Vital physiological behaviors of living organisms are designed to synchronize with the 24-hour day/night cycle of the Earth. They are controlled by endogenous oscillators with free-running periods that only approximate 24-hours. Entraining signals, such as light, correct the period discrepancy, ensuring the internal clocks and, hence, overt behaviors will be in phase with the environment.

The above table illustrates the circadian rhythms of three representative species. The images are of an Arabidopsis seedling (McClung & Salomé & Michael, 2002).

This figure (McClung & Salomé & Michael, 2002) illustrates the complexity of the circadian regulatory systems. Input pathways include light (white, red, and blue) and temperature. At the core of the clock is a set of autonomous oscillators, driven by negative feedback loops and various regulatory connections. These oscillators, taking the influence of input into account, drive various distinct overt rhythms.

Panels

Biology

Circadian Pacemakers
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Phase Response Curves: Measuring the Effects of Entraining Signals upon Core Oscillators and Overt Rhythms

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Phase Response Curves (PRCs). When stimulated by a pulse (e.g. 15 minutes) of light, the pacemaker and thus the overt activities undergo a phase shift. Above are two figures from (Daan & Pintindh, 1976). On the left is the data for two pulses. The upper panel contains raw data (an actogram) and the lower panel summarizes its important features. On the right are phase response curves, which represent data for many pulses. There is one curve for each of four species of nocturnal rodent.

PRCs are illuminating

- PRCs describe the relationship between the clock and entraining signals
- Studying PRCs to perturbations in pacemaker parameters (such as rates of mRNA transcription) elucidates its timing mechanisms
- Understanding phase behavior leads us to the next step – manipulation of phase behavior. For humans this can mean improved performance and safety, especially for those with atypical schedules.

Complex Regulatory Network

Systems Methods

Phase as a Metric

Characteristics of oscillators. Biological oscillatory systems are characterized by certain behaviors, including period, shape/amplitude, and phase. The lower panel illustrates the phase shift induced by a parametric disturbance. Here we measure the phase shift as the distance in time between the peaks in the nominal and disturbed systems.

Comparison of Various Metrics

Metrics using different oscillator characteristics supply different information about parameter importance. For example, the amplitude is highly affected by changes in the rates of protein degradation (red box), while phase is minimally affected (blue box).

References


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