The major proposition of a forthcoming series of contributions will be that the problems of our society can only be solved by science. Volume 1, reviewed herein, implies, by reference (in its very title) to internal rhythms, that chronobiology is the way to do it. Many chronobiologists will agree. As the book proposes, we need to clarify physiological processes as mechanisms of life, from molecular to social, according to temporal measures that (we add MAY) differ from physical time. These time scales of internal periodic processes are described as system time, more strictly than was done earlier by the philosopher Herbert Hörz [1], who has the merit of considering time horizons as well as system times. The book discusses system time in terms of a class of PEP, defined as a class of Periodic Equivalent Processes. According to the book, system time is the quantification (“metering”) of time, which is carried out with the aid of a PEP class.

“Since all living organisms possess for their survival their own temporal organization, it follows that the temporal tuning of internal processes in organisms can be called an intrinsic metering, which exists without metering from the outside or by humans. In this sense (perhaps of an internal quantification), the book’s system times are intrinsic.” (Our free translation.)

A glossary, which should be read first, defines as an example of intrinsic times, the “expression, for instance, of various (about 24-hour) circadian rhythms, documented in all life and in subsystems down to ‘subcellular processes’”.

The book recognizes in the foregoing the ubiquity and critical importance of circadians; it explicitly deals with chronobiology, defined as the “science of body functions” in relation to their characteristics, that undergo, for example, a circadian rhythm, citing a general lexicon [2]. In keeping with the original source [3], a “Citation Classic” of Current Contents, or a glossary in the field [4], rhythms are viewed as intrinsic metering, albeit the PEP approach in the book seems to restrict, perhaps inadvertently and certainly unnecessarily, system time to that of free-running circadian or other rhythms.

Free-running (5; cf. 6) is not found in the book’s glossary; but desynchronization disease is included, with the proper qualification that a desynchronized state need not be harmful. Figure 7-I-A in reference 6 on our website (http://www.msi.umn.edu/~halberg/) shows the desynchronization of a circadian rhythm in rectal temperature in eyeless mice, both time-macroscopically, by eyeballing, and time-microscopically, by time series analysis (7-I-B-D). Control mice with eyes are seen to exhibit a regular 24-h synchronized rhythm; peaks of the rectal temperature in these controls, subjected to a sham-operation, and kept like the eyeless mice in light and darkness alternating at 12-hour intervals, coincide precisely with the straight vertical line at 8:30 pm, with only a few slight exceptions (that also hover around the vertical line on days 3-5, 35 and 49 in Figure 7-I-A in reference 6). By contrast, peaks of rectal temperature in eyeless mice already by the second week and thereafter occurred clearly earlier and earlier, until they were in antiphase with the curve of blind mice by day 22 [6]. The same figure in [6] shows a chronobiologic serial section (IB), thereby assessing, with its uncertainty, an advancing phase in the eyeless mice, by comparison to a much more stable phase in sham-operated controls, both documented in a replication 10 years later, again with their overlapping uncertainties.
The system time for each group is now in the phase domain (IB), only to be transferred next into the period domain, as a result of periodogram analyses of data from control and eyeless mice (Figure 7-I-C in reference 6, 7). The periods of controls hover within 0.05 hours around 24 hours, whereas the periods of eyeless animals are all different from those of controls, averaging 23.4 hours, differing further from each other much more than do controls, a feature to be kept in mind in doing group studies. Figure 7-I-D in reference 6 shows the timing of circadians in serum corticosterone and liver glycogen, referred to the circadian peak in temperature, on the left for mice, again in the phase domain. The length of the period, whether synchronized (top) or desynchronized (bottom), is equated to 360°. One can thus pool data from different individuals, whatever the particular frequency of their rhythm may be, and map internal murine timing, as shown in Figure 7-I-D of reference 6, comparing time relations in the externally synchronized and externally (but not internally) desynchronized groups examined in the phase domain. Therein the period, whatever it may be, is equated to 360°. Figure 7-I-D in ref. 6 compares the circadian system times in both a synchronized (top) and a desynchronized (bottom) state in a woman (right) with that in mice (left).

In the case of studies on circadians in the laboratory, one has a choice, among others, between synchronization by lighting and/or other entraining agents or synchronizers generally (or Uhrzeitgebers in the case of circadians or Kalenderzeitgebers in the case of circannual rhythms). It seems important to remember that by definition, external synchronizers [3] do not “give” body time, but only synchronize internal time with an external (usually cyclic) agent. Chronobiologists, more often than not, determine internal phase relations at an externally impressed frequency, as an alternative to choosing a free-running condition, as in continuous darkness or continuous light or after loss of a primary transducer of the circadian system, such as the eyes, with all other conditions kept the same as much as possible. The synchronized state can be achieved by manipulating lighting alone or by double synchronization with light and feeding time [8]. Thereby, the extent of change (double amplitude) of circadian rhythms can be greatly amplified but their internal phase relations are largely maintained when food is available, e.g., to rodents, only early in the daily dark span [8].

When two synchronizers compete, e.g., food is available only in the daily light span, some rhythms may be advanced, such as that in corneal mitosis, whereas others are delayed, such as those in corticosterone and temperature and internal phase (read: system) relations are drastically different, as is survival time (references in 8). On a restricted diet, the availability of food can override the effect of a lighting cycle for certain variables [3]. The internal endocrine time structure of humans who eat a single daily meal as breakfast (“breakfast-only”), as compared to those on “dinner-only”, is drastically different. A shift in meal timing, while the daily routine is unchanged with respect to other conditions, moves the adrenal cycle, gauged by circulating cortisol, but little, while the temporal location along the 24-hour scale of circadians in glucagon and insulin in blood are changed very much.

In our hands, the mapping of human free-running in isolation from society covered up to 267 days, while that of routine synchronized mapping now extends up to 35 years. Moreover, under presumed free-running conditions, a commonality of external and internal periods, a PEP extended beyond the organism (willy-nilly, each organism is an OPEN system) among physiological and environmental variables points to the need to examine putative causal internal-external interactions [9-12].

The philosophical discussion recapitulates a few – perhaps too few – of the concerns in the development that led to chronobiology from the early 1950s [13-15] to 1969 [3-6]. The genetic basis [13], ubiquity and mechanisms [14] and critical importance [15] of rhythms, described earlier by Fessard [16] as the basis of life (cf. 17), are neither documented nor mentioned. Different periods and putatively underlying mechanisms were then (in the 1950s) sought for different variables in different physiological entities, as illustrated in the book reviewed herein for the heart and circadian systems. The adrenal cortex was found to be a first systemic mechanism for some [14], but not all circadians [3, 6], that naturally led to the pituitary, hypothalamus and pineal, on the one hand and to basic cell cycles in RNA and DNA formation, on the other hand [18]. As longitudinal data accumulated over the past half-century, it became clear not only that periods ranging from circadian to circannual can be found in the same variable, as in 17-ketosteroids [3], but also, as is the case in the heartbeat, that a much broader spectrum of intermodulating cycles can range from 1 second over 1 day to a 10-year periodicity in the same person [19].

For these reviewers, system time is the abscissa of time that covers calendar and/or any physiological or other event-related time from the first sample and/or the first pertinent event (such as the onset of menstruation) to be investigated to the last sample and/or the last pertinent event in a sequence. Any scientific endeavor involving sampling for measurements can be planned in the light of a time horizon [1], that summarizes, as a chronome (from chronos = time and nomos = rule), all pertinent prior information, with the uncertainties involved (3; cf. 1). System time includes “rubbery time”, i.e., transformations of calendar time to a given marker time, such as the spans elapsing between two consecutive onsets of menstruation, that each are equated, e.g., to 360°.
Physiologist Thomas Kenner of Graz, Austria, an active discussant in the book, has rightly described rhythms elsewhere as a feature of everyday physiology [20]. In this context, among others, two papers in the book’s bibliography are of particular interest, both first authored by Max Moser and last authored again by Thomas Kenner [21, 22]. These deal with heart rate variability as a prognostic tool in cardiology, “as a contribution to the problem from a theoretical viewpoint”. In practice as well, focus on heart rate variability; the topic of these papers, resolves risk conditions occurring within the otherwise neglected normal range of physiological variability. Both an over-threshold variability (above the upper 95% prediction limit) of blood pressure, as compared to a reference standard from healthy peers of the same gender and age, and an under-threshold (below the lower 5% prediction limit) heart rate variability, within the system time (of sampling) of a week of monitoring has taught us useful lessons, yet to be tested for use in the prevention of incapacitating disease [23, 24].

The book considers chaos referring to teams working on nonlinear dynamics in Potsdam and Garching, Germany, and reports on a complexity analysis in searching for early signs of sudden cardiac death [25]. A discussion of periodic equivalence requires inferential statistics and the “remove-and-replace” method, time-honored in endocrinology and applied to rhythms [14, 26, 27]. With such qualifications we need marker rhythm statistics to treat the cancer patient by the best compromise between cancer system time (the best one to kill the cancer), and host system time, to avoid the treatment’s toxicity [28] and possibly to prevent the malignancy in the first place. We need system times along the scales of the week and year as well as the day for immunotherapy. Vastly different cycles intermodulate with each other to account for the difference of whether the same total weekly dose of the drug len-tinan stimulates or inhibits a malignancy (Fig. 8-V in ref. 6).

Among contributors to mostly discussions of presentations, four were from philosophy, four from physics (including a physicist-philosopher); they are joined by seven representatives of medicine (one of them also a philosopher), one psychologist and one biologist, at diverse stages of their careers. The book’s transdisciplinary nature, helping to tear down disciplinary barriers [29], is its final merit. This book is warmly recommended to readers fluent in German: it approaches an eminently transdisciplinary problem in an interdisciplinary discussion; it recognizes beyond narrow specialty barriers the ubiquity and indispensability of critical chronobiological system times and horizons. Because of their documented importance, system times and time horizons need consideration by everybody in and beyond science.

This review, focusing on a critical transdisciplinary field long neglected both in physics [30] and in biomedicine, is dedicated with love on her birthday, June 28, to Francine HALBERG. This radiation oncologist participated in the planning of cancer chronotherapy as a high school student [28], with her mother Erna, who made many altruistic contributions to oncochronotherapy that, in the opinion of the founder of the specialty of clinical oncology in the USA [31], benefitted her as well. The broader challenge of treating at times of pertinence vs. those of convenience remains in oncology and much more broadly, in keeping with the scope of the book reviewed herein and the broader series to follow.

REFERENCES


---

BOOK REVIEW. Self-organized system time: An interdisciplinary discussion of the modelling of living systems based on internal rhythms.