

# Chronobiology and chronomics: detecting and applying the cycles of nature

***We monitor our streets to prevent assault and rodents to develop drugs, but not those for whom the drugs are intended. It took over half a century to begin to monitor blood sugar values in patients with insulin-dependent diabetes. Monitoring blood pressure is equally timely and technically feasible for individual home- and website-based personalised care. It also serves basic science and someday perhaps the management of societal illnesses.***

**A**round-the-clock monitoring of blood pressure (BP) and heart rate (HR) can detect Vascular Variability Disorders. VVDs include high BP and/or pulse pressure, that is MESOR (midline-estimating statistic of rhythm) hypertension (MH) and excessive pulse pressure (EPP). For all newly diagnosed hypertensives, at least two 24-hour/7-day records are recommended for the prevention of stroke and other life-threatening diseases. Lifetime-long self-surveillance may be advocated, once the diagnosis of MH or other VVD is confirmed, to validate dosage and timing of treatment. Decades-long records of BP and HR reveal potential signatures of cycles found in solar wind speed, e.g. far-transyears and cis-halfyears (shorter than a standard half-year), of about 16 and 5 months length, respectively. Transyears (more than – ‘trans’ – a calendar year) replace the calendar year in categorising some events, in the incidence patterns of cardiac arrhythmia, sudden death and suicide.

Data from satellites and other modern technologies allow us to apply the advice

of Sir Norman Lockyer, the co-discoverer of helium and the founder of the journal *Nature*: “Surely in meteorology, as in astronomy [and we would add, “and as in personal and societal health care”], *the thing to hunt down is a cycle* [emphasis ours], and if that is not to be found in the temperate zone, then go to the frigid zones or to the torrid zone to look for it; and if found, then above all things, and in whatever manner, lay hold of it, study it, record it and see what it means” (Lockyer, 1874). Miroslav Mikulecky, emeritus professor of internal medicine and statistics at Comenius University, Bratislava, Slovakia, indeed found what he dubbed ‘Halberg’s transyear’ in Mindanao (Philippines) and Brazil as well as in Slovakia for variables ranging from birth rate to the incidence of epilepsy and stroke (see e.g. Kovac and Mikulecky, 2005).

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Sir Norman knew the importance of the cycles generated by our cosmos and like Professor Mikulecky, we followed his advice (Halberg *et al.*, 2006). We argue that through nucleic acid, these cycles eventually become self-sustaining and self-reproducing organisms, including humans, with impacts at the level of society. For all longstanding environmental cycles in the electromagnetic spectrum, whether in the visible range (*photics*, such as the day and the seasons) or beyond (*nonphotics*), biospheric reciprocals in terms of similar period lengths,  $\tau$ , have been found. Nonphotics relate to particle radiation from space weather, broadly galactohelio-ionosphero-geomagnetics, gravity, UV flux and whatever else can be measured in time in our cosmos.

There are more  $\tau$ s than those of about a fraction of a second encountered in the electroencephalogram or about 1 second in the electrocardiogram. There are cycles with  $\tau$ s of  $\sim 1$  day, those of  $\sim 1$ ,  $\sim 2$  and  $\sim 4$  weeks, and  $\sim 5$  months, as well as  $\sim 6$ ,  $\sim 12$  and  $\sim 13$  month (near-transyear), and  $\sim 16$  to  $\sim 21$  month (far-transyear) cycles. There are also  $\sim 11$ ,  $\sim 22$ ,  $\sim 33$ ,  $\sim 50$  and  $\sim 500$  year and myriadennian (Rohde and Muller, 2005) recurring patterns.

### Reciprocity of cycles in and around us

Some cycles have a periodicity measured in millions of years, e.g. the diversity of *genera* on the ocean floor. Equally, for each built-in cycle in living matter an environmental counterpart may be sought (Halberg *et al.*, 2000) and has been found, for the visible day and year (photics) first, and now also for the week and a near-transyear, longer than 12 months by a few weeks (one of the nonphotics).

The  $\tau$  of 24 hours has served to classify three domains within a broad array of frequencies ( $f = 1/\tau$ ). These are circadian ( $\tau = 20$ -28 hours), ultradian ( $\tau < 20$  hours) and infradian ( $\tau > 28$  hours). Many, notably nonphotoc cycles around us and their signatures in us, are nonstationary; they wax and wane in amplitude to the point of disappearing, reappearing and drifting in frequency, bifurcating and rejoining. The built-in nature of the cycles, with periods of their own, amenable to synchronisation by the environment but persisting when the environmental cycle is no longer detected, can be documented. A combination of methods is used to assess uncertainties across entire time series, as well as some concerning variation with time. If, and only if, these procedures have been completed, then these quasi-periodicities can be inferentially statistically described as *Aeolian*, so called because they mimic and may be

related to solar wind speed (SWS) – from the Greek god Aeolus who ruled the winds. These periodicities in the biosphere are the realm of chronobiology, while aligned with weather on earth and in space, they form the basis of chronomics.

A microscopy-in-time revealed cycles in broad time structures with their mechanisms embedded in living matter, and this was resolved as chronobiology. The alignment of time series in biology with series from physics led to chronomics, a telescopy-in-time. The  $\sim 20$ -year population cycles found in religiosity, crime and war can be mapped and examined for associations in underlying putative neuro-endocrine and cellular mechanisms in some motivated persons' blood pressure. These may serve as a starting point for a focus on diseases of nations through the study of individuals. Starting with a focus upon the psychophysiological mechanisms of underlying cycles of diseases of nations, complex relations will have to be resolved – perhaps the major task of applied biomedicine if humanity is to meet the extremist challenges of our time – via chronobioethics.

### Rules of chronobiology

Whether biospheric and environmental cycles have corresponding periods can be tested – and has been documented – once the zero-amplitude (A) assumption of each cycle is rejected (i.e. by ascertaining that the lower limit of the CI or 95% confidence interval of A is positive). CIs of  $\tau$ s can then be compared and may overlap. They can be characterised by intradisciplinary congruence when we deal with time series of the same variables, or from the same discipline such as physics or biology. Congruence is interdisciplinary when the variables are from two different disciplines such as biology *and* physics. There can also be 'transdisciplinary congruence' when other disciplines beyond biology and physics are also involved. Moreover, these environmental-biospheric associations can reveal a 'selective assortment' of congruences of a given physiological variable with different environmental cycles at various frequencies.

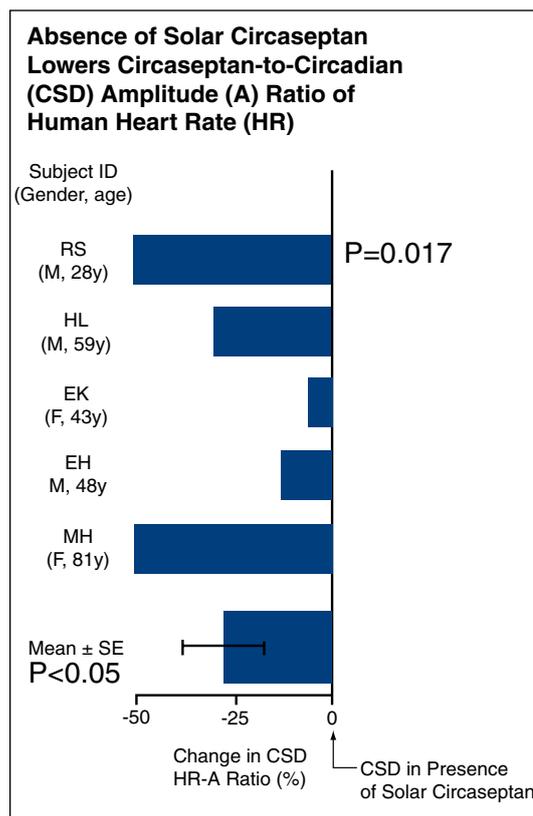
Happenstance can never be ruled out, but must be estimated and rendered unlikely by further steps. 'Consistent subtractive and/or additive behaviour' is examined by the subtraction, up to removal, of an environmental component from the transdisciplinary spectrum or, alternatively, by both the addition and the removal of a component to this spectrum. When changes in the biosphere correspond to those in the environment yet persist in the absence of the latter, we can actually validate

the long-term occurrence of the very environmental cycle which is (transiently) lost.

In summary, there are four main rules:

- Rule 1 is congruence in  $\tau$  (not necessarily in phase), documented by overlapping CIs of infradian  $\tau$ s, in various regions of the spectra from multiples and submultiples of 7 days (multiseptans) (Figure 1) over transyears, up to  $\tau$ s of  $\sim 11$  or  $\sim 22$  years (decadals and didecadals) (Halberg *et al*, 2003) and longer than 30 years (transtridecadals) (Halberg *et al*, 2009).
- Rule 2, a selective assortment of biospheric-cosmic pairing, can be illustrated for an individual's heart rate with a transtridecadal environmental cycle and for blood pressure of the same subject with a didecadal one. A consistent selective pull of the HR, but not of the BP circaseptan phase, also constitutes selective assortment (Halberg *et al*, 2006), and so does at the cis-half-year frequency the parallelism of phases in 17-ketosteroid excretion and of the geomagnetic planetary index Kp (Halberg *et al*, 2008). The application of these first two rules is reminiscent of Mendel's laws of segregation and independent assortment of what became genes.
- Rule 3, a consistent subtractive and/or additive behaviour, is opportunistically examined by subtraction (up to removal) from the transdisciplinary spectrum of an environmental  $\sim 7$ -day component (Figure 1) or of an  $\sim 1.3$ -year component or by the addition of a 7-day (Figure 1) or of a transyear component (Halberg *et al*, 2006). Each entails corresponding changes in the biosphere (damping but not loss, or amplification).
- Rule 4 is concerned with the genetic coding of the biospheric cycle, quantified by cosinor and thus more completely revealed at the molecular level for circadians (Sothorn *et al*, 2009) and perhaps at the atomic level for some circaseptans and for other infradians by a damping effect due to the removal of an environmental component. This rule validates the long-term occurrence of an environmental cycle to the point that it became genetically coded. Damped persistence of the biospheric cycle is hence a transdisciplinary tool pertinent to physics, biology and beyond for an eventual transdisciplinary unified science.

The implications for societal issues can be investigated by mapping photic circadian and circannual cycles in variables as different as



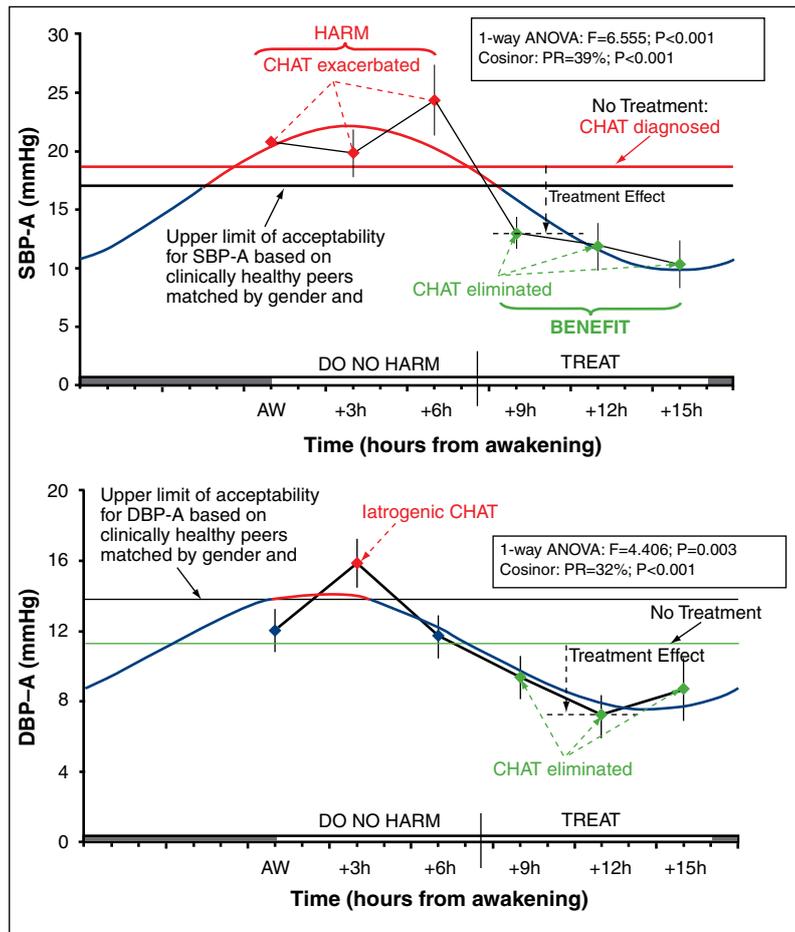
**Figure 1.** An  $\sim 7$ -day spectral component in the HR of five men is less prominent when the solar wind loses its counterpart of corresponding length. Implied, but not shown, is the persistence in the biosphere of an  $\sim 7$ -day component that can be amplified (driven) by a reciprocal component in solar activity.

nucleic acid synthesis, BP and HR. A multitude of infradian nonphotic cycles then can also be found in a multitude of variables occurring in individuals and in the broader biosphere, such as the incidence patterns of sudden cardiac death (Cornélissen *et al*, 2007) and suicide (Halberg *et al*, 2008). Future research into the potential role of the sun has much to gain from physiological monitoring taking place in preventive and curative self-surveillance strategies taught and implemented at primary and secondary education levels.

### Self-help

Chronobiologic steps toward personalised healthcare at home could replace the current, mostly office- or hospital-delivered spot check. This is often only pseudo-evidence-based care as much that relates to everyday physiological variability is lost, being described (and ignored) as “within normal limits”. These limits often serve only to identify a value that may be ‘too high’ or ‘too low’, while a ‘too early’ or ‘too late’ event, or an unacceptable swing around an acceptable mean, remain unassessed. Yet the identification of these VVDs is of critical importance as they may be indicators of a reversible risk. Self-surveillance is in this context useful for everyone and a *sine qua non* for all treated hypertensives.

Without chronobiology, differences in amplitude, phase or frequency in two groups being compared can yield opposite results



**Figure 2.** A popular drug, if prescribed without personalised surveillance, can induce a VVD such as Circadian Hyper-Amplitude-Tension (CHAT). A change in the time when the drug is taken can make the same dose of the same drug in the same person beneficial or vice versa. At one administration time (before noon), Hyzaar induces CHAT in diastolic BP and exacerbates a preexisting CHAT in systolic BP (red). At another time of administration, Hyzaar eliminates a pre-existing VVD (green). These opposite effects were found in tests at six medication times, each administered for about a month, with half-hourly surveillance of BP during the last week of each span. These differences occur as a function of the timing of the drug's use along the scale of 24 hours. Original study by Dr Yoshihiko Watanabe.

at different times. In the individual as well, opposite results can be obtained at different rhythm stages, approximated by clock-hours, as documented in Figure 2. Currently, a vast number of uninformed care providers, blind to large everyday BP and HR variability, treat equally uninformed patients, also blind to variability. Unintentionally because unknowingly, the treatment may induce a circadian overswing (which could be diagnosed with chronobiology) even while all the data lie within so-called normal limits (i.e. no one value is neither too high nor too low). A VVD can represent a greater risk than that of a high BP and can be treated. Two or more VVDs can coexist as vascular variability syndromes, VVSs, with a very high risk of stroke and other life-threatening events (see box). Some VVDs can be eliminated if detected, but otherwise they could be unknowingly iatrogenically induced.

The detection of VVDs can lead to more

extensive preventive treatment and better care (since inferential statistics can be applied to the individual) for previously ignored as well as known conditions – and this can be achieved at much less cost by computer-based self-surveillance within a home-based health programme. Chronobiologic surveillance by apparently complex personalised inferential statistical procedures can actually be implemented automatically for the individual via a website providing inferential statistical analyses. These would prompt treatment or modification of existing measures and so prevent strokes, myocardial infarctions, kidney disease and blindness.

The same monitoring for personal health-care on a large scale also provides research data on societies' health and on any underlying cosmic roots of population disease like crime. One may then try to develop rational countermeasures to roots of society's ills in space weather, just as we already cope with extremes of heat and cold in terrestrial weather with the aid of air conditioning or heating.

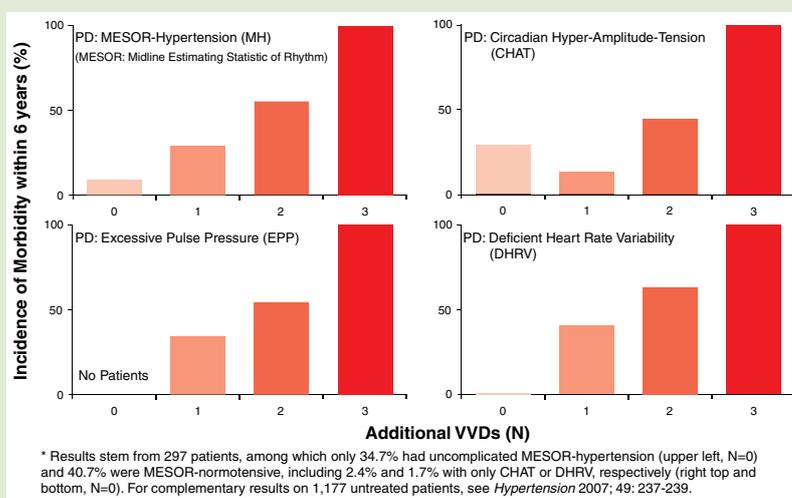
The mapping of cycles shared by living matter and the environment, seen and unseen, constitutes the essential control in a transdisciplinary unified science. These cycles can be resolved by a temporal microscopy (chronobiology) and telescoping (chronomics), which are already available today cost-free worldwide through BIOCOS (corne001@umn.edu) and sooner or later, we trust, through the Phoenix project website (www.phoenix.tc-ieee.org). The Phoenix Group of electrical and electronic engineers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers is planning to develop an inexpensive, cuffless automatic monitor for blood pressure and to construct a website (www.sphygmochron.org) for the collection and analysis of data collected by these instruments.

### Concluding discussion

With respect to critics and fierce opposition to antisepsis (and we would argue also applicable with respect to ignorance of chronobiology and chronomics), Oliver Wendell Holmes elegantly remarked that “medical logic ... does not seem to have been either taught or practised in our schools”. Well over a century later, his statement can also be cited in the context of a new practicable chronobiology and chronomics – the concepts involved are not new though.

Janeway, an opinion leader at Johns Hopkins University, wrote at the turn of the last century (Janeway, 1904): “... *it is essential* that a record of the pressure be made at frequent intervals *at some time previous* [presumably to an

The incidence of VVDs was assessed in a clinic population of 297 patients. Blood pressure (BP) and heart rate (HR) of each subject were monitored around the clock for two days at 15-minute intervals at the start of study. Each record was analysed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, MESOR-hypertension (MH, diagnosed in 176 patients), excessive pulse pressure (EPP), CHAT (a circadian overswing), and a deficient heart rate variability (DHRV) were identified and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every six months for six years, to estimate the relative risk associated with each VVD alone (primary diagnosis, PD) or in combination with 1, 2, or 3 additional VVDs. Earlier work showed that CHAT was associated with a risk of cerebral ischemic event and of nephropathy higher than MH, and that the risks of CHAT, EPP, and DHRV were mostly independent and additive. It thus seemed important to determine the incidence of each VVD, present alone or in combination with one or more additional VVDs. The 176 patients with MH were broken down into 103 (34.7% of the population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVD, 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVDs. In the last group, all three patients had a morbid outcome within six years of the BP monitoring. Ambulatory BP monitoring over only 48 hours, used for diagnosis, is much better than a diagnosis based on casual clinic measurements, yet its results apply only to groups. With this qualification, of the 176 patients with MH, 73 (42.2%) had additional VVDs that further increase their vascular disease risk, and that are not considered in the treatment plan of these patients since current practice does not assess these VVDs. This proportion may be smaller when VVDs are diagnosed on the basis of a 7-day record (available for CHAT). Results related to EPP (bottom left), CHAT (upper right), and DHRV (bottom right) illustrate that these conditions can be present in the absence of MH in as many as 12 (4.0%) of the 297 subjects. Since they do not have MH, it is unlikely that these subjects would be treated from a conventional viewpoint, even though their vascular disease risk can be as high as or even higher than MH. Evidence suggests that treating these conditions may translate into reducing morbidity and/or mortality from vascular disease. Another lesson is that around-the-clock monitoring of BP and HR interpreted chronobiologically is needed, even in the absence of MH, to detect vascular disease risk associated with VVDs such as CHAT and DHRV, that cannot be assessed on the basis of casual clinic measurements, so that non-pharmacologic and/or pharmacologic intervention can be instituted in a timely fashion before the occurrence of adverse outcomes. Once implemented across the board rather than in selected patient populations, vascular disease could be curbed to a much larger extent at relatively low cost if the monitoring is offered directly to the public and care providers become involved only after detection of a VVD. A website has to be built to interest many people and to provide cost-free analyses in exchange for the data, as is now provided worldwide by the BIOCOS project on a small scale (come001@umn.edu). This is an alternative to a polypill that as yet neither detects nor treats VVDs and VVSs.



examination], to establish the normal level and the extent of the periodic variations. When this is done, it may be possible to demonstrate changes of small extent which, lacking this standard for comparison, would be considered within the limits of normal variation.”

In 1974, Frederic C Bartter, then head of the Hypertension-Endocrine Branch at the (US) National Institutes of Health (NIH) and subsequently of the NIH Clinical Center, wrote of a patient whose blood pressure was diagnosed differently by two physicians who saw him at different times of day (Bartter, 1974): “By conventional standards, this patient is clearly normotensive every morning. But the

blood pressure determined each day at six in the afternoon provides especially convincing evidence that this patient is a hypertensive. ... My plea today is that information contained in [data curves compiled under differing circumstances, such as 24-h/7-day a week] become a *routine minimal amount* of information accepted for the description of a patient’s *b by cosinor should become a routine*. It is essential that enough information be collected to allow objective characterisation of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR] ... an estimate of [the amplitude] A itself, and finally an estimate of acrophase,  $\phi$  [a

measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient.”

Today it is documented that some circadian VVDs – notably in combination, as VVSs – entail a risk far exceeding the risk of high blood pressure in itself. These VVDs have raised the risk of having a stroke within six years in MESOR-hypertensives from perhaps 5% to near 100%. For many millions worldwide, the high risk, greater than that of high blood pressure, can be eliminated if the detection of VVDs enters the business plan of every care provider who realises the cost-effectiveness of their detection. Alternatively, or preferably concomitantly, the educable and educated public, notably the community of biologists, may be the agent against apathy and lack of action.

**Figure 3.** Acting on the basis of a conventionally interpreted (chronobiologically uninterpreted) 24-hour blood pressure trace, CHAT remains unrecognized by both those administering treatment and those receiving it. The illustration of Pieter Brueghel's *The Parable of the Blind Leading the Blind* is reproduced by kind permission of the Fototeca della Soprintendenza of the BAS PSAE and of the Polo Museale of the City of Naples.

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