Internal clocks keep all living things ticking -- even you

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Like kids taking apart a fine Swiss watch, scientists are laboring to understand what makes the biological clock that's inside every living creature tick.

Researchers have long known that bacteria, flies, worms, flowers, oak trees and human beings all have tiny internal timepieces that keep them on a roughly 24-hour cycle, the time it takes the Earth to spin once on its axis.

"Living cells can actually tell the time and use this information to control their behavior," said Hugh Nimmo, a plant biologist at the University of Glasgow, Scotland.

Many questions remain to be answered, however, such as how the clocks work at the level of individual molecules. To find out, some scientists are building simple biological clocks in a test tube.

"If you can build it, you really understand it," said Jonathan Arnold, a geneticist at the University of Georgia in Athens. "It's very important that we know how the clock works at the molecular level."

"Biological timekeeping is a core property of life on a revolving planet," said Jay Dunlap, a biochemist at Dartmouth College in Hanover, N.H., and the author of a book on the subject. "Time organization is a vital part of the survival and normal functioning of every species."

These living pacemakers keep running whether it's light or dark. Creatures that live underground or at the bottom of the ocean continue to have timers that they inherited from their ancestors, even though they no longer see the sun shine.

Inner clocks tell people when to wake up and plants when to unfurl their leaves. For small nocturnal mammals, knowing when dawn is coming can mean life or death from a predator. Contrariwise, a fungus may wait to send up its reproductive stalks until after dark to avoid dangerous ultraviolet light.

When clocks go awry, they contribute to miseries such as insomnia, liver disease and cancer, Arnold said. In humans, a gene that the biological clock controls is involved with early-morning heart attacks.

Organic timing mechanisms are governed by one or more clock genes in a cell's DNA. The genes produce specialized proteins - long strings of organic molecules - that control the sequence of bodily functions.

Taken together, the genes and proteins make up a complex regulatory network that fits together like the gears in a watch. As in a clock, the timing can be reset to compensate for daylight saving time, night work, jet lag and even a slightly longer day-night cycle on Mars, if humans ever land there.

People's clock genes may set their sleep patterns. Last summer, Sarah Forbes-Robertson, a British researcher at the Swansea University School of Medicine in Wales, reported that she can tell whether a person is an early riser or a night owl by inspecting a gene called REV-ERB in his or her DNA, taken from a swab on the cheek. A low level of gene activity is associated with sleep, a high level with wakefulness, she said.

"If your peak is earlier than 4 p.m. it would indicate that you are a

natural early bird," she said. "If you peak later than 5 p.m., then you are more of a night owl."

The first clock gene - named "period" - was discovered in 1971. Others followed, with names such as "timeless," "frequency" and, naturally, "clock." Dozens of genes have been identified since then and their elaborate biochemical structures unraveled.

The simplest biological clock is probably the most ancient. It's found in blue-green algae, also known as cyanobacteria, the one-celled creatures that create pond scum. This clock started keeping time about 3.5 billion years ago, when the world was young.

The cyanobacteria clock consists of just three proteins. One of them, shaped like a six-sided ring, looks surprisingly like a cog, or escape wheel, in a mechanical watch, according to Susan Golden, a biologist at Texas A&M University in College Station.

"The gears mesh and turn to crank out a 24-hour timing circuit," Golden reported in the journal *Proceedings of the National Academy of Sciences*.

As organisms grew increasingly complex over millions of years, so did their timing mechanisms.

"In flies, worms and mice, the clock has become more elaborate," said Arnold of the University of Georgia. "Functions once found in one protein have been separated into multiple proteins."

For example, the frequency gene in bread mold, a common fungus, controls 295 other genes, Arnold said.

Humans and other mammals have "master clocks" buried deep inside their brains in bundles of cells called the suprachiasmatic nucleus. The

suprachiasmatic nucleus coordinates peripheral clocks in other organs, including the lungs, liver and kidneys.

According to Nimmo, the Scottish expert, biological clocks evolved separately on four occasions: first in cyanobacteria and later in funguses, plants and animals.

"The essential nature of a clock has led to its arising more than once in the evolution of life," Arnold said.

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ON THE WEB

• "The Biological Clock's Incredible Influence Revealed" (National Science Foundation): tinyurl.com/bdfgm7

• Circadian clocks go in vitro: www.nature.com/msb/journal/v1/ … full/msb4100027.html

• Circadian rhythms: template.bio.warwick.ac.uk/Sta … /amillar/circad.html

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