Aging and active long healthy life in the context of chronobiology

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Abstract
The challenge of aging and supporting active long healthy life of a human is treated herein in the context of the chronobiological theory of bio-system stability. An increase in the energetic efficiency of the structural regulation in the feedback and adapting process of a bio-system results in a reduction of its homeostatic capacity and inhibition of its biorhythms. The occurrence of pathological desynchronoses provokes further escalation of elimination of some elements in the bio-system and finally aging of the latter. The paper offers description of internal and external causes of desynchronoses and some methods of their removal by normalization of hierarchy of biorhythm periods.

Keywords
Aging, Long life, Chronobiology, Biosystems, Biorhythms, Desynchronosis

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Numerous hypotheses on mechanisms of aging give their special attention either to processes of adaptation, genetic programming or error accumulation in metabolism, or in a genome (oxidative stress, etc.) [1–18]. Aging and death at different levels in a bio-system (macromolecules, microstructures, cells, organisms, biocenoses, biosphere) have their own specific features and complexity properties. In this case, maintenance of stability of a higher level bio-system may be provided both by maintaining (restoring) the lower level bio-systems and selective elimination of defective components.

Considering from the point of view of chronobiology, we can identify some common causes responsible for a reduction in the life performance level and death of bio-systems belonging to different hierarchical levels. These common causes are as follows: minimization of energy consumption in adaptation and aging, lowering the levels of functional and restoring processes, and the appearance of pathological desynchronoses falling outside the scope of the current homeostatic capacity of the given bio-system at a specified level. Functional reversible desynchronoses, i.e. a discordance of the bio-rhythms within the self-regulation reserves are essential tools used for an adaptation to external influences and different life performance conditions. But the said discordances in biorhythms of a function, energetics and restoration processes may be turned to pathological irreversible desynchronoses, which are characteristic of and typical for aging at a specified level in the bio-system.

At stages of growing and building-up, the total energy consumption does nothing but increases, and in this case the amount of energy demanded by the external functional processes is greater than that used for the internal regulatory purposes. As the adaptation to the habitual external environment and feedback is completed, the external functional use and the internal regulatory energy consumptions are reducing, and it is applicable to a greater extent in a faster fashion to the internal regulatory energy use. The bio-system demonstrates its higher energy efficiency, but at the same time its homeostatic capacity drops, even if external or internal causes of disorders and damages are not available. The latter are capable of accelerating aging processes and break-down of the bio-system. The common cause of a decline in the homeostatic capacity of a bio-system is adaptation to the usual, regular external influences and minimization of the total energy consumptions. In the process, the probability of errors (damages) both in genome and metabolism as well as in cell organoids is rising, while chances of restoration of them are diminishing. Retardation of biorhythms of macromolecules and microstructures reflects their “aging”. Maintenance of the normal life performance
(the normal periods of biorhythms) in a cell is provided by elimination of defective elements showing certain retarded biorhythms. A daily renewal of intestinal epithelial cells, or for instance, a renewal of erythrocytes, that takes place on the average every three months, should be considered as a way of a corrective action in terms of time management in a bio-system at the level of an organ or at the level of the organism. Those cells, whose biorhythms show a critical deviation from the normal biorhythms of the majority cell population in the enclosing tissue, undergo either apoptosis or malignant transformation. The malignant cells demonstrate an increased fluidity of their membrane and have a greater retardation in biorhythms. Considering this fact, transplantation surgery should pay more attention to provide synchronization between biorhythms of donated stem cells and the host cells in the affected tissue, using for this purpose bio-controlled laser therapy [19].

Adaptation-linked lowering of the functional activity leads to developing of tissue hypoxia and expedites aging. For example, birds in nature do not show evidence of aging before their death, since a bird flight always requires maintenance of a high-level muscle performance.Growing and building-up of a biological organism are suppressing tissue hypoxia. Hypoxia in progress in a human organism is appearing due to retardation of rhythms of alterations of erythrocyte shapes, when the red cell biconcave discs are deformed to slipper elliptic shapes before they enter capillaries. If gel-sol transition partially delays, erythrocytes are not capable of entering capillaries that results in hypoxia progression. In a human, a diminished muscle activity and a reduced blood micro-circulation are compensated by a temporary increased count of cholesterol platelets, which appear first in main blood vessels and later in other smaller-sized circulatory vessels. Because of this the laminar blood flow is transformed to the turbulent one. Mechanical collisions between erythrocytes and platelets favor the rate of gel-sol transitions therein, and this is just the preventive way to avoid hypoxia progression. But the prevalence of such self-regulation in the organism to prevent hypoxia is associated with progression of atherosclerosis affecting blood vessels in the heart and brain, hypertension, stroke and infarction. And it is precisely the major cause of aging and death of a human organism. Another major cause of the aging and death processes is cancerogenesis, which is also associated with hypoxia according to the Warburg effect theory. Professor V.L.Voyeykov suggested (in our verbal communication) that cancer may be treated as a way to control or even avoid hypoxia in an organism, since tumor cells produce active forms of oxygen (AFO). AFO operation is identified as “oxidative stress” which is considered to be one of the most important factors of aging in general. But it should be mentioned that AFO is an actor in any immune reaction provided by the organism, i.e. the organism protection from environmental damaging factors can be realized only under involvement of free radicals. A deficit of AFO may contribute to acceleration of aging in a similar manner, as it does a deficiency of antioxidants. A deficit in AFO in breathing air cannot increase the lifespan as stated by the free-radical effect theory, but it is just the relevant contributor to a sharply reduction of the longevity [3].

In order to provide an active, healthy life of a human organism, it is required to identify interrelations between aging processes at their genetic, cellular, tissue-, organ- and organism-linked levels. These requirements are met by chronobiological studies of an interconnection of hierarchy of biorhythms at the said levels. Functional discordances between biorhythms (physiological desynchronoses) are reversible and needed for adapting and changing the performance modes of the bio-system elements within the homeostatic capacity. In contrast to this, pathological irreversible desynchronoses, falling beyond the scope of the self-regulation reserves, cause death of those elements, whose biorhythms are found to be retarded with critical deviations from certain tolerable profile values or rates. So, stability of a bio-system at its any level can be provided by two opposing strategies as follows: 1. Elimination of defective elements by proteolysis, depolymerization of those macromolecules, lysis of those microstructures and apoptosis of those cells, whose desynchronoses are identified as critical, far beyond the scope of the tolerable homeostatic regulation; 2. Removal of disorders and errors of the elements by reinforcing their restoration biosynthetic processes at the lower level.

Within this context, Strategy 1, as mentioned above, aimed at the maintenance of stability of the bio-system is realized in phases of those rhythms, when energy supply is reduced, or when a deficit in energy supply is available. Strategy 2, as stated above, designed to provide stability of the
bio-system, dominates in periods when sufficient energy resources are available, and its basic feature is an excessive or redundant anabolism [2].

Strategy 1 (let it denote the Passive Strategy of the performance efficiency) implies a reduction of external activity, functional energy consumptions and, more significantly, pronounced cutting of the internal regulatory energy use. An application of this Strategy is reasonable and enjoys priority for maintenance of stability of the bio-system under the conditions of a deficit in external energy supply. The essence of the Passive Strategy can be clearly demonstrated by the following performance cases: rest, cystization, anabiosis, winter sleep and sleep state of an organism in general.

Strategy 2 (let it denote the Active Strategy) comprising re-designing, growing and building-up favors survival of those bio-systems, which are capable to increase not only their external, but also their internal energy consumptions due to a more effective use of an additional external energy and active adaptation to new external environmental conditions. An application of this type of the Strategy is expedient and gives the highest priority in survival to those bio-systems which are able to use the additional external energy supply under availability of sufficient external energy resources for the purposes of their better or higher organization, growth, reproduction and further improvement of their structure.

Variability in the external environment, occurrence of various periods of rhythms of the external energy and availability of the latter to any bio-system require appropriate alternating sequences of Strategy 1 and Strategy 2 responsible for life support. A long-term predominance of only one Strategy increases the probability of loss of stability of the bio-system. Sustained sympaticotonia or vagotonia might be associated with pathology progression and aging acceleration. A prolonged prevalence of the Strategy of the performance efficiency provides for a slowdown in metabolism and a depletion of the self-regulation reserves. If long periods of Strategy 2 of higher activity prevail, it may lead to an aggravation of destructive entropy processes in reference to the restorative anti-entropy processes. The period with an excessive redundant external energy input inevitably results in energy deficit and implies the necessity to going to Strategy 1, the Strategy of the performance efficiency. So, it is evident that pathological desynchronoses are mainly responsible for aging and death of bio-systems.

Best suited for maintaining stability of the bio-system may be such a spectrum of rhythms of alternating sequences of life-supporting Strategy One and Strategy Two, which is capable of providing an optimum relationship between the organism system and the environment and which is capable even of predicting expected phases of the environment variables (it’s a reflection of the pro-action effect). That is the reason that the management of the proper lifestyle, the normal balance between rest and activity, the adequate sequence of circahorianal, circadian, weekly and seasonal rhythms of physical activity, respiration, rest and work, nutrition and some other functions of the organism in concordance with external environment rhythms is of prime importance to slow down aging and keep up health. With aging, a decline in the homeostatic capacity due to feedback and minimization of energy consumptions takes place. As a result, desynchronoses as mandatory elements of self-regulation begin to transform their functional (reversible) nature to pathological irreversible one, while the extreme and the stress-related conditions remain the same. In this situation, stability of the organism is provided not by maintaining stability of the elements (cells), but by eliminating some of them. The reserves of stem cells in a tissue within an affected pathological area are depleted, and irreversible alterations take place in the nervous tissue due to loss of differentiated neurons. Strategy 2 aimed at the stability support prevails at the level of newly synthesized macromolecules, ribosomes, newly born cells, and it is typical for the conditions of tissues and organs immediately upon tissue proliferation, regeneration, growth and building-up.

The maintenance of stability of every bio-system is based on a concordance between the hierarchy of its biorhythms and the time organization of the external environment. Prevalence of gel over sol in cells is favorable in phases of lowering (a deficit in) internal and external energy and gives preference to more efficiently operating cells. In contrast to this, in the phases showing an excessive or redundant external energy, a partial gel-sol transition assigns top priority to those cells which are capable of reasonably utilizing the available excessive energy in order to provide a higher organization and support biosynthesis and reproduc-
tion. An excessive dilution of cytoplasm leads to release of bound calcium and causes again a transitional shift towards gel. Then the cycle is repeated again. The sequences comprising the Passive Strategy alternating with the Active one, targeted at maintaining stability, may exist if the hierarchy of the internal rhythms of the gel-sol transitions is in concordance with the external rhythms of energetics (the hierarchy of environmental space- & helio-physics-related rhythm patterns). However, in order to maintain stability of protocells, they should provide in a selective manner higher sensitivity to some rhythms of the external environment and at the same time to lower it to the others. This can be achieved only by a combination (an integration) of individual gel-sol structures in a common system, based on their mutual energetic interaction and generation of a hierarchy of the gel-sol structures differing in their sizes and oscillation periods. To put it otherwise, creation of a new living cell requires an agreement between the hierarchy of its own intrinsic rhythms of gel-sol transitions and certain extrinsic rhythms of the external environment by selection of some morphological forms and calcium binding & releasing kinetics.

A prerequisite to the formation of the simplest living cell and the maintenance of its stability is the proper alternation of the priorities of the functional and biosynthetical processes by their energy-linked parametric regulation. The functional processes demonstrate the least inertia, while those of biosynthetical nature show the greatest one, and the energy-linked processes possess an intermediate inertia property. The biosynthetical processes feature greater specific energy consumption, as compared with those functional. Considering the above, it should be stated that the simplest living cell may come into existence only if and when a concordance among the functional and biosynthetical rhythms via their common external energy processes is provided.

The principle of the alternating priority in distribution of energy flows in a cell to the assigned processes, showing different energy consumption and lability [19], can explain the hierarchical nature and the endogenous mechanism of the biological clock with their “pendula” swinging in opposite directions. The latter, irrespective of external influences or actions, may be used for correction to provide acting in concordance with the customary regular rhythms of the external environment only, and they do not require a direct genetic regulation. Contrary to the system of a nonlinear chemical oscillator of the Belousov – Zhabotinsky reaction type, the endogenous mechanism of the biological clock is built upon the synchronization of mutually supporting nonlinear oscillations. With this, genetic determination refers to the morphological forms only.

The functional activity of a cell at any evolutional stage caused either by an internal source of imbalance and instability, or an external action, provides an increase in energy output in the cell due to its self-regulation with overshoot. This makes possible to achieve a threshold of energetic activation of the more energy consuming, but less labile process of biosynthesis. And in its turn, the inertial biosynthetical processes by virtue of their self-regulation provide an increase in density of the flow of the synthesized energy that dictates the priority to further elevation of biosynthesis and inhibits at the same time the function, which is limited by the energy output rate and which does not depend on the flow density (the ATP concentration). Upon reaching energy saturation, biosynthesis stops stimulating energy production, and the latter starts decreasing due to the self-regulation. It results in limitation and subsequently retardation of the biosynthesis level, so that the priority is given again to stimulation of the function rate. So, it can be concluded that intermediate values of inertia of the energy balance regulation are responsible for alternating of stimulation and inhibition of the function and biosynthesis and change in their priorities that is best suited to rhythm variables of the external influences and the sequences of the phases and periods of responses by the cell in accordance with its functional activity and biosynthesis parameters.

Figure 1 depicts three areas of the energy-related parametric regulation of the function and biosynthesis, which are differing in their lability and specific energy consumption. Areas designated by 1 define subthreshold values of energetics by density (less than the value for the function) and by energy flow velocity (less than the value for biosynthesis). The function is energetically authorized for those energy flow density values, when biosynthesis remains still blocked. And in contrast to this, biosynthesis is already authorized and released for such values of energy flow rates, when the function is still impossible.
Areas denoted by 2 display ranges of the energetic self-regulation of the function and biosynthesis, which also show differences in the used energy flow rates and densities. Areas 3 illustrating saturation, when the levels of the function and biosynthesis are energetically not controllable, are also different in their energy parameters with respect to the function and biosynthesis. Actually, in a single simple cell we can find not two energetically reciprocally controlled processes, but rather many tens of them, which show also differences in their energetic parameters of the regulation. However, swinging of the biological clock “pendulum” into the opposite direction can be realized under the common energetic interaction even of two processes, differing in their specific energy consumption and lability, and consequently in feedback time constants and durations of the transient process. In general, the labile low energy-consuming processes are regulated by rates or paces, and the inertia energy intensive processes are controlled in their levels.

Feedback of the bio-system by agreeing its biorhythms with those of the external environment, including biorhythms of other bio-systems, which interact with the given bio-system, is accompanied by minimization of energy consumptions and an increase in the performance efficiency. But this favorable, as it may seem, tendency in the biological processes is inevitably associated with a reducing ranges of variation of the periods of own biorhythms of the bio-system, specialized profiling with a decline in the homeostatic capacity and the self-regulation reserves. The price to be paid by the bio-system for feedback is aging, degeneration in noise immunity and reliability in response to unfavorable actions as well as the higher probability of development of phase-, system- and hierarchy-related desynchronoses.

A decrease in mean value, in variability of the period and lowering of amplitude of biorhythms are typical chronodiagnostics signs of aging in any bio-system. However, individuals, who behave like spinning tops throughout their life, demonstrate diminished resistance with age, and “their life days run like calendar sheets taken by the wind”. The sort of external information, including interaction with the other bio-systems, which induced at a young age with a high derivative excessive or redundant anabolism1, cannot be emotionally expressed and is even not capable of compensating catabolism and destructive processes at an old age. The said information becomes customarily acquired by elderly persons, so that it cannot induce any response. Contrastingly, a child actively responds to every new thing or matter. In a child organism, all the cells and organs are far from the balance and feedback in communication, and this is especially true in the period of growth and building-up. Not death, but an increase in the performance efficiency in data processing in the context of feedback is programmed by genetics. Feedback is very useful since it shortens time and cuts expenditures required for decision-making. To prohibit or stop feedback of a bio-system is loss of life thereof. A cancer cell cannot provide feedback and response to signals of the normal intact cells, and it is potentially immortal. Anabiosis, spores, cyst formation and some other forms of input data blocking should be regarded as not life, but life preservation. Loss of data obtained in ontogenesis by a cell or an organism is the price to be paid for transfer of genetic information from one generation to the next generation.

This holds true not only for sexual, but also for vegetative reproduction. So, viruses possess genetic information only, and they cannot be alive outside a cell. And it is only a human who has acquired wisdom, knowledge and expertise to transfer his own individual personalized ontogenetic information with the use paper, magnetic and other data storage media. From this point of view, the problem of biological immortality of homo sapience has been already solved. Gene mutation is one of the ways of feedback and adaptation of
the biocenoses and the biosphere, but this is not applicable to intracellular microstructures, cells or the organism. Can the genetic code be stored in intervals between Big Bang events or not? this is the question related to immortality and continuity of biological life, its origin on the Earth and dissemination in the Universe.

Life of a human is measured not in years, but in biological reference time units, by the actual number of biological information events. According to Russian poet Samuel Marshak, “we know that time is stretchable, and it depend on the content you fill your time.” Varied life scenery, rich in information, is favorable to life prolonging that is measured in standard physical time measuring units. So, a life span of a human is “the art of avoiding life cut-off” due to bad habits, and the art of extending it with adhering a healthy life style. In this case, it should mentioned that not absolutely everything depends on a human: unfavorable genetic inheritance and environment pollution dictate the necessity to develop some fresh specific methods and technologies of early detection & diagnostics, prediction of potential diseases at their preclinical stage, effective prevention and therapy. Based on the successful completion of clinical testing of our original equipment designed for chronodiagnostics and bio-controllable chronophysiotherapy, it should be noted that the most important technologies among them, capable of prolonging active life, are those assessing and improving cell immunity, circahoralian and circadian rhythms of the vegetative nervous status, identification of a limiting organ (affected by hypoxia, arterial or venous hyperemia) and normalization of the relevant rhythm spectrum generated by microcirculation in the affected organ tissues [19–21].

Like any other biological process, aging is of rhythmic nature. The living organism takes always an opportunity to eliminate the produced desynchronoses. V.V. Frolikis called such rejuvenation “vitauct” [5]. But the organism itself is capable of restoring bio-rhythms only by a lowered level of the function of a limiting organ or a limiting system at the expense of adaptation and rise in the performance efficiency of all the other organs and systems. Such temporary improvement of the life performance decreases the homeostatic capacity and cuts off a life span only. Therefore, it is of great significance to identify the limiting organ and restore the proper level of its performance in agreement with the performance of the other organs within the organism. It is a must to treat not a disease and not an affected organ individually, but the patient and his/her organism as a whole. And it is possible only in the regime of bio-control, bio-synchronization of physiotherapeutic effects with the rhythms of the central blood circulation, when and where the rhythms of microcirculation, energy supply, sol-gel transitions, functioning and biosynthesis in cells in the pathology area are automatically rearranged and normalized, accompanied by cancellation of all compensatory alterations in the other organs in the organism [19, 21]. A limiting element, expediting the aging process, may be a deficit in some organ-specific peptides [22]. Administration of specific cytamins may retard aging, but, in order to provide an effective prevention and deceleration of aging, required is removal of limitation not only in the structure (that is undertaken by cytamins in the case in question), but also in functional activity of the respective organ that a prerequisite to the effective use of the cytamins. And removal of the limitation in the functional activity is possible with the use of bio-controlled chronophysiotherapy technologies designed and developed by us [19, 21].

Active long healthy life is possible only in case of prevention and elimination of desynchronoses at the pre-clinical stage of diseases. The necessity of an early detection of the limiting element in a human organism results from the chronobiological theory of bio-system stability. For this purpose needed are not assessments of deviations from the normal parameters of the performance of given organs or changes in morphology of the latter, that has been successfully realized by the existing methods, but a possibility to predict these disorders based on the type, character and degree of desynchronoses, by application of some original chronobiological algorithms and methods of computer analysis designed and developed by us [19, 20].

Transplantation of autologous stem cells reveals new possibilities for active long healthy life. However, the reliable and safety use of this method is possible only in case if the proper concordance among the rhythms of the stem cells and the host cells in the affected tissue within the transplantation area is provided. Our method of bio-controlled laser therapy may be useful for this purpose. The natural process of replacement of the tis-
Sue defects in the organs with its own stem cells is poorly realized by the organism itself, while potentialities of this sort of the process in any organism are huge. Stem cells enter the circulation bed according to a specified scheduled time, so that in the said case maintaining of the proper biorhythm patterns and avoidance of a biorhythm disharmony in any human organism is extremely important.

Among other conditions for active long healthy life, the following should be noticed:

1) an adequate well-balanced nutrition diet, taking into account individual peculiarities and regional area specificity; 2) optimal physical and mental loading (labor) as a method for maintaining Strategy 2 to achieve organism stability; 3) diversity and novelty of external factors, positive emotions, friendly relations, feeling of recognition as a useful social individual; 4) minimization of unfavorable external physical and chemical environmental pollution, optimal ionization and concentration of active forms of oxygen in air; 5) high quality of drinking water according to the relevant physical, chemical and structural characteristics with desired removal of heavy water (D2O); 6) periodical examination of cell immunitiy level with our method of differential thermometry and normalization by applying bio-controlled laser therapy; 7) prevention and normalization of sleep with bio-controlled light therapy; 8) compensation of a deficit in melatonin production by epiphysis with the use of bio-controlled laser therapy; 9) prevention of various somatic diseases, correction of symptoms of menopause, disorders in hormonal functions and psycho-emotional state by applying PC-assisted equipment designed and developed by us for respiratory gymnastics, prevention and treatment of functional disorders in eyesight and hearing with simultaneous chronodiagnostics and improvement of memory with bio-controlled feedback of visual and audible information; 10) prevention of osteoporosis with the method of bio-controlled calcium or xydifon electrophoresis pioneered by us; 11) prevention of chronic venous insufficiency and trombophlebitis with our method of bio-controlled pneumomassage, 12) prevention of arterial hypertension, atherosclerosis, hypoxic disorders, oncological diseases, metabolic syndrome and other age-associated diseases according to V.M. Dilman [4], infections (chlamydia and other parasitic and pathogenic forms of microorganisms and viruses) with bio-controlled chronophysiotherapy.

To extend a lifespan of an organism and decelerate aging, 4 ways have been “invented” by nature. In this context, aging is nothing else but the price to be paid by every organism for its feedback, adaptation, customization to external environment and interrelations between the elements. Ontogenetic memory is always aimed at increasing the efficiency of the interactions. It means that in the feedback process a decrease in free energy and the functional induction of the plasticity (reduction) processes take place, which parametrically depends on the level of a positive energetic disbalance. In a “feedback-completed” system we deal with a lesser amplitude of the energy regulation, deviation in predominance of synthesis or decay of ATP. A decrease in energy supply of the responses during the feedback process (a reduction of the internal regulatory energy inputs) inevitably leads to increasing the probability of damage and elimination of some separate structures, accumulation of errors under influence of external factors which have not been damaging before.

The first way used to slow down aging is typical for arboreal forms of plants, some fungi and fish kinds, which grow all their life, and, in doing so, they decelerate the interactions between the elements and subsystems in their organisms. Growth and building-up of bio-systems of this sort discourage efforts of raising the energetic efficiency. The limitation for this method is misfit to ecological niche and gravity, restrictions on metabolic transport mechanisms and integration of the elements in the organism. Birds have to use this method since, the bird flight requires a high-level muscle performance to be maintained without minimizing energy input.

The second way to decelerate aging is finding of an ecological niche, which, on the contrary, corresponds to Strategy 1, responsible for the stability maintenance, reducing metabolism, lowering a demand in the internal regulatory energy input (typical for tortoises, parasitic organisms, organisms with long anabiosis, hypobiosis, winter dormancy) and decreasing a feedback process rate. However, this way retards aging in terms not of physical, but biological time.

The third way to achieve retardation of aging is restricted solely to human individuals: it greatly excels all other forms of organisms in providing a relation between the lifespan and the
period of growth and morphogenesis. It is only a human subject who shows both adaptation of the spectrum of biorhythms with maximized efficiency and effective alternating of vital activity Strategy 1 with Strategy 2. Not the capacity of homeostasis, but its lability, which is fixed genetically, determines the potential lifespan of a human individual. Extending of the lifespan and retardation of aging are provided by all the factors, which contribute to maintaining the biorhythms harmony: a healthy lifestyle, adequate physical and psychic loading, rational diet, rejection of harmful habits and avoidance of other damaging factors, including unfavorable environmental ones, a fairly regular sleep and work cycle and rhythms of physical activity. An important feature of aging retardation is maintaining of the normal rhythms of the vegetative nervous system status, cell-related and humoral immunity and the normal spectrum of rhythms of blood microcirculation in all organs of the body.

The fourth way to solve the problem of aging in a cardinal manner is feedback elimination, loss or deletion of ontogenetic memory and return to economically inefficient energetics that takes place in unicellular organism division. These simple organisms are “rejuvenated” due to mere loss of their ontogenetic memory. However, such a solution does not differ basically from reproduction of other types of organisms. In fact, the parents’ ontogenetic memory is not inherited by their children. And it is intriguing to learn that we observe in a cultivated cell population an interaction and feedback between the cells, leading to aging of the cell culture, as it is actually the case with the tissue in the organism.

The chronobiological analysis of bio-system stability allows arriving at the following conclusions:

1) The hierarchy of periods of biorhythms, constants of feedback times in regulatory loops and durations of transient processes at each level corresponds to the hierarchy of the levels in the bio-system integration.

2) In the ideal case (stability at its maximum), a time-related organization of bio-systems has a discrete fractal form, and the duration of structural processes is approximately 3000 times higher than that of the functional processes at the same level.

3) Co-evolution of the time-related organization of the external environment and the bio-systems, and, respectively, the processes of onto- and phylogenesis, adaptation, aging, building-up and evolution are determined at all levels by the universal energetic criterion: the maximization of an integral of relationship between the bio-system external energy consumption and its internal regulatory energy expenditures during the corresponding transient process.

4) Stability of any bio-system is determined by its homeostatic capacity, which is characterized by the maximum allowable, without loss of stability, duration of desynchronization, which does not exceed the duration of the corresponding structural restoration process.

5) Functional reversible desynchronoses and conflicts among the targeted energetic functions of optimization of the adjacent hierarchical levels are the basis for development, adaptation and evolution.

6) The maintenance of stability of a bio-system of the higher level can be realized by two alternatives: either by the maintenance of stability of the subsystems and the elements, which do not give rise to desynchronoses with respect to the bio-system as a whole, or by elimination of those elements, which are not energetically optimal for achieving the target function of the highest level bio-system.

7) The strategy of maintaining stability under the conditions of limited external energy resources is aimed at maintaining stability of higher-efficiency elements, which minimize energy consumption designed both for the external performance and the internal self-regulation, but primarily focused on the latter.

8) The strategy of maintaining stability under the conditions of temporarily sufficient or even redundant energy resources is aimed at priority survival (selection) of those bio-systems, which are able to effectively and more operatively use additional energy resources in order to grow their organization and biomass as well as to produce new bio-structures.

9) The bio-systems capable of generating rhythms of the alternation of the passive and the active adaptation, which coincides with the rhythms of the external environment and the energy production, have priority in maintaining stability, progressive evolution and development.

10) To harmonize the fractal structure and the hierarchy of the biorhythm periods with time-related organization of the external environment, the bio-systems generate at the cell level some rhythms of counter-phase oscillations of release, binding and forming deposits of calcium in the corresponding microstructures, fixing the rhythms in the morphology.
of the intracellular calcium deposits. To reduce sensitivity to unfavorable external rhythms, the above counter-phase oscillation rhythms increase calcium concentration in cytosol for the corresponding signals. By reducing local or integral concentration of calcium in cytosol, the cells increase their sensitivity to useful signals and signature stabilizing and correcting rhythms (for example, circadian ones) by adaptive changes in the spectrum of sol-gel transition rhythms, which are responsible for the regulation of all kinds of the intracellular motion and integrative properties of a cell. Habitual or repeated actions are memorized by integrating the receptor proteins into the plasmatic membrane.

11) Similarly, at the organism level, adaptation of the both forms is provided by dynamics of the capillary bed architecture and the regulation of the microcirculation rhythm spectrum by means of energy supply and trophism of tissues and organs, which regulate sensitivity, elaboration of conditioned reflexes, and, in evolution, new neuro-humoral connections and genetically fixed forms of function and morphology.

12) At the level of the biocenosis and the biosphere, in a similar manner, an optimal time organization is fixed by interspecies relationship, the corresponding morphology of populations, consortia, biomes and eco-climatic zones.

13) The hysteresis type of the dependence of sol-gel (phase) transitions in a cell, similar properties of latency and inertia in energy supply of the processes in an organism, the biocenosis and the biosphere can explain the phenomenon of summation of external influences and their information triggering character.

14) Biological memory at the level of the cell and the other bio-systems up to the biosphere as a whole provides, according to the principle of advancing reflection (by P.K. Anokhin), pre-settings of the time organization of the bio-system to the most probable changes in the external environment time organization. This is the basic difference from the memory used in the existing engineering systems.

15) The clock rate of the bio-systems, as opposed to the engineering ones, is referred not to astronomical, but to biological reference time standards, so that in a human organism, for example, an interval between pulses is regarded as the biological time unit.

16) Information biologically valuable signals for bio-systems of any level have multi-frequency codes with an invariant rhythm relation. Any regulation in the bio-systems is of a multiloop multi-frequency nature.

17) Bio-resonances in bio-systems appear only in response to multi-frequency influences, biologically valuable and habitual, where importance are not absolute values of the frequencies, but their relations, adequately fixed in the feedback process (in ontogenesis and evolution), according to the fractal hierarchy of the biorhythms.

18) Chronobiological algorithms for diagnostics of phase-related, system-linked and hierarchical desynchronoses of the bio-systems are simpler and easier-to-use in practice, since they require an assessment of time parameters only, differential modes of evaluation of the dynamics of the processes of the relevant level, but not their absolute values. They allow predicting the directivity of the responses and, using the latter in interactive systems of bio-control, providing stability of the bio-systems. Chronodiagnostics allows predicting progression of diseases even at the early preclinical stage.

19) Bio-rhythmological bio-control, responsible for stability of the bio-systems due to correction of time parameters of the bio-system and elimination of desynchronoses, is biologically more adequate and effective than the other existing methods of influence at the level of function or morphology. It allows correcting the parameters of homeostasis at any level, without upsetting the balance of them. It is especially important in case of deteriorated regulatory possibilities of a given bio-system. For example, bio-controlled chronophysiotherapy, as opposed to conventional physiotherapy, does not upset the balance of the homeostasis parameters, but provides the targeted normalization of them. It excludes negative side effects and is important for treatment of children and elderly population, in case of severe pathologies, when the self-regulation reserves are lowered.

20) Bio-controlled chronophysiotherapy of an organism, as opposed to conventional physiotherapy and medication treatment, permits to reliably avoid unfavorable side effects and exacerbations. It provides the systems approach to treatment with keeping-up stability due tissue cellular memory storage; it makes possible to avoid accustomization, negative compensatory alterations in the other organs and systems, to reduce or in some cases even to exclude the necessity in medication therapy. For example, in elderly patients with arteriosclerosis encephalopathy and
In order to achieve these aims, it is possible to use our original methods, technologies and devices designed for bio-controlled chronophysiotherapy. 22) In order to provide an active long healthy life, in addition to the known requirements for a healthy lifestyle, rational diet and water with negative oxidation-reduction potential and low deuterium content, we have designed and developed some original methods and devices which offer the following: 1) non-invasive assessment of cell immunity with differential thermometry and its restoration with the use of bio-controlled laser therapy, 2) evaluation of disorders in circahiralian и circadian vegetative nervous status rhythms (the device for hourly and daily monitoring of pulse and respiration intervals) and their restoration by eliminating sustained sympathicotonia or vagotonia with PC-assisted respiratory gymnastics, 3) detection of the limiting organ and the associated disorders in the blood microcirculation spectrum rhythm in the area of pathology with the Doppler flowmetry and differential thermometry to identify temperature asymmetry and gradients followed by normalization of them with the use of bio-controlled laser therapy, 4) prevention of atherosclerosis and cognitive disorders, prevention of progression of pathogenic microflora, especially chlamydia, using bio-controlled chronophysiotherapy, as well as an elimination of disorders in vision and hearing, influenza, mental disorders, winter depression, sleep disorders, BMI normalization, improvement in visual and audible information memorization with the use of IT equipment or smartphones.

Conclusions
Stability of bio-systems of any hierarchical level is based on the following: 1) the rhythmic concordance among the energetic, functional and structural processes, 2) correction of the rhythms in relation to the external environment time organization, 3) energetic parametrical dependence of the value and sign of the functional induction of the restoration processes. Aging accelerates due to accumulation of errors and defects at any level, but it should not be simply reduced to them, even when it is impossible to remove the said errors or abnormalities partially or in full. Genetically programmed is not aging itself, but the minimization of energetic expenditures during adaptation of the bio-system functional activity to external environmental factors appearing on a regular basis. Aging decreases the energetic efficiency of the functional induction of the restoration processes. Locking selective sensitivity to certain habitual rhythms of the external factors of Space and biota in a genome and elevating a threshold of sensitivity to some other external influences, considered as noise, is a consequence of evolution of life on the Earth. Aging is associated with the appearance of pathological desynchronoses, with irreversible discordance among the biorhythms, removal of which requires an elimination of some elements with an altered (retarded) biorhythm in the bio-system. The bio-rhythmological bio-control at the cell level makes possible to remove desynchronoses, restore the biorhythms harmony due to the concordance among the functional load and the phases of rhythms.
of increase in the energy supply required for responses. Such synchronization permits to provide a stable increase in the biosynthesis and reduction processes, to maintain or even to partially restore the self-regulation reserves and the homeostatic capacity [19, 21]. Developed are the technologies and devices for chronodiagnostics and bio-controlled chronophysiotherapy, which are capable of retarding the aging process and maintaining health in the human organism. The designed and developed technologies and equipment allow detecting a disease by detecting phase-related, system-linked and hierarchical desynchronoses even at the early pre-clinical stage and eliminate the desynchronoses by synchronization and physiotherapeutic influences with phases of blood filling increase in the area of pathology, using signals from pulse and respiration sensors on a patient [19, 23].

With adaptation of a bio-system of any level to the external environment, the strategy of the efficiency starts prevailing over the active strategy of adaptation with the use of additionally induced energy. It results in reducing the homeostatic capacity and the self-regulation reserves. Aging is a result of a reduction in energetics under adaptation. A decrease in the self-regulation reserves leads to an increase in the probability of damages, defects and a reduction of the possibility to eliminate them. So, an organ in the body may become individually limiting upon exhausting of both methods of elimination of desynchronoses at the lower levels, earlier than the other organs, considering health and stability to unfavorable influences.

For an active long healthy life it is necessary to individually define and eliminate the identified energetic and structural (biosynthesis) limitation of the self-regulation reserves. In doing so, at the molecular level considered should be the organ-specific peptides; in case of transplantation of stem cells we should pay attention to the concordance among the rhythms of the stem cells within the area of transplantation and the rhythms of the recipient's cells at the cell level. To eliminate the limitation of the functional and energetic self-regulation reserves it is required to normalize the vegetative nervous status and the cell immunity rhythms, the spectrum of blood microcirculation rhythms in the limiting organ, having harmonized them with the central blood flow rhythm.

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
The author read the ICMJE criteria for authorship and approved the final manuscript.

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Pre-nosology diagnostics

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Abstract

The present paper deals with prenosological diagnostics as methodology of an estimation of functional states of an organism. Highlighted is its first practical application in space medicine, at long influence of stressful factors, including such factor unusual to terrestrial organisms as weightlessness. Demonstrated is the methodology's wide recognition and use in various areas of medicine and physiology. Health is considered herein as process of the continuous adaptation of an organism to environment conditions. Thus, shown is the connection between transition from health to illness and decrease in adaptable possibilities. Transition from health to illness, an exhaustion and failure of mechanisms of adaptation are described in detail. The classification dividing the prenosological states into physiological norm, prenosological, premorbid and pathological states is used herein. Prenosological studies including diagnostics, screening and control are considered.

Keywords

Prenosological, Space medicine, Stress, Adaptation, Premorbid

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Introduction

Term "pre-nosological state" (R.M. Baevsky, V.P. Kaznacheev, 1978) heaved in sight in another volume of the Big Medical Encyclopedia published more than 30 years ago. The book also gave the definition of pre-nosology diagnostics as a methodology of evaluating functional states of organism on the borderline between the norm and pathology. Today, this methodology has gained a broad enough recognition and is much used in the areas of medicine and physiology. It is significant that pre-nosology diagnostics emerged and was first applied in space medicine fully concentrated on the studies and monitoring of the health of normal people during prolonged exposure to a multitude of stress factors, including microgravity, the most extraordinary one for the human organism. The traditional health definition as absence of disease symptoms could not satisfy space medicine, for its major criteria of health is the abil-