Chronomics: Imaging in time by phase synchronization reveals wide spectral-biospheric resonances beyond short rhythms\(^1\) (“Wenn man über kurze Rhythmen hinausgeht”)

In memoriam – lost future†: Dr.-Ing. habil. Dr. rer. nat. BARBARA SCHACK: 1952–2003

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Setting the stage

Dr. Barbara Schack is no longer with the authors of this paper, who are her students of all ages. After overcoming the deep shock of her death, so that others may benefit from her contributions, we list her biography and bibliography, and illustrate the fruits of intense research by her during the past 15 months with a series of figures prepared by her in Appendix A, qualifying this appendix by emphasizing that any misinterpretations are ours, not hers. We do this against the background of Appendix B, the latter an abstract, qualified in the light of subsequent one-on-one cooperation. Appendix B was never submitted to a meeting in June 2003, since she rescheduled her trip to Minnesota after she received an invitation by Rodolfo Llinas and Urs Ribary to a workshop on magnetoencephalography (MEG). She very gladly accepted this invitation but could not attend. As a co-worker of Herbert Witte, who defines her methods and concepts mathematically in Appendix C, Dr. Schack was involved for many years in the functional imaging of the human brain. Herein, we consider her recently broadened concepts with the inclusion of chronomes, i.e., a temporal imaging of relations between human myocardial infarctions and solar activity. Her methods are applicable to many aspects of chronomics, the imaging of time structures in and around us.

An immediate reason for this note was to communicate this information to those assembled at a workshop on MEG (Cold Spring Harbor, NY, July 30–August 4, 2003). Urs Ribary, the director of the workshop, writes:

The goal of the workshop was to discuss the nature and significance of MEG signals, the state-of-the-art analysis tools and its potential applications in basic and clinical research with focus on oscillatory human brain activity.

Over the past years it became evident that the properties responsible for the mental representations underlying all aspects of cognition and memory from linguistic perception and production to thought can be viewed as functional states in the sensory, motor and

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associative brain systems. Because such cognitive events are encoded in the temporal domain of neuronal activity, electrical pinpointing of the where and when of such activity provides an unsurpassed window into brain function. In particular, the distributed coherent electrical properties of central neuronal ensembles are considered to be a promising avenue of inquiry concerning global brain functions. The intrinsic oscillatory properties of neurons, supported by a large variety of voltage-gated ionic conductances are recognized to be central elements in the generation of the temporal binding required for cognition. Research in neuroscience further indicates that oscillatory activity can be correlated with both sensory acquisition and pre-motor planning, which are non-continuous functions in the time domain. From this perspective, oscillatory activity is viewed as serving a broad temporal binding function, where single-cell oscillators and the conduction time of the intervening pathways support large multicellular thalamo-cortical resonance that is closely linked with cognition and subjective experience. Temporal conjunction is viewed as a form of mapping where sensory inputs that are related to each other are bound by their electrophysiological coincidence. MEG is a truly non-invasive functional brain imaging technique, monitoring the electrical activity of nerve cells within the human brain. The methodology, using state-of-the-art whole-head MEG scanners, allows the localization and monitoring of human brain functions dynamics in three-dimension with a few mm accuracy and with a fast time resolution of less than 1 msec.

Dr. Schack's work and expertise have already contributed to the field of neuroscience, especially the careful description of coherence between theta and gamma oscillations during memory tasks in humans. In addition, Dr. Schack was collaborating with various clinical and basic research investigators and their important findings were published in numerous journals [1–103; cf. 104–108]. Unfortunately Dr. Bärbel Schack was never able to come to the workshop and her expertise could not be integrated with the ongoing discussions. Dr. Bärbel Schack was deeply missed at the workshop and we will keep her in good memory.

Bärbel's brief biography and her bibliography are pertinent further to a broad community of chronobiologists interested in the science of diversity in time and in chronomics, the mapping of chronomes, i.e., time structures and thus also to mapping brain function by MEG.

Personalia

Dr. Barbara (Bärbel) Schack, assistant professor of medical informatics at Friedrich Schiller University in Jena, Germany, drowned while swimming in Lake Owasso, Roseville, Minnesota, in the early morning of July 24, 2003. Bärbel was a master in analyzing transiently phase-coupled oscillations in processes covering widely differing time scales. It is difficult to conceive that Bärbel is no longer with us in person, but her concepts about various types of phase-synchronization, including processes more or less loosely coupled at multiple not necessarily harmonic frequencies and documented facts noted herein remain a treasure for transdisciplinary science.

After a few days of full-time and overtime tête-à-tête discussion and an extensive cooperation for some of the preceding 15 months, Bärbel will be warmly remembered beyond Minnesota by the worldwide group of investigators on problems of the Biosphere and the Cosmos (BIOCOS), as well as, among others, by her collaborators in Jena, Vienna, Salzburg and Berlin. For the Minnesotans, just as for her institute head Prof. Dr. Herbert Witte and her fellow Wolfram Hesse in Jena when they received the news, it proved to be very hard to realize her passing. It must be even more difficult for her family, who wish to make their own arrangements in her memory in private.

To her academic family, the size of which is apparent from the many co-authors in her bibliography (1–103), we are also the bearers of professional developments and findings. Her concepts and results to be further documented were that relations among certain events and processes are so intimately interwoven that they can be mathematically expressed across very broad ranges of frequencies.

Bärbel Schack was born on March 15, 1952, in Waren–Müritz, Seeplatte, a region known for its many lakes, not unlike the state of Minnesota in which she spent the last four days of her life. After finishing high school, she studied mathematics at the University of Yerevan, Armenia, for five years. She earned a diploma in mathematics at Yerevan in 1975, a PhD in mathematics at the Friedrich Schiller University of Jena, in 1980, and a doctorate in engineering (with habilitation, a title and academic level conveying the right to lecture) from the Technical University of Ilmenau, Thüringen, Germany.

Bärbel also earned habilitation from the University of Jena, and was considered the leading candidate for a professorship in "Biosignal Analysis" at the Institute of Biomedical Engineering and Informatics in Ilmenau. Bärbel was a member of the German Society for Biomedical Engineering (DGfMT), the German Society for Medical Informatics, Biometry and Epidemiology (GMDS), the International Organization of Psychophysiology, and the Commission for Scientific Visual Imaging of the Austrian Academy of Sciences. She served as a reviewer for the journals Biological Cybernetics; International Journal of Bifurcation and Chaos; International Journal of Psychophysiology; Psychophysiology; Biomedical Journal; Anesthesiology; Theory in Biosciences, and IEEE Transactions in Biomedical Engineering, and was a member of the Editorial Board of the International Journal of Psychophysiology.

Bärbel arrived in Minnesota in the mid-afternoon of July 20, 2003, with two heavy pieces of luggage. The senior author so valued her coming that he obtained special permission to go to the gate; at the gate he persuaded an employee to go into the plane, where he called her by name and helped her off with her bag. We went to a club, had refreshments, and began a very interesting professional talk. Before we left the airport, Bärbel was offered a choice of staying at a three-star hotel near the University, at a townhome or to a lakeshore home. She emphatically preferred the home on the lake, and when she saw the view, repeated that she much preferred the lake home to a hotel or to anything else in town. The same evening, we continued our professional discussions over dinner, as we did during all other meals except for breakfast, for which Germaine Cornéllissen, the director of our center, had stocked the refrigerator. Dr. Cornéllissen looked after Bärbel, picked her up in the morning and brought her home at night. Her computer ran most of the day, and she received free access for the future to the University of Minnesota’s supercomputer. On the evening before her scheduled afternoon seminar in the department of statistics, she introduced the senior author to some of her methods, and completed further analyses that yielded new findings for all of us. Bärbel was very proud of her good physical shape, emphasized her membership in a fitness club (Turnverein), and on each of three mornings she swam back and forth across the lake (a round-trip distance of about two-thirds of a mile). Sadly, on the fourth morning she did not return alive from her swim.
For Hellmuth Petsche, Emeritus Professor of the Institute for Neurophysiology at the University of Vienna, as he writes in a letter translated from his original German at his request, Bärbel was a scientific daughter. Early on, he also learned first-hand of her basic professional competence, sincerity, unusual ability to work, and above all, of her creativity. He came to esteem her unusual character very highly, using the old German word Lauterkeit, conceivably “unblemished-ness”, to characterize her. He was very pleased to be allowed to become her mentor, and was grateful that she allowed him very intensively to participate in her scientific development. Foremost, it was his endeavor to fortify her belief in herself and to help her become convinced of her own worth. Thanks to her, he could think along with her at the frontier of his science for many years after his becoming emeritus. Prof. Petsche writes further that he also encouraged Bärbel to devote herself fully to endeavors in chronomics, and Bärbel did so even overtime. He and Bärbel were convinced that the work on the diverse Minnesotan time series, which she analyzed with feverish enthusiasm, would become a decisive new and successful step for her better understanding of the complex relations among seemingly independent areas. He describes Bärbel’s interest in enlarging her perspective (by chronobiology and chronomics) by coining the neologism Entgegenfieber, meaning “enthusiastic fever”, in a positive sense.

Like all of us, Wolfgang Klimesch, Professor of the Institute of Psychology at the University of Salzburg, was moved deeply by Bärbel’s death. He wrote:

I became acquainted with her via Prof. Petsche whom with whom we both had/have a close personal and scientific relationship. In the many discussions with Hellmuth Petsche, he was emphasizing repeatedly that Bärbel has those mathematical tools developed that are badly needed for a better understanding of brain oscillations. I was very happy that Bärbel became interested in the idea that even ERP’s can be explained by evoked oscillations. Highly important research was carried out already by other [investigators], but what was needed was a comprehensive program focusing on the development of appropriate methods to analyze phase relations within and among different frequency domains. She was working on that pioneering edge of research. Her paper about n:m phase synchronization in a short-term memory task (published in 2002) is to my knowledge the first of its kind demonstrating phase coupling between theta and gamma rhythms in the human EEG. We were currently working on a manuscript about theta : upper alpha phase synchronization when her death suddenly ended our research. Her emails from her last days in the US were so much emphasizing how excited she is about the kind hospitality and the joy of swimming in the morning.

Bärbel was a gentle friend to me, so interested showing me the application of the complex and elegant mathematical tools she has developed. She was fascinated – as I was – by the idea that these tools allowed completely new insights for a better understanding of the EEG and brain oscillations in particular. I am so grateful that I could join her on her scientific path for almost a year.

With gratefulness and great respect for Bärbel as a friend and scientist, …

Bärbel Schack was pleased by her stay in Minnesota, according to a letter written to Sabine Weiss and another note which describes her experience in Minnesota as “extremely interesting”. “Away from conventional provincialism, there are findings about rhythms of many kinds with insight into their coupling. We tried to sort out the results found thus far for a relation with solar activity of the heart and circulation in disease. The interaction is unbelievable and very clear if one broadens one’s perspective beyond the short [period] rhythms.” Her German text follows. (The insert in [ ] is ours.)


With the shock of her death, Hans-Georg Geissler referred first to Rilke’s “lost future” (109):

Klage

Wem willst Du klagen, Herz? Immer gemiedener ringt sich dein Weg durch die unbegreiflichen Menschen. Mehr noch vergebens vielleicht, da er die Richtung behaelt, Richtung zur Zunkunft behaelt, zu der verlorenen.


Complaint

To whom shall you complain, heart? Ever more shunned your way wrestles through the impenetrable people. The more to no avail perhaps, because it holds to the direction, holds to the direction of the future, to the lost ones.

In the past. You complained? What was it? A fallen berry of Joy, unripe. But now my whole Tree of Joy is breaking, in the storm my slowly grown Tree of Joy is breaking. Most beautiful thing in my invisible landscape, you who made me more knowable to angels, invisible ones.
On a happier earlier note, the senior author wrote to Hans-Georg Geissler (who had introduced him to Bärlbel through his publication with her [40]):

Hier sind wir versammelt zum lübben Tun
Weil die Bärbel Schack kann nicht ruhn
Sie ist unser lieber Lehrer und Gast
Und wir haben so manches von Ihr erfasst
Es verschwinden interdisziplinäre Schranken
Dafür wollen wir Ihnen allerherzlichst danken

Geissler replied:

Wie sehr mich diese Botschaft erfreute;
denn nichts ist besser für älte Leute
als sich am Schaffen anderen zu freuen
und damit die eigene Kraft zu erneuern.

Bärbel Schack war in Minnesota hoch willkommen
Davon haben Ihre Freunde direkt von Ihr vernommen.
Den Owasso-See hatte Sie dreimal
Davon haben Ihre Freunde direkt von Ihr vernommen.

In this sense, we wish to do what Hans-Georg wanted, and it remains our challenge with the modified title of “Future history” rather than concluding as we did above, as an immediate response to the news of Bärbel’s death, with Rilke’s “Complaint” or “lost future”.

Verlorene Zukunft oder eher Zukunftige Geschichte

Bärbel Schack war in Minnesota hoch willkommen
Davon haben Ihre Freunde direkt von Ihr vernommen.
Den Owasso-See hatte Sie dreimal überquert
Eins einstes Mal war Ihr nicht beschert.

Den Owasso-See hatte Sie dreimal
Davon haben Ihre Freunde direkt von Ihr vernommen.

Verlorene Zukunft oder eher Zukunftige Geschichte

In der transdisziplinären Wissenschaft
Hatte Sie überaus produktiv geschafft
Sie hat jedem von uns so sehr Viel geschenkt
Ihr Nachlass soll noch lange in unserer Mitte leben,
Die Hoffnung die wir hier entschieden hegen:
Sonst kommt Bärbel Schack nicht mehr hierher

Oh jeh! würde die Bärbel selbst sicher sagen
Wenn wir über Sie als Verlorene Zukunft klagen!
Diese Fassung von Hans-Georg Geissler adaptiert,
Als erste Reaktion, nach Rilke treffend modifiziert,
Gibt Raum einer gewonnenen Geschichte
Sonnenschein Bärbels Schaffen zunichte.
Die Hoffnung die wir hier entschieden hegen:
Ihr Nachlass soll noch lange in unserer Mitte leben,
Ihre Lektionen die wir so gerne vernommen
Sollen erweitert in transdisziplinäre Lehrbücher kommen

Bärbel besass Kompetenz und Lauterkeit
Diese Bezeichnungen hatte Helmut Petsche bereit
Als Herbert Witta’s Mitarbeiter hat Sie schon belegt
Wes über 10 Grössenordnungen von Frequenzen geht
Oh in Jena, Wien, Minnesota oder Salzburg
Ihr Gedenken ist eine sehr feste Burg
Es ist eine Basis für fieberhaftes Überbrücken
Der vielen heute existierenden Lücken
Das Gehirn mit seinen etlichen vielen Herz
Hängt eng zusammen mit dem wetteifernden Herz
Die Atmung hinkt dann langsam danach

Circadiane Rhythmen sind in jedem Gemach
Dann kommen biologische Wochen und ein Halbjahr
Die beide uns die jahrlöse Geomagnetik gebahr
Winter-Sommer folgen und sind drastisch beim Katzenhai
Aber viel weniger regulär in uns selber dabei
Das humane Circannualsystem wurde uns erst klar
Als uns der Sonnenwind das 1.3-Jahr-lange Tranzyahr gebahr
Wir finden das Tranzyahr in 52 von 52 auch jahrzehntelangen Zeireihen

Die uns Kollegen als Puls und Blutdruck lieben
Dank Wissenschaftern die von der Chronomik verlesen
Nach immer enthusiastisch sich rund um die Uhr messen.
Wiederholt das Tranzyahr die Ubiquität vom Circadiansystem
Aber endogene Aspekte aufzudecken ist nicht so bequem
Sich nicht überlagernde Konfidenzintervalle sind ein Kriterion
Diese finden wir im Tranzyahr und freuen uns schon.
Wenn ohne es zu wissen das biologische Jahr und Tranzyahr

Rhythms with frequencies above 1 Hertz

According to Sabine Weiss, with whom Bärbel worked enthusiastically shortly before she left for the USA: “One of Bärbel’s major interests was the investigation of cerebral oscillations related to human cognitive processing based on electro- and magnetoecephalographic data. [Schack and Weiss extended and adapted] state-of-the-art techniques and developed several new approaches [to gain] new insights into the brain’s activity during different high level cognitive processes, such as thinking, music perception, memory processes and language comprehension (e.g., 26, 29, 34, 47, 54, 92, 102). In particular, she was engaged in developing methods based on the application of an adaptive fit of bivariate autoregressive moving average (ARMA) models. With this approach she was able to investigate dynamic neuronal interaction with high time and frequency resolution. Her coherence and cross phase analyses during memory and language processing revealed a new picture of brain activity accompanying these processes, showing that the engagement of different neuronal networks changes very dynamically during the ongoing cognitive process.

“Beyond the study of many new measures and variables to determine the meaning of neuronal oscillatory activity within different frequencies, [Schack and Weiss’] most splendid step was the application of 1:1 phase synchronization and in particular n:m phase synchronization on EEG data during verbal memory encoding. These results are adding a new dimension towards a theory on the meaning of brain oscillations...
and the functional interplay among neural networks” (according to Sabine Weiss).

**Phase in chronobiology**

In a glossary in 1977 (110), focusing primarily but not exclusively on circadian rhythms (111), we defined “phase” as the “instantaneous value of a biologic variable at a fixed time” and noted that phase usually is considered only as an indication of time (e.g., within a cycle), without indicating the actual value of the variable associated with a phase, i.e., as an abbreviation for phase angle. Such an instantaneous phase within a cycle may be considered in relation to some (e.g., angular) transformation of time, with 1 cycle or period equated to 360°.

We defined “phase angle” as “a time point in a periodicity considered in relation to another specified time point”, as the acrophase, namely as the phase angle referring to the crest time of the [single] cosine curve fitting the data in relation to a specified reference time, such as local midnight or the middle of the rest span. In chronobiology, a meaningful phase angle reference is essential, and the nature of this reference can be made obvious by the notation of one of several (computative, external and internal) acrophases [110]. Use of the term phase angle in biology may thus be limited at best to consideration of macroscopic data. Since the term is unspecific with respect to reference point, it should be replaced by acrophase in any discussion of [time-]microscopic analyses. In composite words such as acrophase, the component phase actually denotes phase angle (the word angle being omitted for the sake of brevity when the prefix acro is used). We refer to an orthophase when a model consisting of a combination of two or more harmonics is used to estimate a rhythm’s timing as the lag from a defined reference time, the orthophase reference, to the crest.

“Acrophase” (\(\phi\), \(\varphi\), \(\Phi\)) is defined as a measure of timing; the lag from a defined reference timepoint (acrophase reference) of the crest time in the function appropriately approximating a rhythm; the phase angle of the crest, in relation to the specified reference timepoint, of a single best-fitting cosine (unless another approximating function is specified).

Units for an acro- or orthophase are angular measures such as degrees and radians; time units: seconds, minutes, hours, days, months, years or decades; or physiological episodic units: number of heartbeats, respirations, etc. Angular measures are directly applicable to any cycle length and hence are proposed for general use because of greater familiarity; degrees (with 360° = period of rhythm) are preferred over radians.

The acrophase and orthophase are microscopic measures of timing and are hence not to be confused with the peak macroscopically determined as the highest point of a recurrent pattern. Three types of acrophases have been considered: the computative, external and internal ones (Figures 1 and 2 in ref. 110, pp. 116 & 117). For example, the circadian acrophase, \(\phi\), may be given in clock hours and minutes on a 24-hour cycle, with midnight as reference timepoint, or the circannual acrophase may be given in months and days on a one-year cycle with December 22nd or June 22nd of the previous year as acrophase references on the northern or southern hemispheres, respectively. This practice is not recommended in itself. It should be accompanied by an indication of timing in degrees (or radians) allowing for direct comparison of acrophases on different cycle lengths.

For some episodic time scales, as well as for, e.g., free-running rhythms with different frequencies, the distance between two physiological events or the period can be equated with 360°. In relation to those two events, one may then express the location of another kind of event (to be studied in relation to events of the first kind).

Other episodic time scales serve students of cardio-respiratory interactions who may express the number of heartbeats not in relation to certain time units but rather to the span elapsed between two consecutive inspirations, whatever the length of that span may be (e.g., 2 heartbeats after start of a given inspiration). By the same token, one may relate the frequency of other physiological phenomena, including changes in mental or physical performance, to the span elapsed between two consecutive awakenings or two consecutive onsets of menstruation or two consecutive events with even lower frequency.

**Acrophase from single and population-mean cosinors below 1 Hertz**

Clinicians have known for over a century and a half that in some patients with convulsive disorders, seizures occur rather consistently at one or another time of day. When each seizure in such patients is assigned to the time of day when it occurred – such data were then available, thanks to the perspicacity of the superintendent of a state hospital for persons with epilepsy – some clearly apparent time-macroscopic patterns are seen, as reported by others earlier and reviewed in 1953 (112). By 1952, we had also determined either the percentage time in which paroxysmal discharge dominated the record or the number of spikes, one or the other in hard copies of 5-minute-long electroencephalograms (EEGs) repeated every 90 minutes for 24 hours during many sleepless 24-hour days (113–116). It seemed of interest to view these time-macroscopic records objectively as rhythms with phases estimated with their uncertainties. Before us, Ed Batschelet – also then concerned with phase at a given fixed single frequency (118) – found some useful information in the domain of phase on other topics and without usually weighting by the amplitude. The cosinor in its broadest sense, had followed Ed with an amplitude-weighted phase that could also be considered as a phase-weighted amplitude (119–126). After that came the cosinor spectrum and the combination of this linear method with nonlinear least squares to estimate confidence intervals for the
period to result in a gliding spectral window, all placed with parameter tests on an inferential statistical basis and thanks to least squares, applicable to unequidistant data.

Figures 1–5 illustrate rhythmicity, called “circadian” (111) along the 24-hour scale in seizure incidence, Figures 1–4, and in paroxysmal EEG discharge, Figure 5 (116, 117; cf. 113–115). The left side of Figure 1 shows that on the average, the number of seizures stacked per unit time and expressed as percentage of series mean can vary greatly in two clinically constituted groups. The data of 6 patients, 4 male and 2 female, with a nocturnal incidence of 11,945 seizures are compared with those from 5 patients, 4 male and 1 female, with a diurnal incidence of 1,997 seizures. By clinical definition they are in antiphase; yet to quantify this time relation, the population-mean cosinor method is applied on the right, to the time-macroscopically displayed data on the left. The 95% confidence intervals non-overlapping the pole (center) provide an estimate of the uncertainties involved. Figure 2 is a summary of seizure incidence for each of 2 patients again based on abundant data. Both Figures 1 (right) and 2 show amplitude-weighted phases as point and interval estimates. In these cases, the hypothesis of “no circadian rhythm” was rejected, a result serving to establish the group rhythm in Figure 1 and the individuals’ rhythms in Figure 2.

Figure 3 plots only phases, but again these are derived with amplitude weighting by the cosinor (119–126) and again the individual’s 95% confidence interval is provided when the zero-amplitude hypothesis is rejected. Because of nonsinusoidality in some cases the hypothesis of no-rhythm cannot be rejected. In these cases, only point estimates are provided, notably in cases with a peak in seizure incidence around arousal. Figure 4 shows again a quantification of the seizure incidence in 6 individuals, including one (subject A) for whom the 95% confidence interval overlaps the pole (center) of the graph, and in such a case, again (only) a point estimate of parameters is given, the failure of hypothesis testing notwithstanding. Figure 5 in turn summarizes EEGs performed about 54 years ago using up bushelbaskets of recording paper (113–117). By inspection of the record on a hard copy, the percentage of time in paroxysmal discharge was measured and different patterns clearly emerge with the rejection of the no-rhythm hypothesis. In all of the single cosinors and in a population-mean cosinor in Figures 1–5, the phases are estimated at a single fixed frequency of 1 cycle in 24-hours.

In other cases, in phase charts one can use “rubbery” time when, for instance, phases are summarized at physiologically similarly meaningful but numerically different frequencies such as a free-running circadian

**Figure 1.** Circadian group rhythm of seizures in patients with convulsive disorder plotted time-macroscopically (left) and analyzed time-microscopically (by population-mean cosinor, right). The elliptical 95% confidence region that does not cover the pole (center) documents the rejection of the zero circadian amplitude assumption (in keeping with a rhythm with a frequency near that fitted). © Halberg.
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**Figure 2.** Individualized single cosinor assessment of seizure incidence in two patients on the same hospital routine. Such information may serve for the timing of medication and for study of etiology. © Halberg.

**Figure 3.** Display only of phase from individualized single cosinor assessment, as shown in Figure 2. Point estimates of phase are given with their 95% confidence arcs, except for cases when the hypothesis of “no circadian rhythm” cannot be rejected. Then, only a point estimate is provided. © Halberg.

**Figure 4.** Time-macroscopic (left) and time-microscopic (right) display of individualized single cosinor assessment of circadian rhythm in seizure incidence of six patients. © Halberg.
Figure 5. The time percent of paroxysmal discharge determined on hard copy EEGs in the 1950s undergoes a circadian rhythm, as was predicted for JS with an acrophase at -348° and a 95% confidence arc extending from -275° to -60°, thus including the point estimate of -26° for JS in Figure 4. The excessively wide arc is a reason for caution in considerations of time lags between the average times of onset of EEG-revealed pathology and of seizure incidence, although the 95% confidence intervals for the two variables greatly overlap one another for JS. Not only seizure incidence, but the temporal placement of circadian rhythms in pathology shows circadians and the acrophase differences between EEG and overt pathology may provide clues about mechanisms and may be considered in timing medication. © Halberg.

Figure 6. A series of daily incidence of myocardial infarction (MI) in Moscow during 1979-1981 (years of high solar activity) (N=85,819) had been analyzed for associations with the local index of geomagnetic disturbance K. A statistically significant global cross-spectral coherence was found at a period of about 3.17 days (bottom). When the data were analyzed for each year separately (not shown), the same result was obtained during the first and third year, but reached statistical significance only in 1979; in 1980, a statistically significant coherence was again found at a shorter-than-3.5-day period. Similar cross-spectral coherences at almost the identical period (3.15 days) were also found with the Bz-GSE, the north-south component of the interplanetary magnetic field (Bz) (top). Statistically significant coherences between MI and Bz were also found for periods of about 26.9, 14.7, and 7.7 days, which correspond approximately to the major harmonic terms of the solar rotation around its axis. Original data of myocardial infarctions in Moscow from Tamara Breus. © Halberg.
frequency of humans or rodents differing among the time series examined (for free-running circadians see section ID of Figure 7 in [127]). Figure 10I in [127] shows the different frequencies of each menstrual cycle with the period lengths in these cases again being equated with 360°. We had also learned, what may again broaden the scope of electro- and magnetoencephalography alike, that the brain in health (128) exhibits circadians, among other rhythms with frequencies higher than 1 Hz, a point pertinent to Bàrbel’s prior work and to that of her many co-investigators! Apart from the brain, we had also learned that circadian phase is important for timing radio- and chemotherapy given to cancer patients (129, 130).

Inferential statistical considerations toward phase relations among time series, summarized by Christopher Bingham

A stationary time series \( \{X_t\} \) and even one that is only locally stationary, can be decomposed as a superposition of many terms of the form \( A_x(f)\cos(2\pi ft - \phi_x(f)) \) where \( f \) is a frequency in cycles per unit time, and \( A_x(f) \) and \( \phi_x(f) \) are random amplitude and phase. Near frequencies where there is periodic or near periodic behavior, \( E[A_x(f)^2] \) tends to be large. In fact, the spectrum \( S_x(f) \) of \( X_t \) is proportional to \( E[A_x(f)^2] \).

The stationarity of the series implies that \( \phi_x(f) \) should have the uniform distribution on the circle \( 0 \leq \phi_x \leq 2\pi \). When \( f_1 \neq f_2, A_x(f_1) \) and \( A_x(f_2) \) should be uncorrelated, as should \( \cos(2\pi \phi_x(f_1)) \), \( \sin(2\pi \phi_x(f_1)) \), \( \cos(2\pi \phi_x(f_2)) \) and \( \sin(2\pi \phi_x(f_2)) \).

Similarly a parallel stationary time series \( Y_t \) can be decomposed as a superposition of terms of the form \( A_y(f)\cos(2\pi ft - \phi_y(f)) \) where \( A_y(f) \) and \( \phi_y(f) \) have similar properties, with the spectrum \( S_y(f) \) proportional to \( E[A_y(f)^2] \).

If the two series are jointly stationary then the cross spectrum \( S_{xy}(f) \) at frequency \( f \) is proportional to the complex quantity \( E[A_x(f)A_y(f)\exp(-i(\phi_x(f) - \phi_y(f)))]) \), where \( i^2 = -1 \). This can be viewed as a weighted expectation of \( \exp(-i(\phi_x(f) - \phi_y(f))) \), the weights being proportional to the product \( A_x(f)A_y(f) \) of the random amplitudes.

The magnitude \( |\rho(f)| \) of the complex coherence \( \rho(f) = S_{xy}(f)/\sqrt{S_x(f)S_y(f)} \), the cross spectrum “adjusted” for the expected size of the random amplitudes, is 0 when the distribution of the phase difference \( \phi_x(f) - \phi_y(f) \) is uniform on the circle so there is no synchronization of the two series at frequency \( f \). The more concentrated is the distribution of \( \phi_x(f) - \phi_y(f) \), the more synchronization there will be and the closer will \( |\rho(f)| \) be to 1.

Thus the squared coherence \( |\rho(f)|^2 \) can be in part considered a measure of how closely linked are the random phases \( \phi_x(f) \) and \( \phi_y(f) \).

Another possible measure of the association between \( \phi_x(f) \) and \( \phi_y(f) \) is the magnitude of the unweighted expectation \( E[\exp(-i(\phi_x(f) - \phi_y(f)))]) \). Like \( |\rho(f)| \), this runs from 0 to 1, with 1 occurring only in the case of perfect synchronization.

When you have \( K \) replicate time series pairs, say \( K \) non-overlapping segments of fixed length, and are able to find estimates \( \hat{A}_{x,k}(f), \hat{A}_{y,k}(f), \hat{\phi}_{x,k}(f), \hat{\phi}_{y,k}(f), k=1,..., K \) of the amplitudes and phases, you can estimate \( |\rho(f)| \) by

\[
|\hat{\rho}(f)| = \sqrt{\frac{1}{K} \sum_{k=1}^{K} \hat{A}_{x,k}(f)\hat{A}_{y,k}(f)\exp(i(\hat{\phi}_{x,k}(f) - \hat{\phi}_{y,k}(f)))^2}.
\]

where the numerator is a weighted average of \( \exp(i(\hat{\phi}_{x,k}(f) - \hat{\phi}_{y,k}(f))) \). Similarly you can estimate \( E[\exp(-i(\phi_x(f) - \phi_y(f)))]) \) by

\[
\hat{\rho}(f) = \frac{1}{K} \sum_{k=1}^{K} \exp(-i(\hat{\phi}_{x,k}(f) - \hat{\phi}_{y,k}(f))).
\]

When there is no phase synchronization so that \( \hat{\phi}_{x,k}(f) - \hat{\phi}_{y,k}(f) \) is uniform on the circle, for moderate \( K \), 2K\(\hat{\rho}(f)^2 \) has approximately a \( \chi^2_2 \) distribution. The use of this statistic for testing uniformity is due to Rayleigh (Batschelet, E. 1981. Circular Statistics in Biology. Academic Press, p. 55).

A disadvantage of the use of PLI rather than \( |\rho(f)| \) is that, when \( \hat{A}_{x,k}(f), \hat{A}_{y,k}(f) \) is small, the distribution of \( \hat{\phi}_{x,k}(f) - \hat{\phi}_{y,k}(f) \) is close to uniform and provides little information about the phase synchronization at frequency \( f \). This will tend to reduce the power of the Rayleigh test as compared to a test based on \( |\rho(f)| \).

Cautionary note

In the case when replicated series are not available, the spectra and cross spectrum are usually estimated by weighted averages of periodograms and the cross-periodogram at frequencies near \( f \). This works well when the true spectra and cross-spectrum change little in the neighborhood of \( f \). The standard approximate tests and confidence intervals concerning coherence assume this near constancy of spectrum and cross-spectrum. When either \( X_t \) or \( Y_t \) has a very sharp spectral peak at frequency \( f \) which rises well above the spectrum at neighboring frequencies, the averages across frequency that make up the spectrum and cross spectrum estimates are dominated by the values of periodograms and cross-periodograms at \( f \) and the stabilizing effect of averaging is defeated. This can greatly damage the accuracy of the standard tests and confidence intervals.

In the extreme, when \( X_t = A_x\cos(2\pi tf - \phi_x) + \eta_t \) and \( Y_t = A_y\cos(2\pi tf - \phi_y) + \eta_t \), where \( (A_x, \phi_x) \) is independent of \( (A_y, \phi_y) \) and \( \{\eta_t\} \) are independent with much smaller variances than \( A_x \) and \( A_y \), the estimated coherence can be close to 1 although \( \{X_t\} \) and \( \{Y_t\} \) are independent of each other. When the coherence can be estimated by averaging across replicate series, this problem does not occur.
Lessons from Bärbel Schack

Bärbel complemented single (series) and population-mean cosinors and linear and nonlinear rhythmometry by the study of instantaneous relations among time series as these relations may change at many frequencies. We were in a position to validate the extreme sensitivity of Bärbel’s methods for time-varying quantification of phase coupling (phase synchronization, as she called it) by anticipating at least some of her results by global coherence published 12 years earlier (131) and recently republished (Figure 6 in reference 132). We had found that myocardial infarctions (MIs) show global cross-spectral coherence at a trial period of 3.16 days (overall and during two of 3 years analyzed separately) with both the north-south component of the interplanetary magnetic field (Bp) and the local geomagnetic index (K) in Moscow during the years 1979–1981, Figure 6a. Independently, Bärbel detected time-variant coherence and phase synchronization at the same frequency between MIs and local K in the same data set. Moreover, she extended the finding to reveal dynamic coherence and phase synchronization most prominently at the same frequency and at other frequencies between MIs and sunspots in 29 years of MIs in Minnesota.

Bärbel found further phase-synchronization at many more frequencies, not only among MIs and interplanetary and terrestrial magnetics, but also among MIs and variables of the solar wind in added cases where no prior information was available. This circumstance leads again to the problem of multiple testing. She found very small differences, i.e., a very tight phase synchronization, as one would expect, among many or almost all frequencies between the original data on MIs in Minnesota and the same data after detrending. This finding constitutes a reference standard, since we might anticipate it when looking at nearly the same time series before and after detrending. The same anticipation is validated for phase-synchronization found by her among geomagnetic indices such as the antipodal index aa, the planetary index Kp or the equatorial indexDst themselves. These findings all serve to validate her technique by the equivalent of good reference standards.

Phase synchronization of solar variables at a half-yearly cycle?

Bärbel was very cautious when her method for detecting phase synchronization picked up a phase relation (she called it “phase synchronization”) at the half-yearly trial period between Wolf’s sunspot numbers and the coronal index of the sun, and thought of possible blurring. At this half-year period, there were peaks in neither of the spectra of these two variables. In other words, she found a relation in two time series in a location without spectral peaks and at a frequency that was not anticipated, and these results require rigorous checking and cannot be interpreted in themselves. As others, we had found the presence of sharp peaks in aa, Kp, and Dst at a frequency of 1 cycle in half a year (133). Peaks at the half-year in geomagnetics can continue to be looked upon as terrestrial, not solar phenomena (133; cf. 131, 134–143). According to McPherron (personal communication), the Russell-McPherron effect depends on the tilt angle of the earth’s axis toward or away from the sun; but the problem also noted by McPherron is that “the historical records are not long enough to define well the statistical significance of various periodicities and correlations”.

The ~1.3 -year

Apart from the purely physical problems, it is interesting to find signatures of a half-year cycle (144) and of the ~1.3 (trans)-year of the solar wind in a number of biological variables. Again, these will have to be checked for whether they are current and/or past signatures of our cosmos in the biosphere (50, 73). On occasion in the human pulse or blood pressure, the amplitude of the trans-year can be greater than that of the 1-year component, i.e., the contribution of the mostly unseen solar wind can exceed that of changes from a hot summer to a cold Minnesotan midcontinental winter.

The helio-geophysical week

Abbott was the first to describe a near-week in rainfall (145). The sun’s magnetism shows a near-week (146), reminiscent of another very wobbly near-week rhythm with a frequency of 1 cycle in ~6.75 days in geomagnetism (131) which is found usually on earth, in data of the past century and again now in the aa-index series accumulated since the nineteenth century to the new millennium. This is at apparent variance with an earlier report (147) of a precise 7-day-week, found by a leading physicist in the data on a geomagnetic index when he happened to examine the series accumulated up to the early 1970s (147). His finding was fully confirmed by us for the span he happened to examine (148). We also found, however, that the spectral component of a precise week length was not reproducible in 22- or 21-year data sections of the geomagnetic index aa accumulated until 2001 (148).

Our finding of an overall near-but-not-precise week (131) in geomagnetics was confirmed by physicists (149, 150). Both the near-week and a precise 7-day human-made component gauging magnetic pollution were next found in Antarctica (151). It is anticipated that the relative prominence of the precise anthropogenic geomagnetic week will increase in amplitude further as a function of further increases in magnetic pollution. Accordingly, the difference between the amplitudes in spectra of aa, other complicating factors being what they are, is likely to disappear and eventually to change sign (148). If so, the way humans change their purely earthly environment can rest on clues from biology, by study of a periodicity believed to be purely social (by many) (152, 153). Bärbel, like us, found near-weekly components in her spectra.

The phase-synchronizations along with coherences among other relations Bärbel found earlier within the human brain along the time scales conventionally used by magneto- and electroencephalographers could be systematically extended along a scale of frequencies covering 10 orders of magnitude and along with the findings of relations of the human heart and the rest of the body to solar activity (131, 154–156). This could be an ambitious project for which chronomics provides maps for cost-effective sampling schemes covering the major cycles now known to be involved in just such long-term studies.

Some rhythms are genetically programmed (154–156), as are developmental trends in biological chronomics (157, 158), and the trends are subject to rhythms (159–161), as is chaos in biology (162, 163). We learned much from Bärbel, and the task at hand, for generations to come, is to continue an extension of phase synchronization by ascertaining the reproduc-
ibility and scope of what she did, preferably with amplitude weighting. Most important are computer routines, enabling time-varying phase-synchronization and coherence studies on unequidistant data that are very common in biology. Linear interpolation but not other methods used by Bärbel to bridge data gaps did introduce demonstrable artifacts in Germaine Cornélissen’s checking. Illustrative examples of Bärbel’s procedures are documented by her graphs in Appendix A, with information of A6 and A7 to be requested only from Herbert Witte.

Epilogue

To implement the wish that Bärbel’s legacy will turn her contributions into an essential of future history, it is hoped that the authors of this eulogy will maintain contact. Certainly replications of work on rhythms with frequencies above 1 Hz should record stages of circadian and circaseptan, among other rhythms including circadecadas and, when possible, vice versa.

Cycles with different frequencies are the reproducible features offering themselves for scientific investigation. Cycles already found characterize the diseases of society such as crime and war (164), that have periods measured in decades, as does spirituality (165); they involve human brains with more specific primary cycles above 1 Hz. The modulation by circadians of pathological electroencephalographic discharge was mapped over 50 years ago (113–117). The different types of seizure incidence were recognized in the 19th century (166). By the 1960s, circadians were mapped in the power of the different regions of the Berger range of the EEG of clinically healthy neurology residents (128). Eventually, human mood was shown to undergo a circadecal change (155) as well as circadian rhythmicity (167). Circadians and about 7-day changes differ for positive vs. negative affect (168).

It would be a surprise if cognition were to prove to be an exception and an even greater finding if this were so. The next step is to study rhythms both above and below 1 Hz by MEG, EEG and otherwise, in the search for mechanisms underlying diseases not only of individuals but also of populations. These are urgent tasks, second in importance to none, as we listen to each day and replace done by the solar wind of components with replacement of its hormone has a parallel in a subtraction and addition approach, with the subtraction and replacement done by the solar wind of components with validatable periods measured in decades. This may be the indispensable safeguard, since as yet there is no invaluable “blank” equivalent, which Bärbel sought for the last 15 months.

Circadecadas influence almost certainly not only the human heart, as various methods suggest, but also the brain. EEGs, MEG and other imaging and physiological approaches may provide clues to conclusions both at frequencies above and below 1 Hz. Bärbel’s methodology, as we see it in a chronomic perspective, brought us from global correlations and cross-spectral coherences to time-varying coherence and complementary time-varying phase-“synchronization”, extending by far the scope of a synchronization reported about half a century ago at a single frequency (169). Concurrent relations among multiple rhythms with different frequencies remain to be explored.

Conclusion

A medieval painter sent a bill to a monastery, charging them “x ducats for enlarging the sky and adding a few stars”. Bärbel in turn enlarged the study of galactic and/or solar influences upon human affairs by phase synchronizations, described at several frequencies. Thereby she enlarged the concept of phase in chronomics. Conceivably she opened the eye of those who, of necessity, first focus exclusively on rhythms within a limited range of more or less specific frequencies, but will greatly benefit immediately by consideration of rhythms with many more frequencies. In a letter to Hans-georg Geissler, included in the title of this memorial, she alludes to rhythms beyond short ones (”Wenn man über kurze Rhythmen hinausgeht”). In any event, we are reminded of the artist’s bill, since she added a star to the sky of science, second to none and priceless, namely herself. If she were to read this, she would say “Oh jeh, I am red-faced!” She need not have been; she deserved this eulogy by virtue of what Hellmuth Petsche called her Lauteurkeit, which is the best description of a scientist who follows whatever goes through her head (mir durch den Kopf geht), as Bärbel put it. In Bärbel, scientists with many interests, and thus transdisciplinary science, had a Kameradin like no other (wir hatten eine Kameradin), who kept on asking questions (presumably Einstein’s advice).

The region of Thuringen, that was home to the composers Johann Sebastian Bach and Franz Liszt, the painter Lucas Cranach, the writers Johann Wolfgang von Goethe, Johann Gottfried Herder and Friedrich Schiller, the poet Christoph Martin Wieland, the industrialist Karl Zeiss, and the physicist and mathematician Ernst Abbe, can now claim Bärbel Schack as a transdisciplinary scientist. Themes of her bibliography fit the diversity of her predecessors. Bärbel built bridges from her disciplines, engineering and mathematics, to endeavors in the letters, the broader humanities, related to language and cognition, all requiring the increasingly more complete mapping of our make-up in time and space, the topics of complementary genomics and chronomics.
Appendix A of figures by Barbara Schack

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Chronobiologic analyses of data on daily mortality from MI in Minnesota during 1968–1996 revealed the presence of about-yearly and about-weekly variations peaking in the winter and on Mondays, respectively, and further an about-10.5-year component similar in

Figure A1. Power spectral densities (PSD) of the daily incidence of mortality from myocardial infarction in Minnesota during 1968–1996 (29 years) (after removal of a linear decreasing trend) (top) and of Wolf numbers (reflecting solar activity) (middle) and of the planetary index of geomagnetic disturbance $K_p$ (bottom) during the same 29-year span were obtained by averaging spectra from 29 consecutive years. Apart from prominent low-frequency components corresponding to the about 10.5-year solar activity cycle, common to all three variables, major spectral peaks are seen for Wolf numbers and $K_p$ at frequencies of about 14 cycles per year (or about 27 days) and harmonics thereof, corresponding to the solar rotation period around its axis.

Figure A1.
length to the solar activity cycle, that accounted for an about 5% difference in the number of deaths occurring during years of maximal versus years of minimal solar activity (154).

In order to further understand any putative influence of solar and/or geomagnetic effects on the incidence of MIs in Minnesota, associations were sought with a number of physical variables retrieved from the web (170), namely the coronal index (CI), the number of sunspots (Wolf numbers; WN) and indices of geomagnetic activity $K_p$, $aa$ and $Dst$. Because the incidence of MIs decreased over the 29-year span investigated herein, the data on MI were linearly detrended.

To this effect, analytical techniques such as phase synchronization, originally developed mostly in the context of brain activity and cognition (1–103; notably 23, 26, 29, 31, 34), were applied to the data on MI mortality in Minnesota, and results were compared with those obtained with the classical approach by spectral analysis. Herein, we focus on relations between WN and MI and between $K_p$ and MI in order to compare putative non-photic effects from the sun or from the earth.

Figure A1 compares the power spectral densities of the detrended MI (top), WN (middle) and $K_p$ (bottom). Not surprisingly, spectral power around one cycle in 27 days is observed for WN and $K_p$, and is likely associated with the solar rotation period. Spectral power is also observed for these two variables as well as for MI around two cycles in 27 days. Whereas the spectral power rapidly decreases at higher frequencies for WN, additional peaks are visible for $K_p$, including one around one cycle in about a week. Some low-frequency components also appear to be common to all three variables.

Figure A2 displays the cross-spectral coherence between MI and Wolf numbers (reflecting solar activity) (left) or the planetary index of geomagnetic disturbance $K_p$ (right) in two selected frequency ranges: the low-frequency region extending from 29 to about 4 years (top), and the about weekly/half-weekly or circaseptan/circasemiseptan region extending from about 7.3 to about 3.3 days (bottom). Cross-spectral coherence is found prominently between MI and Wolf numbers around 10.5 years and between MI and $K_p$ around 1.0 and 0.5 year.
Franz Halberg, Germaine Cornélissen, Christopher Bingham, Herbert Witte, Urs Ribary, Wolfram Hesse, Hellmuth Petsche, Mark Engebretson, Hans-Georg Geissler, Sabine Weiss §, Wolfgang Klimesch, Peter Rappelsberger, George Katinas, Othild Schwartzkopff

Figure A3a.

variable 1: number of deaths from MI on that day
notations 2: linearly detrended MI
3: coronal index CI
4: Wolf number
5: planetary geomagnetic index Kp
6: antipodal geomagnetic index aa
7: equatorial index Dst

color scala:
1: sign. different from zero phase synchronization
0: not sign. different from zero phase synchronization
sign. level: 95 %
number of trials: 29
number of simulations: 100

Figure A3b.

intersection of test results against surrogate data and noise
Chronomics: imaging in time by phase synchronization reveals wide spectral-biospheric resonances beyond short rhythms

Figure A3. Illustration of three different approaches to determine non-zero phase synchronization between pairs of variables. The data set consists of the daily incidence of mortality from myocardial infarction (MI) in Minnesota during 1968-1996 (29 years) (variable 1), the same data after removal of a linear decreasing trend (variable 2), and different physical environmental variables reflecting the influence of the sun (coronal index and Wolf numbers, variables 3 and 4, respectively) or that of geomagnetism (the planetary index of geomagnetic disturbance $K_p$, the antipodal index of geomagnetic disturbance $a_a$, and the equatorial index of geomagnetic activity Dst, variables 5, 6, and 7, respectively). Thresholds for the phase synchronization index computed at each time-frequency for each pair of variables were computed either by random permutation of trials, here represented by 29 1-year spans, used as replications (Figure A3a), by simulation of noise series (Figure A3b), or theoretically, according to the Raleigh distribution (Figure A3c). Anticipated results are obtained, such as the identical time-frequency structure of MI and detrended MI, and the very close—but not identical—time-frequency structure of $K_p$, $a_a$, and Dst, $K_p$ and $a_a$ being very similar to each other but both showing some slight differences, mostly at higher frequencies, with Dst, and the similarity in the low-frequency region between the two solar variables. Results are also very similar irrespective of the approach selected to determine the thresholds of statistical significance, giving added credence to the results, the unresolved problem of multiple testing notwithstanding.

Figure A3c.

most prominent with respect to WN. Cross-spectral coherence is also found around one and two cycles per year, primarily in relation to $K_p$. At higher frequencies, cross-spectral coherence around two cycles per week with WN and around one cycle per week with $K_p$ are noteworthy.

Because phase is often a more sensitive parameter than amplitude, a method of phase synchronization was used to investigate any associations of MI with respect to WN and $K_p$. In order to apply this technique, several trials of the same process are needed. Since in this context there is no specific ‘event’ (such as the presentation of a stimulus or a test routine) to which trials can be referred as phase zero, the original time series were arbitrarily subdivided into 29 yearly subspans, considered as replications or ‘trials’. The phase synchronization index quantifies the variation of phases among the different ‘trials’ (years) for each time-frequency pair. The phase synchronization index ranges between zero (no synchronization) and one (total synchronization). To test for non-zero phase synchronization, several approaches were followed. First, the method proposed by Rodriguez et al. (171) was performed, which consists of calculating the phase differences for each of 100 randomly chosen trial pairs (the data of one variable during one year being matched...
Results of non-zero phase synchronization between MI or detrended MI and each of the physical variables are very similar and are identical when relying on the Raleigh test (Figure A3c) (118). CI and WN are very similar at low frequencies. Kp and aa have a phase synchronization index above threshold for almost all time-frequency pairs, suggesting that these two variables are very similar but not necessarily identical. Great similarity is also observed between either Kp or aa and Dst, differences occurring primarily at high frequencies, a finding making good geophysical sense. In addition, there is non-zero phase synchronization found consistently at some specific frequencies between MI (or detrended MI) and each of the physical variables.

Figure A4 compares results obtained by random permutation of trials (years) (top) or by random permutation of samples (data) (bottom) for the case of MI versus WN (left) or Kp (right). For a description of the data set, see Figure A3.

Figures A3a-c illustrate non-zero phase synchronizations between pairs of variables, computed according to each of the 3 approaches described above. It can be seen that results are very similar irrespective of the approach used. As expected, there is practically no time-spectral difference between MI and detrended MI (except for the lowest frequency corresponding to the removal of the linear trend). Results of non-zero phase synchronization between MI or detrended MI and each of the physical variables are very similar and are identical when relying on the Raleigh test (Figure A3c) (118). CI and WN are very similar at low frequencies. Kp and aa have a phase synchronization index above threshold for almost all time-frequency pairs, suggesting that these two variables are very similar but not necessarily identical. Great similarity is also observed between either Kp or aa and Dst, differences occurring primarily at high frequencies, a finding making good geophysical sense. In addition, there is non-zero phase synchronization found consistently at some specific frequencies between MI (or detrended MI) and each of the physical variables.

Figure A4 compares results obtained by random permutation of trials (years) (top) or by random permutation of samples (data) (bottom) for the case of MI versus WN (left) or Kp (right). Results appear similar whether
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Figure A5. Results from non-zero phase synchronization between MI and Wolf numbers (left) or the planetary geomagnetic disturbance index Kp (right) at the 5% (top) or 1% (bottom) nominal or, rather, ordering probability level. For a description of the data set, see Figure A3.

the random permutations are performed on trials or on samples. MI also seems to exhibit more phase synchronization with respect to WN than with respect to Kp.

Using the approach by random permutation of trials, Figure A5 compares non-zero phase synchronizations between MI and WN (left) or Kp (right) using the upper 95% (top) or 99% (bottom) quantile from the distributions to reflect associations statistically significant at the nominal 5% or 1% probability level (without correction for multiple testing).

The conclusion that MI is more closely associated with solar activity (WN) than with geomagnetic disturbance (Kp) is also reached from the instantaneous cross-spectral coherence results around one cycle per 10.5 years, shown in Figure A6. An association between mortality from MI and WN (top) or Kp (bottom) at a frequency of one cycle in about 10.5 years (solar activity cycle) is documented by dynamic power, coherence and cross-phase analyses of detrended data filtered with a narrow band (0.04 to 0.16 cycle/year or 6.25 to 25 years) filter. Figure A6 shows the dynamic power and coherence of the two pairs of variables analyzed as bivariate processes. The results indicate a much stronger association of MI with solar activity than with geomagnetic activity, occurring only intermittently.

Coherence of MI with the different physical variables is displayed again in Figure A7 (top). It can be seen that the strong association of MI with WN is very similar to that observed between MI and CI, another index of solar activity. By contrast, the weak or absence of coherence between MI and Kp is similar to results between MI and aa or Dst, two other indices of geomagnetic activity. Figure A7 (bottom) also shows results from cross phase analyses, which are slightly positive, indicating that at the frequency tested of one cycle in 10.5 years, mortality from MI in Minnesota follows tightly Wolf (sunspot) numbers. In the second half of the 29-year record, MI is practically in
phase also with the three geomagnetic indices, the phases being almost zero with respect to $K_p$ and $aa$, and almost in antiphase (5.22 years) with respect to $Dst$, as anticipated since magnetic storms are associated with large positive values of $K_p$ and $aa$ but large negative values of $Dst$.

Results from global analyses shown in Figure A2 suggest that at a frequency of about one cycle per week, the association is stronger between MI and geomagnetics than between MI and solar activity. We may resonate with different environmental drummers to a different extent at different frequencies, but the resonance as such is beyond a reasonable doubt.

**Figure A6.** Results from dynamic coherence between MI and Wolf numbers (top) or geomagnetic activity (bottom) at a frequency of about one cycle in 10.5 years (solar activity cycle). Mortality from MI in Minnesota (1968-1996) appears to be more closely associated with solar activity than with geomagnetic disturbance at this relatively low frequency, since the coherence with Wolf numbers reaches 0.5 during most of the middle part of the 29-year record, but remains close to zero in relation to $K_p$.

**Figure A7.** Results shown in Figure A6 are further corroborated by the similarity around one cycle in 10.5 years of instantaneous coherences with respect to both the coronal index and Wolf numbers on the one hand, and among the three indices of geomagnetic activity $K_p$, $aa$, and $Dst$ on the other hand (top). Moreover, instantaneous cross phases are invariably close to zero and slightly positive (bottom), indicating that the dynamics of MI follow tightly those of the physical environmental variables. The near-antiphase seen with respect to $Dst$ stems from the fact that magnetic storms are associated with large positive values of $K_p$ and $aa$, but large negative values of $Dst$. 
Appendix B
Temporal mapping, chronomics, of environmental associations with human cerebral and related physiology and pathology

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AIM. To explore amplitude and phase relations of putative cyclic associations among environmental and biospheric variables, many involving the human brain, heart and circulation, with individual and societal health-related consequences.

BACKGROUND. An international transdisciplinary project on the biosphere and the cosmos (BIOCOS) aims at producing an atlas of inferentially statistically documented time structures (chronomes), consisting of 1. a broad spectrum of cycles, with frequencies covering over 10 orders of magnitude, from those of many hertz in the brain to decade-long cycles of the human circulation and motivation, criminality and international battles, 2. deterministic chaos, gauged by indices such as the correlation dimension and approximate entropy, and 3. trends in cyclic and/or chaotic endpoints as a function of age, disease risk or pathology.

MATERIALS AND METHODS. Archives and accumulating databases of physiological and pathological variables were analyzed by spectral, cross-spectral and phase synchronization methods combined with superposed epochs and other addition and subtraction methods. The latter extend the endocrinological removal and hormone replacement by manipulating or exploiting the presence (addition) or absence (subtraction) of socio-eco-cosmologic variables, such as series of the satellite-recorded acceleration changes in the solar wind or changes in the north-south vectorial component of the interplanetary magnetic field, that may be of interest in themselves in physics and by their association in the biosphere of interest also to disciplines as varied as physiology and sociology or pathology and criminality.

Figure B1. Spectra of Wolf numbers (reflecting solar activity) (top left) and the daily incidence of myocardial infarction (MI) in Moscow during 1979–1981 (top right) reveal prominent low-frequency changes in both variables and a prominent weekly and half-weekly variation in MI. Despite the relatively small amplitudes of components with periods of about 4.7 and 2.7 days (arrows), a phase synchronization method developed by Bärbel Schack who prepared this graph suggests that MI and solar activity share a common time regime at these two frequencies.
RESULTS. Already available items of future atlases are mapped: ultra- as well as infra-annual spectral components, the latter with circadecadal, circadecadal and circuinquidecadal phenomena, displayed in both the frequency or period and the phase domains, complement about 24-hour (circadian), about-weekly (circaseptan), about-monthly (circatriquintan), about-half-yearly (circasemianual), about-yearly (circannual) and separate, trans- (somewhat longer than) annual changes, among others. The lower half of Figure B1 shows an example of time-varying phase synchronization between two variables on the abscessa; spectra of these variables are seen on top, with cycles per year on the abscessa on top. Relations of amplitudes and phases were resolved elsewhere, with emphasis on diverse functions, some involving the human brain, others the electrical activity of a single eukaryotic cell or the behavior of bacteria, among a host of other morphological and physiological variables in the biosphere. The relative importance of competing photic and non-photic synchronizers is illustrated elsewhere (50, 73, 154; cf. 131, 148, 154, 164).

DISCUSSION. Long-standing controversies that led to the universal acceptance of a heliobiology in the then-Soviet Union, persisting unchanged in current Russian science, on the one hand, and often unwarranted western bias on the other hand, can be resolved by inferential statistical chronomics, yielding the recognition of the putative roles of tempo-spatial factors, including geography and ethnicity as well as solar cycle stage and number. The chronomes of the human brain involve phenomena relating to problems of our day. The resolution of identifiable cyclic mechanisms allows focus upon human motivation for religious activity and upon major diseases of our society, whose cycles are now documented not only upon the crimes committed by individuals, such as homicides, but by the chronomics of a series of international battles covering 2,556 years.

Appendix C by Herbert Witte
Methodological amplification in a physical-engineering perspective: Comments on the mathematics underlying Barbara Schack’s methodology

For a sinusoidal signal
\[ x(t) = c \cdot \cos(2\pi ft + \Theta) = a \cdot \cos(2\pi ft) + b \cdot \sin(2\pi ft) \]
with
\[ c = \sqrt{a^2 + b^2} \quad \text{and} \quad \Theta = \arctan\left(\frac{-b}{a}\right), \]
the instantaneous phase is \( \Phi(f, t) = 2\pi ft + \Theta \), where \( f \) is the frequency and \( \Theta \) is the zero phase (phase \( \Phi(f, t) \) at \( t = 0 \)). Note that \( \Phi(f, t) = 2\pi ft + \Theta \) is a linear time function with slope \( 2\pi f \). n:m phase coupling between two oscillations can be defined by
\[ |n\Phi_1(f, m, t) - m\Phi_2(f, n, t)| < \sigma \]
(1)

with \( \Phi_1(f, m, t) = 2\pi ft + \Theta_m \), \( \Phi_2(f, n, t) = 2\pi ft + \Theta_n \) and \( f_m/n_n \approx m/n \), where for coupled oscillators \( n \) and \( m \) are integers that describe the ratio of the frequencies and \( \sigma \) is a small positive constant.

Multiples of the instantaneous phases, which are linear time functions with slopes \( 2\pi f_m \) and \( 2\pi f_n \) for sinusoidal signals, lead to identical slopes and comparable zero phases.

For identical frequencies \( m/n = 1 \) (1:1 phase coupling), the phase difference (shift) can be given by
\[ \Delta\Phi(f, t) \big|_{f_m = f_n = f} = \Phi_1(f, t) - \Phi_2(f, t) = \Theta_1 - \Theta_2 \]
(2)

Synchronization effects can be observed in coupled oscillating systems and phase shifts result from signal propagation (signal transfer through a system), i.e. if two oscillations show a stable 1:1 phase coupling, then they can be synchronized with \( \Delta\Phi(f, t) < \sigma \) or phase shifted \( \Delta\Phi(f, t) > 0 \) with the constraint \( \text{VAR}(\Delta\Phi(f, t)) < \lambda \), where \( \sigma \) and \( \lambda \) are small positive constants. Synchronization in a dual oscillator system means the existence of certain relations between their phases and frequencies, i.e. equ. (1) is often used for the definition of synchronization. Therefore, n:m phase coupling, n:m synchronization and n:m phase synchronization (used by Bärbel Schack) are used as synonyms in this field.

Both models are important for the interpretation of results but the observed data can be analyzed by the same methods. In contrast to our definition of a signal given above, in statistical time series analysis, signals are often defined as zero mean valued stationary random signals, i.e. amplitude and phase are random variables. For non-stationary signals, time-varying analysis methods can be seen as efficient tools. Therefore, time-varying spectral analysis methods have been developed and applied by Bärbel Schack.

Time-varying coherence and cross-phase spectrum
Time-varying methods have been introduced by Schack et al. (13–15) for estimating time-varying spectra and spectral parameters, i.e. non-stationarity can be assumed for two signals investigated. Accordingly, the time-varying (instantaneous) cross-spectral coherence and cross-phase spectrum can be given in general by
\[ \hat{\gamma}_{12}^2(f, t) = \frac{\left| \hat{S}_{12}(f, t) \right|^2}{\hat{S}_{11}(f, t) \cdot \hat{S}_{22}(f, t)} \]
\[ 0 \leq \hat{\gamma}_{12}^2(f, t) \leq 1 \]

(3)

\[ \Phi_{12}^*(f, t) = \arctan\left( \frac{\text{Im}\{\hat{S}_{12}^*(f, t)\}}{\text{Re}\{\hat{S}_{12}^*(f, t)\}} \right) \]
(4)
where \( Re\{\cdot\} \) and \( Im\{\cdot\} \) denote the real and the imaginary parts of a complex spectrum, \( S_{11}(f,t) \) and \( S_{22}(f,t) \) are the estimated time-varying autospectra and \( S_{12}(f,t) \) is the estimated time-varying cross-spectrum, as functions of discrete frequencies and time.

The time-varying cross-phase spectrum can be expressed (according to equ.(2)) as the instantaneous phase differences for each frequency as a function of time. According to equ. (1) and (2), a 1:1 synchronization of two signals (common frequency components \( f_{m}=f_{n} \)) can be stated, if the conditions \( |\Delta \Phi(f,t)| < \sigma \) and \( \gamma_{m=2}(f,t) > x_{k} \) are fulfilled: The threshold value \( x_{k} \) designates statistically significant coherence values (e.g. significance level at 5%) and depends on the estimation method and signal properties, i.e. by means of the cross-spectral coherence values, the estimation accuracy of the cross-phase can be obtained. Two signals (signal components) are shifted in erroneous low mean values if the single trial phases accumulate in the neighbourhood of the saltus \([\pi, \pi]\). Therefore, an averaging may result with the constraint \( \text{VAR}[\Delta \Phi(f,t)] < \lambda_{k} \), where \( \sigma \) and \( \lambda \) are small positive constants.

The cross-spectral coherence values depend on the noise content (signal-to-noise-ratio) of both investigated signals. Therefore, the deviation of the cross-spectral coherence spectra (coherence values) are possible. The cross-spectral coherence is

- a measure of the accuracy of the cross-phase estimation,
- the squared linear correlation coefficient for each frequency component,
- a measure of phase stability or stability of phase coupling
and/or gives
- the fraction at a system’s response that is due to the input and
- the amount of common information with regard of oscillations within certain frequency bands.

A mean time-varying cross-spectral coherence can be obtained by

\[
\hat{T}_{12}^{2}(f,t) = \frac{1}{(k)} \left( \frac{\gamma_{12}^{2}(f,t)_{k}}{\gamma_{11}^{2}(f,t)_{k} + \gamma_{22}^{2}(f,t)_{k}} \right) \tag{5}
\]

where \( \{\} \) denotes averaging (for each time point) and \( \gamma_{12}^{2}(f,t)_{k} \) is the time-varying cross-spectral coherence estimation of the \( k \)-th trial. The cross-phase is defined in the interval [-\( \pi \), \( \pi \)]. Therefore, an averaging may result in erroneous low mean values if the single trial phases accumulate in the neighbourhood of the saltus \( \pm \pi \). Thus, the coordinates on the unit circle (\( Re=\cos \), \( Im=\sin \)) are averaged and the mean time-varying cross-spectrum \( \Phi_{12}(f,t) \) is calculated by

\[
\Phi_{12}(f,t) = \text{arctan}\left( \frac{\sin(\Phi_{12}(f,t)_{k})}{\cos(\Phi_{12}(f,t)_{k})} \right) \tag{6}
\]

where \( \Phi_{12}(f,t)_{k} \) is the time-varying cross-phase spectrum estimation of the \( k \)-th trial. From the mean coordinates of the phase on the unit circle the so-called time-variant phase coherence spectrum \([2]\) can be derived

\[
\hat{k}_{\Phi}(f,t) = \sqrt{\left(\cos(\Phi_{12}(f,t)_{k})\right)^{2} + \left(\sin(\Phi_{12}(f,t)_{k})\right)^{2}} \tag{7}
\]

This time variant parameter can be used for the quantification of the stability of time-variant cross-phase at a frequency \( \omega \).

**Phase coupling and synchronization indices**

From now on, a shortened text of Bärbel Schack (in preparation) is used to explain the synchronization parameters introduced by Bärbel (our comments are cursive).

The evaluation of phase synchronization presumes the calculation of instantaneous phases. Widespread approaches are (a) the Hilbert transform and (b) the convolution with a complex wavelet (she used another method, the Gabor expansion described in (38)). In contrast to the Hilbert transform approach, which requires narrow band pass filtering for each frequency of interest, Gabor expansion allows to calculate instantaneous phases for the whole frequency range at once.

**Phase locking index**

The circular statistics for phases at a fixed time point after a stimulus onset evaluates phase locking with regard to an event. Therefore, in order to quantify the phase variation with respect to a stimulus onset, the phases \( \Phi_{m}(f_{m},t)_{k} \), \( k=1,...,K \) were calculated for each single trial \( k \). The so-called phase locking index (PLI) is defined by

\[
\text{PLI}(f_{m},t) = \left| e^{i \Phi_{m}(f_{m},t)_{k}} \right| , \quad j = \sqrt{1} . \tag{8}
\]

The PLI represents the circular statistics for instantaneous phases of the signal for the set of trials and ranges between zero and one. An increased \( \text{PLI}(f_{m},t) \) indicates stronger phase locking to the onset for a certain frequency \( f_{m} \) at time point \( t \).

**Phase synchronization index**

A stable relationship between phases of two oscillations with the same frequency may be evaluated by the 1:1 phase synchronization index. Let \( \Phi_{1}(f_{m},t)_{k}^{(m)}, \Phi_{2}(f_{m},t)_{k}^{(m)} \) be the instantaneous phases of two signal components for the frequency \( f_{m} \) at time point \( t \) of the \( k \)-th trial. From phase differences (according to equ. 2) of each trial \( k \)

\[
\Delta \Phi(f_{m},t)_{k} = \Phi_{1}(f_{m},t)_{k} - \Phi_{2}(f_{m},t)_{k} \mod 2\pi \tag{9}
\]

the 1:1 phase synchronization index is calculated according to

\[
\Gamma_{\Phi}(f_{m},t) = \left| e^{i \Delta \Phi(f_{m},t)_{k}} \right| , \quad j = \sqrt{-1} . \tag{10}
\]

Equivalently to the PLI, the 1:1 phase synchronization index ranges between zero and one. An increased 1:1 phase synchronization index hints to a strong phase relationship between oscillations of frequency \( f_{m} \) measured at two different sites. In contrast to the phase locking index, 1:1 phase synchronization indices are more sensitive to phase differences than the PLI.
n:m phase synchronization index

Phase synchronization described above may be seen as a special case of synchronization of two oscillators with arbitrary frequencies. The synchronization between two oscillations with different frequencies may be described as follows. Let \( \Phi(f_n, t)^{(k)} \) be the instantaneous phases of two oscillators with frequencies \( f_n \) and \( f_m \) of one or two signal components of the k-th trial with the n:m frequency relationship. The generalized phase difference is calculated according to equ. (1)

\[
n \cdot f_n = m \cdot f_m
\]

\[
\Delta \Phi(f_n, f_m, t)^{(k)} = n \cdot \Phi_1(f_n, t)^{(k)} - m \cdot \Phi_2(f_m, t)^{(k)} \mod 2\pi
\]

The n:m phase synchronization index is defined by

\[
\Gamma_{\Phi}^2(f_n, f_m, t) = \left| \frac{e^{-i \Delta \Phi(f_n, f_m, t)^{(k)}}}{\sqrt{f_n}} \right|, \quad k = \sqrt{-1}
\]

The n:m phase synchronization index may be calculated for the arbitrary frequency pair \((f_n, f_m)\), \(m \neq n\) of one or two signal components.

REFERENCES

including full bibliography of PD Dr. Bärbel Schack

A Journals cited in SCI and/or with peer review process

1 Thiele (Schack) B. Eine Umkehrformel für einfache stationäre Punktprozesse endlicher Intensität im \( \mathbb{R}^2 \), Math.Nachr. 1979; \(91\): 171–179.


Chronomics: imaging in time by phase synchronization reveals wide spectral-biospheric resonances beyond short rhythms


B Short communications in SCI journals


Franz Halberg, Germaine Cornélissen, Christopher Bingham, Herbert Witte, Urs Ribary, Wolfram Hesse, Hellmuth Petsche, Mark Engebretson, Hans-Georg Geissler, Sabine Weiss, Wolfgang Klimesch, Peter Rappelsberger, George Katinas, Othold Schwartzkopff


137  Schack B, Seidel G, Krause W, Heinrich F. Coherence Analysis of the Ongoing EEG by Means of Microstates of Synchronous Oscill
Chromosomes: imaging in time by phase synchronization reveals wide spectral-biospheric resonances beyond short rhythms

D Book articles


103 Witte H, Schack B. Quantification of phase coupling and information transfer between electroencephalographic (EEG) signals: Analysis strategies, models and simulations. Theory in Biosciences, in press.

Other articles cited


145 Abbot CG. Solar variation and weather, a summary of the evidence, completely illustrated and documented. Washington DC: Smithsonian Miscellaneous Collections 146, No. 3 (Publ. 4545); 1963. 67 pp. + 4 plates.
149 Roederer JG. Are magnetic storms hazardous to your health? Eos, Transactions, American Geophysical Union 1995; 76:441, 444–445.