The Symphony of Life

Importance, Interaction, and Visualization of Biological Rhythms

BY MAXIMILIAN MOSER, MATTHIAS FRÜHWIRTH, AND THOMAS KENNER

Biological rhythms in a wide range of frequencies are present in the whole organism as well as within each living cell. Some of these rhythms reflect adaptations to cosmic cycles and help to anticipate changes in the environment. Others integrate and coordinate body functions. Extensive coordination has been found between different rhythms, indicating a systemic temporal cooperation. Rhythms and their interaction might be more important for our health than was realized before. Disturbance of the circadian rhythms by night-shift work or jet lag not only disturbs our metabolic balance but also increases the risk of cancer as well as cardiovascular diseases, which together account for 70% of all causes of death in industrialized countries. Rhythms in the organism obviously stabilize the systemic functions. They maintain organismic stability by calibrating the system’s characteristics during sleep and rest when rhythms are also most present. Regulation curves in time and space are crucial for controlling physiological long-term stability. To be continuously aware of its properties, an autopoietic system may vary its parameters at different frequencies simultaneously, according to what our body does, e.g., in heart rate variability (HRV). Methods such as autocronometric imaging [27], [28] allow the visualization of the body’s proprietary rhythms, which are present in long-term heartbeat and brain wave recordings. Similar to spatial X-ray images of the body, they provide a temporal image of our time structure.

Tuning and synchronization of rhythms reduces energy expenditure. Huygens already observed the synchronization between two pendulum clocks mounted on a wall. The synchronization occurred and became stable spontaneously and obviously reduced the drain of energy. It turned out later that synchronization is a frequent phenomenon observed in bodies’ rhythms and can be found, for example, between heartbeat and respiration and between blood pressure and blood perfusion rhythms, especially when we relax or sleep. At times when energy consumption is expected to be minimal, our body is working most efficiently.

In two recent papers [1], [2], an additional aspect explaining the necessity of oscillations has been introduced. Chemical reactions need a certain environment, for example, reducing or oxidizing. As space is limited in a cell, temporal compartmentalization allows different environments to occur in the same space unit but at different times. No transport is needed and the same space can be used for subsequent chemical processes that would not be possible simultaneously [1] due to differing enzymatic and chemical requirements. A similar concept may also apply to more complex organs and even organismic processes. Systole and diastole, inspiration and expiration, work and relaxation, wakefulness and sleep, and exhausting and recreational states cannot happen efficiently at the same time. Temporal compartmentalization is probably the most efficient way to mediate between these polarities and provide periods for both poles. The understanding of the cyclic nature of our live opens a new and very exciting insight into our bodies’ functioning. The biological time and its oscillations gain more attention and importance as these interrelations are understood.

Cosmic Connections

Since aeons, organismic life has been exposed to various cosmic cycles, the most evident of which is the rotation of the earth resulting in the geological day, which occurred about a billion \((10^{12})\) times during the last 3,000 million years since life occurred. Although for a long time these external influences were thought to be responsible for the cycling physiological patterns, we know since the work of Aschoff [3] that our bodies’ clocks are working independently, but triggered by Zeitgebers cues, which help to establish and stabilize biological rhythms. Temporal adaptations to the external cycles of dark and light or cold and warmth, consequently, have found their ways into the human genome. Regulation centers such as the suprachiasmatic nuclei or the pituitary are involved in the coordination of the internal circadian cycles as well as several genes of the so-called clock, cryptochrome, and period families [4]. The biological significance of an internalized image of external rhythms is obvious as it helps to anticipate changes of the external environment. The ergotropic functions of work (collecting or hunting for food), fight, and flight are mainly needed during the day, the trophotropic analogs of digestion, immune system function, and regeneration are maintained during the rest phase, which in human beings is the night. This separation allows for a coordinated adaptation of the organism to either ergotropy or trophotropy.

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Additionally, the change of heart rate, hormone levels, and electrolytes, to mention just a few parameters varying during the circadian cycle, exposes the internal sensors to different systemic levels, recalibrating them and facilitating their autonomous work.

**The Body Works Like an Orchestra**

Besides the circadian rhythm, chronobiology observes a notable amount of rhythms at all organismic levels and over several orders of time magnitude [5]–[7]. The rhythmic orchestra investigated up to now ranges from milliseconds of a nerve discharge to the annual rhythms of hibernation (Figure 1). Although circadian and long-term rhythms help to anticipate the environmental changes connected to the earth’s and solar movements, the faster ultradian rhythms organize the interplay between different organ systems. There is a horizontal orchestration of body functions comparable to the themes of a symphony and a vertical orchestration comparable to the rhythmic interaction between different instruments in a music ensemble. Forty-eight octaves are available for the human organism of which ten are audible to the human ear. Longer cycles of seven 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. The occurrence of tooth change (~7 years), puberty (~14 years), and adolescence (~21 years) also follows such cyclicity. The whole life span, which is expected to be around 78 years for a subject born in United States in 2001, is the longest cycle observed in the human life.

On the other end of the spectrum, very short periods of length, of microseconds, may be found in the clockwork of the receptor channels present on the surface of cells [8]. Musically speaking, 48 octaves can be counted from the frequency of a fast ion channel (29,000 Hz) to the average human lifetime (~78 years), which is about six times the range of a stage piano.

Recent investigations give hints that the different rhythms are interconnected, at least in healthy subjects, by phase coupling [9], synchronization [10]–[12], or mutual modulation [5], [13], [14]. As in a symphonic orchestra, different oscillators cooperate within and between cells and organs from plants [15] to man. The resulting time network supports organismic regulation and is an 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 shows up short after birth and becomes synchronized with the external day during the first

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### Table: Spectrum of Biological Rhythms

<table>
<thead>
<tr>
<th>Body Rhythms</th>
<th>Period Duration (log)</th>
<th>Cosmic Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Expectancy</td>
<td>78 years</td>
<td>Sunspot Cycle</td>
</tr>
<tr>
<td>Developmental Rhythms</td>
<td>7 years</td>
<td>Annual Solar Cycle</td>
</tr>
<tr>
<td>Seasonal Growth and Behavior</td>
<td>1 year</td>
<td>Lunar Cycle</td>
</tr>
<tr>
<td>Reproduction</td>
<td>1 month</td>
<td>Earth Rotation</td>
</tr>
<tr>
<td>Sleep-Wakefulness</td>
<td>1 day</td>
<td>Metabolism</td>
</tr>
<tr>
<td>Autonomous Equilibrium</td>
<td></td>
<td>Rhythmic Transport and Distribution</td>
</tr>
<tr>
<td>Sleep Cycles</td>
<td>1 hour</td>
<td>Information</td>
</tr>
<tr>
<td>Smooth Muscle Tone</td>
<td></td>
<td>Functional System</td>
</tr>
<tr>
<td>Blood Distribution</td>
<td>1 min</td>
<td></td>
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<tr>
<td>Peristalsis</td>
<td>1 s</td>
<td></td>
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<tr>
<td>Blood Pressure</td>
<td>0.1 s</td>
<td></td>
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<tr>
<td>Respiration</td>
<td>0.01 s</td>
<td></td>
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<tr>
<td>Heartbeat</td>
<td>0.001 s</td>
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<tr>
<td>EEG Nerval Action</td>
<td>0.0001 s</td>
<td></td>
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</table>

**Fig. 1.** Spectrum of biological rhythms identified in the human organism (modified after [5]).
16–20 weeks of human life [16]. Toddlers exposed to a light-cycle program display improved growth and circadian entrainment when compared with those exposed to continuous dim or bright light [17], [18].

The terrestrial movement around the sun results in the geological year and is responded by a circannual cycle in organisms living under its influence. The period of the lunar cycle is possibly found in the female menstrual cycle, although today only some studies find a significant connection [19]–[21] 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 [22].

As already mentioned, it seems favorable for the organism to orchestrate its functions in synchrony with external conductors such as cosmic rhythms and also to synchronize the internal rhythms 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 [23], [24], feeding [10], and temperature [25] are the most important. The onset of light in the morning triggers a couple of hormonal reactions, which turn down the immune cell response, the readiness to sleep, and the production of growth hormone and melatonin [23]. On the other hand, heart rate, vigilance, the secretion of epinephrine, cortisol, and other hormones necessary for wakeful activities are turned up. It is easily understandable that this has to be done in synchrony and coordination, otherwise the resulting chaos would neither allow for a vigilant day nor a restful sleep. Shorter rhythms than the circadian do not reflect cosmic cycles, although some authors claim a connection between body rhythms and solar events [26], some of which may display ultradian cycles.

**Bodies’ Own Time Symphony**

One of the most prominent cycles of short duration is the heartbeat, the period of which is modulated by and can be used to gain insight into a couple of other body cycles. This HRV is easily obtained noninvasively from a 24-h Holter ECG and mirrors the rhythmic activity of the vagal and sympathetic nervous system controlling the action of the heart. The autonomic activity is always cyclic, generated by oscillators in the brain stem. As the autonomic modulation of the heart rate is proportional to sympathetic or vagal tone, information about the sympathicovagal balance can be extracted from the amplitude of heart rate variability, thus giving access to the state of the autonomic nervous system, which governs almost all body functions.

An impressive overview about rhythms present in a subject can be obtained by time-variant analysis of HRV. We have developed a special method to visualize these rhythms from longtime recordings of HRV [27], [28] (also see www.heartbalance.com). The resulting graph called an autochronic image (in Greek, autos means self or proprietary and chronos means time) is a portrait of the rhythms modulating and moving the beat of the most central organ of the body (Figure 2). This activity is also closely connected to our emotional state and state of consciousness, to work strain or relaxation (Figure 3).

The autochronic image has since been used extensively in projects of occupational health promotion [29], shift work, and even space medicine [30], [31] to diagnose sleep quality and rhythm disturbances (Figures 4 and 5). The heart rate is synchronized with several other cycles, as, for example, the respiratory cycle, the blood pressure rhythm, and the rhythm of peripheral circulation. This synchronization is needed for survival.
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 the well-tuned sleep.

The orchestration of the rhythmic system has a horizontal and a vertical aspect. Horizontally, rhythms such as 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. As mentioned, this has been investigated recently in yeast cells [1], [2], and the rhythmicity becomes most pronounced under nutrient-restricted conditions. Interestingly, nutrient restriction also has been found to prolong life [32], [33], which tightens the connection between rhythmicity, health, and longevity.

Vertically, rhythms such as heartbeat and respiration coordinate with each other to “give me five” (slap hands) every four or so cycles. In an orchestra, this would correspond to the rhythmic interaction present between different instruments during the play, e.g., the relation of the violins to the slow contrabass. The coordination can be a phase coupling, a mutual modulation, or a synchronization [9], [11]. The obtained synchronization obviously saves energy, such as clocks synchronizing their beats if mounted on the same wall [34], indicating that the synchronized state is the one with lower energy expenditure.

Rhythmic gene regulation is also important for normal embryonic development [35]. During development, time structures in gene expression and cell division are translated into spatial shape, which makes precise timing most crucial to translate the precise shape of
the developing structures [36]. It appears reasonable, therefore, that abnormal development found in cancer cells might originate from disturbances of rhythms. Severely disturbed rhythms, have, in fact, been found in cancer patients as it should be expected.

**Circadian Rhythm Disturbances in Cancer**

Circadian rhythms are disturbed in cancer patients, with regard to heart rate and HRV [37], [38]. Sleep quality is extremely reduced in cancer patients [39], which also hints at a disturbed circadian system [40].

In a study performed in a German cancer clinic by our group, it was especially the circadian profile of the sympathetically mediated low-frequency HRV around 0.1 Hz that differentiated between healthy subjects and all cancer patient groups [38]. Disturbances of biological rhythms can also be found in cancer cells and vessels supporting cancer tissue. Cancer cells divide rather slowly as long as their metabolism is limited, and they are not connected to the circulation. The vascularization that makes cancer tissue really harmful is evoked by angiogenetic hormones secreted by certain cancer cells. These new vessels sprouting from normal vessels lack normal development and appear disorganized and chaotic due to their rapid growth [41], [42]. Smooth muscle cells in the vascular wall of these vessels are missing, so that they do not respond to the hormones regulating normal vessel diameter in a circadian profile. As there is no temporal restriction to growth, the connected cancer cells grow faster than normal cells. In addition, a chaotic circadian temperature profile can be observed [42]–[44]. The cancer tissues seem to be different in their rhythms from those of the remaining organism. The resulting desynchronization 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, which was not synchronized with the circadian rhythm, compared with the synchronized patterns of controls [45]. The circadian clock, representing the most intensively investigated rhythm, is increasingly recognized as an important tumor suppressor [46].

**Ultradian Rhythms**

Ultradian body rhythms oscillate faster than daily but are usually whole-number multiples of the circadian rhythms.
One example is the basal rest and activity cycle, which controls deep and rapid eye movement phases of our sleep in an approximately 90-min pattern corresponding to 16 cycles per day. These rhythms are phase coupled to the circadian rhythms in healthy subjects so that their ups and downs appear approximately at the same time each day. Short-period rhythms are present in the human circulation and permit the study of the possible benefits of oscillating parameters establishing homeodynamic [47] 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 a dependence between blood pressure and the heart rate was found. Increasing the pressure in the carotid sinus (the location responsible for sensing the blood pressure value) leads to a compensatory reduction of heart rate via vagal pathways (Figure 6) in a classical experiment performed by Koch [48]. 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 mmHg. As physiological sensors adapt to each steady stimulus, the blood pressure regulation would shift and become unstable after a while, if no variation in the pressure occurred. A slight variation of the heart rate (which is found in the HRV mentioned previously) prevents this adaptation by a resulting continuous variability of blood pressure. Thus, the blood pressure regulation loop obtains the necessary feedback to estimate the amount of heart rate change required for a certain increase or decrease of blood pressure.

The small oscillations present in the organism support the self-calibration of the organismic functions. Blood pressure is therefore obviously not controlled by a single neuronal center, which sets the scheduled value to 120 mmHg. It is rather the result of a democratically achieved regulation curve that 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 most sensitive close to this value and,
hence, most stable for the circulation. Opting for a stable supply of blood and oxygen, it is not surprising that the organism shifts its normal blood pressure value to this turning point. This is especially the case under resting conditions, where more regular oscillations with higher amplitudes occur. Under ergotropic conditions, the metabolic needs determine heart rate and blood pressure, and HRV becomes small or disappears as it loses its importance for regulation. Consequently, rhythms are mostly found when the energy expenditure has to be minimized, which is during the economic and quiet periods of the night and during rest. There is a second instance where rhythms might occur especially in well-trained subjects. Long time periods of equal exercise also do not supply changes of blood pressure necessary to prevent blood pressure drifts. Accordingly, rhythmic variations of heart rate can appear under these conditions.

It is not yet known whether such sigmoid regulation curves such as the one shown in Figure 6 exist for hormones as well. Given the known pulsatile secretion of hormones, it seems very likely that other control loops are maintained in a similar fashion, again especially under conditions of rest, where the hormonal pulsing becomes most pronounced [49], [50]. Oscillations in this context obviously act as search functions seeking points of optimal regulation in our organism. Recent work has connected the decline of the dynamic range of environmental cues in modern societies to observed biological dysfunctions, such as insulin insensitivity and metabolic diseases [51]. A dynamic system lacking variability is more likely to lose its points of calibration.

**Chronamins**

If decreased rhythms are harmful, an enhancement of rhythmicity can be expected to improve organismic function. Modern life has restricted rhythmicity due to artificial light, controlled temperature, and restriction of outdoor activities. Like vitamins lacking in modern food, rhythms are missing in modern life. This knowledge could help provide therapies based on chronamins [38] and lifestyle approaches providing dynamic environmental cues [51], [52]. In musical instruments, long-term stability of sound is achieved by playing, i.e., vibrating the instrument for a period of time. This stable state may even be mimicked by vibrating the instrument artificially [53]. In several studies not yet published in English, we found therapies based on art and rhythmicity very successful in improving subjective as well as physiological sleep quality and well-being. Heart rate dropped in the treated subjects, and autonomic circadian amplitude increased. In construction workers, the number of accidents dropped from 12% of workers per annum to zero in a company of 300 workers [29]. Sleep quality significantly improved only in the rhythm therapy group, whereas the control group treated just with simple gymnastics did not show this improvement.

As we are taking part in various revolutions in our understanding of life, one of them 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 [54], chronobiology is now dismantling the secrets of our hidden time shape. This is also interesting from a philosophical point of view, as natural science gains access to an area that is not physical matter, a substance, its concentration, energy, or 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 (Figure 6). This has consequences for an understanding of health and its maintenance. As early as the 1930s, the extract of the pineal gland, the source of the circadian hormone melatonin, was used as a remedy against cancer with surprising success [55]. Even today, melatonin contained in the pineal gland is considered to be helpful against certain tumors. There is strong evidence that the observed sleep quality improvement and beneficial immunological effects of melatonin [56] are only present if melatonin is administered in the evening [57], thereby improving also the amplitude of circadian rhythmicity. 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 increasingly utilize the human rhythms to support their therapies [58]. Playing in harmony with the body’s orchestra is obviously not only more graceful and charming but also more effective than just playing loud.

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Fig. 7. (a) The physical anatomy of the human body has been described and investigated scientifically since the work of Andrea Vesalius. (b) Medical science has only recently become aware of the complex patterns of body rhythms accessible, e.g., by spectrogram analysis of long-term heart rate recordings (autochronic image). Body rhythms display distinct times of chaos (mainly during the day) and order (during well-slept nights). They are orchestrated horizontally, e.g., by the circadian clock, which conducts the temporal order of different organs as well as vertically, by the rhythmic interaction of parameters such as respiration and circulation. These become visible in the 4:1 integer ratio of the pulse-respiration quotient (b, green line) achieved during sleep and during periods of rest. ((a) from [54]).

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References