

## Human Chronobiology

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## Abstract

Brief introduction to Chronobiology, followed by considerations on the landmarks of this new field of biological science, focussed on its implications on human physiology and behaviour, as well as its applications to medicine and social organization. Periodicals, Internet sites and relevant literature dedicated to Chronobiology are included to help newcomers.

**Key-words:** biological clocks, biological rhythms, chronobiology.

## Clocks & Rhythms

**Humanity has been oscillating since its origins**, following both environmental cycles and obeying bodily urges such as hunger or sleep. Biological rhythms, or regular fluctuations of body functions, have long been recognized, in empirical terms, in all living organisms, but it was not until the beginning of the 18<sup>th</sup> century that the question of the determination of rhythmicity was raised in what may be understood as the birth of modern chronobiology. Jean Jacques d'Ortous de Mairan, a French astronomer, showed that a plant kept in isolation from the natural environment, in constant lighting conditions, maintained its periodic leaf movements approximately coinciding with the day/night cycle (Moore-Ede et al., 1982).

Almost three centuries later, we repeat the basic procedure, temporal isolation, in order to witness the ticks of what came to be recognized as the biological clocks (Garfield, 1988a&1988b). The expression "biological clock" is an apt choice for producing surprise and thus became popular; nevertheless, it implies discrete structures with "cogs and wheels" which may not necessarily be the case. A much better expression is "timing system", opening room for functional circuits linking different parts of the organisms (Moore, 1999).

Biological rhythms, in a strict sense, are generated endogenously and adjusted to environmental cycles by organic timing systems (Aschoff, 1976). In a broader sense, biological rhythms may be defined as all regular oscillations expressed by an organism, or population of organisms, independently of the endogenous or exogenous origin of the oscillation.

Examples of biological rhythms in this broader sense:

- 1) respiratory and cardiac cycles do not show entrainment to environmental cycles although they may be modulated by external stimuli;
- 2) the 7-day rhythm represented by the human week might be determined endogenously (Halberg, 1983&1985; Aveni, 1995), but not necessarily so (Zerubavel, 1985).

Unless otherwise stated, we will use the expression "biological rhythms" in this second, broader sense. Moreover, biological rhythms may refer to periodicities observed in a species but not in the individual – gestation, puberty, menopause and the life cycle itself, are examples of such rhythms.

## A Wide Spectrum

**There is a wide spectrum of biological rhythms**, from fast oscillations in pacemaker neurons (Minors & Waterhouse, 1981) to seasonal changes in hormone secretion (Aschoff, 1981). The parameter frequency has been adopted for the classification of biological rhythms as circadian (one cycle per 24h); ultradian (faster rhythms) and infradian (slower rhythms). (Halberg, 1959). Rhythms which are synchronized to external cycles are referred to as "circarhythms" (Aschoff, 1979), such as circadian, circalunar, circatidal, circannual - the prefix *circa* allowing for a range along which the frequency may vary, e.g. from one cycle each 20 to 28h for the circadian.

A biological rhythm may be approximately depicted by a cosine curve in which we identify the *amplitude* of the oscillation, its *phases* and *period*, although other formats may express a rhythm with better accuracy, such as a triangular form depicting the pulsatile episodes of hormone plasma concentration.

In all cases it is clear that the linear representation of the dynamics of a biological variable as a mean omits its obvious time-dependent nature, thus inviting us to reconsider some dogmas of normality, such as usual timeless interpretation of normal temperature as a straight line around 36.5°C. The  $\pm 0.5^\circ\text{C}$  that usually follows that figure, although admitting variability, does not imply the now obvious "time-of-day" effect. 35.5°C at 05:00h is normal as is 37.5°C around 18:00h in a diurnally-active, healthy individual, and this variation is not entirely due to direct posture, exercise, or metabolic effects on thermoregulation, since the fluctuation also happens in individuals under constant conditions such as temperature and illumination, fed intravenously in a continuous manner (Minors & Waterhouse, 1981).

## Homeostasis Revisited

**The invitation to revisit classical data** may be one the most relevant contributions of Chronobiology to contemporary biological thinking.

Homeostasis may vary, said Martin Moore-Ede (1986) to the select audience at the 1986 meeting of the American Physiological Society, suggesting the adjective "predictive" rather than "reactive" to qualify homeostasis. Alternatively, *rheostasis*, or "the physiology of change", in the words of Nicholas Mrosovsky (1990), may be a more powerful key, able to encompass a wider range of phenomena, which, until recently, were shown as limited to closed systems.

Another expression, *homeodynamics*, is discussed by Goodwin (1997), who advocates a model composed of chaotic generators and several interacting oscillators, a system able to cope with a changing environment.

## Internal Temporal Order

Cortisol secretion peaks about an hour before we wake-up, which coincides with the rise of core temperature; by the end of the day core temperature starts declining after reaching its peak; in a couple of hours sleep comes followed by increased secretion of growth hormone, and so on (Copinschi et al., 1999). We are facing what has been named by Moore-Ede and Sulzman (1981) "Internal Temporal Order". Physiological functions succeed each other more or less regularly, some of them causally linked, such as in the hipothalamo-pituitary-adrenal axis of hormone control, some of them only temporally coupled such as the Growth Hormone-Slow Wave Sleep (Van Cauter et al., 1998).

Maintenance of the Internal Temporal Order equals good health condition, as the adverse effects on health of "jet lag" or shiftwork unambiguously demonstrate (Folkard et al., 1986). Since the demonstrations of Dorothy Krieger (1979) among others, we have sufficient reasons to assume that the presence of a neurotransmitter at a synapse is not the only condition for its efficacy – the readiness of the membrane plays the other essential role; the parallel controls of neurotransmitter liberation and post-synaptic membrane configuration need a temporal link in order to function properly - and this is granted by the coordinate functioning of the timing systems.

Phase maps of a multitude of physiological variables have been proposed by several authors (Moore-Ede et al., 1982).

Internal Temporal Order refers to more or less stable phase relationships between variables in an individual organism. External relationships between individual and environment, social interactions included, may constitute what may be called an External Temporal Order. The usefulness of such a concept has yet to be put to the test.

## Synchronization

**Entrainment or synchronization** of human biological rhythms to environmental cycles has been studied mostly in the circadian range; circadian rhythms are readily observable as well as their synchronizing environmental cues.

Jurgen Aschoff (1954) coined the word *zeitgeber* (german word for "time giver") which is now widely employed together with entraining or synchronizing agent. It is worth noting that the loose usage of such terms has led to a confusion which may be characterized by the expressions "light as a zeitgeber", "mother as a zeitgeber", etc.

The confusion resides in the now well-known fact that light per se (as any other environmental cue) shows distinct and even opposite effects on the circadian timing system of organisms, including humans.

In the middle of the day light has no effect; in the beginning of the night light produces a phase advance (the circadian system runs faster) whereas by the

end of the night the same light slows down the system. This phenomenon is usually depicted in a graphic form known as a phase response curve (PRC). There are atlases of PRC's for several species readily available in the Internet, see Internet Chronobiology sites list at the end of this review.

## **Social Cycles**

**Social cycles**, comprising working and leisure hours, have been suggested to be the most powerful if not the only zeitgeber for humans (Aschoff & Wever, 1976). Relatively recent studies have demonstrated important effects of light/dark cycles upon human circadian rhythmicity, including phase advances and delays of the core temperature rhythm (Shanahan et al., 1997). In the last section of this review we will come back to these effects of the LD cycle, as they have been employed in clinical studies on depression and re-entrainment of shiftworkers and airplane crews.

The fact that social cycles do entrain circadian rhythms raises the issue of the range of stimuli (nature of the time cues) able to synchronize humans. A common wristwatch may be a suitable example of the complex nature of the social time cue. Although two persons may see the same hour on a watch, the conditioned effects on each individual may lead to opposite changes in their behaviour and underlying physiological adjustments.

Regularly spaced sounds of a gong signalling moments for urine collection were able to synchronize circadian rhythms of an isolated individual under otherwise constant conditions (Aschoff & Wever, 1976). One can predict sunrise and sunset as producing distinct synchronizing consequences in a farmer when compared to his urban cousin, and so on.

Not only human rhythms are entrained by social cycles, as has been elegantly demonstrated by Mrosovsky et al. (1989) and his pulse of female synchronizing male hamsters. Furthermore, a zeitgeber effective in an adult may not produce any synchronizing effect on an infant or on an elderly person.

## **From Womb to Tomb**

**Human biological rhythmicity changes with age** (Davis, 1981). Intrauterine rhythms in the human fetus (rest/activity) have been described and are assumed to be synchronized, if not "exogenously" determined by the mother (Weaver & Reppert, 1989).

Birth can be considered a physiological revolution in several aspects, temporal regulation being one of the most prominent – time cues change in nature and mode of acting on the body.

During his first days a newborn baby shows practically only ultradian rhythms, the most conspicuous being the 3-4h sleep/wake cycle (Meier-Koll, 1979). The following weeks witness the increasing presence of circadian rhythmicity, with

the remarkable characteristic of large individual differences in the age from the second week to the eighth (Menna-Barreto et al., 1993).

The picture we are able to draw is of a gradual coalescence of ultradian into a circadian pattern as in the sleep/wake changing pattern. Family routines compose the temporal setting during infancy and represent the first markedly external impositions upon the timing system of the developing individual with which he will learn to negotiate (Tomioka & Tomioka, 1991).

School life is another "time-mark", when what may be called "the temporal range" is enlarged and enriched by new social interactions. New temporal challenges may come up such as changes in school schedules and increasing constraints on time available for sleep; those challenges proceed into adolescence with the well recognized restriction-extension pattern of the sleep/wake cycle – shorter sleep episodes during the week alternate with longer sleep episodes during the weekends (Andrade et al., 1993; Bearpark & Michie, 1987). This pattern can be associated with the complaints of excessive daytime sleepiness accompanying puberty, although hormonal changes seem to play an important role as well, promoting a phase delay in circadian rhythms at that age. The effects of this phase delay – delayed sleep onset and delayed wake-up time – associated with the new social demands, compose a well known setting for temporal struggles between teenagers and parents (Carskadon et al., 1980).

Adults, especially in industrialized urban areas, play with their biological timing systems, scheduling work at irregular hours, extending wakefulness, eating at odd times, and so on.

Awareness of the consequences of such tampering with our timing systems has been increasing since the demonstration of incidence of mistakes in radar-signal detection by navy crews submitted to non-24h work/rest cycles (Colquhoun et al., 1996).

Biological rhythmicity in the elderly is known to show decreases both in amplitude and strength of the circadian component (Monk et al., 1992). Those decreases may be a natural step in ontogeny, due to cell death in the timing systems of the Central Nervous System, weakening of zeitgeber action, decreased coupling between parts of the timing system and/or effector mechanisms. Alternatively, the decreases might represent secondary effects of diseases or attenuation of other functional capacities.

Very active and healthy elderly do not necessarily show the decrease in amplitude and strength mentioned above (Touitou et al., 1997; Ceolim & Menna-Barreto, 1999). The challenge here is to link the aging process to the already known components of the timing system, such as the suprachiasmatic nuclei of the anterior hypothalamus and the genes controlling aspects of circadian rhythmicity which are being identified contemporaneously (Cashmore et al., 1999; Gekakis et al., 1998). Genetic manipulation of life-cycle duration seems to be the next step ahead, since molecular biology is paving the way into the fruit fly and the mouse timing systems

(Wilsbacher & Takahashi, 1998). It must be stressed however that changes in life expectancy call for associated better quality of life, which includes wiser time management. In this respect, human chronobiology may offer relevant contributions in the near future.

## **Individual Differences**

Larks, or morning people, and owls, evening types, are part of our everyday experience with a striking characteristic concerning the variability of phase allocation of circadian rhythmicity in humans. Evidence points to genetic determination of the "chronotype" and the variability of types itself suggests either a loose control by selective forces or an adaptive advantage for the species, able to occupy a larger portion of the 24h cycle. Chronotypes may be identified by specially-devised questionnaires (Horne & Östberg, 1976).

Short and long sleepers were defined in the seventies by Webb (1979), being an easily recognizable individual difference in sleep-duration preference. Sleep-duration preferences may be assessed by measuring the sleep phase along two to three consecutive weeks in a situation as free of temporal constraints as can be devised.

Attempts to associate chronotype or sleep duration type to differences in performance do not show any consistent result, although there is a strong social prejudice against evening types and long sleepers, as contrasted to morning active and short sleeping types. Chronobiology might be of help in clarifying and perhaps changing this widespread prejudice.

## **Research - History**

**Research on human rhythms** started in the 17<sup>th</sup> century, when Sartorius built a floating room, suspended over strings where he slept and spent most of his waking time. Body weight circadian and monthly rhythms were thus detected. In the 18<sup>th</sup> century, Virey wrote a doctoral thesis on the fluctuations of temperature as a marker of health and disease, thus anticipating research performed in the second half of the 20<sup>th</sup> century (Reinberg & Smolensky, 1983).

Jurgen Aschoff in Germany, Franz Halberg in the United States, and Alain Reinberg in France are the immediate fathers of contemporary chronobiology, all of them with important contributions on human rhythms. Aschoff is famous for his isolation-unit experiments in Andechs, Germany, summarized by Wever (1979); Franz Halberg in Minnesota produced an enormous amount of data and coined most of the chronobiological jargon in use today; to Alain Reinberg we owe the beginnings of chronopharmacology, especially the asthma studies. Contemporary chronobiology is marked by molecular biology and new possibilities of intervention in human rhythmicity represented by light therapies and melatonin studies (Wilsbacher & Takahashi, 1998; Arendt, 1998; Morin, 1999; Cashmore et al., 1999).

## Eliminating External Timing

**Isolation experiments** in humans were indeed crucial for the recognition of the relevance of biological rhythmicity. The demonstration of persistence of biological rhythms in the absence of external cycles, associated with the identification of structures in the CNS of mammals participating in the generation of circadian rhythms, made possible the scenario for the recognition of chronobiology as a scientific field (Aschoff, 1960).

In isolation studies humans show free-running rhythms in sleep/wake states, core temperature, urine volume and composition, and hormone secretion, among others. Those studies have been conducted in caves or in specially-built facilities called Isolation Units (Minors & Waterhouse, 1981). Although extremely important for the demonstration of the endogenous determination of biological rhythms, it is important to draw attention to two points: 1) Temporal isolation is an artificial environment, especially for humans; 2) Biological rhythms tend to show disruption after long periods of isolation, which may be the consequence of the artificial environment.

Free-running rhythms never match 24 hours: in humans they are slower than synchronized rhythms, somewhere in the vicinity of 24.3h; in other species they may be faster or slower. Human free-running rhythms were at first thought to be slower, with a period of around 25h (Wever, 1979); but recent evidence showed that the presumed values should be corrected in order to account for a phenomenon called internal masking (Minors & Waterhouse, 1989). Constant routine protocols were devised with subjects kept awake for 36 consecutive hours (Minors & Waterhouse, 1989), in an attempt to control masking.

In order to prevent errors eventually induced by isolation, demasking or purification protocols are now being employed to edit data collected in the field. An example of this procedure: in an investigation on the effects of abrupt phase changes (someone starting to work night shifts) where core-temperature data are collected with electronic probes and recorded every minute, values are corrected by a positive factor when the individual is asleep or resting and by a negative factor when the individual is active (Minors & Waterhouse, 1989) in an attempt to control masking.

## Windows in Time

**Timing of data collection** has always been a central issue in questions regarding chronobiology (Halberg, 1959). Not only the definition of the moment of data collection, but also the interval and number of "visits" to the biological system under study, must be taken into consideration. It is generally accepted a minimum of four data points per cycle investigated for at least three full cycles (Minors & Waterhouse, 1988).

Longitudinal designs are recommended as a means to circumvent interindividual variability, although care must be taken in order to minimize



interferences of the data collection procedure over the rhythm under study. A clear example of this negotiation is the design of sleep/wake cycle studies: one can either rely on polysonographic data and have the subjects sleep in the lab for two or three days or trust the subject's adherence to a protocol requiring maintenance of sleep logs for two to three consecutive weeks. Depending on the question one is asking, the discomfort of the polysonography wiring or the errors involved in self-measurements may be tolerated.

## Individual Times?

**The problem of individual differences** may be approached by synchronizing subjects to the same time cues; this may reduce variability but may be technically difficult; moreover it does not account for individual characteristics such as morningness/eveningness. Consider a morning type whose core temperature peaks at 15:00h and an evening type with a peak at 20:00h; mean temperature peak at the midpoint 17:30h may be misleading information, although both of them may be perfectly synchronized to the same 24h routine. The solution here resides in choosing a distinctive phase of marker rhythm, generally the phase when core temperature reaches its highest (*acrophase*) or its lowest (*bathyphase*) values as time reference, and adjusting the phases of different subjects (Minors & Waterhouse, 1981). Cortisol and melatonin peak plasma concentrations have been used as marker rhythms recently (Copinschi et al., 1999).

Quite another problem is the variability in values, not in time. Suppose two healthy individuals whose heart rate oscillates between 60 and 100 bpm, in one case, and 40 to 80 bpm in the other. Although oscillating in distinct ranges, the temporal patterns may be markedly similar. Since the relevant question in chronobiological studies is the temporal pattern of the variables, their absolute values may vary between subjects as long as the amplitude of the oscillations remains within similar ranges.

Classical reports on human biological rhythms relied mostly on direct visual inspection of time series plotted along a time axis, generally with the size of the rhythm under investigation. Thus, a circadian rhythm appears as a vertical sequence of consecutive days, plotted as continuous or discrete events on a 24h time axis. Very often the abscissae are extended to 48h in what is called "double plot" to allow inspection of transient phenomena or non-24h rhythms such as those in free-running conditions.

Most of the statistical analyses consisted of comparisons of mean diurnal against nocturnal values – a rhythm was said to exist when the difference between the means became significant (Hellbrugge, 1960). A step ahead was taken when analyses of variance comparing several data points were performed – the independent variable being the time points of data collection. Post-hoc analyses are necessary for comparisons between particular data points.

Spectral analyses based on Fourier Transforms are a powerful resource for the detection of regular oscillations in a time series, with the clear advantage of identifying composition of frequencies (DePrins & Malbecq, 1983).

The Cosinor technique, especially devised for the detection of biological rhythms, in its early and classical version, allowed the analysis of a single frequency (Nelson et al., 1979). In biological systems the simultaneous presence of periodicities of different frequency are more of a rule than an exception – besides the more obvious circadian component, biological rhythms generally show modulations by both infradian and ultradian components (Tsai et al., 1989). Other tools have been proposed (Sokolov & Bushell, 1978; Minors & Waterhouse, 1981). There are new softwares especially designed for the processing and analyses of biological rhythms, such as “El Temps”, produced by Antoni Diez-Noguera of the University of Barcelona and available at: <http://www.ub.es/dpfisiv/soft/ElTemps>.

Ultradian rhythms have been studied with the help of the new tools of non-linear dynamic systems, which seem to be appropriate for the multidetermined biological functions (Glass & Mackey, 1988). The idea of a stable system, showing recurrent states along a regular cycle, is certainly familiar to chronobiologists. Furthermore, this approach is ready to accept disturbances elicited by external signals given at certain points in time, disrupting the former cycle and eventually rebuilding it at another point, which is again what chronobiologists see in real life.

Chronobiology's contribution to research resides not only on the unveiling of oscillations in all biological systems, but also in calling the attention of investigators to the time and frequency domains of the phenomena under scrutiny. Fundamental concepts such as homeostasis are being reanalysed – homeodynamics (Goodwin, 1997) or rhoestasis (Mrozovsky, 1990) might become more suitable as a general principle of living systems, in the sense that they emphasize its oscillatory character. Collecting data in these days may thus be described as opening windows in time, according to protocols designed to take oscillations into account. Moreover, technology now offers several possibilities for automatic monitoring, recording, and transference of data (Miles & Broughton, 1990).

## **Chrono-Health**

**A healthy human being oscillates** regularly throughout life. This sentence may summarize the relevant contribution of chronobiology to contemporary medicine (Moore-Ede et al., 1982).

Neurology, psychiatry, and endocrinology (Kleitman, 1949; Richter, 1965; Boyar et al., 1972<sup>a,b</sup>) were the branches of medical practice most immediately receptive to the emerging concepts. Pediatrics (Aserinsky & Kleitman, 1955; Parmelee, 1961), cardiology (Halberg, 1986) and oncology (Hrushesky, 1985) came next, followed by gerontology (Richardson, 1990) and immunology (Plytycz & Seljelid, 1997).

In spite of the growing evidence, formal teaching of chronobiology at medical schools is in its infancy (Cambrosio & Keating, 1983), sometimes as a singular course, sometimes spread over other courses such as Physiology, Neurosciences, and Sleep&Consciousness.

## **Breaking clocks**

**Jet-lag and shiftwork** are expressions readily linked to applications of chronobiology in these days of fast time-zone changes and flexible working hours. The adverse effects of submitting our timing system to abrupt phase shifts of *zeitgeber* are today universally recognized (Manfredini et al, 1998; Boggild & Knutsson, 1999). The relevant questions have become: 1) how to minimize these effects (Eastman & Martin, 1999), and 2) the origin of important interindividual differences in tolerance to such shifts (Folkard & Monk, 1981; Menna-Barreto et al., 1993). Hospital routines are one of the important issues, not only from the clinical point of view but also from a legal perspective (Gaspar et al., 1998; Grossman, 1997).

## **Currently Published Periodicals on Chronobiology**

Biological Rhythm Research. 4 issues/year. Official organ of the European Society for Chronobiology. Editor: W. J. Rietveld (Department of Physiology, University of Leiden, P.O. Box 9604, 2300 RC Leiden, Holanda). Published by Swets & Zeitlinger Publishers, P.O. Box 825, 2160 SZ Lisse, Netherlands.

Chronobiology International. 6 issues/year. A Journal of Basic and Applied Biological Rhythm Research, bimestral. Official organ of the International Society for Chronobiology. Editors: Michael H. Smolensky (University of Texas, Houston, Health Science Center, P.O. Box 20186, Houston, TX, EUA. Fax: (713) 745-1956) e Ludger Rensing (Cell Biology FB2, University of Bremen, P.O. Box 330440, D-28334 Bremen, Alemanha. Fax: (49-421) 218-4042). Published by Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106-3780, EUA.

Journal of Biological Rhythms. 4 issues/year. Official organ fo the Society for Research on Biological Rhythms. Editor: Fred W. Turek (Department of Neurobiology and Physiology, Northwestern University, 2153 North Campus Drive, Evanston, IL 60208-3520, EUA. Fax: (708) 467-4065). Published by SAGE Science Press, 2455 Teller Road, Thousand Oaks, CA 91320, EUA.

Rythmes, Bulletin du Groupe d'Étude des Rythmes Biologiques. 4 issues/year. Bulletin of the Société Francophone de Chronobiologie. Editor: Bernard Canguilhem (Institut de Physiologie, Faculté de Médecine, 4 rue Kirschleger F67085 Strasbourg, CEDEX, França). Published by the Société Francophone de Chronobiologie, at the Université de Strasbourg.

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<http://www.crono.icb.usp.br/>  
<http://johnsonlab.biology.vanderbilt.edu/prcatlas/prcatlas.html>

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