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CHRONOMICS AND GENETICS

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A b s t r a c t

The mapping of time structures, chronomes, constitutes an endeavor spawned by chronobiology: chronomics. This cartography in time shows signatures on the surface of the earth, cycles, also accumulating in life on the earth's surface. We append a glossary of these and other cycles, the names being coined in the light of approximate cycle length. These findings are transdisciplinary, in view of their broad representation and critical importance in the biosphere. Suggestions of mechanisms are derived from an analytical statistical documentation of characteristics with superposed epochs and superposed cycles and other „remove-and-replace" approaches. These approaches use the spontaneously changing presence or absence of an environmental, cyclic or other factor for the study of any corresponding changes in the biosphere. We illustrate the indispensability of the mapping of rhythm characteristics in broader structures, chronomes, along several or all available different time scales. We present results from a cooperative cartography of about 10, about 20, and about 50-year rhythms in the context of a broad endeavor concerned with the Bɪosphere and the Cosmos, the BIOCOS project. The participants in this project are our co-authors worldwide, beyond Brno and Minneapolis; the studies of human blood pressure and heart rate around the clock and along the week may provide the evidence for those influences that Mendel sought in meteorology and climatology.

K e y w o r d s

Chronomics, Chronobiology, History of science, History of statistics, Time series, Wolf's relative sunspot numbers

INTRODUCTION

The mapping of time structures, chronomes, constitutes an endeavor spawned by chronobiology: chronomics. This cartography in time shows signatures on the surface of the earth of the about 21-year (circadidecadal or circavigintunennian) Hale cycle in the polarity of sunspots. Circadidecadals complement about 10.5-year (circadecadal or circaundecennian) and about 50-year (circaquindecadal or circasemicentennian) cycles, also accumulating in life on the earth's surface. We append a glossary of these and other cycles, the names being coined in the light of approximate cycle length. Many of the unselected, seemingly ubiquitous infra-annual cycles are inferentially statistically validated with their uncertainties. These findings are transdisciplinary, in view of their broad representation and critical importance in the biosphere. Suggestions of mechanisms are derived from an analytical statistical documentation of characteristics with superposed epochs (with control epochs) and/or superposed cycles and other "remove-and-replace" approaches. These approaches use the spontaneously changing presence or absence of an environmental, cyclic or other factor for the study of any corresponding changes in the biosphere. Hints of putative partial endogenicity stem from non-overlapping 95% confidence intervals of near-matching biospherical and physical periods in variables that were linked by the foregoing methods. Solar flares, storms in the interplanetary magnetic field, major geomagnetic and/or cosmic ray disturbances, that all exhibit cycles, may play a role as potential synchronizers of multidecadal cycles built into populations. They may also elicit, as single events, sequences of rhythmically recurring, very different effects, i.e., feedsideward intermodulations, to be revealed by a phase-response curve.

In the light of the foregoing, we illustrate the indispensability of the mapping of rhythm characteristics in broader structures, chronomes, along several or all available different time scales. The results of this mapping, chronomics, can be used to plan the system time of future studies and to interpret results in the context of a broader time horizon, e.g., in health care or basic science. This mapping is done in Brno, the birthplace of genetics. We draw a parallel between the mapping of the genome, genomics, spawned by genetics, and that of chronomics, an offshoot of chronobiology. We present results from a cooperative cartography of about 10, about 20, and about 50-year rhythms in the context of a broad endeavor concerned with the BIosphere and the Cosmos, the BIOCOS project. The participants in this project are our co-authors worldwide, beyond Brno and Minneapolis; the studies of human blood pressure and heart rate around the clock and along the week may provide the evidence for those influences that Mendel sought in meteorology and climatology.

A very broad concern for diverse changes with time led Herbert Hörz to philosophically coin the terms "system time" and "time horizon" (*1*). We here apply these terms empirically from the viewpoint of chronomics, the cartography of time structures, i.e., chronomes (*2*). Empirically, the time scale, along which we intend to sample in a given observational, clinical or experimental test or other study, may be called the system time. The complementary time horizon in turn includes all retrievable, inferentially statistically analyzed pertinent prior information. The time horizon thus consists of the rhythm, chaos and/or trend characteristics and of their changes with time in the variable(s) under consideration. The durations and temporal locations of the timepoints at which earlier sampling was done have to be specified, of course, as system times and their sum constitutes the time horizon, enlarged by each addition. These characteristics become useful only after as many as possible observations made with all previously used system times are summarized as chronomes. The chronobiologic aspects of parts of ontogeny and phylogeny are being documented for one or a few variables in the rat, piglet, and human newborn. A synthesis of these different results shows an initial prominence of circaseptans, ascertained in a comparative physiological time horizon, which is as yet limited to early human and other post-uterine life and to early stages of crayfish development. One can then add that circaseptans can also be more prominent than circadians in *Acetabularia acetabulum,* a unicellular plant. By contrast, in as yet very limited time series of observations on E. coli and cyanobacteria, circaseptans, albeit present, have a smaller amplitude as compared to circadians.

Along such lines, much more study is required to attempt to track evolution chronobiologically. Incomplete information, again restricted to a few test pilots, is available for the case of the human heart rate, blood pressure, and their variabilities. Eventually, all biological variables will require systematic mapping, whether for tracking an internal integrative as well as external adaptive Darwinian evolution on the one hand (*3*), and for reference values in health and disease on the other hand (*4*).

An international project on the Biosphere and the Cosmos, BIOCOS, has enlarged the transdisciplinary time horizon and torn down barriers for students of physiology in general, including the circulation. Archival studies complement physiological monitoring to reveal multidecadal changes in the chronomes not only of blood pressure and heart rate, but also in the incidences of disease such as strokes and myocardial infarctions. These latter conditions carry circaquindecadal and circadecadal cyclic signatures, respectively.

We illustrate the need for mapping chronomes by showing what could happen when any mapping already accomplished remains ignored (albeit it should constitute a useful time horizon). We also indicate the putative utility of a time horizon to health care and basic science, once the mapping proceeds, for instance for the detection of CHAT (short for **c**ircadian **h**yper-**a**mplitude-**t**ension). The long-term major public health task of picking up in time the elevated risk of vascular disease in adults can be documented. It is to be complemented eventually in the human newborn at birth, if not at conception. We seek disease risk detection in the physiological range, for the clinics an endeavor requiring the collection of reference values. Work toward this goal provides, as a dividend, a broad time horizon, emerging from a network of international cooperation; we may reap ample dividends first and foremost for the interpretation of studies along the system time of long-term lifetime monitoring, implemented by a test pilot by self-measurement of 11 variables about 5 times on most days for over 3 decades and by another colleague automatically every 30 minutes for well over a decade for blood pressure and heart rate. Systematic monitoring leads to pre-habilitation for eventually replacing or reducing the need for rehabilitation after catastrophic disease has occurred (*4*).

From genetics to chronomes in Brno

The signature of Johann Gregor Mendel, the founder of genetics, is present, beyond his mid-19th-century Brno, throughout the world of genetics and now genomics, and is currently making headlines with stem-cell research and human cloning. Also present in the contemporary mind of investigators involved in BIOCOS is the mapping of time structures in the human circulation and around us, the chronomes in the organism and the environment. This mapping endeavor, associated in Brno, and the title of this presentation reflect the thread leading from Johann Gregor to the Brno chronobiology team from the Department of Functional Diagnostics and Rehabilitation and the Department of Physiology. The pea patch in front of the Brno abbey, cultivated by Mendel, was not his only interest (*5*). Mendel published only two papers on plant hybridization; he published much more extensively in the field of meteorology. In private correspondence, Mendel was concerned about the "telluric and cosmic influences" (*6*) that enable some but not most other hybrids to survive severe environmental conditions. Could he have anticipated chronomics (*2*) more than chronobiology (*7*), the study of the built-in mechanisms of human time structures, documented by studies, among others, on twins reared apart to be genetically based (*8*)?

Mendel would certainly enjoy the documentation, by the BIOCOS team, that genomes have incorporated more and more of the cycles of the very environment in which they evolved, not only by an adaptive natural selection but also by an integrative evolution (*3*). Some of the evidence is obtained as circadian amplitudes from the fit of a 24-hour cosine curve to the heart rates of twins reared apart. When these amplitudes are analyzed by intraclass correlation coefficients, they reveal heritability (*8*). Chronomics, the mapping of the expression of genes in the form of chronomes, consisting of multifrequency rhythms in us and their interactions with those outside us, is well under way in Brno to answer whether the results, in the otherwise neglected physiological range, are a curiosity of certain Asians or also apply to some extent to other populations, including Caucasians. The scope of these results is being checked at Brno's St. Anne's Hospital by Pavel Homolka and Jarmila Siegelova with 7-day/24-hour monitoring. As a start, over 100 such 7-day series have already accumulated. The 24-hour profile is a rather false gold standard, a fact documented elsewhere (*9, 10*).

Need to separate transient 24-h CHAT from 7-day CHAT

In a seemingly healthy woman in her 60s (years, CH), the circadian amplitude of systolic blood pressure was only transiently elevated. For the ensuing 6 years, the usually longer than 1-week profiles were all acceptable in terms of the circadian amplitude. In this case, the initial elevation of the circadian amplitude was associated, on different days, with trouble at work, bad memories and grief, all recorded prospectively in a diary, as described elsewhere (10). The patient did have intermittent systolic and diastolic **c**ircadian **h**yper-**a**mplitude-**t**ension, CHAT. Her case was a transient **24-hour** CHAT, not only initially but also 6 years later, yet not for a sufficient time to diagnose "**7-day** CHAT" based on a 7-day or, in such cases of transient or **24-hour** CHAT, based on a much longer record. Initially, the woman CH had a very high blood pressure for 5 consecutive days, but again not for the rest of over 20 days of the first monitoring, so that in long profiles, except for a very psychologically taxing (emotional) event, her blood pressure MESOR, a chronome-adjusted mean (not shown), was below the upper chronobiologic limit. (The last profile, however, after 6 years had an elevated MESOR, as confirmed by the time course of indices other than the MESOR such as the percent time elevation and the hyperbaric index, which were all elevated only transiently, in association with emotions or at the end of the 6-year monitoring span.)

Had one acted based on the 5 days of initial MESOR-hypertension and treated for the intervening 6 years, one might have had side effects and unnecessary expense. In view of the chronobiologic diagnosis, the patient remained untreated and was doing well six years later. Other similar cases (*9–12*) include that of a cardiologist who had very high pressures for 48 hours but an overall acceptable 7-day profile not only to start with, but also 7 years later at the age of 93 (*12*). In the interim he was untreated, but was doing very well. Nonetheless, such long intervals between monitoring, as in the case of the cardiologist, are not recommended. The minimal system time in these cases was the 7-day/24-hour monitoring, preferably on a yearly or, if indicated, by a transient abnormality more often, as in the case of the woman CH. The real time horizons will be the lifelong perspectives, provided by such test pilots, a majority of them physicians themselves (*12–14*). But there is another side to this story. Only controlled large chronobiologic trials, preferably with timed treatment, can decide at what level non-drug or drug treatment is indicated.

Building further on quicksand

A recent article by *Vasan et al.* based on the Framingham Study suggests that high normal values should be treated (*15*). Before one adheres to such a recommendation, a point mentioned by Panza in an editorial (*16*) on this article (*15*) concerns the lack of reliability of the conventional diagnosis. The editorial, entitled "High-normal blood pressure – more 'high' than 'normal'", comments on the risk of cardiovascular disease among a subgroup of the Framingham Heart Study population without hypertension at base line, classified according to their base-line blood pressure. The authors found that the participants with high-normal blood pressure (systolic pressure of 130 to 139 mm Hg, diastolic pressure of 85 to 89 mm Hg, or both) had higher rates of cardiovascular events than those with optimal blood pressure (defined as systolic pressure of less than 120 mm Hg and diastolic pressure of less than 80 mm Hg). These findings lend further credence to the theory that high-normal blood pressure must be categorized differently from normal or optimal blood pressure.

Certain aspects of the study affect its clinical relevance. First, blood pressure measurements were obtained at single time points. Given the variability of blood pressure, particularly in this borderline range, these measurements may not represent the average value during daily activities (*16*). The realization is overdue that the "high normals" were so diagnosed by virtue of a snapshot on a roller coaster with 40% or more uncertainty (*17*). This uncertainty must be eliminated before solid recommendations for the treatment of individual patients can be made. The uncertainties even of 24-hour or longer profiles, including 5-day profiles, have been demonstrated (*9*). A spontaneous remark by an editor on a paper published by us in his journal seems pertinent (18; cf. 19):

Talking about "blood pressure" as a single figure is similar to knowing the average height of a mountain range: an interesting statistic, but completely useless to a pilot trying to make it through a mountain pass alive. Realistically, we need to consider not merely the mean [average] stress on an aging vascular endothelial cell, but the "peaks" that it has to "fly over" as well. Aging vessels are–to an extent–the end result of such stresses. *Halberg et al*. suggest that many patients may be apparently normotensive [with normal blood pressure], yet (because of circadian peaks in blood pressure) have the catastrophic risks of any other severely hypertensive patient. They recommend that [medical practitioners] avoid "flying blind" and begin to measure peak pressures more accurately if we are to avoid disaster.

Chronobiologic guidelines for archivization

Bohumil Fiser et al. have greatly broadened the time horizon in archivization by showing a 50-year cycle in stroke incidence in the Czech Republic as in Minnesota (*20, 21*). The proper coding for medical chronomics, relating to natality, morbidity and mortality, is overdue and is an urgent governmental task. Like the maintenance of clean air, clean water, and clean and safe streets, the surveillance by monitoring and proper archivization could become a service on the immediately practical side (*22*); but perhaps, it may have to be privatized if people do not value what is offered free of cost.

From heliobiology to chronobiology

The physico-chemical environment on earth and beyond has a number of more or less periodic features that may be classified as photic (or more broadly as obvious and sensed environmental temperature effects included) and non-photic (hidden; subtle). The sun and earth are both magnets. Helio- and geomagnetics contribute with galactic cosmic rays their share of non-photic effects that can be traced by auroras, sunspots, and recently by recordings not only on earth but also from vehicles in space. The photic effects are now known to be coded in the genome as circadian and circannual systems (*7*). Among non-photic environmental effects, we have found first a near-week in the environment (*23*), confirmed by physicists (*24*), shown in environmental geophysical activity. Germaine Cornélissen has also just found proof from studies on twins that the week as well is anchored in our genes (*25*). The geomagnetic half-year and non-photic biological associations are also mapped with about 10.5-year and other components of solar activity, and in the frequency domain. We can summarize these and other results from mapping rhythms into rules of procedure based on the proposition that during a billion or so years on or in earth, life had to integrate into a cyclic environment not only by adjusting to cycles but also by coding them as features of organismic and environmental adaptation (*26*) or integration in genomes (*3*). The finding by others (*27–29*) of a half-year component in the geomagnetic index K_p led us first to show its particular prominence in a phase-weighted cosinor spectrum (30), and further to the finding of a circasemiannual near-matching periodicity in a vast number of biological phenomena. While the biological week led to the geophysical week, the information on the half-year, emphasized to us by the geophysicist Armin Grave (*27*), led us to the detection of a circasemiannual component in many variables of the biosphere and to an amplification of the proposition of an internal evolution (*3, 31*).

Results from mapping rhythms in chronomes

More generally we propose:

1. Any old or newly observed periodicity in the physico-chemical or socio-ecological environment should prompt the search for a near-match in biology as a putative synchronizer or influencer and/or, what seems at least equally likely, as a feature built into organisms. Thus, we find circasemiannuals in the birth rate at high latitudes (*32*), in body weight and height at birth (*33, 34*), in gain in weight and height during the first 15 months of life (*35*). There is a cross-spectral coherence coefficient with K_p of 0.74 at 5.91 months, away from a spectral peak, in the blood pressure and heart rate of a clinically healthy man who self-measured these and 9 other variables for over 3 decades (>.5 million values) (*21*). There is further a half-yearly component in the circulating melatonin of human pregnancies with intrauterine growth retardation (*36*) (but not in clinically healthy pregnancies). At middle latitudes, at a solar activity minimum, but not in the ascending stage of solar activity, human circulating melatonin exhibits a circasemiannual component by night (*37*) and a circannual during the daylight hours, whereas melatonin shows a circasemiannual component at noon at high latitudes (37; cf. 38). Test 2 (for a circasemiannual component in nightly melatonin of subjects at middle latitude) works at solar minimum but not in the ascending stage of solar activity. Thus, frequencies interact and some intermodulations constitute new testable items to be fitted into an ever broader picture puzzle that may turn into novel chronome maps. Circasemiannuals further characterize the vasopressin-containing nuclei of the human hypothalamus (*39*), the incidence of hallucinations (*40*), and most prominently the incidence of status epilepticus, during a 3-year span of intensive magnetic activity (*23*).

2. When we find a biologically new periodicity, previously regarded as purely societal (*41, 42*), we have to search for a near-match in the natural physical

environment. If there is not a very prominent near-match in the environment, the new periodicity such as that of a biological free-running week found in the urinary 17-ketosteroid excretion of a healthy man (*43*), we may speculate that the week may stem from one that was present prominently in an ancient past, when rhythmicity, such as that of a week or of a half-week, existed or the periodicity came about in response to internal needs, as a feature of an internal integrative evolution (*3*), complementing a Darwinian adaptive evolution by natural selection (*26*). The latter internal mechanism was the original hypothesis (*31*) until we found an average about 6.75-day periodicity in a 59-year record of K_p, Figure 4, which was subsequently corroborated by a similar near (but not exactly) matching component in 110 years of data on another geomagnetic index, aa (24), and now by our analysis of 134 years of data on aa; the amplitude of the near-match of the biological week about 130 years ago was weak, as it is now (*44, 45*). As originally postulated (*3, 31*), internal conditions may still have played the major role in acquiring a genetically anchored week (*31*). Unquestionably, however, on the average there is a near, but not exactly 7-day peaklet in geomagnetic pulsations also recorded in the presumably less polluted Antarctic by a stand-alone magnetometer, 610 km from the nearest habitat; albeit small, it has the largest amplitude in that spectral region (*25*).

3. Biological rhythms without an environmental near-match may point to the disappearance in the course of life's development on earth, of corresponding near-matching natural physical environmental cycles. Like the foregoing ones, this possibility has to be qualified by the circumstance of an internal evolution, postulating that some periodicities came about for matters of internal coordination, exclusively or at least primarily for this reason. Of course, matters of sheer chance by random mutations cannot be excluded. The information of today may have to be qualified tomorrow.

A current challenge is the search for a possible environmental counterpart for about 8-hourly rhythms in vasoactive substances such as norepinephrine and epinephrine (only on an equidistant isocaloric diet thus far) (*46*) and (under ordinary conditions but not invariably) in the case of endothelin-1 in the human circulation (*47–49*) and in the population density of endotheliocytes in mouse ear (*50*) and in venous human (*51*) and portal pig blood melatonin (*52*). Whether an 8-hour periodicity in endothelin is a key connecting rhythms and chaos pertains to the search for a similar periodicity in other vasoactive substances under ordinary conditions, such as in the case of substance P. It will take further studies to see whether the complementary aspects of chronos and chaos in our lives intersect at about-circaoctohoran features as a mechanism in its own right, coded in our genes, or whether 8-hour rhythms merely represent, as the third harmonic, the waveform, of a fundamental circadian system physiology.

4. In their growth and development, individuals and populations of human beings and other multi- or unicellulars, eu- or prokaryotes, have already proved to be living fossils that may replay, in their rhythmic dynamics during ontogeny, the

sequences that occurred during the development of life (*23, 53*). Crayfish (*54*) may be a better subject of study in this context than human beings (*55, 56*), rats (*57*) or pigs (*58*), for the investigation of the biological week, since a circaseptan is present with an amplitude larger than that of the circadian in crayfish locomotor activity at 6 months of age.

5. For any endeavor in any clinical and/or purely scientific context, maps from preferably automatic monitoring along more than the time scale chosen for recording (i.e., the system chronome) are desirable. Monitoring and analyses are best planned by considering all complementary chronome information (chronome horizon); based on the latter, the T (the duration of recording providing the number of replications) and the Δt (the interval(s) between consecutive observations) (for data density) are estimated. In spatial travel, we may use, in addition to our city map, a large world map, and after arrival in a new location, again a new city map. Similarly, we have mapped in time and space, among many other aspects of the human brain, religious motivation in Alaska (*59*) and then in 103 countries around the world (*60*). East and west of Greenwich and north and south of the equator, in nations near the equator and in those closer to the poles, we have found about 21-year signatures of the Hale cycle in this presumably brain-related index of religious activity. A lesser 21- and a major about 50-year cycle were found in homicides. More 50-year cycles were including one in international battles over the past 2,556 years. Chronome mapping complements geographic mapping in dealing with the health or disease of individuals or societies. Chronomics, rather than single-sample- or 24-hour-based spotchecks, are best combined with a broader time horizon, wherein chronomics complements genomics and proteomics, even as we trace ancestors in science (*61*) or in our evolution or make preparation with safeguards, as we venture into space.

Confounding nonsense becomes new information *with* chronomics

The role of multidecadal rhythms is illustrated by the example of the excretion of metabolites of steroidal hormones (17–KS); over several years, a decrease with age (P<0.001) was demonstrated during the ensuing several years, in the same subject there was an increase with age (P<0.001). When all data over 15 years were used, it was clear that one was dealing with a spontaneous about 10-year cycle (P<0.001). In different stages of this cycle, there were spans of positive, negative, and no correlations with age. Nonsense correlations may also account for much controversy attempting to relate biological variables to environmental ones, such as Wolf's relative sunspot numbers, WN, and the geomagnetic activity index, $K_{p.}$ A nonsense correlation thus occurs not only between steroids and age, but also between steroids and helio- or geomagnetic indices, if cycles shown on the right of this figure are ignored. These results can be generalized. Unmapped biological cycles corresponding in length to those of solar activity will be confounders with ignorance hidden by the term "secularity". Confounding and irreproducible results are inescapable when rhythmic functions are involved yet ignored. This prompts the rhetorical question: What variables are not rhythmic?

On the positive side, the time relations of solar activity to steroid excretion were found with the right timing (a small lead in phase) for a putative role played by the sun in affecting hormones that relate to resistance to disease (*7, 21, 43, 53*). This hint from both the periods and the phases involved is strengthened by a cross-spectral coherence between the two variables, 17KS and WN. A partial chronome map of periods showing rhythms with many frequencies modulating a prominent circadian component was found. This and similar information can be usefully considered in all investigations that involve studies with system times corresponding to just one component in the spectrum of a given variable investigated, such as steroid excretion and innumerable others. What may appear to be focused research on the circadian system may actually be subject to a host of intermodulations.

Multidecadal rhythms may relate to the non-photic environment, a possibility suggested first by a scrutiny of mechanisms by superposed epochs with controlled epochs, by superposed cycles and by following spontaneous changes in solar or geomagnetic activity, for associations in the biosphere when certain components in the spectrum of the sun are present, or absent, i.e., by an approach comparable in endocrinology to the removal of a gland and its replacement by its hormone. The story of these decadal and multidecadal rhythms in the past few years repeats the story of circadians, which, only half a century ago, were regarded as trivial associations of emotions, exercise and diet, until a genetic basis was clarified.

Non-overlapping 95% confidence intervals between environmental cycles and the near-matching biological cycles, the two associated by the "remove-and-replace" approaches just discussed, suggest that some decadal or multidecadal rhythms are anchored in our gene pool. The intermodulations among cyclic mechanisms in the broader chronomes, in and around us, resolved by time series analysis, replace, as time-specified feedsidewards, the time-unqualified feedbacks or feedforwards (*2*).

Chronometa-analysis

Chronomics can provide much new information where the naked eye, even when accompanied by an analysis of variance, has limitations (*62*) or fails (*63, 64; cf. 52*). In an elegant study, thoroughly carried out, c-Fos immunoreactive cells in suprachiasmatic nuclei (SCN) of rats were studied around the clock at 2-hour intervals. The rats had been previously synchronized under two different lighting regimens, one group in light (L) for 16 hours and darkness (D) for 8 hours, i.e., LD16:8, the other on the opposite photofraction, in LD8:16. For the 24 hours of the experiment, the rats had been released into continuous darkness as a prolongation of the dark span. Each data series taken off the published graph was analyzed by a single cosinor at a trial period of 24 hours (notwithstanding an uncertainty that could not be clarified concerning one outlier). Parameter tests were applied for the purpose of two kinds of comparisons: first, of any effect of the lighting regimens on the SCN as a whole and separately on each part of the suprachiasmatic nucleus, and second, a comparison was made of the dorsomedial vs. ventrolateral part of the SCN on each of the two lighting regimens.

The circadian amplitude differed between the dorsomedial and ventrolateral parts only for rats that had been kept in LD16:8 and not for rats that were kept on the regimen with a short photofraction, LD8:16, which displays the fitted cosine curves as a function of time to the data expressed as a percentage of the series mean. There is thus an effect of one of the lighting regimens on the circadian amplitude of the c-Fos immunoreactive cells, even after the difference in MESOR has been taken into account, showing an effect in rats exposed to the long but not in those on the short photofraction.

The latter results, irrespective of timing, can be regarded as particularly pertinent in any comparison of biological chronomes exposed to more vs. less light per day. This problem was considered with focus on multiseptan rather than circadian rhythms, for comparisons of dental chronomes in contemporary vs. ancient civilizations, the latter without artificial light (*65*). From a methodological viewpoint, the quantitative inferences that can be drawn by chronomics provide a more powerful approach than an analysis of variance (*66*). The merits of discussing separately the different characteristics of rhythms add the consideration of the amplitude to that of an average (for the sake of brevity, the phase difference also apparent when the zero phase became "light on" is here not considered). Our results are intended to show that the scope of time-macroscopically valuable research can be extended by quantification via chronomics. In another case cited, chronomics have detected and quantified a melatonin rhythm objectively (*52*). There, the naked eye not only failed to quantify multiple components (*52*) but missed the occurrence of a rhythm as such (*63, 64*). In each case, major macroscopic opinion leaders were involved.

Problems for the future: 7-day/24-hour monitoring of newborns' blood pressure dynamics

Based on the maximum sampling allowed by the "ethics" of the time, blood pressure and heart rate could be autonomically measured half-hourly on healthy human newborns only for 48 hours. Such data in 1985–86, summarized by cosinor as a group phenomenon, show a circadian rhythm of systolic blood pressure in the case of a positive (top) but not in that of a negative (bottom) family history (FH) of high blood pressure and/or other vascular disease. During the years 1987–89, the circadian amplitude of blood pressure in newborns had increased with statistical significance in babies with a negative, but not in babies with a positive FH. We sought but could not find any difference in the way the babies were handled, except that the years 1985–86 coincided with a solar minimum, and the ensuing years with the ascending stage of solar activity in the about 10.5-year sunspot cycle. Clearly, we needed data over spans longer than 48 hours to understand circulatory dynamics in the first week of life, a task to be accomplished in keeping with the then still-prevailing “ethic” that healthy newborns are not to be monitored for more than 48 hours at half-hour intervals. The solution came from the circumstance that some babies could be studied for 48 hours during the first two days, while others could be studied during some other two consecutive days in the course of the first post-natal week. Thereby, we could explore, with serially independent sampling, any weekly component in the data pooled (from dozens of babies, eventually from a total of 164 babies, each providing 48-hour series). From the integration of such separate 48-hour observations a weekly pattern could be constructed, found to differ as a function of family history, in the time domain.

Longitudinal sampling on the same individual in health for the first 40 days of life has confirmed the initial great prominence of the biological week (*67*). The systematic individualized sampling of groups of babies in health is indicated preferably for longer than the first week of life, to seek a test in the newborn that should assess the risk of developing a high blood pressure later in life, irrespective of solar cycle stage. In considering these results that should prompt further work, we undertook, during the past decade, the hazardous journey from the newborn’s putative sensitivity to the solar cycle stage to broader effects of the cosmos that appear perhaps in the form of magnetolability and lead to associations of morbidity and mortality and many human affairs with various aspects of our physical environment.

For practical vascular disease risk assessment at all ages, we require long-term, at least week-long monitoring (until lifetime surveillance becomes practical), as the basis of a preventive health care that acts before the *fait accompli* of a disease, that detects changes in the usual value range and responds to the changes in dynamics therein. On the positive side, this is documented for adults based on a summary of 2,736 individuals monitored by 158,177 measurements. The steps taken by the Brno chronobiologic team, in well over 100 published titles within a decade, starting with the timing of aspirin (*68*) and most recently dealing with circadecadal cycles (*69*), and even earlier in the footsteps of Mendel’s concern for meteorology, all led to a cooperation between Brno and Minnesota. Our original approach to the prevention of vascular disease that worked on a population basis at different ages for 2 years was overpowered by the solar cycle at the very sensitive pre- and perhaps perinatal age that may be characterized by magnetolability under circumstances yet to be elucidated. We are trying to make a confounder into a friend by pertinent methodology (*70*). Whether these chronomes will also elucidate intentionality (*71*) and the dimensions of physicists approaching emotions, the mind and spirituality in purely physicomathematical terms, remains to be seen. This 82-year-old can tell about this beginning, but others will live to complete it. From a physical viewpoint, the prominent Stanford professor emeritus William Tiller writes (*71*):

The goal of science is to gain a reliable description of our natural phenomena, so as to allow accurate prediction within appropriate limits, of nature's behavior as a function of an ever-changing environment ...

Indeed we need

internally self-consistent knowledge about the relationships between different phenomena and different things.

(For "different things" read "cycles".) In these definitions, with which we agree, useful but as yet missing information relates to the time horizon, the information on the very many rhythms as they organize chaos and undergo trends, i.e., the information on the chronomes of an ever-changing demography. There is a need for mapping by chronomics the entities involved in these cycles, indeed the sets of phenomena that share the wave particle duality (*71*). Against this background, the mapping of quasi-spontaneous cycles in religious activity and the mapping of other cycles related to the brain, some perhaps antithetical ones such as those involved in criminality and war, may be the challenge of those interested in both the ills of the individual that seem to be much more amenable to an empirical approach and the ills of society that are much in the forefront since the terrorist attacks of September 11, 2001, and require an even more urgent solution.

Glossary

The introduction of terms here has been guided as previously (*72, 73*) by the consideration of brevity, but also of familiarity with at least part of a neologism (the ringing of a bell) and most importantly by staying away from implying any mechanism involved. Instead, the basis of the terms is the numerical indication of the length of the period, in preference usually to the (reciprocal) frequency, since a majority of people can think easier in the time than in the frequency domain, notably in the case of long periods. Exceptions such as "ultradian" and "infradian", relating to frequencies rather than to periods, are prompted by the desire for using the precedents of "ultraviolet" or "ultrasound" for frequencies higher than the visible or audible, and likewise we have the precedents of "infrared" and "infrasound" for frequencies lower than the visible or audible. Many terms will require compromise to reach a unified transdisciplinary terminology in view of the discrepancies between the frequencies introduced by physicists and engineers on the one hand and those of biologists on the other. For biomedicine, the very low frequencies of the physicists are relatively very high. The terms here prepared or their equivalents in English will have to replace the "high", "low", "very low", and "ultralow" frequencies currently used by scholars in heart rate variability, as HF, LF, VLF, and ULF. It is not only clear that these frequencies are far from being the lowest, when heart rate variability is shown to exhibit a circadecadal rhythm. Eventually, the currently broadened system time for an ECG from a few minutes to 24 hours or to a few weeks, but as yet only on demand, will be switched to continuous surveillance with as-one-goes windowing, compacting, and broader and broader recycling by repeated passes over the larger and larger accumulating data set by broader and broader moving cosinor windows.

A c k n o w l e d g e m e n t

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