

Biological Oscillators

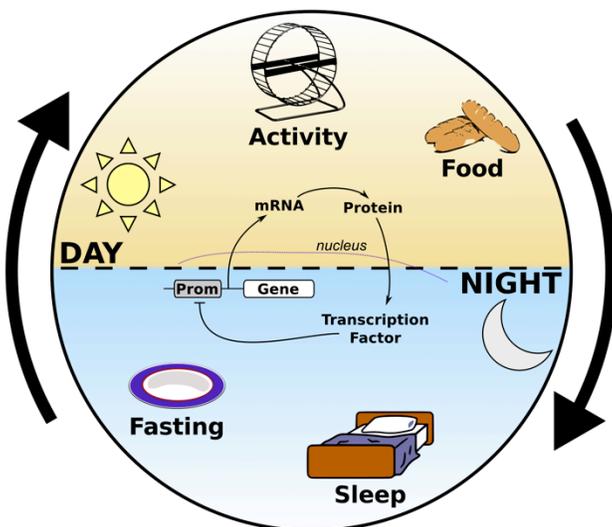
Periodic fluctuations in biological processes are found at all levels of life and are frequently the result of changes to gene expression. These rhythms play key roles in a variety of important processes, including circadian regulation, metabolism, embryo development, neuron firing, and cardiac rhythms. Oscillating gene regulatory networks function as finely tuned dynamic systems in which time-delayed negative feedback gives rise to sustained rhythms. Such rhythms display robustness to biological noise and evolutionary mutations while remaining acutely sensitive to such environmental cues as light or temperature.

The essential characteristics of biological oscillators can be represented by biophysical networks with many interacting species. Through the application of modeling and simulation tightly linked to experiment, systems biology provides a way to study such biophysical networks and hence to understand the mechanistic foundations of biological oscillators. Systems biology employs systematic measurement technologies such as genomics, bioinformatics, and proteomics to quantitatively measure the behavior of groups of interacting components in biophysical networks and harnesses mathematical and computational models to describe and predict dynamical behaviors.

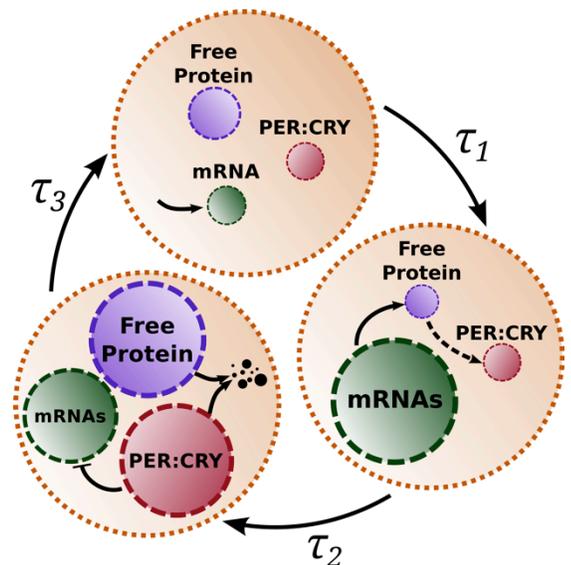
Why Is Systems and Control Theory Relevant?

Regulation, tracking, interactions, adaptation, robustness, communication, signaling, sensitivity, identification, dynamics, stability/instability, and causality are all concepts that are crucial in biological oscillators and have counterparts in the systems and control domain. Systems and control theory can be harnessed for

- Modeling of biological oscillators,
- Understanding the mechanisms of robustness and sensitivity,
- Reverse engineering of biological oscillators, and
- Control (e.g., in pharmaceutical regulation) and design (e.g., in synthetic biology) of rhythmic biological processes.



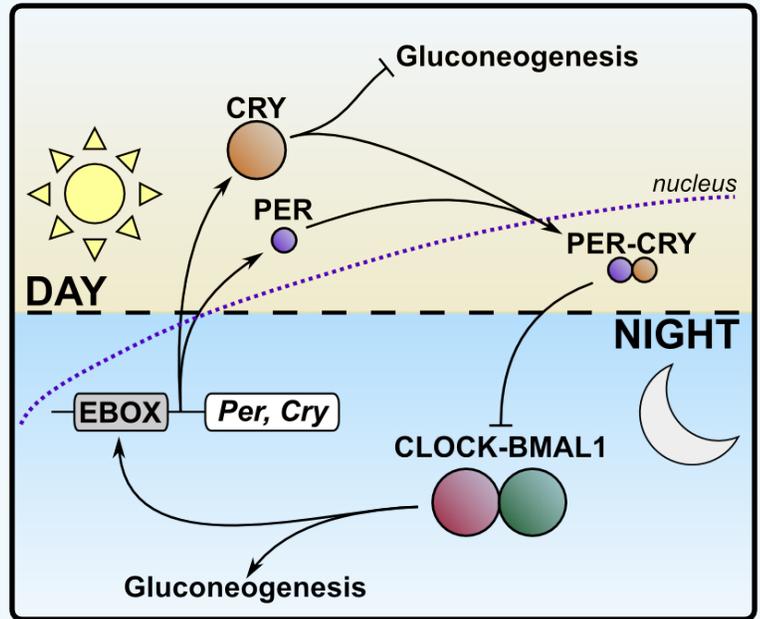
Genetic regulatory networks help coordinate important oscillatory behaviors, including circadian rhythms, shown here. Rhythmic light/dark cues optimize metabolic pathways for expected energy intake and demand.



Sustained oscillations result from multiple sources of time delays. Transcription, translation, and degradation of repressive complexes (PER-CRY in mammalian circadian rhythms) all contribute to the oscillatory period.

Example: Circadian Control of Mammalian Metabolic Pathways

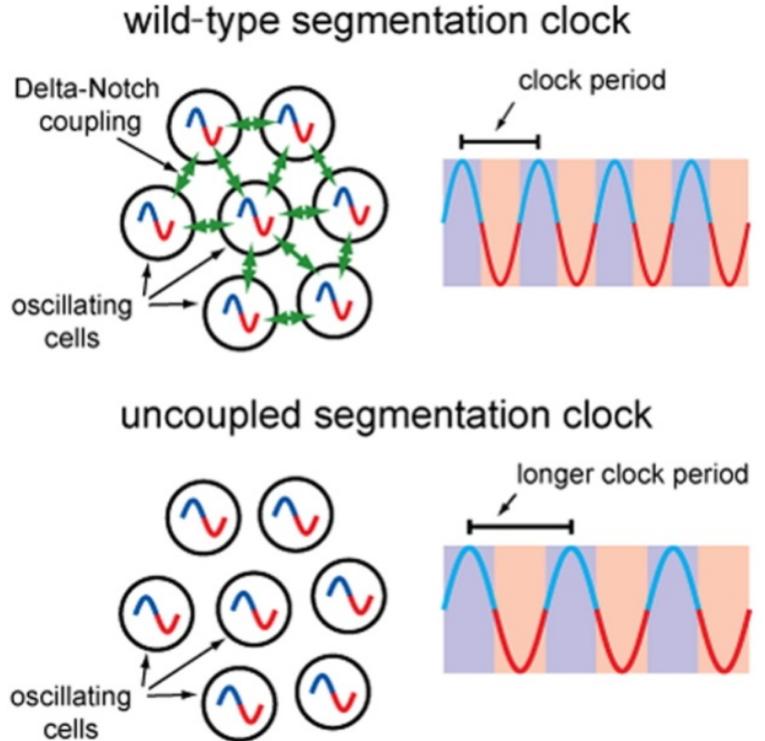
In mammals, circadian rhythms control the activity of many key metabolic pathways. For example, in the liver, the production of new glucose from energy reserves is repressed during the day, when meals are common, and activated at night, when they are scarce. However, in our current 24-hour society, circadian disturbances such as jet lag and shift work are also manifested as metabolic disorders. Without a keen understanding of the processes involved, appropriate behavioral or pharmaceutical therapies for long-term circadian disorders are difficult to find. By applying systems and control methodologies to models of circadian rhythms, the additional metabolic burden of irregular light schedules could possibly be alleviated.



Circadian rhythms control many aspects of mammalian metabolism, including the creation of new glucose in the liver (gluconeogenesis).

Example: How Is Network Oscillation Behavior Established From Cell Autonomous Oscillations?

Most biological rhythms are generated by a population of cellular oscillators coupled through intercellular signaling. One such system where this occurs is the segmentation clock shown at right, which governs the synchronized development of vertebrate embryos. Recent experimental evidence shows that the collective period of all cells may differ significantly from the autonomous period in the presence of intercellular delays. Although this phenomenon has been investigated using delay-coupled phase oscillators, a better understanding of the biological mechanisms that govern coupled oscillators is critical to connecting genetic regulatory networks to tissue-level oscillatory behavior.



Coupling independent oscillators can result in a collective period different than that of each cell. (Source: L. Herrgen et al., *Curr. Biol.* 20, 1244, 2010)