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## Commentary

# Ultradian rhythms: Life's dance to the music of time\*

**Keywords.** Biological morphology; cell–cell interactions; cellular growth; development; emergent behaviour; intercellular signalling; oscillations

## 1. Background

A recent and updated translation of a book, earlier published in Russian in 2021, contains a fascinating account of the development of a central theme in our understanding of the kinetics of cellular growth and development (Brodsky 2022). The book deals with the twin concepts of ultradian (i.e. about one hour period) signals and cell-to-cell communication. The author, Vsevolod Ya. Brodsky, has performed a major service by discussing in a comprehensive manner studies on high-frequency oscillations in intercellular communication. The book will be especially valuable to readers who are not familiar with the extensive Russian literature on the subject, much of which has been ignored elsewhere. The present Commentary uses it as a take-off point in order to highlight issues that are common to the area of biological rhythms generally and ultradian oscillations in particular. In view of the importance of the book, we critique it towards the latter part of the Commentary in the style of a book review.

## 2. Oscillatory phenomena in living systems

To begin with a point of terminology: conventionally, biological rhythms are broadly categorised as circadian, or near-24 hours, and ultradian. Ultradian, which can also be loosely expressed as ‘high frequency’, refers to diverse processes that recur at intervals substantially smaller than 24 hours. Neuronal oscillations and several biochemical oscillations fall in this class, as does the cell division cycle. This classification does not cover all rhythmic phenomena in the living world. For instance, rhythms that occur at markedly longer intervals than a day, such as tidal (lunar) rhythms, the ‘periodical cicadas’ (Simon and Cooley 2022) and some flowering rhythms are ignored. Perhaps the term ‘infradian rhythm’ needs to be used more often (Engelmann 2015), for there are many such examples of plant rhythms.

The so-called lower eukaryotes (represented by single-celled protists, yeasts, as well as ‘higher fungi’), animals (e.g., crayfish, mice, rats, quail), and plants (e.g., mosses, ferns, and monocots to flowering plants) have proved extremely useful in unravelling the molecular mechanisms that lie behind the functioning of living systems. They have set a firm foundation for studies on the cells, tissues, and entire individuals belonging to the so-called higher species. Our understanding of human physiology and disease has grown thereby. Among such studies, the investigation of how the functioning of cells and tissues is organized temporally, in other words, how they ‘keep time’, has proved especially fruitful. Synchrony and coherence in biological time-keeping help us in deciphering core processes and events that are likely to be basic to animals and plants (Gilbert *et al.* 2020; Kembro *et al.* 2023). They involve coherent processes that appear to be highly evolved and elaborately organized. As stated, we

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\*Dedicated to the memory of Wolfgang Engelmann: warm friend, excellent scientist, eminent teacher.

are taking advantage of a recently published book to comment on the aspect of coherence that deals with integration in time.

Contemporary attempts to address the issue bring powerful new techniques to bear on an age-old enigma, namely, the apparent stability of the living state. In a universe where an increase in disorder would seem to be a necessary consequence of thermodynamics, islands of self-organization may seem only remotely possible. Yet, provided that conditions are held within acceptable limits, the growth, development, and maintenance of living organisms proceed apace robustly. Textbooks illustrate the seemingly monotonic progression from egg to adult with still photographs or drawings of stereotypical stages. However, the photographs mask continuous progression as well as a great deal of back-and-forth change. Rhythmic temporal dynamics are a basic feature of cells and tissues. The apparent stability of living organisms disguises the enormous complexity behind its construction, of which studies of rhythmicity reveal one aspect.

### 3. Rhythms as indicators of temporal stability

Viewed as assemblages of matter, living organisms exhibit two characteristic features. They are open in a thermodynamic sense, almost always function not far from equilibrium, and are intrinsically prone to disorder. At the same time, they display intricate spatial and temporal regularities, including coordinated autonomous behaviour that is suggestive of agency. The explanation of the apparent paradox lies in kinetic mechanisms, not thermodynamics. Prigogine and co-workers showed that rather than entropy reaching a maximum, which is what happens when a closed system is at equilibrium, the *rate* of entropy production can attain a minimum in an open system. But that is a useful thermodynamic criterion only close to a steady-state (Prigogine and Stengers 1984). However, unlike thermodynamics, kinetics can account for spatio-temporal order in open, far-from-equilibrium systems that operate irreversibly. Consequently, the modelling of such systems is the approach of choice for explaining patterns in living organisms. The problem becomes one of identifying which of the molecular processes that go on inside cells are responsible for giving rise to oscillatory and rhythmic patterns in time, and when coupled with intercellular communication between cells (via diffusion, active transport, fluid movement, or something else), also in space.

The identification has to be on a case-by-case basis, because only rarely can one hope to come up with general principles for spatio-temporal patterns. Two prominent exceptions are the works of Turing (1952), who drew attention to the importance of positive (activatory) and negative (inhibitory) effectors; and, building on that, the work of Gierer and Meinhardt (1972), who emphasized that activation had to occur at short-range and inhibition at long-range. In sum, one looks for functional explanations for biological order based on temporal oscillations. Living processes can be studied from two aspects: in terms of the mechanistic aspects of their functioning, and in terms of their evolutionary history (Nanjundiah and Morange 2015). Functional explanations address the ‘how’ question; they require, besides biochemical and biophysical details of the molecular structures of components, an understanding of their synthesis, inter-conversion and regulation, and the kinetics of those processes. That leaves open the evolutionary or ‘why’ question, which is really two questions: what was responsible for the origin of a particular temporal (or spatial) ordered pattern, and what is responsible for its continued maintenance?

As shown by the terms ‘ultradian signals’ and ‘cell-to-cell communication’, Brodsky’s book (Brodsky 2022) attempts to bring together two concepts. He more or less restricts the ultradian topic to rhythms with periods around one hour, and uses the Latin-derived word ‘circahoralian’ for about an hour (the window is given as roughly 20 to 120 minutes) to emphasize it. More rapid ultradian oscillations and rhythms (especially in the brain, and nervous and muscular tissues) are discussed to a lesser extent. In those instances where they have been tested, e.g., metabolic, glycolytic, and cell division cycles, ultradian oscillations are not temperature-compensated, are not sustained, and are not persistent – unless they are set up under strictly controlled experimental conditions, as in open-flow systems (Lloyd 2020). Ultradian rhythms both in the yeast *Saccharomyces cerevisiae* (Salgado et al. 2002) and in *Avena* stomata regulation (Brogårdh and Johnsson 1974; Johnsson 2015) are slowed down and perturbed by lithium ions. Furthermore, not all signals are oscillatory: for instance, signals that activate a switch between alternative biochemical pathways via a threshold value of an effector substance (e.g., in  $\text{Ca}^{2+}$  signalling for membrane-associated channel opening). During signal transmission, receptive and responsive functions are by their nature inherently transient, and are often characterized by rapid phenomena over time scales of milliseconds

(or even microseconds or less), and are characteristic of the highly sensitive, responsive, and motor elements between cells and tissues. On the other hand, circadian rhythms have periodicities bunched around 24 hours (not exactly 24, whence ‘circa’); activity cycles are typical examples. They are found in organisms from some bacteria, e.g., some cyanobacteria to humans (Bhadra *et al.* 2017), and are therefore likely to have been present in the last universal common ancestor. Similarly, lithium ions slow down circadian rhythms in plants (e.g., of *Kalanchoë*), small mammals, and humans (Engelmann 1973): they are concerned with the coordination, coherence, and timekeeping necessities for organisms in tune with their naturally fluctuating nutritional, behavioural, environmental, and geophysical requirements. Usually the period is independent of temperature over ranges favouring continued sustenance, survival, and vitality. Ultradian rhythms have been designated ‘the dynamic signatures of life’; they serve the intrinsic timekeeping functions for ‘homeodynamics’, i.e., that essential and characteristic intracellular requirement (Lloyd *et al.* 2001; Yates and Yates 2008). The most important message arising out of research on rhythms is clear: the familiar and once useful concept of ‘*homeostasis*’ (our italics) is an out-dated oversimplification and the phrase ‘homeostatic maximum stationary state’, or ‘plateau’, should be used instead in future editions of publications and textbooks.

The integrated and coherent molecular mechanisms that lie behind the functioning of living organisms remain among the central unsolved problems of biology. Although the elucidation of many of the relevant processes constitutes a major achievement of biochemical endeavour, the resultant total picture we have at that level of organization is still lacking in being able to tackle the emergence of the functioning of whole cells, *in situ* tissues, organs, and whole organisms, let alone many aspects of behaviour. Biological timekeeping and the deciphering of synchrony and coherence in the model protists, as described by Brodsky (2022), continue to provide detailed information on the core processes and events typical of ancestral characteristics basic to more highly evolved and elaborated animals and plants. The most recent attempts to achieve a synthesis bring several powerful new techniques to bear on the enigma mentioned earlier: what accounts for the seemingly stable persistence – over the short to medium term – of the living state?

#### 4. The Brodsky book

We have referred earlier to the ‘how’ and ‘why’ questions, which respectively imply mechanistic and evolutionary viewpoints. Brodsky (2022) addresses the ‘how’ question, and in the course of doing so provides a sample of the wide range of possible answers. As we have pointed out, ultradian oscillations tend not to be autonomous, sustained or temperature-compensated. However, in *Acanthamoeba castellanii* (Lloyd *et al.* 1982), as in at least six other species of protists and three of yeasts (Lloyd 1992; Kippert and Lloyd 1995; Murray *et al.* 2001), temperature compensation leading to quantized increments in cell division cycle durations has been demonstrated. These characteristics reveal that there is an underlying rhythmic timekeeping function, and that the phenomena are therefore not ‘merely’ oscillations.

The contents of the book are organized as follows. Ultradian/circahoralian rhythms are described in four chapters, focusing on the presentation of cellular rhythms, the nature of the rhythms (e.g., a discussion on their fractal structure) and search for the mechanisms (‘the pacemaker’). Direct cell-to-cell communication is discussed in the next seven chapters. The last 40 or so of the 246 pages that make up the book contain chapters under the heading ‘Medical and Biological Supplements’. Here the reader gets concentrated and stimulating discussions on topics broadly related, but not fundamental in a mechanistic sense, to the hard core of the main themes. Some of the chapter titles cover themes that are being intensively pursued in molecular detail, but are still not comprehensively understood. They include ‘The Origin of Multicellularity’, still a contentious and necessarily hypothetical evolutionary major step; ‘Aging’, with all the varied accompaniments of human decline, and the illnesses of old age; ‘Protein Metabolism’, more precisely turnover times, synthesis, and catabolic breakdown; ‘Cell–Cell Interactions’, intercellular communication by electrical or biochemical mechanisms; ‘Signal Factors as Medicines’, containing material of potentially therapeutic relevance; ‘Sleep and Wakefulness’, perhaps the most exciting and rapidly advancing, yet still incompletely understood, area of biochemistry and physiology; and other topically research-intensive and attractive titles (e.g., ‘Synchronization of Oscillations’, ‘Models for Studies’, ‘Signal Transduction Factors’, ‘Communication Systems in Sponges, Plants and Bacteria’).



The book presents and summarizes a vast amount of relevant experimental data. Many results originate from studies in the author's own department and have been collected over several years. Only a few topics can be mentioned here (see also the summary of the book). The data on ultradian (circahoralian) rhythms concern their distribution, nature, and importance in biochemistry and physiology. Rhythms of protein synthesis and cell mass, enzyme activity, ATP and cAMP concentration, pH, and cellular respiration are considered with examples from bacteria, protists, and mammalian cells, as well as integral rhythms of human respiration, pulse, and behaviour. The temperature dependence of the period of the oscillations is discussed and it is pointed out that the robustness of circadian rhythms to temperature ('temperature compensation') is also found in several ultradian rhythms. Using cell cultures, mechanisms of direct intercellular interactions have been extensively investigated. Signalling factors have been found, and the triggered processes leading to synchronization of cell and organ functions as a result from cell-to-cell contact in the population determined. A feature of the book is that the fractal nature of ultradian rhythms is studied in the context of cellular properties. Fractals, or entities that exhibit self-similarity at several scales, can be geometric, statistical, or dynamical in nature. When applied to time series, their relationships persist across multiple time scales important for physiology and biochemistry (Aon *et al.* 2008). The implication is that rhythms must have evolved in such a manner as to result in their harmonious integration at different time scales. The outcome is an emergent property of living systems.

The historical surveys in this magisterial book stimulate reflection about omissions. One is that some features from the history of plant studies could have been presented or extended. Taking up the latter first, the presence of circadian rhythms in plants was first documented in 1729 by the French astronomer Jean Jacques Ortous de Mairan by his observing the daily leaf movements of *Mimosa* that persisted in constant darkness. The typically thorough studies of Charles Darwin (1880) on the movements of plants during their growth should have been cited; and we would also remind the reader of Darwin's pioneering book *The power of movement in plants* (written with the assistance of his son Francis Darwin; Darwin 1880). The helical growth movements of many plant species often have an ultradian (circahoralian) period. The fundamental interaction between gravitropism and these movements has been studied extensively and it is quite clear that gravity affects these rhythms that also exist, though to a lesser degree, in plants under weightlessness (Johnsson *et al.* 2009). Ultradian trophic plant leaf movements in the minute range were studied early by J. C. Bose (1913) in *Mimosa* and *Desmodium* leaves, and recently by A. Pfeiffer *et al.* (2016). And likewise, cell-to-cell contacts in plants were reported very early: the so-called plasmodesmata (diameter about 50–60 nm), 'tubes' connecting plant cells, were discovered already in the 1880s. The term plasmodesmata was used first by Strasburger as early as 1901.

The list of references totals almost 800 and covers about 35 pages. The reader can find references that are usually not presented in English texts or papers, but point to the extensive Russian language literature. This section can be a source for interesting reading. Still, there are surprising omissions. Three significant contributions have been missed out. The first is the epochal 1952 publication by Turing, in which cell-to-cell communication via diffusible chemicals was shown to be capable of producing spatio-temporally ordered concentration distributions, including oscillatory patterns, in groups of cells forming a ring (Turing 1952). That paper is a cornerstone in the whole area of reaction–diffusion systems and their role in morphogenesis (for a recent survey, see Jahanbakhsh and Milinkovitch 2022 and Hunter 2023). Another missing element is the now-famous work of Belousov and Zhabotinski, which demonstrated convincingly that an apparently closed system of chemicals in solution can exhibit spatio-temporal rhythms, something that was seriously doubted at one time (Belousov 1959; Zhabotinsky 1964; Barzykina 2020; see Winfree 1980 for a topological treatment of biological rhythms, and Winfree 1984 for the fascinating history of the discovery of the Belousov–Zhabotinsky oscillator). Then there is the path-breaking paper by Cowan (1972) which outlined a purely hydraulic model for ultradian transpiration oscillations in plants. The model withstood many later attempts at falsification (see, e.g., Johnsson *et al.* 1979); its predictive value is high and it can be incorporated into a scheme that involves biochemical oscillators. It involves only physical components of the plant system, but all the same predicts very complicated, ultradian oscillatory water regulation (Prytz *et al.* 2003a, b). Results from plants growing in a space experiment on-board the International Space Station show that gravity amplifies, and microgravity decreases, circumnutations in *Arabidopsis thaliana* stems (Johnsson *et al.* 2009).

Of two volumes relevant to the work being discussed (Goldbeter 1989, 1997), the first, which deals with the interplay of experiment and theory in diverse systems, is not cited; the second, which offers valuable insights into building specific models, does get mentioned. Goodwin's book *Temporal organisation in cells* (1963), based on

his epochal oscillator model, is cited, but no mention is made of the huge secondary literature it spawned in diverse fields. For example, one would like to know the extent of the influence Waddington – he was Goodwin’s mentor at the time – had on the book. Some of the secondary work was by Goodwin himself (Goodwin 1963, 1976, 1993, and 1994); we also refer to Goodwin’s paper with others in 1963, 2000, with Briere (1991), and Jaeger (2002). Although well-cited in the reference list, the startling early experimental and mathematical modelling work of Don Gilbert receives scant attention (see Winfree 1980 and Kate Gilbert *et al.* 2020). However, these omissions are minor quibbles that detract little from this massive undertaking.

Smaller mistakes and spelling errors will be submitted to the author – they are unavoidable in such a rich volume as the present one. But one must be pointed out: on page 151, it says that the ultradian side-leaf movements of *Desmodium gyrans* are independent of temperature and Sharma *et al.* (2003) is cited. This statement is not correct, since the cited paper states explicitly that the ultradian oscillations of the side leaflets are temperature-dependent.

## 5. Rhythmicity and evolution

What is the answer to the ‘why’ question? Why are there rhythms at all? In the case of ultradian rhythms, one can come up with an explanation that posits a selective advantage of the rhythm *per se*, with the precise reason behind the advantage depending on the rhythm in question (e.g., Nanjundiah 1988). Alternatively, rhythmic behaviour could have originated as a compromise between the twin demands of adapting to a signal and remaining sensitive to changes in it; or as a spin-off from having to ensure stability in a system of biochemical reactions that involved positive and negative feedbacks (Higgins 1967). In both those situations, natural selection would not have favoured rhythmicity *per se*, but would have acted on the physiological variables that were responsible for its origin – feedbacks, adaptation, and so on. In the case of circadian rhythms, the most obvious explanation would seem to be that in a world governed by a 24-hour light–dark cycle on account of the sun, a 24-hour intrinsic rhythmicity is obviously adaptive. Since the light–dark cycle must have long preceded the origin of living organisms, the evolution of circadian activity rhythms may well be the most spectacular example of what C. H. Waddington called genetic assimilation, by which he meant the transition of an environmentally driven response to an intrinsic, genetically based activity (Waddington 1953). This raises the interesting question of the interplay between environmentally driven changes and those that result from natural selection for the origin of complexity. D. C. Wallace (2013) has usefully summarized the current post-Darwinian view of the origins of biological complexity by pointing out that natural selection may not account for several features that could have arisen instead as a consequence of energy flow for over four billion years and the accumulation of information (consciousness and the functioning of the human brain being examples). Indeed, Alfred Russel Wallace (1908, 1911) was of the view that ‘natural selection is not the all-powerful, all-sufficient and only cause of the development of organic forms’ (Lloyd 2015). There are other causes, such as the endless possibilities afforded by the dynamics of complex systems (Lloyd 2020).

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