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Why Life Oscillates – Biological Rhythms and Health

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Abstract— **A multitude of biological rhythms have been identified in the whole organism as well as within each living cell. Some of these rhythms reflect adaptations to our environment, while others run on their own. Recent evidence shows that these rhythms and their interaction might be more important not only for recreation but also for our health. Disturbance of the circadian rhythms by jet lag or shift work not only disturbs our metabolic balance but also increases the incidence of cancer. Rhythms in the organism obviously stabilize systemic functions: They increase organismic stability by calibrating the system's characteristics. Regulation curves in time and space are crucial for controlling physiological long-term stability. To be continuously aware of its properties an autopetic system may vary its parameters slightly over several time scales at different frequencies—akin to what our body does, e.g. in heart-rate variability.**

I. Introduction

Tuning and synchronization of rhythms saves energy: It was Huygens who observed that clocks on a wall tend to synchronize their beats. It turned out later that synchronisation is a very common phenomenon observed in bodies' rhythms and can be found, for example, when we relax or sleep. At such times energy consumption is minimal, our body working most efficiently.

Temporal compartmentalization allows polar events to occur in the same space unit: there are polarities in the universe of our body, which cannot happen simultaneously. Systole and diastole, inspiration and expiration, work and relaxation, wakefulness and sleep, reductive and oxidative states cannot be performed efficiently at the same time and place. Temporal compartmentalization is probably the most efficient way to mediate between these polarities. Chronobiology and chronomedicine are opening a new and very exciting understanding of our bodies' regulation. The biological time and its oscillations gain more attention and importance as these interrelations are understood.

During Aeons, organismic life has been exposed to various cosmic rhythms. These rhythms consequently have found their ways into the organismic coordination as well as into the human genome. Hormone centres like the suprachiasmatic nuclei or the pituitary are involved in circadian regulation as well as several genes of the clock, cryptochrome and period families [1]. Although in the past most emphasis has been put on the circadian cycle resulting from the variation of light during each day it is but one of the many rhythms observed in living organisms as well as in every cell of our body. The biological significance of these now internalized rhythms are obvious and help to anticipate the needs of life: The ergotropic functions of fight and flight are separated into the day, the trophotropic digestion, immune system function and regeneration into the resting period, which in human beings is the night. Additionally, the change of heart-rate, hormone levels and electrolytes, to mention just a few parameters changing during the circadian cycle, exposes the internal sensors to different systemic levels recalibrating them and facilitating their auto-regulative work.

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II. The Symphonic Orchestra of Our Body

Besides the circadian rhythm, chronobiology observes a notable amount of different rhythms at all organismic levels and over several orders of time scale magnitude [2–4]. The rhythmic orchestra investigated up to now ranges from milliseconds of a nerve discharge to the annual rhythms of hibernation. Even longer cycles of 7 years can be found, for example, in the biography of celebrities like Goethe, who used to change the lady he adored with such clear periodicity. Recent investigations give hints that the different rhythms are interconnected, at least in healthy subjects, by phase-coupling [5], synchronization [6–8] or mutual modulation [2, 9] and that the different rhythms cooperate like a symphonic orchestra from plants [10] to man. The resulting time network might be a background for organismic regulation, which is a most important precondition for the maintenance of normal development and health. Consequently, there is now increasing evidence that the destruction of the biological rhythms and their synchronization results in the loss of health.

The circadian rhythm itself is the organismic response to the daily turn of the earth around its axis and becomes synchronized during the first weeks of human life [11]. Children exposed to a light cycle program displayed improved growth and circadian entrainment compared to continuous dim or bright light [12, 13]. The terrestrial movement around the sun results in the geological year and is responded to by a circannual cycle in organisms living under its influence. The period of the lunar cycle is possibly found today in the female menstrual cycle, although only some studies find a significant connection [14–16], most likely due to the light pollution present in urban societies, thus obscuring the lunar influence. In many traditional societies social life during the year was organized in synchronicity with the lunar cycle [17].

In response to external influences all of these cycles have been internalized into organisms. Complicated neuronal integrators and genetic control utilizing at least 8 genes are present to coordinate, for example, the circadian rhythms [18].

It seems favourable for the organism to orchestrate its functions in synchrony with external conductors like cosmic rhythms as well as among each other. This is the case in the circadian rhythms, which are synchronized with the external day and night by ''zeitgebers'', of which light [18, 20] feeding [7] and temperature [19] are the most important. The onset of light in the morning triggers a couple of reactions, which turn down the immune system, the readiness to sleep and the production of growth hormone and melatonin [18], and on the other hand, turn up heart-rate, vigilance, the secretion of epinephrine and other hormones necessary for wakeful activities. It is easily understandable, that this has to be done in a synchronized and coordinated way, otherwise the resulting chaos would neither allow for a vigilant day nor a restful sleep. Shorter cycles than the circadian rhythms do not depend on cosmic events, although some authors claim a connection between body rhythms and solar events [21], some of which may have ultradian cycles. One of the most prominent cycles of short duration is the heart rhythm, which is modulated by and can be used to display a couple of other body cycles. It is easily obtained non-invasively from a 24-hour Holter ECG and has therefore gained attention to create an overview about rhythms present in a subject [22–24]. Information about the sympathico-vagal balance is also contained in the rhythms of heart-rate variability, thus giving access to the state of the autonomic nervous system, which is important for the coordination of different body functions. The heart-rate itself is synchronized to several other cycles, as for example the respiratory cycle, the blood pressure rhythm and the rhythm of peripheral circulation. This synchronization is especially strong during rest and relaxation, and is not present if subjects are under increased stress and strain—these conditions do not allow for tuning, and consequently spend more metabolic energy than a well-tuned sleep.

The orchestration of the rhythmic system obviously has a horizontal and a vertical aspect: Horizontally, rhythms like the circadian conduct the sequences necessary for the daily activities at the time they are needed. This corresponds to the sequence of themes in a symphony. The temporal compartmentalization arising from this gesture permits oxidative and reductive reactions to run undisturbed alongside of each other within the same spatial compartment. In yeast cells this has been investigated recently [25], and becomes most pronounced under nutrient-restricted conditions. Interestingly, this condition not only improves the rhythmicity but has also been implicated in prolonging life [26, 27], which might shed light on the connection between rhythmicity and health.

Vertically, rhythms like heartbeat and respiration coordinate with each other to ''give me five'' (slap hands) every 4 or so cycles. In an orchestra, this would correspond to the rhythmic interaction present between different instruments during the play—e.g., to the relation of the violins to the slow contrabass. The coordination can be a phase-coupling, a mutual modulation or a synchronization [5, 8]. The hand slapping obviously saves energy—like clocks synchronizing their beats if mounted on the same wall [28], indicating that the synchronized state is the one with lower energy.

Rhythmic gene regulation is also important for normal embryonic development [29]. During development time structures in gene expression and cell division are trans-translated into spatial shape, which makes precise timing most crucial to obtain the precise shape of the developing structures [30]. It appears reasonable, therefore, that abnormal development found in cancer cells might be connected to disturbances of rhythms. This is, in fact, the case across several time scales as one might expect if the different rhythms are interconnected and networked.

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Rhythm Disturbances in Cancer

Circadian scale rhythms have been found to be disturbed in cancer patients concerning heart-rate and heart-rate variability [31, 32]. Sleep quality is extremely reduced in cancer patients [33], a fact which hints at a disturbed circadian system [34].

In a study performed in a German cancer clinic it was especially the circadian profile of the sympathetically mediated low frequency heart-rate variability around 0.1 Hz, which was able to differentiate between healthy subjects and all cancer patient groups. Disturbances of biological rhythms can also be found in cancer cells and vessels supporting cancer tissue. Cancer cells divide rather slowly, as their metabolism is limited as long as they do not connect to the circulation. The vascularization that makes cancer tissue really harmful for the organism takes the form of these sprouting from normal vessels, and is evoked by angiogenetic hormones secreted by certain cancer cells. These new vessels lack normal development and appear disorganized and chaotic compared to normal vessels [35, 36]. Due to their fast development smooth muscle cells in the vascular wall of these vessels are missing, so that they do not respond to the circadian profile of the hormones regulating normal vessel diameter. As there is no temporal restriction to growth, the connected cancer cells grow faster than normal cells. In addition, chaotic behaviour can be observed in the circadian temperature profile of these cancer tissues [35, 37, 38]. Cancer tissues seem to separate their rhythms from those of the remaining organism. The resulting desynchonization weakens the circadian oscillation and decreases the amplitude of the circadian profile in cancer patients. As early as the 1980s Bartsch and coworkers found a disturbed melatonin excretion in breast cancer patients that was not synchronized with the circadian rhythm compared to the synchronized patterns of controls [39]. The circadian clock, representing the most intensively investigated rhythm, is increasingly recognized as an important tumour suppressor [40].

ULTRADIAN RHYTHMS

Ultradian body rhythms oscillate faster than daily but are usually phase-coupled to the circadian rhythm in healthy subjects. Examples are the ‘‘basal rest and activity cycle’’ (BRAC), which controls deep and rapid eye movement phases of our sleep in an approximately 90 min pattern. These rhythms are phase-coupled to the circadian rhythms in healthy subjects, which means that their ups and downs appear approximately each day at the same time. Short-period rhythms are present in the human circulation, and permit the study of the possible benefits of oscillating parameters establishing homeodynamic [41] equilibria in the body. Blood pressure control has been studied as early as the 1930s: the blood pressure loop was disconnected under experimental conditions and dependence between blood pressure and heart-rate was found. Increasing the pressure in the carotid sinus (which is responsible for sensing the blood pressure value) lead to a compensatory reduction of heart-rate in a classical experiment performed by Koch [42] via vagal pathways. Along the range of different pressures a sigmoidal shape of the resulting regulation curve was found. Interestingly the steepest part or point of inflection of this regulation curve is located almost exactly where the normal systolic blood pressure can be found, at around 120 mm Hg. As physiological sensors adapt to a steady signal the blood pressure regulation would probably shift and become unstable after a while, if no variation in pressure would occur. A slight variation of heart-rate (known as heart-rate variability today) found in healthy subjects prevents this adaptation by a resulting continuous variability of blood pressure. As a consequence the blood pressure regulation gets the necessary feedback to recalibrate by the amount of pressure change achieved by a certain increase or decrease of heartrate.

So the small oscillations present in the organism support the self-calibration of the organismic functions. Obviously, blood pressure in this framework is not controlled by a single neuron or group of neurons, which give the information “120 mm Hg’’. It is rather the result of a perhaps ‘‘democratically’’ obtained regulation curve which integrates all relevant parameters, such as the elastic properties of vessels, blood volume, blood viscosity and peripheral resistance. At the inflection point the strongest interconnection between heart-rate and blood pressure can be found, making regulation around this values most sensitive, and hence, stable for the circulation. Opting for stability in such a crucial supply, it is not surprising that the organism selects this turning point to be the normal value of blood pressure under resting conditions.

It is not yet known whether such curves exist for hormonal parameters as well, but, given the recently discovered oscillating secretion of hormones, it seems very likely that other control loops are maintained in a similar fashion.

This could mean that different oscillations also act as search functions seeking points of inflection in our organismic regulation. It seems remarkable that recent work in that context has connected the decline of the dynamic range of environmental cues to observed biological dysfunctions, like insulin insensitivity and metabolic diseases [43]. A dynamic system lacking variability is more likely to lose its calibration points. On the other hand this knowledge could help provide therapies based on ‘‘Chronamins’’ [44] and life-style approaches providing dynamic environmental cues [32, 43]. In musical instruments long-term stability of sound is also achieved by playing, i.e. vibrating the instrument for a period of time. This stable state may also be mimicked by vibrating the instrument artificially [45]. Nowadays we are taking part in various scientific revolutions, one of which might be based on the results of modern chronobiology. Like Andrea Vesalius, who so beautifully described the spatial aspects of our body, giving access to the anatomical shape of our muscles and bones [46], chronobiology is now dismantling the secrets of our hidden time shape. This is also interesting from a philosophical point of view, as science gains access to something that is less a physical matter, not a chemical substance, not its concentration, not energy and not even space—it is time and its biological structure. In a way we are discovering what could be called an anatomy and a histology of time represented in the different rhythms acting in our body and the symphonic orchestra playing the tune of our life. This has consequences for an understanding of health and its maintenance. For example as early as the 1930s the extract of the pineal gland was used as a remedy against cancer with varying success [47]. Even today melatonin contained in the pineal gland is considered to be helpful against certain tumours. The question as to whether a simple high melatonin level is beneficial or a whether special timing of the melatonin application is necessary to improve the organismic resistance to cancer has not yet been clearly answered. There is, however, strong evidence that sleep quality improvement and beneficial immunological effects of melatonin [48] are only present if melatonin is administered in the evening [49]. Many new achievements of applied chronobiology, such as the application of medication in a timed fashion, give us an inkling that the future medical profession will utilize the human rhythms increasingly to support their therapies [50]. Playing in harmony with the body's orchestra is obviously not only more graceful and charming, but more effective than just playing loud.

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