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Chronomedicine

Definitions and Aims

Chronobiology (from *chronos*, time; *bios*, life; and *logos*, science) investigates the mechanisms underlying variability in the otherwise unassessed physiological range, including rhythms found in us, resonating with cycles around us. Broad time structures (chronomes) consisting of deterministic chaos and trends organized by rhythms are found in organisms and in their environments. They are mapped by chronomics as the reference values for both an applied chronomedicine and a basic chronobiology. Chronomics quantify health, identifying new disease risks, diagnosing predisease and overt illness, enabling timely and timed treatment (R_x), and validating the short- and long-term efficacy of a given R_x on an inferential statistical individualized (as well as population) basis. Chronomics-based mapping includes the cartography of rhythms in us and around us and of their associations, with **hypothesis testing** and parameter **estimation** yielding ***P*-values** and 95% **confidence intervals** for the everyday preventive as well as curative self- or professional care of a given patient, rather than only for research on groups.

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Introduction

About-daily **circadian** and about-yearly (circannual) rhythms, popularly biological clocks and calendars and broadly biological time measurement, are some of the many more features of intermodulating rhythms with widely differing frequencies including those of the action potentials in the human brain and heart at the high-frequency end. Near the other end of the rhythm spectrum are about 11-year and multidecadal cycles, not only outside us, but also within us, influencing other components such as circadians. Rhythms, **chaos**, and (e.g. age-related) trends are chronome components interacting as feed-sidewards, time-specified intermodulations requiring inferential statistical quantification, replacing time-unqualified feedbacks and feedforwards.

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Historical Development

Confusing variability in blood eosinophil cells was resolved by averaging and stacking data over the 24-hour day. Time plots (chronograms) revealed to the naked eye large amplitude rhythms dependent upon the adrenal cortex as a cyclic mechanism preparatory for daily activity. The temporal placement of this and other rhythms could be manipulated by shifts, among others, of lighting or feeding regimens and was altered by magnetic storms. Experiments in continuous light or darkness at constant temperature and humidity or studies of humans in isolation from society documented endogenous features of "circa" rhythms that persisted with a period slightly but statistically, significantly different from their exact societal daily, weekly, yearly, or decadal counterpart. These studies led to the coinage of "circadian" and other "circa" rhythms. A circadian system was extended to hormones influencing these cells and other endocrines, to the nervous and other systems, and eventually to nucleic acid formation, as well as to the effects of drugs, magnetic storms, and other physical agents such as noise or radiation. A genetic basis of biological circadian rhythms is now documented, *inter alia*, by studies on human twins reared apart (*see* **Twin Analysis**) and by chemical mutagenesis (*see* **Mutagenicity Study**) and gene transfer in fruit flies. The prefix "circa" (about) conveys the desynchronized feature and the fact that rhythm characteristics can only be defined with some statistical uncertainty.

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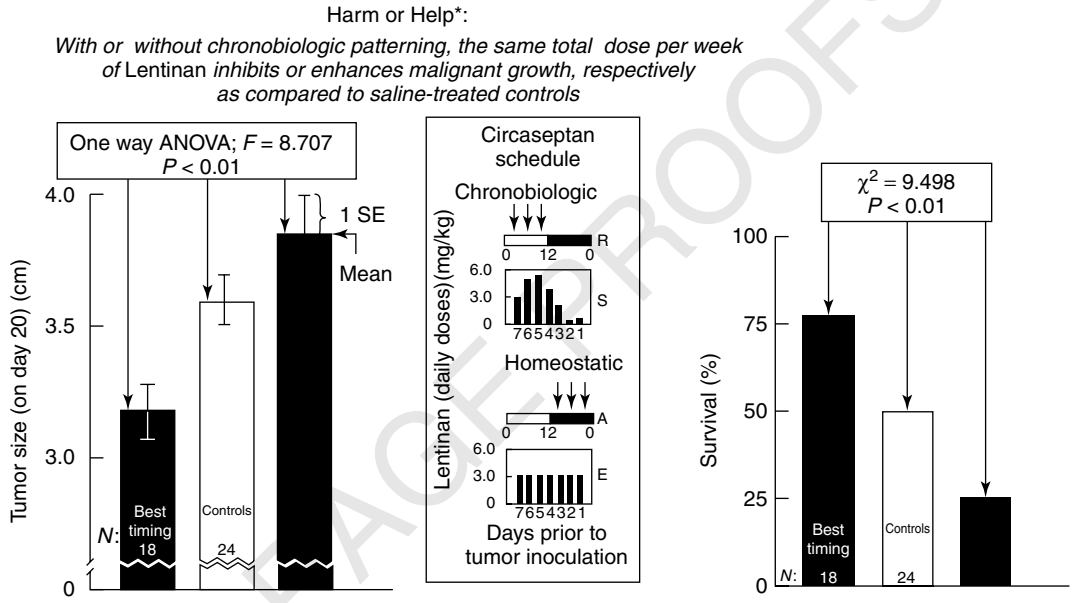
In isolation from society, nearly identical frequencies were found for cardiovascular and geomagnetic rhythms, the latter gauged by the planetary disturbance index, K_p. What is more conclusive, "subtraction" to the point of disappearance and reamplification of environmental cycles' amplitudes was associated with dampened and amplified biological rhythms with corresponding frequency, respectively. Without causal implications, such findings provide strong hints of associations, rendering it essential to examine and compare the frequencies and phases of biological and environmental rhythms. A desynchronization as a free-run of biological rhythms must be documented not only from societal and other artificial, for example, lighting schedules but also from magnetic or other terrestrial, atmospheric, solar and galactic, for example, cosmic ray and/or other near-matching environmental cycles. The latter may pull and amplify a biological rhythm without necessarily synchronizing it.

Different Types of Study

B2A12039 For **longitudinal** "womb-to-tomb" monitoring in the laboratory, sensors are available for the telemetry of B2A03042 many vital functions. Transverse or **cross-sectional** studies are often linked systematically into a hybrid (linked cross-sectional) design with repeated measures for spans of days, weeks, years, or decades on different variables of human subjects or groups being compared (*see* **Longitudinal Data Analysis, Overview**). B2A12039

Landmark Studies

Nonrandom patterns of morbidity and mortality from different causes stem largely from the times (e.g. hours) of changing resistance. Ubiquitous rhythms account for the difference between life and death, as a function only of timing, when in the experimental laboratory the same stimulus – noise, *X*-irradiation, an endotoxin, or a drug – is applied with the same dose or intensity under the same conditions to similar groups of inbred animals at different rhythm stages (e.g. 4 hours apart covering 24 hours). Fundamental life processes, RNA and DNA synthesis, exhibit reproducible rhythms underlying a circadian cell cycle, with important applications in cancer chronotherapy with chemicals or radiation. When anticancer drugs act at a specific stage of the cell cycle, it is important to time their administration in such a way as to optimize tumor cell kill. The concurrent aim is to minimize the damage to target organs, when pertinent rhythms are in antiphase or to separate, before treatment, the timing of host and cancer rhythms as much as possible, for example, by manipulating mealtimes. Findings on the critical importance of the circadian system have led to the fields of chronopharmacology and chronotherapy. Rhythms



* Key: treatment during active (A) or rest (R) span with sinusoidal weekly pattern (S) or equal daily doses (E); $P < 0.01$. Difference in size corresponds to 50% difference in survival time; $N = N$ of animals.
Therapeutic optimization by timing drug administration according to biologic week and day.
Halberg E and Halberg F: Chronobiologia 7:95-120,1980.

Figure 1(a) The administration pattern of an immunomodulating drug accounts for the difference between the inhibition and stimulation of a subsequently implanted malignant growth. The conventional fixed daily dose pattern shortens survival time rather than lengthening it, as does a sinusoidally varying pattern adjusted to the body's rhythms, the *raison d'être* of chronotherapy. What remains to be proved in humans is that by resolving a time structure in both circadian and circaseptan aspects, clinical chronotherapy benefits from multifrequency timing, as it does from the use of circadian rhythmicity. See Figure 1b. © Halberg

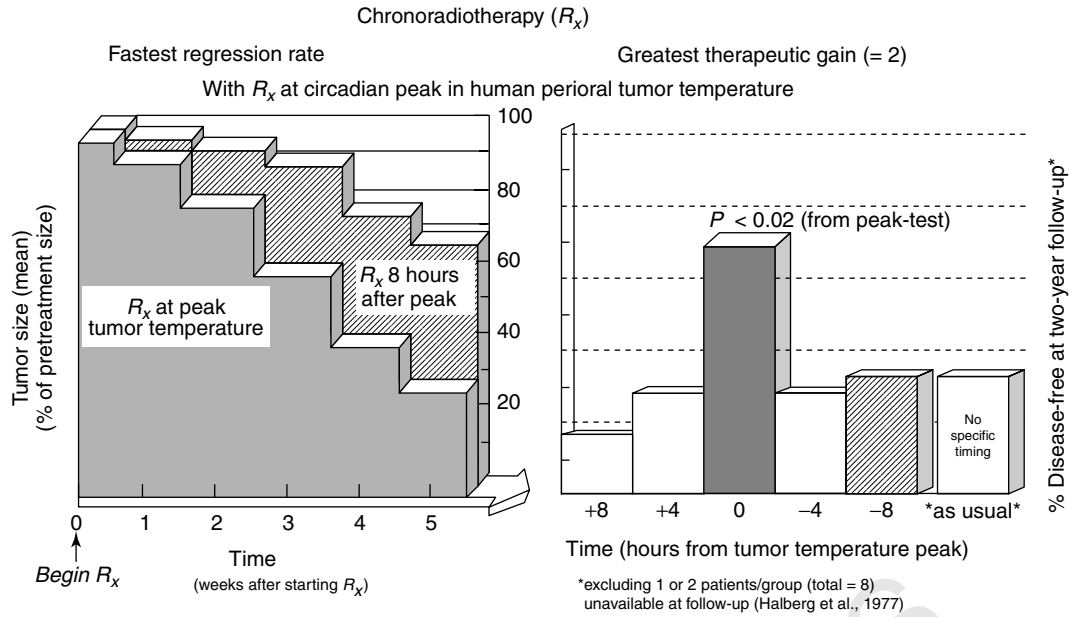


Figure 1(b) Doubling of two-year disease-free survival by radiotherapy administered at the circadian peak of tumor temperature. © Halberg

with other-than-circadian frequencies also matter: pretreatment with a sinusoidally patterned daily (and hourly) administration of the same total weekly dose of the immunomodulator lentinan can inhibit a subsequently implanted immunocytoma growth, when pretreatment with conventional equal daily doses enhances the same malignant growth in rats (●Figure 1(a)). The use of tumor temperature as a marker rhythm to guide perioral cancer radiotherapy, as compared to the usual time-unspecified treatment, has doubled the two-year disease-free survival rate (Figure 1(b)). Further optimization involves about-weekly and circadian considerations in keeping with Figure 1(a).

Other Clinical Uses of Chronomics

Chronome mapping leads to: (i) a positive definition of health in the light of reference standards for new endpoints (see Figure 2); (ii) a better understanding of mechanisms underlying changes of chronomes in healthy development (Figure 3) and against this reference standard, an earlier recognition of any disease process; (iii) the detection of chronome alterations before changes outside the physiological range occur, detecting predisease longitudinally in the stroke-prone, spontaneously hypertensive rat and in humans; and (iv) the opportunity to act preventively and rationally rather than after the fact of overt disease (Figure 4). A chronomic interpretation of serial data yields a location index (the MESOR (**m**idline **e**stimating **s**tatistic **o**f **r**hythm)) usually more accurate and more precise than the arithmetic **mean** (being associated with a smaller bias owing to the temporal placement of measurements and with a smaller **standard error** once other deterministic variation is accounted for) (Figure 5). This improved average, of great merit in itself, is only a dividend from the major merit of chronomics, namely, the provision of intuitively meaningful endpoints of dynamic changes (such as amplitudes, phases, and frequencies of rhythms), which convey useful information in their own right (Figure 2).

Examples are the disease risks: chronome alterations of heart rate variability, CAHRV, such as a **d**ecreased (under-threshold) **h**eart **r**ate **v**ariability (DHRV), and an excessive (over-threshold) variability of blood pressure (circadian hyper-amplitude-tension, CHAT). CHAT describes a blood pressure profile with an amplitude above the upper 95% prediction limit of healthy peers matched by gender

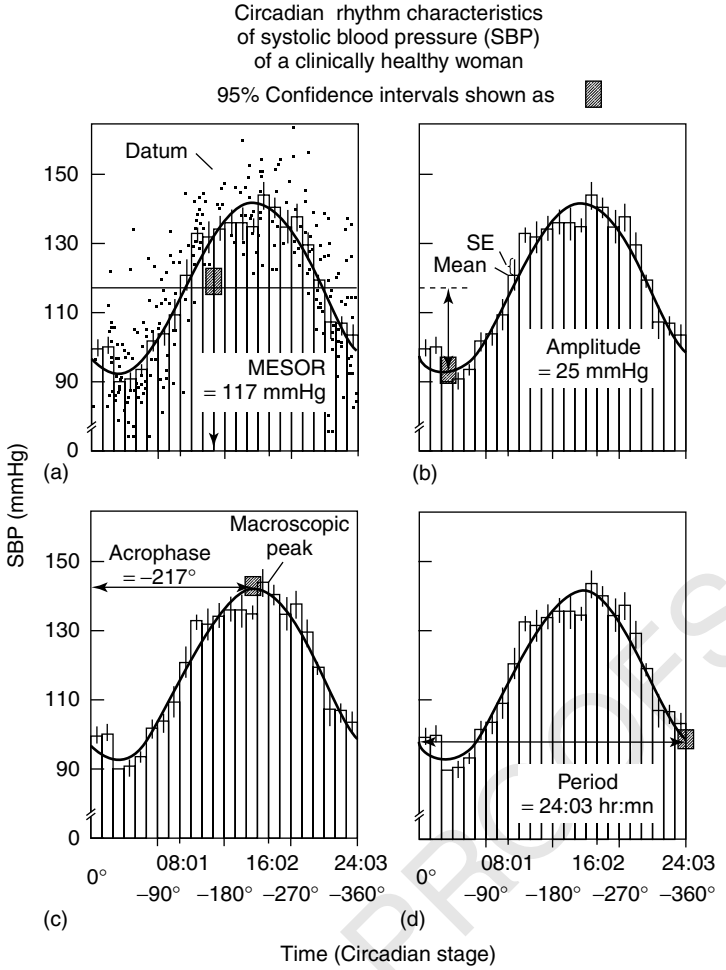
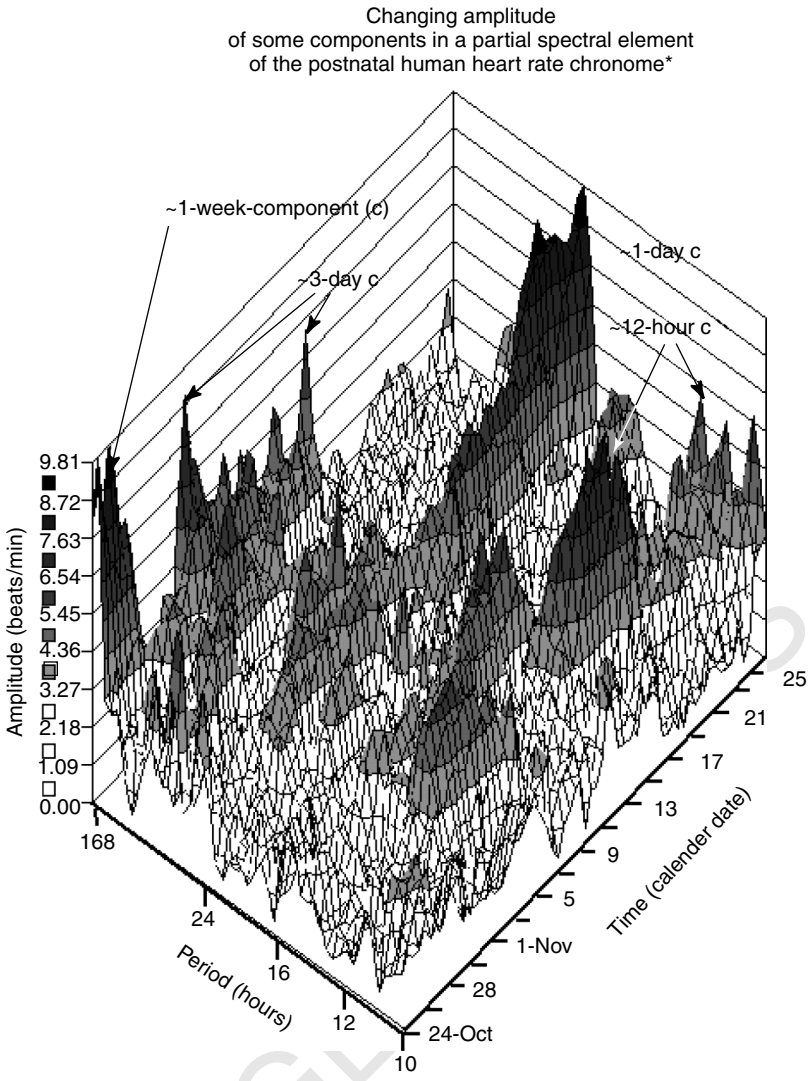


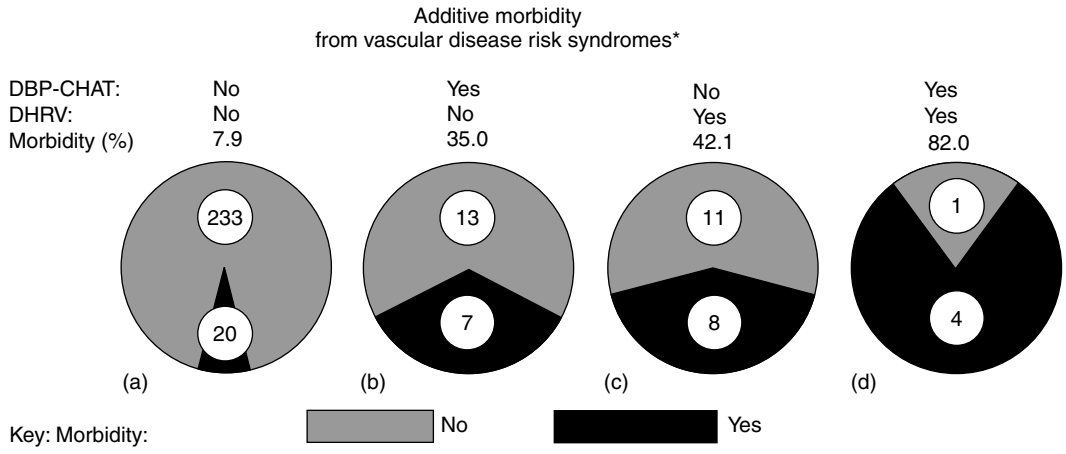
Figure 2 Illustration of circadian rhythm characteristics of systolic blood pressure (SBP) of a clinically healthy woman estimated by linear–nonlinear least squares. Although the data (dots; (a)) were collected during a 9-day span and were analyzed as a longitudinal time series, the results are displayed after the data have been stacked over an idealized cycle with a period that was estimated before stacking to be 24:03 hours (d). The 95% confidence interval for the period estimate is much less than 1 hour, as can be seen from the rectangle at the tip of the arrow (d). Point-and-interval estimates are also shown for the MESOR, a rhythm-adjusted mean (a), for the amplitude, a measure of half the extent of predictable change within a cycle (b), and for the acrophase, a measure of the timing of overall high values recurring in each cycle (c). The results also serve to indicate the large variability in systolic blood pressure, which is predictable to a large extent. They question the reliability, validity, and pertinence of single measurements used today for screening, diagnosis, and treatment of blood pressure disorders. © Halberg

and age. CHAT can be a response during only a few days to stimuli such as conflict or grief (transient CHAT). CHAT beyond a week-long monitoring should prompt further monitoring. Patients with diastolic CHAT, whether MESOR-normotensive or MESOR-hypertensive, have a 720% increase in the risk of cerebral ischemic events. The diagnosis of CHAT requires both that data be collected around the clock and that the circadian amplitude be estimated and compared with available reference values. DHRV (decreased **h**eart **r**ate **v**ariability) is a deficient heart rate jitter, (defined as a 24-hour standard deviation of heart rate below the lower 5% prediction limit of healthy peers) which carries a 550% increase in the



* in a healthy boy, born 19.10.1992, whose heart rate was measured at mostly 30-minute intervals from 20.10 for the ensuing 40 days, and analyzed as a moving spectrum in separate weekly intervals, displaced in 12-hour increments through the data set. An initially greater prominence of infradians (see ~1 week c, left), shown by height and color, corresponding to a larger amplitude, contrasts with the prominence of circadians and circasemidians in later weeks of life, while any ultradians with still higher frequencies and any trends and chaos, two other chronome elements, are here unassessed.

Figure 3 Early infradian over circadian prominence of human heart rate after birth. The oblique age scale ascends from the bottom middle to the right; trial periods are shown along a scale that ascends from the bottom middle to the left. Along the vertical scale of amplitudes initially no circadian peak, only an infradian (about-weekly) component is seen. The circadian and circasemidian components become noticeable by peaking several weeks later. © Halberg



* DBP-CHAT: Diastolic circadian hyper-amplitude-tension.
DHRV: Deficient heart rate variability.
Morbidity: Cerebral ischemia, myocardial infarction, nephropathy and/or retinopathy during 6 years, without (a), with single (b, c) or both (d) disease risk syndromes.

7-day / 24-hour monitoring can detect in the neglected normal range abnormality in variabilities of blood pressure and heart rate that make the difference between <8 and 80% morbidity.

Q1 **Figure 4** Pie charts compare the incidence of morbid vascular events among four groups of patients: •(a) Those with an acceptable blood pressure and heart rate variability; patients diagnosed with either (b). an excessive (above-threshold) circadian amplitude of diastolic blood pressure (DBP-CHAT, or (c) a decreased (below-threshold) heart rate variability (DHRV, alone, and (d)patients diagnosed with both conditions. Results from a 6-year prospective study on 297 (121 MESOR-normotensive and 176 treated MESOR-hypertensive) patients, who each contributed a 48-hour record of blood pressure and heart rate measurements at 15-minute intervals at the start of study. The incidence of morbid events was checked at 6-month intervals for 6 years. Each patient's circadian characteristics of blood pressure and heart rate was interpreted in the light of reference standards obtained from independent studies of presumably clinically healthy subjects, matched by gender and age. CHAT (**c**ircadian **h**yper-**a**mplitude-**t**ension) was defined as a circadian amplitude of blood pressure above the upper (95% prediction) limit of acceptability and DHRV (as a 48-hour standard deviation of heart rate below the lower limit of acceptability. Findings of Kuniaki Otsuka, in keeping with earlier studies of the spontaneously hypertensive stroke-prone Okamoto rat, and in keeping with human studies in Minnesota, Taiwan, Japan, Italy, and Germany, where outcomes are available with a 28-year perspective. © Halberg

risk of coronary artery disease and can be determined along with a check for CHAT by ambulatory monitoring without electrodes. When both CHAT and DHRV coexist, there is a doubling of the risk of vascular diseases (Figure 4).

Statistical Concepts, Problems, and Solutions

Periodograms, Power Spectra, and Single (Usually Multiple-component) Linear-nonlinear Cosinors

B2A12065 In the precomputer era, periodograms (*see* **Spectral Analysis**) used at first necessitated equidistant data over several integer cycles of the components characterizing the data. The computations were time-consuming and data could not always be obtained at regular intervals. Self-measurements of blood pressure or heart rate, for example, are not possible while sleeping. An alarm clock used to prompt a self-measurement leads to disturbance, which may affect the measurements and hence may prevent the rigorous assessment of spontaneous variation. Undue caution at the beginning of the computer era led to very conservative power spectra, with a great deal of smoothing. As the ubiquity of circadians was documented, **least-squares** procedures offered themselves B2A09024 for the test of anticipated rhythms in unequidistant data such as those collected in isolation from society

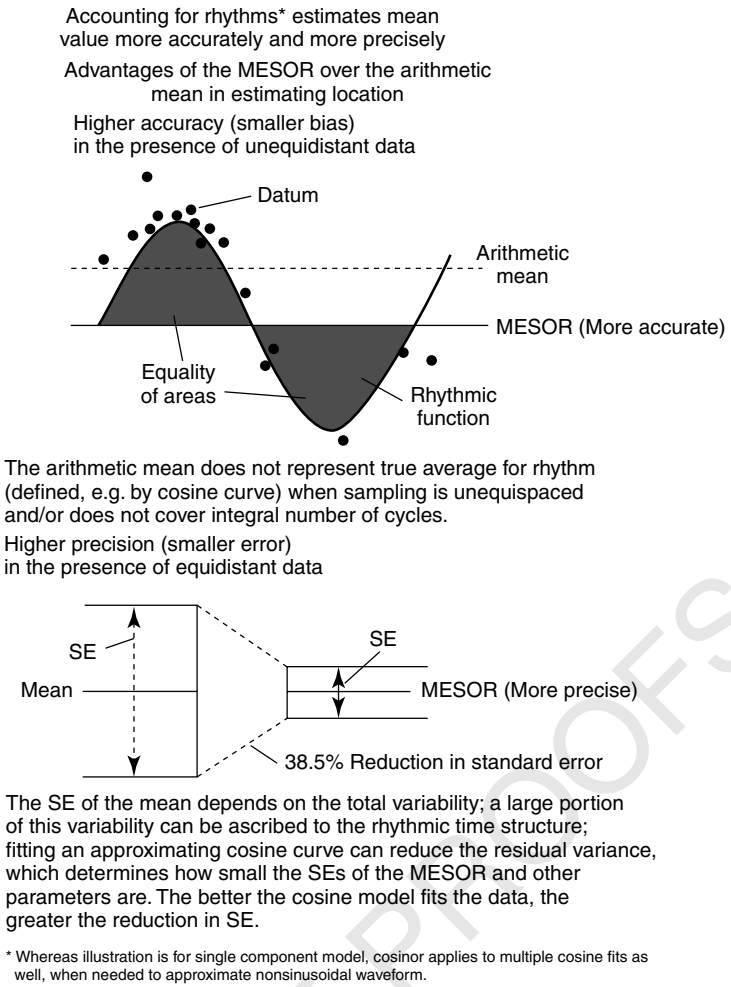


Figure 5 In the presence of periodicities, the use of statistics to resolve the time structure (chronome) usually yields a more accurate (a) and more precise (b) estimate of location (the MESOR, a rhythm-adjusted mean) than the arithmetic average. © Halberg

in caves, without a clock. Thus, the single cosinor was developed. Here *single* refers to the analysis of a single series by the fit of one or, usually, of several components when the data allow it. The addition of harmonic terms in the model quantifies the waveform when it is nonsinusoidal. The results are displayed along both rectangular and polar coordinates as point estimates and 95% confidence intervals. For time series spanning more than one or a few cycles, a chronobiologic serial section can be used, wherein the single cosinor is applied to successive consecutive or partly overlapping intervals to examine how the characteristics of a rhythm with a given frequency vary as a function of time. For long series involving components of several frequencies, chronobiologic serial sections of several orders can be applied to the original data or to the parameters obtained in a previous pass.

Least-squares procedures are well suited to the situation where anticipated rhythmic components have known approximate periods (τ_i). The least-squares fit of a model such as

$$Y(t) = \sum_{j=0}^{q} a_j t^j + \sum_{i=1}^{p} A_i \cos\left(\frac{2\pi t}{\tau i} + \phi_i\right) + \varepsilon(t)$$

detects a rhythm with period τ_i by the zero-amplitude test ($H_0 : A_i = 0$). Confidence and/or prediction limits are derived for the parameters of all rhythmic components, whether they represent several physiologically different (multifrequency) rhythms and/or harmonics quantifying a nonsinusoidal waveform. In addition, any superimposed trend is detected by nonzero **polynomial** coefficients (a_j). Least-squares techniques to assess rhythms in short and sparse series led to several important developments. B2A09038

1. Parameter comparisons: these can check for changes occurring on an individual basis, for example, to determine whether a given antihypertensive drug has lowered the circadian blood pressure amplitude of a patient with CHAT, or whether it is preferable to administer such a treatment at one versus another circadian stage.
2. Gliding spectral windows in combination with cumulative sums (CUSUM) (*see* **Quality Control in Laboratory Medicine**, Figure 6), ascertain that an effect of treatment occurs and persists with statistical significance in the given patient, when his/her blood pressure, in response to antihypertensive treatment, leaves the decision interval. B2A06016
3. Phase zero trials: the parsimonious single cosinor method relying on prior information (such as the critical importance of circadian stage in relation to treatment efficacy) accounts for powerful chronobiologic pilots that are always useful but are named "phase zero trials" since usually they should precede the customary Phase I–III **clinical trials**, which then could be carried out at the "right time" determined in the phase zero trial. B2A01009

For different signal-to-noise ratios and a relatively small number of subjects (≤ 20), in a hardly ever random (but rather somewhat periodic) world, the power of the single cosinor method exceeds that of a one-way analysis of variance (*see* **Experimental Design**), assuming that the (usually considered six) test times are equidistributed within one (e.g. circadian) cycle. The dangers of relying on a two-timepoint approach need to be stressed whenever the precise phase information is lacking and/or the individual's rhythm may be desynchronized in phase or period. The merit of a six-timepoint design at the outset is its amenability to cost-effectively determine the optimal time and the likely gain to be derived from timing. For instance, in a six-subject, six-timepoint pilot study, the particular tested anticlotting properties of treatment with daily low doses of aspirin were optimal when the drug was administered shortly after awakening (Figure 7). B2A16021

Indications for Linear–Nonlinear Least-squares Cosinors, Spectra, and Cross-spectra

The time structure of a variable is usually synchronized by the environment. Transient changes are associated with the expression of partly endogenous variations when an organism is studied under conditions rendered as constant as possible in terms of illumination, temperature, humidity, access to food and water, and so on. Persisting rhythms assume periods, which usually remain close to their environmental match, yet differ with statistical significance, albeit slightly, from the period of the environmental cycle with which they had been synchronized earlier.

Nonlinear least-squares techniques (*see* **Nonlinear Regression**) generally serve to estimate the period(s) with other rhythm characteristics. The combination of linear and nonlinear least squares relies on guess estimates from the former to assess by the latter the persisting circadian rhythms in the absence of time clues. Evidence accumulates for the desynchronization from societal schedules of about-weekly (circaseptan) rhythms *in vitro* and *in vivo*, and for their frequency multiplication to about-3.5-day (circasemiseptan) rhythms after enucleation and/or mutation in unicells. B2A09034

Methodological Challenge in Finding Out that Stormy Weather in Space Is a Health Hazard

The combined use on existing extensive databases of spectral coherence, superposed epochs, and other remove-and-replace approaches, as in **endocrinology** (allowing nature to ablate and replace certain frequencies, e.g. of the velocity changes in the solar wind), has yielded consistent results suggesting that magnetic storms are consistently associated with a decreased heart rate variability, a physiological basis for an increased localized **incidence** of myocardial infarctions and strokes. Notably in the Arctic, around-the-clock electrocardiograms covering seven days allowed the comparison of data from days with high versus low geomagnetic activity. The long-term B2A08015 B2A03075

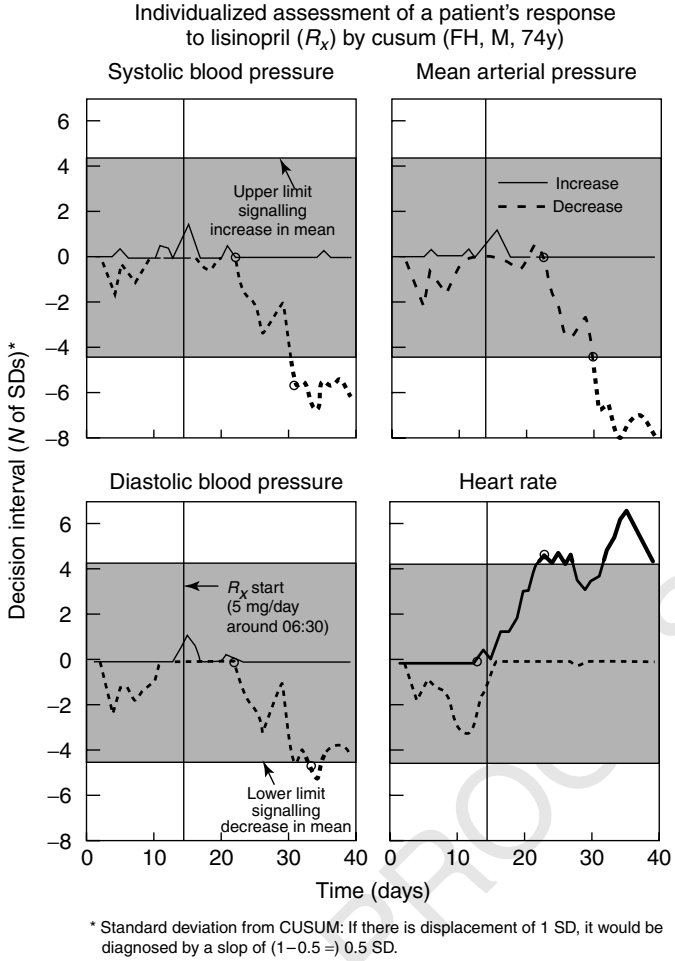


Figure 6 Control charts of daily mean values of blood pressure and heart rate data collected at 15-minute intervals around the clock. While the series of daily means is proceeding "in control" (i.e. at the pretreatment mean value), the CUSUM comprises two line graphs, signaling an increase or decrease in mean, respectively, that generally stay within the shaded "decision interval", plotted here as the horizontal lines at 4.4 and -4.4 SD. When the dashed curve breaks out of the decision interval boundary, it provides the validation of a decrease in daily blood pressure mean. The time at which the mean changed is estimated by tracking the line segment leading to the breakout back to the last occasion on which it lay on the horizontal axis. Thus, in the case of systolic blood pressure, the breakout occurs on day 30 (16 days after the start of treatment with the drug lisinopril) and the shift in pressure is estimated to have occurred on day 22 (8 days after lisinopril treatment started). © Halberg

concomitant systematic monitoring of physiological variables for alignment with ongoing physical monitoring is the aim of an international chronome initiative seeking information in different geographic/geomagnetic locations as reference values for chronomedicine, while also examining questions about mechanisms of external–internal chronome interactions.

Population-mean Cosinor

This method, based on **multivariate** statistics, was developed for drawing inferences to be generalized by checking the extent of similarity of single-cosinor estimates among individuals selected at random from a homogeneous population. B2A13047

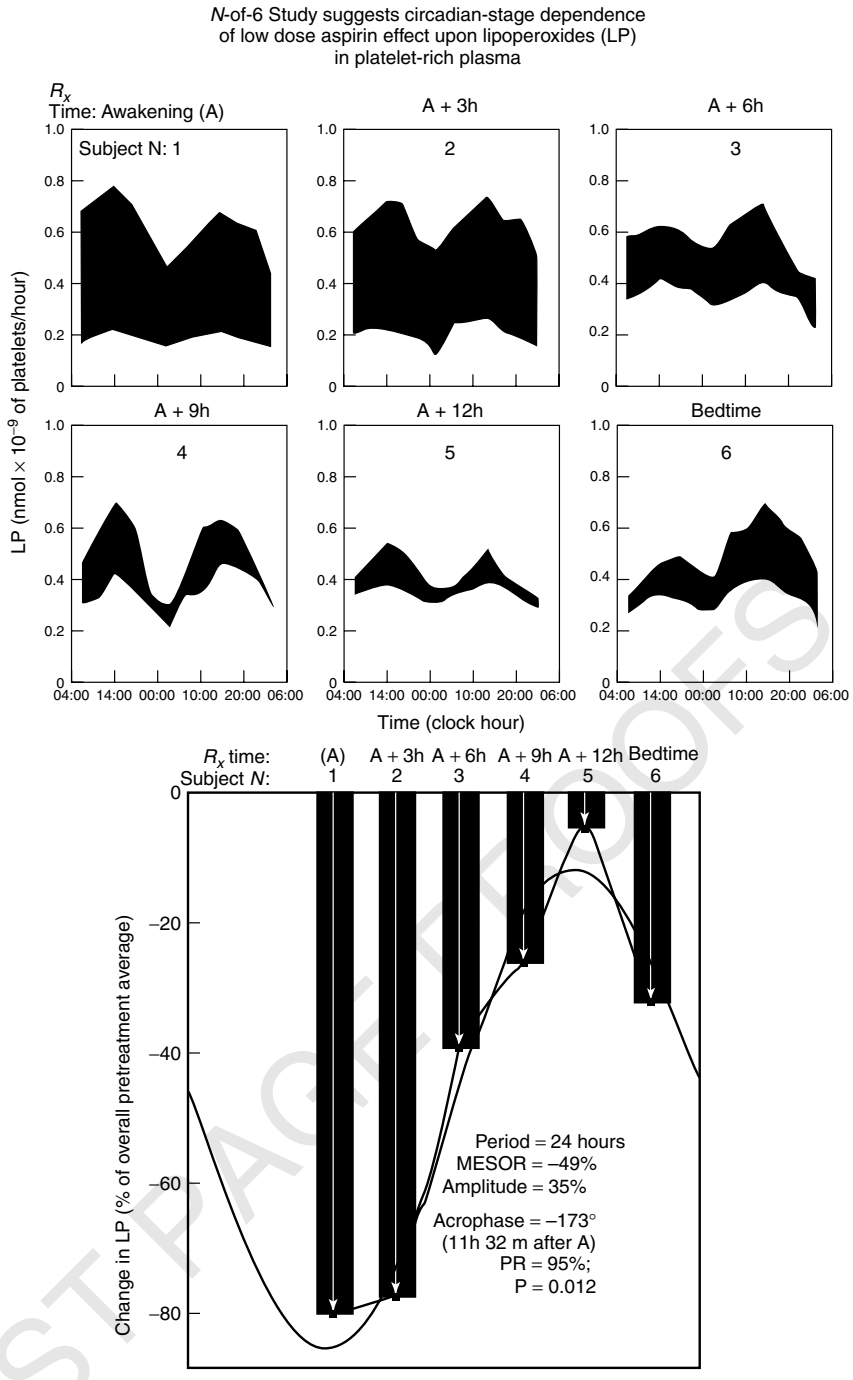


Figure 7 Power of "phase zero" chronobiologic pilots: by randomly assigning similar subjects to six different circadian stages, each to receive 100 mg/day of aspirin for one week, a large amplitude response rhythm can be assessed indicating that the lowering of lipoperoxides (LP) in platelet-rich plasma (a desired effect to prevent myocardial infarction) is maximal when aspirin is taken shortly after awakening and that aspirin does not have this effect when it is given 12 hours later.

Time-specified Reference Standards: Chronodesms

This chronobiologic alternative for usual value ranges collects serial data from clinically healthy subjects to derive reference limits (such as 90% prediction intervals) that account for multifrequency rhythms, age trends (from womb to tomb), and differences as a function of gender and ethnicity, considering both changes in mean value and **variance**. These limits are for the interpretation of single values and for that of rhythm parameters (parameterdesms) and noise characteristics. This approach to the monitoring of blood pressure and heart rate identifies patients with CHAT or DHRV, among others.

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Measures of Excess and Deficit and Beyond with Signal Averaging

The recognition of chronomes provides more reliable answers to the question whether and when a time series is too high or too low and detects alterations in time structure in the absence of changes in operating an overall average. Chronomics compares endpoints of anticipated periodic components with a pertinent chronodesm to determine the extent, timing, and duration of any excess (or deficit) by numerical integration of the area (under and/or over the curve) delineated by the data when they are outside time-specified limits and the limits themselves (*see* **Bioequivalence**). The time when most of the excess (deficit) occurs serves for diagnosis and for timing any intervention.

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Control Charts

To assess an individual's trends in mean or in other chronome characteristics, cosinor methods are applied in intervals that are progressively displaced throughout the accumulating **time series**. This chronobiologic serial section can be combined with a self-starting cumulative sum (CUSUM) to detect chronome alterations or to assess the response to a given intervention (*see* **Quality Control in Laboratory Medicine**). Such an individualized approach, first used in chronomedicine for the monitoring of epileptic seizures and for adjusting treatment, is particularly indicated in assessing blood pressure and heart rate. Hawkins' self-starting CUSUM detects a shift in mean (MESOR, circadian amplitude, and/or any other pertinent chronome endpoint or chrone) and indicates when the change may have occurred. Moreover, the boundaries of the decision interval can be determined even from relatively few data prior to a given intervention. Gliding spectral windows provide a view, from above or from the side, of the change in both amplitude and period.

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Anticipated Developments

Some nondrug treatments or an antihypertensive drug can lower an excessive circadian blood pressure amplitude when given at the right time (rhythm stage) or raise it when given at the wrong time. For instance, an α-adrenoceptor antagonist given for benign prostatic hypertrophy in the evening raises the circadian blood pressure amplitude, but fails to have this effect when given in the morning, when the circadian blood pressure amplitude is restored within acceptable limits. Further clinical trials will have to examine the degree of generality of the finding already made, that the actual incidence of adverse vascular events can be reduced by antihypertensive agents capable of lowering an excessive circadian blood pressure amplitude when given at the right time.

Deterministic chaos theory of heart rate variability has associated complexity, if not irregularity, with health, while regularity (periodicity) has been regarded as an index of disease, with the focus primarily on spectral components with periods of seconds or a few minutes. Results along the 24-hour scale reveal that the circadian variation is better defined in health than in the presence of heart disease. Concomitant assessment of various chronome elements reveals rhythms in endpoints of "chaos". Trends in both rhythmic and chaotic endpoints are found as a function of age and in disease versus health. For example, the correlation dimension of fractal scaling separates healthy subjects from patients with coronary artery disease at 2 A.M., but not at 10 A.M. or 2 P.M. Sampling around the clock not only reveals a circadian rhythm in the correlation dimension of cardiac interbeat intervals in health, but also a variance transposition of an endpoint of chaos from the 24-hour to the 12-hour region of the rhythm spectrum, as a new feature of CAHRV in patients with heart disease.

Chronome-specified Interactions

Chronome-specified interactions among two or more different variables have been called feed-sidewards. Those among three rhythmic entities such as the pineal–pituitary–adrenocortical interactions have been modeled *in vitro*. A rhythmic sequence of stimulation, no-effect, and inhibition by a third entity, a modulator, such as the pineal, upon the interaction of two other entities, the actor and reactor, such as the pituitary and the adrenal, is gauged by the *in vitro* production of corticosterone (see Figure 8). Another feed-sideward applies to DNA labeling in bone. An ACTH analog leads to a circadian sequence of stimulation, no-effect, and inhibition. Studies of feed-sidewards will have to be extended to multiple interactions at several (e.g. circadian and about 7-day rhythmic) chronome components, since the results can be critically important (Figure 1), as different as the stimulation versus the inhibition of a malignant growth.

Automatic Closing of the Loop Between a Chronodiagnosis and Chronotherapy

Longitudinal monitoring of vital signs for surveillance has been advocated, at least for at-risk individuals. Rather than loosing all original data except those collected just prior to an event, as done in the black box of an airplane, the data steadily accumulating over years or decades can be analyzed in relatively short spans to extract the pertinent spectral, chaotic, and trend (chronome) characteristics. Endpoints extracted from such windows are stored, thus compacting the available information as a summary for each day and then for each week or for a longer span. The information is thus progressively

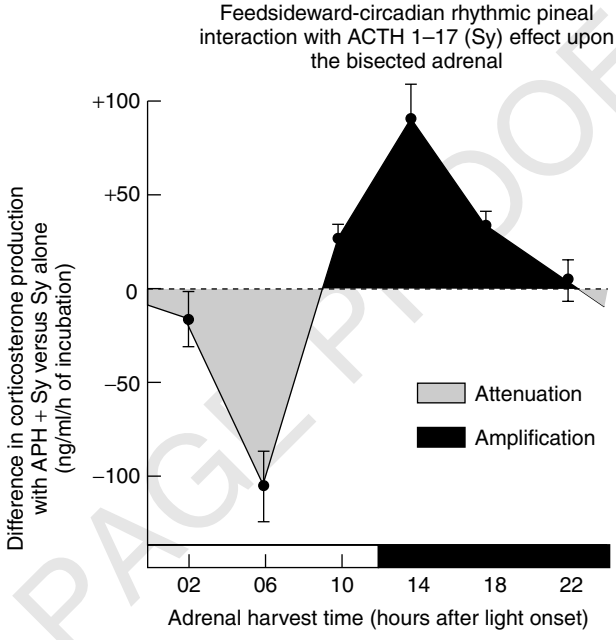

Figure 8 Much controversy can be resolved by studying the effect of the interaction by more than two entities at different rhythm stages: a third entity may modulate, in a predictable insofar as rhythmic fashion, the effect of a first entity upon a second. Predictable sequences of attenuation, no-effect and amplification can then be found. A case in point is corticosterone production by bisected adrenals stimulated by ACTH 1–17 (Sy) in the presence versus absence of pineal homogenate (APH). Such chronomodulations are part of (time-specified) feed-sidewards, for example, of rhythmic sequences of attenuation, no-effect and amplification by a modulator upon the interaction of an actor and a reactor. The figure summarizes five studies. © Halberg

updated as the window is displaced in repeated passes as-one-goes, while components with progressively lower frequencies are thus gradually resolved. This continuous examining, compacting, and recycling of information can detect the earliest chronome alterations at one or the other frequency, which may indicate an increased disease risk and can prompt the institution of countermeasures.

Automatic monitoring devices, miniaturized for long-term ambulatory use, some implanted under the skin or in the heart, are already available for research. The windowing, compacting, and recycling of telemetered data could provide a continuous medical examination, eventually available to everybody, thus contributing a thorough objective history of vital signs, preferably retrieved in response to the push of a button. Eventually, the loop may be closed for automatic chronome-adjusted treatment with drug pumps and/or electrical treatment devices. Another merit of the chronome approach versus the airplane's black box may be the much more complete history of long-term antecedents to avoid the "crash" of catastrophic disease by timely and timed treatment.

Further Reading

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Abstract: Chronobiology (from *chronos*, time; *bios*, life; and *logos*, science) investigates the mechanisms underlying variability in the otherwise unassessed physiological range, including rhythms found in us, resonating with cycles around us. Broad time structures (chronomes) consisting of deterministic chaos and trends organized by rhythms are found in organisms and in their environments. They are mapped by chronomics as the reference values for both an applied chronomedicine and a basic chronobiology. Chronomics quantify health, identifying new disease risks, diagnosing predisease and overt illness, enabling timely and timed treatment (R_x), and validating the short- and long-term efficacy of a given R_x on an inferential statistical individualized (as well as population) basis.

Keywords: chronobiology; chronome; chronomics; circadian; cosignor; time series

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