscillations is a time-delayed negative feedback loop (Leloup, 2009). The cause of the delay between gene transcription and protein activity is, therefore, important to understand. Kuczenski et al. (2007) developed a model specifically to explore the hypothesis that an interval timer creates the necessary delay. They showed that their mechanism was better at explaining mRNA and protein time series than other mechanisms. They then placed it in a complex model of the clock and demonstrated that this complete model accurately reproduced wild type and mutant phenotypes (such as decreased levels of per mRNA and protein in a simulated *pdp* knockout). Other modelers have incorporated post-translational processes like phosphorylation into a model and demonstrated that they led to new insights, such as how the clock could maintain robust oscillations despite constant levels of key clock transcripts (Leise and Moin, 2007; Risau-Gusman and Gleiser, 2012). The result is an improved understanding of the clock, but also a proliferation of models that are similar in complexity, but different in which biological experiments