

BIOLOGICAL CLOCK

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Biological Clock

Primary Disciplinary Field(s): Chronobiology, Neuroscience, Physiology, Genetics

1. Core Definition and Terminology

The term **Biological Clock** refers to the intrinsic, self-sustaining mechanism present within virtually all living organisms--from single-celled cyanobacteria to complex mammals--that regulates the timing of physiological processes and behavioral patterns. This internal timekeeping system ensures that activities are synchronized with the environmental cycle, most notably the 24-hour cycle of light and darkness. The activities governed by this mechanism are collectively known as **biological rhythms** or **biorhythms**.

The most widely studied and prominent of these rhythms is the circadian rhythm (from the Latin *circa diem*, meaning 'about a day'), which dictates the oscillation between periods of activity and rest. Crucially, the biological clock operates endogenously; that is, the rhythm persists even when an organism is isolated from all external temporal cues (a state known as 'free-running'). The internal mechanism maintains a period length close to, though often slightly longer or shorter than, the precise 24-hour solar day, necessitating periodic fine-tuning by external signals.

As noted in preliminary psychological definitions, the biological clock involves a fundamental pattern of activity and rest within a 24-hour period, functioning as an **internal clock**. In humans, this function is highly integrated with the central nervous system, particularly the hypothalamus, enabling the predictable alternation between wakefulness and sleep. The primary purpose of this highly conserved evolutionary mechanism is to anticipate predictable environmental changes, allowing the organism to prepare metabolically and behaviorally for optimal performance, feeding, and survival.

2. Neurological Localization: The Suprachiasmatic Nucleus (SCN)

In mammals, the central biological clock, often termed the **master pacemaker**, is localized within the suprachiasmatic nucleus (SCN), a tiny pair of nuclei situated in the anterior part of the hypothalamus, directly above the optic chiasm. The SCN is composed of approximately 20,000 neurons per side, and these cells exhibit synchronized, self-generated rhythmic electrical and biochemical activity. This centralized structure integrates timing information and relays it to various regions of the brain and body.

The SCN receives crucial non-image-forming light information directly from specialized photoreceptors in the retina--specifically, the intrinsically photosensitive retinal ganglion cells (ipRGCs), which contain the photopigment melanopsin. This dedicated pathway, known as the retinohypothalamic tract, allows environmental light to directly impinge upon the SCN, serving as

the most powerful external cue for resetting the clock. The SCN uses this light input to continuously adjust its internal rhythm, ensuring it remains synchronized, or **entrained**, to the 24-hour external day.

The SCN orchestrates systemic timing by sending signals via neural and humoral pathways. Key outputs include regulation of the autonomic nervous system, body temperature, and the rhythmic secretion of hormones, particularly **melatonin** from the pineal gland. Melatonin production typically increases during the subjective night, acting as a powerful signal of darkness and promoting sleep. Thus, the SCN acts as the conductor, establishing temporal coherence across the multitude of peripheral clocks located throughout the body's organs and tissues.

3. Molecular Mechanisms and Genetics

At the cellular level, the biological clock is governed by a complex and highly conserved molecular machinery known as the **Transcriptional-Translational Feedback Loop (TTFL)**. This loop involves a set of core clock genes whose protein products cyclically inhibit their own transcription over approximately 24 hours. This fundamental genetic mechanism drives the cellular oscillation that underpins the entire biological rhythm.

The central positive elements of the loop involve the transcription factors **CLOCK** (Circadian Locomotor Output Cycles Kaput) and **BMAL1** (Brain and Muscle ARNT-Like 1). These proteins heterodimerize and bind to E-box elements in the promoters of target genes, activating the transcription of the negative elements, primarily the **Period** (*Per1*, *Per2*, *Per3*) and **Cryptochrome** (*Cry1*, *Cry2*) genes. As levels of PER and CRY proteins accumulate in the cytoplasm, they form complexes and translocate back into the nucleus. Once in the nucleus, the PER/CRY complexes bind to and inhibit the CLOCK/BMAL1 complex, shutting down their own transcription.

As transcription is inhibited, the existing PER and CRY proteins are gradually degraded, relieving the inhibitory pressure on the CLOCK/BMAL1 complex. This allows the cycle to restart, creating a self-sustaining oscillation that takes approximately 24 hours to complete. This intricate molecular dance is regulated by various post-translational modifications, particularly phosphorylation by kinases such as Casein Kinase 1 Delta (CK1 δ) and Epsilon (CK1 ϵ), which fine-tune the timing and stability of the clock proteins. The synchronization of these TTFLs across millions of cells within the SCN creates the robust, centralized rhythm observed at the organismal level.

4. The Role of External Cues (Zeitgebers)

While the biological clock is endogenous, its period rarely matches exactly 24.0 hours, making it susceptible to drifting out of sync with the external world. Therefore, the clock must be regularly reset or **entrained** by external environmental cues, known as **Zeitgebers** (German for 'time-

givers'). Entrainment is the process by which the internal periodicity is precisely synchronized to the 24-hour day.

The most potent and dominant Zeitgeber for nearly all species, including humans, is **light**. As detailed previously, light information reaching the SCN provides the necessary signal for phase shifts--advancing or delaying the internal clock. Light exposure early in the subjective night typically causes a phase delay, pushing the clock later, while light exposure late in the subjective night causes a phase advance, pulling the clock earlier. This sensitivity to light forms the basis for treating many circadian rhythm disorders.

Beyond light, other factors serve as non-photic Zeitgebers, influencing the peripheral clocks and, to a lesser extent, the SCN. These include **feeding times**, physical activity, social interactions, and ambient temperature cycles. The strict timing of meals, for instance, is critical for entraining metabolic clocks in the liver and pancreas. Disruption of these non-photic cues, such as highly variable meal times common in shift work, can lead to internal desynchronization, where the central clock is aligned with the light cycle, but peripheral clocks are out of phase with the SCN.

5. Types of Biological Rhythms

Biological clocks do not only govern 24-hour cycles; they are responsible for maintaining temporal organization across multiple timescales. Rhythms are broadly categorized based on their period length:

Circadian Rhythms: Rhythms with a period of approximately 24 hours (e.g., the sleep-wake cycle, core body temperature fluctuations, cortisol secretion). These are the direct manifestations of the SCN master clock.

Ultradian Rhythms: Rhythms that cycle more frequently than 24 hours (i.e., periods shorter than a day). Examples include cycles of rapid eye movement (REM) and non-REM sleep (approximately 90 minutes), hormone pulsatility (e.g., growth hormone), and cycles of appetite and attention span.

Infradian Rhythms: Rhythms that cycle less frequently than once every 24 hours (i.e., periods longer than a day). The most notable example in humans is the menstrual cycle (approximately 28 days). Seasonal changes in behavior, such as hibernation in some animals, also fall under this category.

While the SCN is primarily known as the pacemaker for circadian rhythms, all these rhythms are interconnected. The precise coordination between different rhythm types is essential for maintaining homeostasis and adapting to long-term environmental demands. For example, seasonal changes mediated by infradian rhythms influence the amplitude and phase of circadian rhythms, preparing the organism for changes in photoperiod (day length).

6. Significance and Impact on Health (Chronobiology)

The field dedicated to the study of biological rhythms and their mechanisms is **Chronobiology**. This discipline emphasizes that health is fundamentally dependent on robust and properly timed biological rhythms. The biological clock exerts influence over nearly every physiological system, including metabolism, immunity, DNA repair, cardiovascular function, and cognitive performance.

Disruption of the biological clock, often termed **circadian misalignment** or desynchronization, is increasingly recognized as a significant public health issue. Common causes of misalignment include shift work, frequent transmeridian travel (jet lag), and poor light hygiene (e.g., exposure to blue light at night). Consequences of chronic circadian disruption are profound and include increased risk for metabolic disorders such as **Type 2 Diabetes** and obesity, cardiovascular disease, impaired immune function, certain cancers (particularly breast and prostate cancer in shift workers), and mood disorders like depression.

The understanding of rhythmic physiological processes has led to the development of **Chronopharmacology**, the study of how the timing of drug administration affects its efficacy and toxicity. Since the activity of enzymes, drug receptors, and metabolic pathways varies rhythmically over 24 hours, timing drug delivery to coincide with the peak sensitivity of the target tissue can optimize therapeutic outcomes and minimize side effects. Examples include administering chemotherapy at times when healthy cells are most protected or prescribing statins in the evening when cholesterol synthesis peaks.

7. Disorders and Clinical Implications

Disorders directly related to the malfunction or misalignment of the biological clock are classified as **Circadian Rhythm Sleep-Wake Disorders (CRSWD)**. These disorders involve persistent or recurrent patterns of sleep disruption due to alterations of the circadian system or a misalignment between the endogenous rhythm and the required external schedule. Common intrinsic CRSWDs include Delayed Sleep Phase Syndrome (DSPS) and Advanced Sleep Phase Syndrome (ASPS).

In **DSPS**, the patient's internal clock runs later than normal, leading to difficulty falling asleep at conventional times and difficulty waking up in the morning. Conversely, in **ASPS**, the clock runs earlier, resulting in very early evening sleep onset and extremely early morning awakenings. Extrinsic CRSWDs include Shift Work Disorder and Jet Lag Disorder, where the internal clock is healthy but is repeatedly forced out of sync by environmental demands.

Therapeutic approaches for CRSWDs focus on **entrainment manipulation**. These interventions rely on leveraging the power of Zeitgebers, specifically precisely timed light exposure (phototherapy) and timed administration of melatonin. Bright light therapy, often administered via light boxes, is used to shift the phase of the SCN. For example, morning light is used to advance

the clock in DSPS patients. Furthermore, behavioral strategies, such as maintaining strict sleep schedules and controlling environmental light exposure in the hours before bed, are crucial components of restoring temporal alignment and optimizing the function of the biological clock.

Further Reading

[Circadian rhythm \(Wikipedia\)](#)

[Suprachiasmatic nucleus \(Wikipedia\)](#)

[National Institute of General Medical Sciences: Circadian Rhythms](#)

[Sleep Foundation: Circadian Rhythm](#)

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