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What gets you going first thing?

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BIOLOGICAL SCIENCE

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The study of time represents one of the great transdisciplinary themes of scientific research, from space time in physics and deep time in geology, through to circadian time in biology and the search for lost time in literature. Amid these overlapping interests, it is easy to forget that the investigation into time was, for a considerable period, stalled by a desire to square all empirical advance with scriptural considerations.

It was perhaps in geology that time matured as a topic, under the gaze of James Hutton (1726-97) who wrote: "Great things are not understood without the analysing of many operations, and the combination of time with many events happening in succession." In a previous century, approximately coinciding with Newton's investigations into extra-planetary motion, Jean-Jacques d'Ortous de Mairan was inquiring into the nature of terrestrial rotation and making occasional digressions into the diurnal rhythms of Mimosa plants deprived of natural light. As Russell Foster and Leon Kreitzman report in this fascinating book, de Mairan's experiments were some of the earliest scientific explorations of the temporal correlations established between the living and non-living universe.

Since the early work of De Mairan, there has been great progress in the study of biological time, with the discovery of infraridian, circadian and ultraridian rhythms (less than a day, daily and more than a day), such as heartbeats, sleep-wake cycles and reproductive cycles. One of the enduring early findings was made by Erwin Bunning, who established that circadian clocks, when kept in constant conditions to control for rhythmical cues from the environment, "free run" with a periodicity close to our 24-hour solar cycle. This demonstrated that the rhythm was endogenously generated, and that the role of exogenous cues (the "Zeitgeber") was to entrain the clock to coincide more precisely with sunrise and sunset.

There were those who doubted that organisms could maintain such perfect time. They argued that without a constant source of regularity imposed from outside, based on classical inputs such as planetary motion, biology would succumb to entropy and become disordered. This is a debate that goes beyond discussion of biological clocks; it is about sources of order in living systems and mechanisms for minimising dissipation.

In his book *What is Life*, the physicist Erwin Schrodinger distinguishes between the order from disorder principle, and the order from order principle, following on from an earlier distinction made by the physicist Max Planck between dynamical and statistical laws. Dynamical laws, such as Newton's laws of planetary motion, hold true because statistical irregularities disappear at absolute zero. While the temperature of the galaxy never falls this low, it is sufficiently low that this dynamical system behaves as if thermal fluctuations play an insignificant role. The same idea applies to the working of a mechanical clock where thermal noise can be minimised. Thus in these cases, we observe order (regular time) from order (the orderly interactions of the mechanical components of the clock).

An example of a statistical law is Boyle's law, which states that, at constant temperature and quantity, there is an exact inverse relationship between the temperature and volume of an ideal gas. Unlike the mechanical clock, in which the components are themselves orderly, producing orderly behaviour, in a gas the components are all disordered and produce order through an averaging of a multitude of independent, random trajectories. This is statistical order (or average order) and it forms the basis of regularity in most biological processes.

Foster and Kreitzman recount the debates on this subject between the geologist Frank Brown Jr and the chronobiologist (time biologist) Colin Pittendrigh. Brown refused to accept that circadian rhythms could emerge as statistical regularities, and posited the existence of geophysical forces, such as magnetism and cosmic radiation as driving forces. One particular source of incredulity for Brown was the so-called Q10 law, which states that for every 10xC increase in temperature there is a doubling of the metabolic rate. Since many organisms move freely among environments of widely varying temperature, Brown could not see how a constant clock, based on statistical metabolic dynamics, could remain accurate. Pittendrigh performed numerous ingenious experiments to demonstrate the endogeneity and robustness of the rhythm. This robustness is now commonly accepted, however the mechanisms producing order across temperatures remain somewhat elusive.

The mechanisms producing order from disorder, described in the book, are a special case of regulatory dynamics. Following the discovery of the structure of DNA in the cell in 1953 by Crick and Watson, molecular biologists determined that genes that encode proteins are able to activate or inhibit other genes. In other words, genes and proteins form networks of activation and inhibition, in which genes express proteins that bind to regions of DNA, causing further genes to express additional proteins or stop expressing existing proteins. Francois Jaçob and Jacques Monod explored in depth a class of these networks (the operon) in bacteria and showed that they implemented feedback loops, much like a thermostat, to regulate the concentration of proteins as they are required by cellular processes. And just like the oscillations of a thermostat that arise from delays in responding to variations in ambient temperature, there is oscillation in proteins as a result of delays in their expression and decay.

The basis of the organismal circadian rhythm is an elaborate gene regulatory network within cells that produces cells capable of synthesising proteins whose concentrations vary in a periodic fashion. This periodicity results from a combination of negative feedback and time delays. It transpires that organisms are aggregates of thousands of cellular clocks, each beating out rhythms according to the statistical regularities emerging from their own feedback loops, and coming together as a statistical unity to give us our sense of time.

The book goes on to explore circannual rhythms, those with a period of a year, responsible for coordinating migration. These are dependent on seasonal variation in daylight, leading to variation in the concentrations of melatonin liberated during the dark hours from the pineal gland. There is an exploration of the species-specific variation in the neuroanatomical localisation of clock centres in the brain, and a discussion of the evolutionary context in which this variation might be understood. There is even a short chapter on coping with jet lag.

There is a great deal of interest in this book. While the study of biological clocks is a topic of great interest in itself, biological clocks are also illustrative of some of the most challenging problems in theoretical biology, biological physics and biological computation. The book presents the full richness of this system as it appears across species, in a style that is informative to lay readers and professionals, while presenting some of the personalities and disagreements that make science so much fun.

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