The portrait stamp issued in the USSR: Makhmud Eivasow, 148 years old.

The portrait stamp issued in Colombia: Javier Pereira, 167 years old.
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JOURNAL INFORMATION

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Artem Chefranov and Sergey Chefranov are outstanding Russian mathematicians who have solved one of the seven fundamental Millennium Prize problems formulated by Clay Mathematics Institute: the smooth solution of the Navier-Stokes equation is existent.

\[
\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = \frac{\eta}{\rho} \Delta u_i - \frac{1}{\rho} \frac{\partial}{\partial x_i} \left( p - \left( \zeta + \frac{\eta}{3} \right) \frac{\partial u_i}{\partial x_i} \right), \
\Delta = \frac{\partial^2}{\partial x_i \partial x_i}
\]

\[
\frac{\partial \xi}{\partial t} = T \frac{\partial \xi}{\partial t} + \frac{p}{\rho} \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial t} \left( \rho \xi \right) + \Phi_0 \frac{\partial \rho}{\partial t}
\]

\[
\rho \Phi_0 = \frac{1}{4} \left( \frac{\partial}{\partial t} \left( \rho \xi \right) + \rho \frac{\partial \rho}{\partial t} \right) + \Phi_0 \frac{\partial \rho}{\partial t}
\]

\[
\begin{align*}
B_i(t) &= \int_0^t d\tau V_i(\tau) \\
\frac{\partial u_i}{\partial t} + (u_j + V_j(t)) \frac{\partial u_i}{\partial x_j} &= 0
\end{align*}
\]

\[
\begin{align*}
\mu (\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi)) &= \delta(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi)) \\
\frac{\partial \delta(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi))}{\partial x_m} &= -A_{km} \frac{\partial \delta(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi))}{\partial \xi_k}
\end{align*}
\]

\[
H = \omega_k u_k = \int d^2 \xi (u_{0k} \omega_{0k} + t \omega_{0j} \frac{\partial}{\partial \xi_j} (\bar{u}_0^2 + 2 \xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi))
\]

\[
\begin{align*}
\hat{A}(t) &= 1 + t \mu(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi)) \\
\hat{A}(t) &= 1 + t \mu(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi))
\end{align*}
\]

\[
\begin{align*}
\langle u_i \rangle &= \int d^2 \xi (u_{0i} \omega_{0i}) \frac{1}{\det \hat{A}(\xi)} \exp \left[ -\frac{(\xi - \bar{x} + \bar{B}(t) + \bar{u}_0(\xi))^2}{4 \mu} \right]
\end{align*}
\]
Dear Reader!

The topics of the present issue of our journal are addressing the problem of longevity and a healthy life. We open our topical discussion with a unique article presenting new data on the performance of the cardiovascular system in individuals aged over 90. We are sure it will contribute to a better understanding of some specific age-related features in a human organism. The other papers of outstanding scientists published herein should complete our analysis of challenges associated with longevity and prolongation of human life.

And there is one more fascinating important message for our readership:

S.G. Chefranov, our Editorial Board Member, Doctor of Physical and Mathematical Sciences, devotes most of his research efforts to hemodynamics treated by him from the standpoint of mathematics. His papers are often found in our journal, and they always offer an excellent mathematical analysis of blood circulation processes in a human body. The most accurate description of hemodynamics as an integral part of hydrodynamics is developed by him in the context of the Navier-Stokes equations. The said equations are considered as very complicated, so that till the present no analytical solution for any moment of time has been found. Moreover, the equations are considered as much too complicated to be soluble for arbitrary smooth initial conditions. At the same time, the Navier-Stokes (NS) equation is widely used for numerical modeling in various fields of applications: from non-stationary vortex air flows in aircraft designing up to forecasting of weather phenomena that is of great importance for aviation, industry in general and even human health. However, at present, errors in computation and prediction based on the NS equation cannot be systematically realized and reduced because of the absence of not only a smooth analytical solution, but even the proof of the existence of such solution for any finite time to the three-dimensional (3D) Navier-Stokes equation. The problem of establishing this proof for the 3D Navier-Stokes equation (for a relatively simple approximation, where the described medium is regarded as incompressible one) is included into the list of seven fundamental unresolved mathematical problems of the Millennium formulated by the Clay Mathematical Institute (USA). And now, it gives us great pleasure to announce that our Editorial Board has received a fresh article by S.G. Chefranov, co-authored
with his son, where their original analytical smooth solution to the 3D Navier-Stokes equation is offered, covering even the most complicated description case: vortex flows of the viscous compressible medium (actually, all media are compressible with varying degrees). It is undeniably a huge success! Moreover, the elegance of the found solution supports the well-known principle in science: the true discovery always implies beauty and elegance both from the viewpoints of scientific logics and mathematics!

Our Readers should notice that, when deriving the hemodynamic equations by G.M. Poyedintsev - O. K. Voronova, which form the foundation of the theory of cardiometry, a new structural mode of the fluid flow was discovered, which was given the name "the third flow mode" to differ it from the well-known laminar and turbulent ones. The third flow mode is characterized by minimized energy consumptions. By this means evidence has been submitted that the purpose of the performance of the entire cardiovascular system is to generate and properly maintain the third mode of the blood flow in our organism. The discovery has given impetus to creating a new fundamental science: cardiometry.

Most attention has been concentrated by S.G. Chefranov on the mathematical description of specific features of the third flow mode using the Navier-Stokes equation. And now we are prepared to present his new paper where the credit for the solution of one of the above seven Millennium problems is given to S.G.Chefranov and his son. It turns out the two topics of primary concern: the NS equation in mathematics and human hemodynamics are very closely related subjects. This excellent scientific achievement deserves respect and recognition! So, it might be thought that we deal not only with an outstanding scientific achievement, but also with a highly promising research tool for further development of the theory of cardiometry.

There is no doubt the pioneering advancements of our scientists will make a great contribution to the development of research methodology in natural sciences in general.

We are sure this issue of the journal will not have gone unnoticed by the research community, and the hot topics hereof will have all the chances of receiving ample interest by those who is acquiring knowledge, expertise and understanding through thought and experience in science.

Editorial Board
Cardiometry
Analysis of the cardiovascular system performance in long-living individuals

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Abstract
The paper presents some interesting data and findings on the study of the performance of the cardiovascular system in long-living individuals aged over 90. In this case, highland area individuals of this class are compared with those in flatland areas. For the purpose of the study, the cardiometric technology has been used that allows identifying age-related features in the said long-liver cohorts. The conclusions thereupon reveal the features of an individual age-related state, the assessment of which may find practical applications by researchers involved in gerontology.

Keywords
Gerontology, Cardiovascular system, Hemodynamics, Metabolic processes, ECG, RHEO, Stress index

Introduction
Gerontology focuses its attention to studies on the phenomena of longevity at all levels: from life conditions and environment up to and including physiology of a human organism [1–5]. Nevertheless there are no unambiguous conclusions on an understanding what might be the cause for the longevity phenomenon. It can be explained by the fact that until now medicine does not have any clear-cut criteria applicable to the performance of a healthy human organism. Thus, when examining athletes, characteristics of their physiological conditioning states, to a greater extent, may be interpreted as significant pathology cases. In other words, we have to state that at the present no well-defined definitions to describe the boundary between the norm and pathology are available. As opposed to other existing methods, it is just cardiometry that is capable of accurately identifying the boundaries of the norm and pathology. To meet the challenge, the developers of the cardiometric technology arrived at an original idea to examine two different cohorts of long-living individuals and obtain new data which could interpret the phenomenon of longevity in a new way [6-10]. The aim of our studies was to confirm the unique informative capabilities of cardiometry, when examining age-associated changes in long-living persons.

Materials and methods
Individuals aged 90 to 100 years have been examined by us as follows: one group of them lived in a mountain region, 1200 m above sea level, in Costa-Rica, and another group covered long-livers in flatlands in the South of Russia. To carry out the comparative studies, the following most informative parameters have been analyzed by us:
1. Metabolic processes in cardiac muscles: lactate, phosphocreatine and oxygen concentration parameters (in conventional units).
2. Hemodynamics: SV (stroke volume) percentage of the early diastole PV1 volume; parameter RV1 in %. PV1 is the volume of blood entering the heart ventricle in the early diastole (ml);
PV2 is the volume of blood entering the heart ventricle in the atrial systole (ml);
PV5 is pumping function of the aorta (ml).

An important aspect is the measurement of the above listed parameters during the orthostatic test. All the measured data have been summa-
The paper presents the relevant cardiometric ECG and Rheographic records. In total, 8 long-living persons have been covered by the studies. Results of examination of long-living individuals with the use of cardiometric technology Taking into account the fact that classical cardiology cannot provide a comparative analysis of any age-related changes in a healthy heart, we offer fresh cardiometric criteria which are capable of revealing new, previously unknown, dynamics of age-related changes in the performance of the cardiovascular system in human subjects. Table 1 below herein contains examination data obtained in our above mentioned studies on the heart performance covering the long-liver cohorts. Figures 1 to 8 given below in the paper display some recorded ECG and Rheo curves which have been used as the main sources of the analyzed information pertaining to the comparison studies.

Table 1. Data on metabolism, hemodynamics and system indicators of long-livers

<table>
<thead>
<tr>
<th>№</th>
<th>ID name of long-liver</th>
<th>Year of birth</th>
<th>Lactate (3–7)</th>
<th>O$_2$ (0.5–0.55; 0.6–0.65; 0.7–0.85)</th>
<th>PCr</th>
<th>RV1 (60%)</th>
<th>PV1</th>
<th>PV2</th>
<th>PV5</th>
<th>Stress Index (150–300)</th>
<th>Ortho-test</th>
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<td>1</td>
<td>X1, Costa-Rica</td>
<td>1925</td>
<td>39.6</td>
<td>0.16</td>
<td>0.36</td>
<td>norm</td>
<td>norm</td>
<td>+4%</td>
<td>+13%</td>
<td></td>
<td>Lying Lying</td>
</tr>
<tr>
<td>2</td>
<td>X2, Costa-Rica</td>
<td>1915</td>
<td>12.68</td>
<td>0.07</td>
<td>1.81</td>
<td>norm</td>
<td>norm</td>
<td>+9%</td>
<td>norm</td>
<td></td>
<td>Lying</td>
</tr>
<tr>
<td>3</td>
<td>X3, Costa-Rica</td>
<td>1926</td>
<td>7.21</td>
<td>0.28</td>
<td>1.99</td>
<td>norm</td>
<td>-24%</td>
<td>+4%</td>
<td>norm</td>
<td></td>
<td>Lying</td>
</tr>
<tr>
<td>4</td>
<td>X4, Costa-Rica</td>
<td>1919</td>
<td>10.61</td>
<td>0.07</td>
<td>1.05</td>
<td>norm</td>
<td>58.24</td>
<td>norm</td>
<td>norm</td>
<td>22/18</td>
<td>Lying</td>
</tr>
<tr>
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<td>X5, Costa-Rica</td>
<td>1923</td>
<td>5.44</td>
<td>0.52</td>
<td>6.50</td>
<td>norm</td>
<td>48.97</td>
<td>norm</td>
<td>norm</td>
<td>213/371</td>
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<td>X6, Russia</td>
<td>1928</td>
<td>7.80</td>
<td>0.05</td>
<td>1.82</td>
<td>norm</td>
<td>71.59</td>
<td>norm</td>
<td>+1%</td>
<td>728/247</td>
<td>Lying</td>
</tr>
<tr>
<td>7</td>
<td>X7, Russia</td>
<td>1924</td>
<td>1.79</td>
<td>0.77</td>
<td>4.03</td>
<td>norm</td>
<td>45.35</td>
<td>norm</td>
<td>norm</td>
<td>829/1074</td>
<td>Lying</td>
</tr>
<tr>
<td>8</td>
<td>X8, Russia</td>
<td>1926</td>
<td>22.14</td>
<td>0.43</td>
<td>2.39</td>
<td>norm</td>
<td>70.63</td>
<td>norm</td>
<td>norm</td>
<td>239/935</td>
<td>Lying</td>
</tr>
</tbody>
</table>

Note: Lactate, oxygen (O$_2$) and phosphocreatine (PCr) concentration indices are given in the table in conventional units.
Figure 2. ECG and Rheo of X2; A: lying position and B: sitting position (year of birth: 1915)

1. Ca++ deficit;
2. Coronary blood flow is weakened;
3. Low level of oxygen concentration;
4. Load on atria (PV2) detected.
1. Endocarditis;
2. Coronary blood flow is reduced. It affects hemodynamics and is reflected in blood volume deficiency in the early diastole (PV1). Load on atria (PV2) detected.
Figure 4. ECG and Rheo of X4; A: lying position, and B: sitting position (year of birth: 1919)

1. Ca++ deficit;
2. Extrasystole due to the increased number of fibroblasts in cardiac muscle (danger!)
3. The aorta is dilated;
4. Very low level of oxygen concentration in muscle cells detected;
5. Low level of phosphocreatine concentration detected;
6. Low stress index indicating severe state;
7. Nevertheless, hemodynamics is O.K.
Figure 5. ECG and Rheo of X5; A: lying position, B: sitting position, and C: standing position (year of birth: 1923)

1. The aorta is dilated;
2. High diastolic pressure is detected;
3. Coronary blood flow is insufficient;
Consequence: the early diastole blood volume percentage referred to stroke volume is reduced (RV1);
4. All other indicators are O.K.
Figure 6. ECG and Rheo of X6; A: lying position, and B: sitting position (year of birth: 1928)
1. Very low level of oxygen concentration in cardiac muscle cells;
2. The IVS contractility is significantly reduced.
Figure 7. ECG and Rheo of X7; A: lying position, B: sitting position (year of birth: 1924)
1. High stress index indicates over-tension of the organism as a whole;
2. Low level of lactate concentration is an indication of weakness of myocardium. Nevertheless, the hemodynamic parameters are within the norm.

Figure 8. ECG and Rheo of X8; A: lying position, and B: sitting position (year of birth: 1926)
1. Increased level of lactate concentration detected;
2. Other parameters are within the norm.
Upon analysis of the above mentioned cardiometric data, it has been found that no common pronounced problem of aging is available in the examined cohorts of the long-living individuals. A reduced coronary blood flow was detected in three long-livers. A decreased level of oxygen concentration in blood was identified in two individuals of the said class. Other parameters should be treated as individual peculiarities for each of the examined persons.

It should be noticed that the comparative analysis of Costa-Rican long-living subjects, who live in the regions 1200 m above sea level, and the Russian long-livers from Russian flatlands is worthy of being discussed.

So, the highland long-living persons show a dilation of the aorta. It should be attributed to hypoxia, a consequence of which is an increased carbon dioxide level in the organism that results in the dilation of blood vessels. It leads to a disbalance in hemodynamics, especially under physical loads. Evidence supporting this fact is demonstrated in Table 1 given above herein. Actually, observed is insufficiency of blood filling in the aorta that produces a deficit in the coronary blood flow.

Conclusions
1. The amplitude of cardiac muscle contraction reduces with age. It is related to a depletion of the total ATP energy resources in general.
2. The detected changes in the performance of the cardiovascular system of the long-living subjects show their individual peculiarities.
3. It has been found that the primary cause of hemodynamic changes in the long-livers is abnormal respiration which is responsible for alterations in the balance between oxygen and carbon dioxide in blood.
4. All other changes detected in the studies should not be classified as those age-related, since they are also often reported for middle-aged individuals.
5. The cardiometric technology makes possible to issue the proper recommendations on how to maintain the cardiovascular system in a healthy state for a long period of life that may be used as useful strategy to prolong a healthy life.

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 authors read the ICMJE criteria for authorship and approved the final manuscript.

References
V.B. Simonenko, S.V. Magayeva

The Siege of Leningrad: Discoveries in Biology and Medicine

This unique book has been released to offer a scrutinized analysis of physiology of those who suffered under the deadliest blockade of a city in human history. The authors present factual evidence showing how starvation conditions and the most unfavorable psychological factors during the Second War period affected physiology of the Leningrad inhabitants. This book describes not only the story of the siege as heroic resistance and stoical survival, but it also gives an attempt to scientifically analyze how changes in nutrition of the people under those circumstances influenced human physiology. The studies carried out by the scientists cover both blockade and post-blockade time.

Language of publication: Russian only.
The new analytical solution of the 3D Navier-Stokes equation for compressible medium clarifies the sixth Millennium Prize problem

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Abstract
The limitations of capabilities of the existing mathematical weather prediction (including forecasting for weather-sensitive individuals) cannot be duly realized nowadays due to the fact that till now there is no proof of the existence and uniqueness of smooth solutions of the three-dimensional (3D) Navier-Stokes equation (in any finite period of time).

We have obtained a new analytical solution of the Cauchy problem of this equation in an unbounded space, which has finite energy for any values of time.

Keywords
Hydrodynamics, Compressibility, Viscosity, Turbulence, Vortex waves

Introduction
1. The proper understanding of many processes in nature and engineering systems is closely connected with the existence of the fundamental and applied problem of turbulence, which remains unsolved for more than a century due to the absence of exact analytical nonstationary smooth vortex solutions of the Navier – Stokes (NS) equation. The development of the statistical approach to its solution gave a lot of interesting results, but at the same time led to a new, still unsolved, problem of the closure in the description of different moments of the vortex field, an approximated solution of which was proposed by Kolmogorov A.N., Geizenberg V. et al. [1].

In order to solve the problem of turbulence, in its turn, it is required to properly understand the mechanism of the appearance of randomness due to instability of a deterministic continual dynamic system described by the NS equation. In this case, the problem of the appearance and development of turbulence is linked to the problem of self-organization of coherent structures emerging from chaos and to the associated issues of nonrandom randomness in an individual life of a human and in life spans of living species treated in the context of the Sinai billiards [2].

However, till the present, an analytically smooth on the whole time axis nonstationary solution of the three-dimensional (3D) NS equation has not been found and even the corresponding theorem of the existence and uniqueness of such solution has not yet been proven [1].

Actually, up to date in hydrodynamics only a few exact solutions are well known, but, however, none of them is nonstationary and at the same time is defined in an unbounded (or with periodic boundary conditions) space [1–4]. Only weak nonstationary solutions describing, for example, dynamics and interactions between singular vortex objects in the two-dimensional (2D) and three-dimensional (3D) ideal incompressible medium are known [3, 5, 6]. At the same time, for the 3D ideal medium flows there are some conceptual ideas on a possibility of the existence of nonstationary solutions of the Euler – Helmholtz (EH) equation only on an unbounded interval of time $0 \leq t < t_0$ (see [1, 3, 6, 7] and the references given therein). This time value for incompressible medium is determined exclusively by the 3D effect of vortex filament stretching, which may lead to an explosive unbounded growth of the enstrophy (the integral of the squared
vorticity over space) in finite time $t_0$ [1, 3, 6, 7]. On the other hand, known are the exact stationary modes of flows of the viscous incompressible medium in the form of the Burgers and Sullivan [3] vortices for which this, potentially dangerous with respect to appearance of singularity, effect of the vortex stretching is accurately compensated by the effect of the viscosity. For these solutions, however, a convergent integral of energy over the entire unbounded space does not exist.

2. As a result, for almost two hundred years (since 1827–1845), open remains the issue on the existence of smooth nonstationary divergent and divergent-free solutions of the 3D NS equation in an unbounded (or with periodic boundary condition) space and on an unbounded interval of time [8–12]. And the significance of this problem is determined not only by mathematical, but also by practical interest, owing to both the fundamental and applied problem of predictability in hydrometeorology and other related fields that might be the case with the applications of the methods utilized for the NS equation computational solution [9, 10].

Therefore, in 2000 the problem of the existence of a smooth nonstationary vortex solution of the 3D NS equation on an unbounded interval of time was included by Clay Mathematics Institute into the list of the seven fundamental Millennium Prize problems under number six [8, 9, 11, 12]. However, at the same time, in [8] it is proposed to consider this problem solution not for the full NS equation [4], but only for the equation, derived from it in assumption that the divergence of incompressible medium velocity field is equal to zero. Evidently, such a definition a priori assumes that for divergent flows (having a nonzero velocity field divergence) the full NS equation obviously cannot have smooth solutions on an unbounded time interval. Actually, in [12] written is the following: “The Millennium Prize problem refers to incompressible flows, as it is known that the compressible ones behave disgustingly”. Thereupon, an example of appearance of the shock wave in compressible medium when an object moves therein with a velocity higher than the velocity of sound in this medium is given in [12]. However, it is clear that the viscosity forces do not allow for real singularity for any flow characteristics, that, as a result, does not exclude a possibility of the existence of smooth divergent solutions of the full NS equation.

3. Up to date, as we know, a direct proof of impossibility of the existence of smooth divergent solutions of the full NS equation has not been obtained yet, and therefore the problem formulation in [8] allows in full a generalization for the case of divergent compressible medium flows that is the matter under consideration in this paper.

Actually, in the present paper on the basis of the theory [13] found is a new analytical nonstationary vortex solution of the full 3D NS equation which because just to the finiteness of the viscosity forces (which are modeled by adding of the velocity field of the random Gaussian delta correlated in time to the velocity field [10]) remains smooth for any arbitrary large periods of time. At the same time, the NS equation solution may be extended in Sobolev space $H^p(R^3)$ for any $q \geq 1$ and $t \geq t_0$, where $t_0$ – is a minimum time of singularity (collapse) appearance for the corresponding exact solution of the EH and Riemann – Hopf (RH) equations in case of zero viscosity.

The norm in Sobolev space $H^p(R^3)$ is determined in the form [14]:

$$
\|u\|_{H^p(R^3)} = \left( \sum_{j=0}^{q-1} \int \left| \partial_x^j u(x) \right|^2 \right)^{1/2} (B.1)
$$

Let us note that in [14] formulated is a local theorem of the existence of a 3D EH equation solution of the divergent-free ideal compressible fluid flow. According to this theorem, a smooth EH equation solution exists if the initial velocity field $u_0$ belongs to the Sobolev space $H^p(R^3)$ when $q \geq 3$, and the very solution corresponds to the class

$$
\tilde{u} \in C \left( \left[ 0, t_0 \right]; H^q \right) \cap C^1 \left( \left[ 0, t_0 \right]; H^{q-1} \right),
$$

where the norm is determined in (B.1). At the same time, for the considered herein exact EH and RH equation solution in case of the divergent ideal compressible medium flow there exists the possibility for extension of this solution for times $t \geq t_0$ only in Sobolev space $H^p(R^3)$. And there is no possibility for its extension in Sobolev space $H^p(R^3)$ by time $t_0 \geq t_0$ when $q = 1$ is instead of the condition $q \geq 3$ of the theorem in [14].

The finite value of the velocity field divergence corresponds to the obtained NS equation analytical solution, that indicates an inconsistency of the above “quasi evident” a priori assumption on the absence of smooth divergent 3D vortex solutions of the full NS equation.

The noted method for taking into account the viscosity is a particular example of turbulence modeling, when instead of a random force a random velocity field is entered [15]. In [15], however, treated is only the spatially
inhomogeneous large-scale random velocity field and excluded is the drift part of this velocity which depends only on time. At the same time, just the averaging over the random velocity field, which depends only on time, provides the proper modeling of the effective viscosity (in assumption that this velocity is Gaussian and delta – correlated in time) in the present paper. Besides, it is important that this method for modeling the viscosity effect does not change the structure typical for viscosity force \( \bar{F} \), which is entered into the NS equation and, as an example, for the incompressible medium, having the form

\[
\bar{F} = \nu \Delta \bar{u} \quad [3].
\]

Actually, it is well known [15], that the existence of a NS equation solution is proven in case if to the conventional viscosity force added is a member which is proportional to a higher derivative (of the velocity of flow \( \bar{u} \)) of the form

\[
\Delta^\alpha \bar{u}, \alpha \geq \frac{5}{4}
\]

(see [16,17]) and which is responsible for changes of the viscosity force structure typical for the initial NS equation.

Besides, it is shown that an elimination of the singularity of the solutions of the EH, RH and NS equations takes place even in case of an introduction of a sufficiently great coefficient of external friction \( \mu \), satisfying the condition (5.3) and corresponding to the substitution

\[
\nu \Delta \bar{u} \rightarrow -\mu \bar{u}
\]

in the NS equation.

The new solution of the 3D NS equation is found under the condition of the zero total balance of normal stresses caused by pressure and the viscosity of the compressible medium divergent flow that, as shown in paragraph 2 hereof, corresponds to the sufficient condition of positive definiteness of the integral entropy growth rate. It allows reducing the NS equation solution to the solution of the 3D analog of the Burgers equation, and then to the solution of the 3D RH equation and its generalization for the case of taking into account the viscosity force (the external friction or the above effective friction related to the random velocity field).

Let us also note that in general case the vortex solutions of the 3D RH equations coincide with the 3D EH equation solutions for describing the ideal compressible medium vortex flows with the nonzero velocity field divergence [10, 13].

In fact, all real media are more or less compressible, and their flows should be described just by the divergent solutions of the full NS equation. On the other hand, the divergent flows for a conditionally incompressible medium may also correspond to the presence of distributed sources and drains, modeling of which is successfully used in relativistic and non-relativistic hydrodynamics [18–21].

4. Let us notice that in [22] obtained is also an exact solution of the 3D RH equation, which describes, however, only in terms of the Lagrangian variables, an explosive evolution with time for the matrix of the first derivatives of the velocity field. It does not provide a possibility for obtaining on its basis an exact solution of the 3D EH equation for the vortex field, as it has been performed in [13] in the Eulerian representation of the solution. At the same time, the present paper shows that the obtained in [13] exact solution of the 3D RH equation for the velocity field (see formula (3.7) below) in the Lagrangian representation gives for the evolution of the matrix of first derivatives of the velocity field an expression (3.14), which exactly coincides with the formula given in [22] (see formula (30) in [22]).

Also found are new analytical solutions for the evolution of vortex intensities and helicity of the Lagrangian fluid particle in the 1D and 3D cases. In [23] considered is the similar in structure form of the EH equation solution (see formula (23) in [23]) on the basis of an application of a combination of the Eulerian and Lagrangian descriptions in the representation of the vortex lines. However, it does not permit to explicitly describe the peculiarities (including the enstrophy singularity) of the evolution with time for vorticity. The discovered herein description of the evolution vorticity in the Lagrangian representation for the 2D and 3D case (see (4.4) n (4.5)) may be considered as a concretization of the obtained in [23] form of the EH equation solution for the case of the inertial fluid particles motion.

Besides, herein specified is a new necessary and sufficient criterion for the realization of the explosive singularity (collapse) in a finite time (see (3.11), (3.12)) for the nonviscous RH and EH equation solutions in the 1D, 2D and 3D cases. At the same time, in [22] given is an integral criterion in the form of (3.13) (see formula (38) in [21]), which determines only the sufficient condition for the realization of a solution collapse. Besides, for example, for the case of the ini-
tial divergent-free velocity field, the collapse is possible only according to the necessary and sufficient criterion (3.12), but it cannot be established from the criterion (3.13). At the same time, from the completed in [22] consideration of the explosive mode for the 3D RH equation solution made is a conclusion about impossibility of extension of this solution by an infinite time in the Sobolev space $H^2(R^3)$, that differs from the above mentioned result indicated herein.

In the 2D case we have an exact correspondence between the criterion (3.11) and the similar criterion given in [24] (see formula (9) in [24]) in connection with the solution of the problem of flame front propagation (generated by self-sustained exothermic chemical reaction) on the basis of a simplified version of the Sivashinsky equation [25]:

$$
\frac{\partial f}{\partial t} - \frac{1}{2} U_s \left( \nabla f \right)^2 = \gamma_0 f \tag{B.2}
$$

In the equation (B.2), the function

$$
x_s = f(x_1, x_2, t)
$$

determines the flame front representing the boundary between combustion agent ($x_3 > 0$) and combustion products ($x_3 < 0$), where $U_s$ and $\gamma_0$ are constant positive values characterizing the front propagation velocity and the combustion intensity, respectively. With $\gamma_0 = 0$ the equation (B.2) coincides with the Hamilton – Jacobi equation for a free non-relativistic particle. The proposed herein exact RH equation solution (3.7) in the 2D case (to be more exact, in its consideration of the explosive mode for the 3D case (to be more exact, in its exact RH equation solution (3.7) in connection with the criterion (3.11) in the 2D and 3D cases. It is achieved on the basis of the corresponding analytical solution of the EH, RH and NS equations both for the case of the zero viscosity and the case with taking into account the external friction or the effective viscosity. As a result, not approximately, as usual, but exactly solved has been the problem of the closure in the theory of turbulence, which remained unsolved for a long time, despite multiple attempts for searching at least for its approximate solution [1]. Herein we have succeeded in finding the solution due to establishing a relatively simple and clear dependence on the initial condition for the obtained exact EH and RH equation solution for the velocity field (3.7) and the vortex field ((4.1) and (4.2)), which is absent, for example, in the well known exact Burgers equation solution, obtained with the use of the nonlinear Cole – Hopf transformations.

In particular, due to this fact, based on the exact solution (4.2), obtained can be an estimation for the integrals of the vorticity field in the 3D case close to the moment of solution singularity:

$$
\Omega_{3(2m)} = \int d^3x \omega^m \approx O\left( \frac{1}{(t_0 - t)^{m-1}} \right) \text{ and}
$$

$$
\Omega_{3(n)} = \int d^3x \omega^m \approx O\left( \frac{1}{(t_0 - t)^{m-1}} \right),
$$

when $m = 1, 2, 3...$. Thus, the following inequality is evident:

$$
\frac{\Omega_{3(2m)}}{\Omega_{3(n)}} \cong O\left( \frac{1}{t_0 - t} \right) \gg 1; \tag{B.3}
$$

It demonstrates a strong intermittency of the vortex field in the vicinity of singularity.

Let us note, that usually the inequality

$$
\Omega_{3(2m)} > \Omega_{3(n)},
$$

actually, is regarded to be true under a strong vortex intermittency [15], but in the past it was impossible to derive it from the exact solution of the closure problem in the theory of turbulence, as it was done, when obtaining the estimation (B.3).

6. In conclusion hereof, based on an analysis of the exact closed solution of the enstrophy balance equation (5.6) and the rate of integral kinetic energy change in (6.1)–(6.4), discussed is a possibility of the existence of not only divergent, but also smooth divergent-free NS equation solutions on an unbounded time interval.

1. The Navier-Stokes (NS) and Euler-Helmholtz (EH) equations

The equation of the motion of the compressible medium may be written as follows [4]:

$$
\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = \frac{\rho}{\rho} \frac{\partial p}{\partial x_j} (p - (\zeta + \eta) \frac{\partial u_i}{\partial x_j});
$$

$$
\Delta = \frac{\partial^2}{\partial x_i \partial x_j} \tag{1.1}
$$

$$
\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x_i} (\rho u_i) = 0 \tag{1.2}
$$

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It follows from the form of the second member in the right side (1.1) that for the viscous compressible divergent flow the normal stresses are determined not only by pressure, but also by the velocity field divergence. In (1.1.1), (1.2) \( u_i \) – is a velocity of medium; in repeated indices implied is a summation from 1 to \( n \) (where \( n \) – is dimensionality of space, and later treated will be the cases, when \( n = 1, 2, 3 \)), a \( p, \rho, \eta, \zeta \) – is a pressure, a density, a constant coefficient of the viscosity and the constant coefficient of the second viscosity of medium, respectively [4].

For the incompressible medium with a constant density \( \rho = \rho_0 \) from equation (1.1), in the 3D case (when \( n = 3 \)) after curl operation from left and right sides, the following Euler – Helmholtz (EH) equation is obtained:

\[
\frac{\partial \omega_i}{\partial t} + u_i \frac{\partial \omega_i}{\partial x_i} = \omega_i \frac{\partial u_i}{\partial x_k} - \omega_i \text{div} \overline{u} + \nu \Delta \omega_i.
\]

In (1.3) \( \omega = \text{rot} u \), and \( v = \eta / \rho_0 = \text{const} \) – is a coefficient of molecular kinetic viscosity.

For the case of the compressible medium, the equation (1.3) also takes place, but only if \( \eta / \rho = \text{const} \) and the curl from the second member in the right side (1.1) is equal to zero. In particular, it occurs in the case if the second member in the right side is equal to zero (1.1) that corresponds to the zero total balance of the normal stresses produced by pressure and viscosity of the divergent medium flow.

In [13] obtained an exact vortex solution of the 3D Riemann-Hopf (RH) equation (which coincides with (1.1) when vanishing the right side (1.1)) in case of arbitrary, smooth, vanishing at infinity, initial conditions. It coincides with the exact EH equation solution (1.3) for the compressible nonviscous medium (when in (1.3) the last member in the right side is equal to zero). At the same time, in [13], in particular, it is demonstrated that the obtained smooth solution may exist only on a bounded interval of time \( 0 \leq t < t_o \) (where the value \( t_o \) is determined further from equation (3.11)).

Further (in paragraph 3 herein) it is demonstrated that for any arbitrarily small value of the effective viscosity (introduced instead of the last member in the right side (1.3)) obtained can be an exact solution of the equations (1.1) – (1.3) which exists even on an unbounded time interval.

2. Energy and entropy balance equations

1. Usually, when considering the system of four equations (1.1), (1.2) for five unknown functions, introduced is an additional condition of a relation (an equation of the medium state) between density and pressure in order to make equal the number of the equations and the number of the unknown functions. The representation of the equation of state for a nonequilibrium vortex flow needs to be specified. Instead of this, for the closure of the system (1.1), (1.2) usually utilized is an approximation of the velocity zero divergence for the incompressible medium, that is reasonable, in particular, in case of relatively lower (if to compare with sound velocity) medium motion velocities.

Let us derive a similar equation, which closes the system (1.1), (1.2) for the compressible medium divergent flow and which will substitute the condition of equality to zero of the velocity field divergence for the incompressible fluid flow.

For this purpose, we obtain the energy and entropy balance equations which follow from (1.1), (1.2) as well as from the conventional thermodynamic relations [26]. In case of a single-component medium, these relations have the following form [26] (see (14.3), (15.6) and (15.7) in [26]):

\[
\begin{align*}
\mathcal{E} &= Ts - \frac{p}{\rho} + \Phi \\
-sdT + \frac{dp}{\rho} &= d\Phi \\
\frac{d\mathcal{E}}{dt} &= Tds + \frac{p}{\rho^2}d\rho
\end{align*}
\]

In (2.1) – (2.3) \( T \) – is a temperature, \( s, \Phi \) – are internal energy, entropy and thermodynamic potential or the Gibbs free energy (units of medium mass), respectively [26]. At the same time, the equation (2.3) immediately follows from the equation (14.3) in [26], and it exactly coincides with the equation (2.1) and (2.2) (which coincides with the equation (15.7) and (15.6) in [26], respectively) at any \( \Phi \). For the considered single-component medium under condition of the constant amount of the particles therein, we assume below that in (2.1) and (2.2) \( d\Phi = 0 \) and \( \Phi = \Phi_0 = \text{const} \).

The equation (2.3) is further used in the following form (see also [4] on page 272):

\[
\frac{\partial \mathcal{E}}{\partial t} = T \frac{\partial s}{\partial t} + \frac{p}{\rho^2} \frac{\partial \rho}{\partial t}
\]

2. Based on the equations (1.1), (1.2), we may obtain the equation of the balance of the integral kinetic energy

\[
E = \frac{1}{2} \int d^nx \rho u^2
\]
as follows:

\[
\frac{dE}{dt} = -\eta \int d^nx (\frac{\partial u_i}{\partial x_i} + \frac{\partial \zeta}{\partial x_i})^2 + \int d^nx \left[ p - (\zeta + \frac{\eta}{3}) \text{div} \overline{u} \right] \text{div} \overline{u}
\]
For the incompressible viscous medium, the divergent-free flow formula (2.5) exactly coincides with the formula (16.3) in [4], and it serves as its generalization for the case of the compressible viscous medium flow. To derive the equation (2.5) it is enough to scalarly multiply the equation (1.1) by the vector \( \rho u \), multiply the equation (1.2) by the scalar \( \frac{\nabla u^2}{2} \), add the obtained expression and integrate over the entire space.

Let us notice, that in case of an ideal (nonviscous) medium, from (2.5) it follows that integral kinetic energy is an invariant only for the divergent-free flows, and for the divergent flows as an invariant should be only the total integral energy

\[ E_s = \int d^3 x (\rho \frac{\nabla u^2}{2} + \rho \delta) , \]

conservation of which is assumed to be for the viscous medium, too [4].

Let us derive an equation of the total energy balance for the viscous compressible medium and the corresponding equation of entropy balance, on the basis of the equations (1.1), (1.2), (2.1) and (2.4). As opposed to the derivation given in [4], let us immediately use the equation (2.1) written taking into account the above equality \( \Phi = \Phi_\varepsilon = \text{const} \). As a result, considering (2.1), we have the following from (2.4):

\[ \frac{\partial}{\partial t} (\rho \delta) = T \frac{\partial}{\partial t} (\rho s) + \Phi_\varepsilon \frac{\partial \rho}{\partial t} \]  

(2.6)

In the equation (2.6), the second member in the right side, taking into account (1.2), is convenient to represent in the form

\[ \Phi_\varepsilon \frac{\partial \rho}{\partial t} = - \text{div}(\Phi_\varepsilon \rho \delta) . \]

At the same time, from (1.1), (1.2) and (2.6) we obtain the following total energy balance equation:

\[ \frac{\partial}{\partial t} \left( \rho \left( \frac{\nabla u^2}{2} + \rho \delta \right) \right) = \]

\[ - \frac{\partial}{\partial x_k} \left[ u_k \left( \frac{\rho \nabla u^2}{2} + \Phi_\varepsilon \right) + p - \left( \rho \delta + \frac{\rho}{3} \text{div} \delta \right) \frac{\partial}{\partial x_k} \left( \frac{\nabla u^2}{2} \right) \right] + \]

\[ + T \frac{\partial}{\partial t} (\rho s) = \frac{B}{T} , \]

where expression \( B \) is given in (2.7).

The energy and entropy balance equations (2.7), (2.8) do not coincide with the equations given in [4] in the formula (49.3) and (49.4), respectively. However, from the balance equation (2.7) we may obtain exactly these equations (49.3), (49.4) and the given in [4] integral entropy balance equation (49.6) as well. For this purpose, in (2.7) we should use instead of the equation (2.6) its equivalent representation

\[ \frac{\partial}{\partial t} (\rho s) = (\varepsilon + p) \frac{\partial}{\partial t} - \rho T \frac{\partial}{\partial t} \frac{s}{\rho} \]

(applied in [4] without taking into account (2.1), but assuming the equality \( \Phi = \Phi_\varepsilon = \text{const} \)). It is more significant that, in addition thereto, to provide the coincidence of (2.7) with (49.3) in [4], the pressure gradient in (2.7), according to [4], should be expressed in the form of

\[ \frac{\partial p}{\partial x_k} = \rho \frac{\partial}{\partial x_k} \left( \varepsilon + p \right) - \rho T \frac{\partial}{\partial x_k} \frac{s}{\rho} , \]

which follows from the thermodynamic relation (2.3) (if to add member \( dp/\rho \), to the left and right side (2.3)),

Such thermodynamic representation for the pressure gradient which enters into (2.7) (and in (1.1)), corresponds to the conventional representation of pressure, which completely describes normal stresses for the compressible and incompressible medium only in case of the zero viscosity. It does not correspond to that new representation of pressure, which appears just in case of description of the viscous compressible hydrodynamics in (1.1) due to appearance of additional normal stresses, proportional to the velocity field divergence (see [4] page 275).

This statement on incompletely adequate representation of the pressure gradient (in formulas (2.7) and (1.1)) on the basis of the application of the thermodynamic relation (2.3) is further confirmed by the obtained in next clause fundamental relation (2.10) between the rates of with-time change of the integral entropy and the integral kinetic energy. Actually, the relation (2.10) immediately follows from (2.5) and the integral entropy balance equation, written just in the form of (2.9) on the basis of (2.8). On the other hand, this relation (2.10) obviously cannot be obtained from (2.5) and the integral entropy balance equation in the form given in [4] (see page 275).

4. From the entropy balance equation (2.8), the integral entropy balance equation

\[ S = \int d^3 x s \rho \]

in the given below form follows (for simplicity’s sake, herein as well as in (2.7) and (2.8) we do not use members, which describe flows generated by the temperature gradient):


\[
\frac{d}{dt} S = \eta \int d^3 x \left( \frac{1}{T} \partial_i u_i + \frac{2}{3} \text{div} u \right) - \int d^3 x \frac{1}{T} \text{div} \left[ p - (\zeta + \frac{2}{3} \text{div} u) \right] \tag{2.9}
\]

The balance equation (2.9), as already noted in the previous clause hereof, significantly differs from the integral entropy balance equation given in [4] (see formula (49.6) in [4]).

From (2.9) and (2.5), in case of constant temperature \( T = T_0 \) in (2.9), it immediately follows that the given fundamental relation is exactly satisfied:

\[
T_0 \frac{dS}{dt} = -\frac{dE}{dt} \tag{2.10}
\]

(it is also given in [4] page 422) between the rate of the mechanical energy change and the rate of the integral entropy growth.

The expression for the rate \( dE / dt \), given in formula (79.1) in [4], is not derived immediately from (1.1), (1.2), as it is done for the equation (2.5), but entered only on the basis of the relation (2.10), resulting from the presented in [4] integral entropy balance equation (49.6). At the same time, it is clear, that it is just the formula (2.5) for value \( dE / dt \) that provides a generalization of the formula (16.3) in [4] for the case of the compressible medium divergent flows, and it is not the formula (79.1), as stated in [4] without substantiation of derivation (79.1) on the basis of the Navier – Stokes equation (1.1) and the continuity equation (1.2).

Thus, it is evident from (2.5) and (2.9), that the negative definiteness of the integral kinetic energy dissipation rate and the corresponding positive definiteness of the integral entropy growth rate are possible in the compressible medium divergent flows only under condition of vanishing the second member in the right side (2.5) and (2.9), when the following relation is satisfied:

\[
p = (\zeta + \frac{2}{3} \text{div} u) \tag{2.11}
\]

The equation (2.11) demonstrates that the rate of decrease in the divergent flows integral kinetic energy in (2.5) is determined by only viscous dissipation, as it is the case with the divergent-free flows (see (16.3) in [4]). When satisfying the equation (2.11), the positively determined value of the rate of the integral entropy growth in (2.9) is found to be significantly less than the growth rate of the integral entropy given in formula (49.6) in [4]. Actually, in (49.6) there is a member present, which is proportional to the second viscosity coefficient, and in (2.9) such a member is absent under condition (2.11). The relative decrease in the kinetic energy dissipation rate in (2.5), if to compare with the expression (79.1) in [4], corresponds to the said entropy growth rate decrease in (2.9) under condition (2.11). At the same time, at least a similarity to the minimum entropy production by I. Prigogine (see in [10]) takes place.

Thus, for the compressible medium divergent flows formulated is an additional equation (2.11), which closes this system (1.1), (1.2), based on the requirement of the positive definiteness of the integral entropy growth rate in (2.9) and the negative definiteness of the integral kinetic energy dissipation rate in (2.5). Therefore, the equation (2.11) for the compressible medium divergent flows must substitute the condition of the nondivergency, usually applied for the closure of the system (1.1), (1.2) in case of the incompressible medium approaching.

3. A new divergent solution of the NS equation

1. The condition (2.11) defines an exact mutual compensation between the normal stresses of pressure and the normal viscous stresses of the compressible divergent flow. As a result of such compensation, vanishing is the second member in the second side of equation (1.1). At the same time, the equation (1.1) exactly coincides with the n-dimensional generalization of the Burgers equation:

\[
\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = \frac{\eta}{\rho} \Delta u_i \tag{3.1}
\]

In this case, the system (1.2), (3.1) is already closed and describes the evolution of the density and the medium inertial motion velocity field with decaying available, which should be attributed only to the action of the shear viscous stresses, corresponding to the nonzero right side of the equation (3.1).

If in (3.1) the viscosity coefficient is equal to zero, from (3.1) we obtain the n-dimensional RH equation, for which in [13] obtained is an exact vortex solution, considered further and generalized for the case of taking into account the external friction or the effective viscosity. Let us notice that, as opposed to the given herein and in [13] consideration of the vortex solutions, previously studied was only a vortex-free solution of the equation (3.1), which corresponds to the potential flow and which is obtained when using the modification of the nonlinear Cole – Hopf transformation [27, 28].

Suppose that in (3.1) carried out is the substitution \( u_i \rightarrow u_i + V(t) \), where \( V(t) \) is a random Gaussian delta-correlated with-time velocity field, for which the following relations take place:
\[ \langle V_i(t) V_j(t) \rangle = 2 \nu \delta_{ij} \delta(t - \tau) \]
\[ \langle V_i(t) \rangle = 0 \]
(3.2)

In (3.2) \( \delta_{ij} \) is the Kronecker symbol, \( \delta \) is a delta function of Dirac – Heaviside, and the coefficient \( \nu \) characterizes the viscosity force effect. In general case, it may depend on time, describing the effective turbulent viscosity, but also it might coincide with the constant coefficient of the kinematic molecular viscosity, when the considered random velocity field corresponds to the operation of averaging over the random Gaussian field \( V(t) \).

When deriving the equations (3.4) from (3.1), (3.2) except inequality (3.3) used is the following relation (which is a consequence of the Furutsu – Novikov formula [29-31]):

\[ \langle V_i \frac{\partial u_i}{\partial x} \rangle = -\nu \Delta \langle u_i \rangle \]
(3.5)

The equation (3.4), also without condition (3.3), may correspond to the equation (3.1) as well, if together with (3.5) the following equalities hold:

\[ \langle u_i \rangle = u_i, \]
\[ \langle u_j \frac{\partial u_i}{\partial x} \rangle = u_i \frac{\partial u_j}{\partial x_j} \]
(see [31]) and if in (3.1) the substitution

\[ \frac{\eta}{\rho} \rightarrow \min(\frac{\eta}{\rho}) = \nu \]

is carried out before. Such disconnecting of the correlations is possible in case of an exact disintegration of the time scales related to the large-scale inertial motions and the motions with the typical scale of the viscous dissipation [23].

2. Instead of approximate solving (see [32]) the problem of closure when considering the equation (3.4) in order to find the average velocity field \( \langle u_i \rangle \), let us use the initial equation, from which exactly evident is just the equation (3.4). This initial equation has the form of the RH n-dimensional equation [10, 13, 22]:

\[ \frac{\partial u_i}{\partial t} + (u_j + V_j(t)) \frac{\partial u_i}{\partial x_j} = 0 \]
(3.6)

If to apply the curl operation to the left side of the equation (1.3.6), we obtain just the Helmholtz equation (1.3), where only the member \( \nu \Delta \omega_i \) should be deleted and where the substitution \( \tilde{u} \rightarrow \tilde{u} + \tilde{V}(t) \) should be carried out.

The equation (3.6), as shown in [14], has the following exact solution for the case of an arbitrary dimensionality of the space \( (n = 1, 2, 3, \text{etc.}) \):

\[ u_i(\tilde{x}, t) = \frac{1}{(2\pi)^{n/2}} \int d\xi \delta(\xi - \tilde{x} + \tilde{B}(t) + \tilde{u}_0(\tilde{\xi})) |\det \hat{A}| \]

where

\[ \hat{A} = A_{nm} = \delta_{nm} + \nu \frac{\partial u_n}{\partial x_m}, \]

\[ \det \hat{A} \] – are determinants of the matrix \( \hat{A} \), and \( u_0(\tilde{x}) \) is an arbitrary smooth initial velocity field. The solution (3.7) satisfies the equation (3.6) only at times for which with any spatial coordinate values the value of the matrix \( \hat{A} \) determinant is positive, i.e. \( \det \hat{A} > 0 \). Therefore everywhere we shall take it into account, and, respectively, the modulus sign when writing \( \det \hat{A} \), will not be used, unless otherwise specified.

The solution (3.7) only in case of the initial velocity field potentiality is a potential vortex-free one and corresponds to the zero vortex field for all subsequent time moments. On the contrary, it is the vortex one and determines the vortex field evolution in case of a nonzero initial vortex field (see the next paragraph herein). Further, let us discuss the vortex solutions only (3.7). Let us note, however, that in [24] obtained is just the potential solution of the 2D RH equation (3.6) (at \( \hat{B} = 0 \).
in (3.6)) in the Lagrangian representation, which exactly follows from (3.7) at \( n = 2 \), as already mentioned in Introduction hereof in connection with the possibility of description of the Sivashinsky equation (B.2) solution, using the potential solution (3.7). For the 1D case with \( n = 1 \) we have
\[
\det \mathbf{A} = 1 + t \frac{d u_{01}}{d \xi}.
\]
in (3.7), and the solution (3.7) exactly coincides with the solutions given in [33, 34]. The solution (3.7) is found if applied has been an integral representation for the implicit solution of the equation (3.6) in the form of
\[
u(t) = \int d^2 \xi \exp -\frac{1}{4\nu t} \left( \frac{\xi - \bar{\xi}}{\nu t} - t \bar{u}(\bar{\xi}, t) \right)^2 \]
with the use of the delta-function and the following identities [13]:
\[
\delta(\bar{\xi} - \bar{x} + \mathbf{B}(t) + t \bar{u}(\bar{\xi}, t)) \equiv \delta(\bar{\xi} - \bar{x} + \mathbf{B}(t) + t \bar{u}_0(\bar{\xi})) \det \mathbf{A};
\]
\[
\frac{\partial \delta(\bar{\xi} - \bar{x} + \mathbf{B}(t) + t \bar{u}_0(\bar{\xi}))}{\partial \xi_m} \equiv -A_{km}^{-1} \frac{\partial \delta(\bar{\xi} - \bar{x} + \mathbf{B}(t) + t \bar{u}_0(\bar{\xi}))}{\partial \xi_k};
\]
(3.8)
\[
\delta(\bar{\xi}_1 - \bar{\xi} + t(\bar{u}_0(\bar{\xi})) - \bar{u}_0(\bar{\xi})) \equiv \frac{\delta(\bar{\xi}_1 - \bar{\xi})}{\det \mathbf{A}}.
\]
(3.9)
where \( A_{km}^{-1} \) is the matrix inverse to the matrix \( A_{km} \).

After averaging over the random field \( B(t) \) (with Gaussian density of probabilities distribution) from (3.7) we can obtain the following exact solution of equation (3.4) (and the equation (1.1) under the condition (2.11)):
\[
\langle u_0 \rangle = \int d^2 \xi \hat{u}_0(\bar{\xi}) \left| \det \mathbf{A} \right| \frac{1}{\sqrt{2\pi \nu t}} \frac{1}{\left( 2\sqrt{\pi \nu t} \right)^n} \exp -\frac{1}{4\nu t} \left( \frac{\bar{\xi} - \bar{x} - t \bar{u}_0(\bar{\xi}))}{4\nu t} \right)^2
\]
(3.10)
The averaged solution (3.10), as opposed to (3.7), is already arbitrarily smooth in any unbounded span of time change, and not only just under the condition of positivity of the matrix \( \mathbf{A} \) determinant.

3. Without taking into account the viscosity forces, when in (3.7) \( \mathbf{B}(t) = 0 \), the smooth solution (3.7), as already noted, is determined only under the condition \( \det \mathbf{A} > 0 \) [13]. It corresponds to the bounded interval of timewhile the value of the bounded minimum time of the existence of the solution \( t_0 \) is computed from the solution of the following algebraic equation of order \( n \) (and further minimization of the obtained expression, which depends on spatial coordinates, by these coordinates):
\[
\det \mathbf{A} = 1 + t \frac{d u_{01}}{d \xi} = 0, n = 1
\]
\[
\det \mathbf{A} = 1 + t \frac{d u_{01}}{d \xi} + t^2 \frac{d^2 u_{01}}{d \xi^2} = 0, n = 2
\]
\[
\det \mathbf{A} = 1 + t \frac{d u_{01}}{d \xi} + t^2 (\frac{d \hat{U}_{012}}{d \xi} + \frac{d \hat{U}_{013}}{d \xi} + \frac{d \hat{U}_{023}}{d \xi}) = 0, n = 3
\]
(3.11)
where \( \hat{U}_{0j} \) is the determinant of the 3D matrix \( U_{0mn} = \frac{\partial u_{0m}}{\partial \xi_n} \) and
\[
\hat{U}_{012} = \frac{\partial u_{01}}{\partial \xi_1} \frac{\partial u_{02}}{\partial \xi_2} - \frac{\partial u_{01}}{\partial \xi_2} \frac{\partial u_{02}}{\partial \xi_1},
\]
is the determinant of the similar matrix in the 2D case for variables \( x_p, x_q \). At the same time it is possible to change the determinant condition, obtained in [24] in connection with the problem of flame propagation, studied on the basis of the Sivashinsky equation (B.2).

For an exact coincidence it is necessary to substitute
\[
t \to b(t) = \frac{U_s(\exp(\gamma t) - 1)}{\gamma}
\]
in (3.11).

In the 1D case at \( n = 1 \) from (3.11) we have the minimum time for singularity appearing
\[
t_0 = \frac{1}{\max \left( \frac{d u_{01}(x)}{d x} \right)} > 0.
\]
In particular, at the initial distribution
\[
u_0(x_1) = a \exp(-\frac{x_1^2}{L_1^2}), a > 0
\]
we obtain
\[
t_0 = \frac{L_1}{a} \sqrt{\frac{\pi}{2}}
\]
for the value
\[
x_1 = x_{1_{\text{max}}} = \frac{L_1}{a} \sqrt{\frac{\pi}{2}}.
\]
At the same time, the singularity realization itself may take place only with positive values of the coordinate \( x_j > 0 \), when the equation (3.11) has a positive solution for the time value. It means that the singularity (collapse) of the smooth solution never occurs in case when the initial velocity field is other than zero only at negative values of the spatial coordinate \( x_j < 0 \).

The value of the wave breaking time \( t_0 \) is computed similarly at \( n = 1 \), too. Thus, for (3.11) in the 2D case (with the initial velocity field under the zero divergence) for the initial function of the flow in the form
\[
\psi_0(x_1, x_2) = a \sqrt{L_1 L_2} \exp(-\frac{x_1^2}{L_1^2} - \frac{x_2^2}{L_2^2}), a > 0
\]
the minimum value of the time of the existence of the smooth solution is equal to
\[
t_0 = \frac{e \sqrt{L_1 L_2}}{2a}
\]
The indicated minimum time of the existence of the smooth solution in the treated example is realized for the spatial variable values corresponding to ellipse points
\[ \frac{x_1^2}{L_1^2} + \frac{x_2^2}{L_2^2} = 1. \]

According to (3.11), the necessary condition of the singularity realization is the condition of the existence of the real positive solution of the quadratic (at \( n = 2 \)) or cubic (at \( n = 3 \)) equation in relation to time variable \( t \). For example, in the case of the 2D flow with the zero initial divergence of velocity field \( \text{div}u_0 = 0 \) the necessary and sufficient condition for the singularity (collapse) solution realization in finite time according to (3.11) is the following:
\[ \det U_{022} < 0 \quad (3.12) \]

For the considered above example from (3.12), the inequality
\[ \frac{x_1^2}{L_1^2} + \frac{x_2^2}{L_2^2} > \frac{1}{2}, \]
follows, in case when it is satisfied for \( n = 2 \) there is a real positive solution of the quadratic equation in (3.11), for which found is the given above minimum value of the collapse time
\[ t_0 = \frac{e_{\text{det}LL}}{2a} > 0. \]

On the contrary, if the initial velocity field is defined in the form of a carrier in the domain
\[ \frac{x_1^2}{L_1^2} + \frac{x_2^2}{L_2^2} \leq \frac{1}{2}, \]
the inequality (3.12) breaks down, and appearance of the singularity in a finite time becomes impossible, and the solution remains smooth for an unbounded time even without taking into account the viscosity effect.

The condition of the existence of the real positive solution of the equation (3.11) (see, for example, (3.12)) is necessary and sufficient for the realization of singularity (collapse) of the solution as opposed to the sufficient, but not necessary integral criterion, proposed in [22] (see formula (38) in [22]) and written in the following form:
\[ \frac{dL_0}{dt}{\mid}_{t=0} = -\int d^3x \text{div}u_0 \det^2 \hat{U}_0 > 0; \]
\[ I = \int d^3x \det^2 \hat{U} \quad (3.13) \]

Actually, according to this criterion, proposed in [22], the solution collapse is impossible for the case when the initial velocity field is divergent-free, i.e. \( \text{div}u_0 = 0 \). At the same time, however, violation of the criterion (3.13) does not exclude a possibility of the solution collapse by virtue of the fact that criterion (3.13) does not determine the necessary condition for the collapse realization. Indeed, in the considered above example (when determining the minimum time of the collapse realization
\[ t_0 = \frac{e_{\text{det}LL}}{2a} \]
for the 2D compressible flow, the initial condition corresponds just to the initial velocity field with \( \text{div}u_0 = 0 \) in (3.11) at \( n = 2 \).

4. An exact solution of the EH and Riemann-Hopf (RH) equations

1. The velocity field (3.7) is in conformation with the exact solution for the vortex field having the form [13] in the 2D and 3D cases as follows:
\[ \omega (\tilde{x}, \tilde{t}) = \int d^3\xi \omega_0 (\tilde{\xi}) \delta (\tilde{\xi} - \tilde{x} + \tilde{B}(t) + \tilde{u}_0 (\tilde{\xi})) \]
\[ \omega (\tilde{x}, \tilde{t}) = \int d^3\xi (\omega_0 (\tilde{\xi}) + t \omega_0 \frac{\partial \omega_0 (\tilde{\xi})}{\partial \tilde{\xi}}). \]
where \( \tilde{\omega}_0 = rot \tilde{u}_0 \) in (4.2) and \( \omega_0 \) is the initial distribution of vorticity in the 2D case in (4.1). The solution

At the same time, the expression (3.14) precisely coincides with the given in [21] formula (30) for the Lagrangian with-time evolution of the matrix of the first derivatives of velocity that satisfies the 3D RH equation (3.6) in [22] the equation (3.6) is considered only at \( \tilde{B}(t) = 0 \). In particular, in the 1D case at \( n = 1 \) from (3.7) and (3.8) we obtain the following particular case of formula (3.14) in the Lagrangian representation:
\[ \frac{\hat{\omega} (\tilde{x}, t)}{\hat{x}} = \frac{du_0 (a)}{da} + t \frac{du_0 (a)}{da}, \quad (3.15) \]

where \( a \) is the coordinate of a fluid particle at the initial moment of time \( t = 0 \).

The solution (3.15) also coincides with the formula (14) in [22] and describes a catastrophic process of the collapse of a simple wave in a finite time \( t_c \), the estimation of which is given herein above on the basis of the equation (3.11) solution when applying the Euler variables.
(4.2), (3.7) corresponds to the following exact expression for helicity:
\[
H = \omega_i u_i = \int d^3 \xi (u_{i,\alpha} \alpha_{i,\beta} + t \omega_{i,\alpha} \frac{\partial}{\partial \xi_j} \frac{\partial^2}{\partial \xi_i^2} (\xi_j)) \cdot \delta(\vec{\xi} - \vec{x} + \vec{B}(t) + t \vec{u}_0(\vec{\xi}))
\]  

The representations for the 3D vortex (4.2) and velocity (3.7) fields exactly satisfy the 3D Helmholtz equation (1.3), where, as mentioned above, it is necessary to remove the last member in the right side (1.3) and enter the random velocity field $\vec{V}(t)$ for describing the viscosity forces. It may be verified by the direct substitution of the solution (4.2) and (3.7) into (1.3). For this purpose, when considering the nonlinear terms, it is necessary to use the equality
\[
\delta(\vec{\xi} - \vec{x} + \vec{B}(t) + t \vec{u}_0(\vec{\xi})) \cdot 
\delta(\vec{\xi}_1 - \vec{\xi} + \vec{B}(t) + t \vec{u}_0(\vec{\xi}_1)) = 
\delta(\vec{\xi}_1 - \vec{x} + \vec{B}(t) + t \vec{u}_0(\vec{\xi}_1)) \cdot 
\delta(\vec{\xi}_1 - \vec{\xi} + t(\vec{u}_0(\vec{\xi}_1) - \vec{u}_0(\vec{\xi})))
\]
and the following identities: (3.8), (3.9)
\[
\omega_{i,\alpha}(\vec{\xi}) = A^{-1}_{\alpha \xi i}(\omega_{i,\alpha} + t \omega_{i,\alpha} \frac{\partial u_{i,\alpha}}{\partial \xi_j})
\]
After averaging in (4.1) and (4.3) over the random Gaussian field $\vec{B}(t)$ taking into account (3.2), we obtain expressions where under integral sign in (4.1)–(4.3) the delta-function is substituted by an exponent with the normalizing multiplier as it is the case with (3.10). Only after the said averaging provided the existence of not only the averaged vortex and helicity field values, but also the corresponding highest derivatives and higher moments in any time span. In particular, it takes place when for the enstrophy value (the integral of the vorticity square over the entire space) and higher moments of the vortex field, for which the explicit analytical expressions are obtained in an elementary way in the next paragraph without solving any closure problem.

2. In the Lagrangian variables, the expressions, which correspond to the Eulerian vortex (4.1), (4.2) and helicity (4.3) fields, may be presented in the following form (in case when $\vec{B}(t) = 0$):
\[
\omega(\vec{a}, t) = \frac{\omega_{i,\alpha}(\vec{a})}{\det A(\vec{a}, t)} 
\omega_{i,\alpha}(\vec{a}, t) = \frac{(\omega_{\alpha,\beta}(\vec{a}) + t \omega_{\alpha,\beta}(\vec{a}) \frac{\partial u_{\alpha,\beta}(\vec{a})}{\partial \xi_\alpha})}{\det A(\vec{a})} 
\omega(\vec{a}, t) = \frac{(u_{\alpha,\beta}(\vec{a}) \omega_{\alpha,\beta}(\vec{a}) + t \omega_{\alpha,\beta}(\vec{a}) \frac{\partial u_{\alpha,\beta}(\vec{a})}{\partial \xi_\alpha})}{\det A(\vec{a})}
\]
and the following identities: (3.8), (3.9)

In (4.7) $J = \det (\partial x_\mu / \partial a_\mu)$ is the Jacobian transformation to the Lagrangian variables $\vec{a}$. At the same time, $\partial \omega_{\alpha,\beta}(\vec{a}) / \partial \xi_\alpha$ is a new Cauchy invariant (coinciding with the initial vorticity) which is characterized by the zero divergence $\partial \omega_{\alpha,\beta}(\vec{a}) / \partial a_\mu = 0$ and
\[
\frac{d \vec{R}}{dt} = \vec{V}_v(\vec{a}, t)
\]
where $\vec{V}_v$ is the velocity component being normal to the vorticity vector so that for the component we have $d \vec{V}_v / dt \neq 0$ [22]. As opposed to (4.1) and (4.2), the expression (4.7) does not give an explicit representation for the EH equation solution, since in (4.7) no definite relation for the Jacobian $J$ and the vector $\vec{R}$ is provided. At the same time, there exists a structural correspondence between (4.7) and (4.1), (4.2), and for case of the Lagrangian fluid particles motion due to inertia, at least, for the Jacobian in (4.7) may be used the explicit representation $J = \det \hat{A}$, where $\det \hat{A}$ is determined from (3.11).

5. Equation of enstrophy balance and due consideration of external friction

1. Disregarding the viscosity force (i.e. without averaging in (4.1) and (4.2) over the random field $\vec{B}(t)$) from (4.1), (4.2) it follows that the enstrophy values conforming with them in the 2D and 3D cases allow for an exact closed description and take on the form [14]:
\[
\Omega_2 = \int d^2 \xi \omega^2(\vec{\xi}, t) = 
\int d^2 \xi \omega^2(\vec{\xi}) / \det \hat{A}
\]
\[
\Omega_3 = \int d^3 x \omega^3(\mathbf{x}, t) = \\
\int d^3 \xi (\omega_{00} + t \omega_{0j}) \frac{\partial u_{0i}}{\partial \xi_j}^3 / \det A
\]

(5.2)

To write the expressions indicated in (5.1) and (5.2) above, there has been no necessity to solve the closure problem which usually exists in the theory of turbulence. In our case, we succeed in avoiding this problem due to a comparatively simple representation of the exact solution of the Helmholtz nonlinear equation utilized for the description of the vortex flow of an ideal compressible medium.

The expressions (5.1) and (5.2) tend to approach infinity in a finite time \( t_0' \) determined from the solution of the algebraic equation (3.11) and subsequent minimization of this solution with the use of the space coordinates.

Using the exact solution of the EH equation in the form of (4.1) and (4.2), we can obtain a closed description of the with-time evolution not only for enstrophy, as it was the case with (5.1) and (5.2), but also for any other higher moments of a vortex field.

For example, in the 2D case, from (4.1), taking into account (3.8), we will obtain:

\[
\Omega_{2(\omega)} = \int d^2 x \omega^2 = \\
\int d^2 \xi \frac{\omega_{00}(\xi)}{\det^{m-1} A} = \\
\Omega_{2(\omega)} = \int d^2 \omega \omega_{00}(\xi) \frac{\det^{m-1} A}{\det A}
\]

In Introduction hereof, presented has been the estimation (B.3) for a relation of different moments in the 3D vortex field that was obtained on the basis of the expressions of the similar type from (4.2) and (3.8).

To obtain (B.3), utilized is also the estimation \( \hat{A} \equiv O(t_0 - t) \) which is realized in the limit \( t \to t_0' \). The quantity of the collapse minimum time \( t_0' \) is computed in this case on the basis of (3.11).

2. Let’s take into account the external friction now. For this purpose, in the equation (1.3) we should replace \( \nu = -\mu_\omega \). In doing so, from the expressions (3.7), (4.1) and (4.2) we can obtain an exact solution, which is found from (3.7), (4.1) and (4.2) by carrying-out the substitution of the time variable \( t \) for a new variable

\[
\tau = \frac{1 - \exp(-t \mu)}{\mu} \quad [13].
\]

Changes of the new time variable \( \tau \) take place now within the finite ranges from \( \tau = 0 \) (for \( t = 0 \)) to \( \tau = 1 / \mu \) (at \( t \to \infty \)). It leads to the fact that in case, when under the given initial conditions the following inequality

\[
\mu > \frac{1}{t_0'}, \quad (5.3)
\]

holds, then the value \( \det \hat{A} > 0 \) in the denominator (5.1) and (5.2) cannot go to zero at any moment of time, since the necessary and sufficient condition for realization of the singularity is no longer met for any instant of time (3.11), where the substitution \( t \to \tau(t) \) should be made.

Subject to the condition (5.3), the solution of the 3D EH equation is smooth in an unbounded span of time \( t \). The corresponding analytical divergent vortex solution of the 3D NS equation (where the relation (2.11) for pressure should be taken into account and where carried out should be the substitution of the first term in the right side (1.1)

\[
\frac{\eta}{\rho} \Delta u_i \rightarrow -\mu u_i; \mu = \text{const}
\]

also remains smooth at any \( t \geq 0 \) subject to the condition (5.3). We should also notice that when the values of parameters are formally coinciding \( \mu = -\gamma_\omega \) (see the Sivashinsky equation (B.2)), the equality \( \tau(t) = b(t) \) takes place subject to the condition that the singularity has been realized (3.11) with \( n = 2 \) and in accordance with the solution of the Sivashinsky equation in [24].

3. It should be noted that for flows of the nonviscous (ideal) incompressible fluid with the zero divergence of the velocity field an explosive growth of enstrophy is characteristic of the 3D flows only, and enstrophy for the 2D flows should be viewed as an invariant. A different situation arises with the divergent flows of the compressible medium under consideration herein.

Actually, for the divergent flows of the nonviscous medium, the equations of enstrophy balance in the 2D and 3D cases, which follow from the EH equation (1.3) (at \( v = 0 \) in (1.3)), hold true as given below:

\[
\frac{d\Omega_3}{dt} = -\int d^2 \xi \omega \omega^2 \text{div} \bar{u}
\]

\[
\frac{d\Omega_3}{dt} = 2 \int d^2 \xi \omega \omega^2 \frac{\partial u - \partial u}{\partial \xi_i} - \int d^2 \xi \omega \omega^2 \text{div} \bar{u} 
\]

(5.4)

It can be seen from (5.4) that in the 3D case the evolution of enstrophy \( \Omega_3 \) with time is determined not only by the effect of stretching of vortex filaments (by the first term to the right), but also by the second term as well, determined by the finiteness of the value of the velocity field divergence. As to the 2D flow, the with-time evolution of enstrophy \( \Omega_3 \) occurs only, if the flow velocity field divergence is other than zero.
In order to solve (3.7), the value of the divergence of the velocity field is of the form [13]:

$$\frac{\partial u_i}{\partial x_i} = \partial \frac{\partial}{\partial t} = \partial \frac{\partial}{\partial t} - \partial \frac{\partial}{\partial t} = 0$$  \hspace{1cm} (5.5)

An integral over the entire unbounded space from the right side (5.5) is equal to zero by virtue of the fact that the identities (3.9) hold and subject to the condition of becoming zero at infinity for the initial velocity field. As a result, for the solution in question, the equality \( \int d^3 x \text{div} \mathbf{u} = 0 \) takes place, which is responsible for the fulfillment of the law of conservation of full mass of fluid and an exact mutual integral compensation of intensities of the distributed sources and drains.

For the 3D case in (5.4), based on (3.7), (3.8), (3.9), (4.2), and (5.5), we can formulate exact expressions for the first term and the second one in the right side (5.4), which describe the contribution to a growth rate of enstrophy due to the effect of stretching of vortex filaments and due to the non-zero divergence of the velocity field, accordingly. It is not difficult to see that the same expressions for the above two terms can be also obtained by direct differentiation of the expression for enstrophy in (5.2) that results in formulation of an equality as follows:

$$d^3 \mathbf{\xi} \frac{\partial}{\partial t} \delta(\mathbf{\xi} - \mathbf{x} + \mathbf{B}(t) + t \mathbf{\bar{u}}_{\rho}(\mathbf{\xi}))$$  \hspace{1cm} (5.6)

In (5.6) the first and the second terms in the right side are exactly in conformance with the corresponding first and second terms in the right side (5.4). From (5.6) it follows that

for the non-viscous case both of these terms tend to approach infinity at \( t \to t_0 \), when \( \det \mathbf{A} \to 0 \) according to (3.11). The first term in the right side (5.6) corresponds to the effect of stretching of the vortex filaments. Its expression under integral sign is proportional to the value \( O(1/\det \mathbf{A}) \). It is evident that it makes a relatively lesser contribution to the rate of explosive growth of enstrophy as against the second term in (5.6), the expression of which under the integral sign is proportional to the value \( O(1/\det \mathbf{A}) \) and which exists only for the case with the divergent flows with a nonzero divergence of the velocity field.

Since, as noted above, taking into account the viscosity (in particular, under due consideration of the external friction, when the condition (5.3) is met) leads to a regularization even of divergent solutions of the NS equation, it might be expected that it is also possible for solutions with the zero-divergence. As for them, a similar regularization, probably, would be possible because of a comparatively weaker (in the above mentioned sense) effect of stretching of the vortex lines as against the process of a wave collapse in the divergent flow. This issue will be also treated in the next paragraph herein.

4. From (2.11) and (5.5), upon averaging the Gaussian probability distribution for random field \( B_k(t) \) we obtain with due account of (3.2) the following representation for pressure

$$\left\langle p \right\rangle = \left\langle \zeta + \frac{\eta}{3} \right\rangle \cdot$$

$$\cdot d^3 \mathbf{\xi} \frac{\partial}{\partial t} \frac{1}{(2\sqrt{\pi \nu})^3} \cdot \exp\left[-\frac{(\mathbf{\xi} - \mathbf{x} + t \mathbf{\bar{u}}_{\rho}(\mathbf{\xi}))^2}{4\nu t}\right]$$.

(5.7)

An expression for the density conforming with the equations (1.2) and (3.6) takes the form [12]:

$$\rho = \int d^3 \mathbf{\xi} \frac{\rho_{\rho}}{(2\sqrt{\pi \nu})^3} \cdot \exp\left[-\frac{(\mathbf{\xi} - \mathbf{x} + t \mathbf{\bar{u}}_{\rho}(\mathbf{\xi}))^2}{4\nu t}\right]$$.

(5.8)

Upon averaging in (5.8) with due consideration of (3.2) we can write an expression which is smooth at any times for the medium density as follows

$$\left\langle \rho \right\rangle = \int \exp\left[-\frac{(\mathbf{\xi} - \mathbf{x} + t \mathbf{\bar{u}}_{\rho}(\mathbf{\xi}))^2}{4\nu t}\right]$$.

By replacing \( \rho \to \mathbf{\omega}, \rho_{\rho} \to \mathbf{\omega}_{\rho} \) in (5.9) we obtain an expression for the 2D vortex field, since the expressions (5.8) and (4.1) have the same structure.

6. On the existence of divergent-free solutions of the NS equation

The found smooth divergent solution of the NS equation (1.1) in the form (3.10), (5.7), as stated above, by virtue of the fact that there is its analytical representation for arbitrary smooth initial conditions is just the proof that the solution of the NS equation really is existent and unique. It is of importance that in order to model the viscosity effect, it is precisely the random Gaussian delta-correlated with-time velocity field that has been introduced for that purpose, that leads to an effective viscosity force, which is structurally exactly in conformance with the viscosity force in the NS equation, as distinct from the derivatives treated in [16, 17], which are higher than the Laplacian, in computation of the viscosity force in the NS equation.

Let us perform a comparative analysis of integral values for the divergent
and divergent-free flows which characterize the evolution of the integral kinetic energy with time, the finiteness of which in [8] is the major criterion supporting the evidence of the existence of a solution of the NS equation.

For this purpose, let us consider the equation of the balance of the integral kinetic energy (2.5) on the condition (2.11) that has replaced the assumption of the zero divergence of the velocity field and that has provided the closure of the system of the equations (1.1), (1.2) for the case of the divergent flows of the compressible medium. In doing so, from (2.5) we can write an expression as given below

\[
\frac{dE}{dt} = -\eta F;
\]

(6.1)

\[ F = \int d^3 x (\frac{\partial u}{\partial x})^2 \]

The equation of the balance (6.1) in its form is exactly coincides with the equation of the balance of the integral kinetic energy for the divergent-free flow of incompressible fluid, as indicated in [4] (please, see formula (16.3)). Unlike the formula (16.3) from [4], there is in the formula (6.1) just the divergent velocity field, which has the nonzero divergence and which describes the motion of the compressible medium. In this case, for the divergent flow, the functional F in (6.1) is connected with enstrophy

\[ \Omega_s = \int d^3 x (\text{rot} \vec{u})^2 \]

by the following relationship:

\[ F = \Omega_s + D_s; \]

\[ D_s = \int d^3 x (\text{div} \vec{u})^2 \]

As this takes place, for the divergent solution of the NS equation, the right side (6.2), with other conditions being equal, obviously exceeds the value of the functional \( F = F_0 = \Omega_s \) for the solution with the zero divergence of the velocity field.

For the obtained exact solution, the expression for enstrophy \( \Omega_s \) in the right side (6.2) takes the form (5.2), and for the integral of the square of the divergence from (5.5) and (3.8) we arrive at an expression as given below:

\[ D_s = \int d^3 x \left( \frac{\partial \det A}{\partial t} \right)^2 / \det A \]

(6.3)

From comparison of (6.3) and (5.2) it follows that in the vicinity if the singularity of the solution at \( t \to t_0 \) (see (3.11)) the values of the first and the second terms in the right side (6.2) are of the same order of magnitude.

Besides, for functional F in (6.1) let us make upper estimate with the use of the Koshi-Bunyakovsky inequality as follows:

\[ F^2 = \left[ \int d^3 x u^2 \Delta \vec{u} \right]^2 \leq \int d^3 x u^2 \left[ \int d^3 x (\Delta \vec{u})^2 \right] = \int d^3 x u^2 \left[ \int d^3 x \left( (\text{rot} \vec{u})^2 + (\text{grad} \vec{u})^2 \right) \right] \]

(6.4)

According to (6.2) – (6.4), the divergent flows, with other conditions being equal, demonstrate obviously a higher value of functional F as against the divergent-free flows, which for the ad-dend in the square brackets in the right side is absent (6.4).

From the preceding, it is clear that a conclusion must be made that the smooth divergent-free solutions of the NS equation are existent because of the fact of the proven existence of the divergent smooth solutions of the NS equation on an unbounded time interval with due consideration of the effective viscosity or external friction subject to the condition (5.3).

Conclusions

Therefore, in (3.10), (5.7) and (5.9) represented is the analytical solution of the NS equation (1.1) and the equation of continuity (1.2) for the divergent flows which have a non-zero divergence of the velocity field (5.5). From (3.10), boundedness of the energy integral in the 3D case

\[ E_0 = \frac{1}{2} \int d^3 x \vec{u}^2 \]

obviously follows, too, that meets the main requirement, when formulating the problem of the existence of a solution of the NS equation [8]. Besides, satisfied is the requirement specified in [8] for unbounded smoothness of solutions for any time intervals, when describing velocity and pressure fields.

We should notice that for the found solution of the equation (3.7) even without averaging (for example, in the case \( \vec{B}(t) = 0 \) the energy integral

\[ E_\infty = \frac{1}{2} \int d^3 x \vec{u}^2 = \]

(6.4)

remains finite for any finite moment of time, while at the limit \( t \to \infty \) energy also tends to approach infinity in a power-raise manner as \( O(t^\alpha) \) (refer to (3.11)). In this case, the solution (3.7), (4.2) can be extended by any finite time \( t_0 \geq t_0 \) in the Sobolev space \( H^\alpha(R^3) \). It means that for the case with the ideal (nonviscous) medium the flow energy meets the requirement specified in [8] to prove the existence of the solution of the NS equation.

At the same time, however, the integral of enstrophy in (5.2) demonstrates an explosive unbounded growth (in a finite time \( t_0 \) determined from (3.11)), when

\[ \Omega_s \equiv O(\frac{1}{t_0 - t}) \]

in case with the unique positive real root of the equation (3.11). By this is meant that the obtained exact solu-
tion of the EH equation in the form (3.7) and (4.2) cannot be further extended in the Sobolev space \( H^1(R^3) \) by a time \( t_\epsilon \geq t_\rho \), i.e. even at \( q = 1 \) when defining the norm (B.1). Only considering the viscosity makes possible to avoid the said singular behavior of enstrophy and higher moments of a vortex field which is to say that there is a possibility of extending the solutions of the EH and NS equations for any \( t \geq t_\rho \) in Sobolev space \( H^q(R^3) \) even at any \( q \geq 1 \).

In [7], under formulating the problem of the existence of a solution of the 3D NS equation, it has been offered to impose restrictions to considering only cases of solutions with the zero divergence of the velocity field. Therewith in [7] noted is importance of treatment of those particular 3D flows, for which the effect of stretching of vortex filaments in a finite time may lead to a limitation on the existence of solutions of the NS equation in the small (im Kleinen) only.

The reached conclusion that there are smooth divergent solutions of the 3D NS equation at the expense of considering even small viscosity bears witness to an admissibility of a positive solution of the problem of the existence of smooth divergent-free solutions on an unbounded interval of time as well. Really, as it has been established in (5.6), the effect of stretching of vortex filaments makes a considerably lesser contribution to the realization of the singularity of the solution than the effect of collapse of a vortex wave in the divergent compressible flow. This possibility is suggested by the inequality (6.4) as well as the equality (6.2), which determine the value of rate of change in the integral kinetic energy.

It should be also stressed that the exact solution of the EH and RH equations found in [13] gives a closed description of the with-time evolution of enstrophy and any higher moments of the vortex, velocity, pressure and density fields. The possibility of a closed statistic description for modes of turbulence without pressure (modeled with the linear 3D RH equation (3.6)) was mentioned first in 1991 in [13]. We should note that the paper by A.M. Polyakov [35] published in 1995 develops for the 3D RH equation with a random white-noise type force (Delta-correlated with time) a general theoretical field approach to the theory of turbulence and establishes a relationship between the breakdown of the Galilean invariance and intermittency. With this, however, only for 1D case found was a concrete solution of the problem of the closure in the form (refer to formula (41) in [35]) of an explicit expression for distribution of probability \( \psi(x, y) \) at points being at a distance \( y \) from each other.

This paper offers a fresh approach capable of considering also exactly pressure on the basis of which an analytical solution of the full NS equation for a flow of the viscous compressible fluid has been found. In doing so, actually, the main problem of the theory of turbulence has been resolved [1], when the precise representation for a joint characteristic functional of the velocity and density fields (the pressure field in this case is uniquely defined from (2.11)) is provided. In the past, it was generally accepted that the main problem of the theory of turbulence in case with the compressible fluid could not be solved, and in [1] in this connection it was stated: "Unfortunately, this general problem is too difficult, and at present an approach to finding a full solution thereof cannot be seen." (please, refer to [1] P.177).

Utilizing the proposed exact solutions of the EH, RH and NS equations, modeling of turbulent modes can be provided, including modeling performed on the basis of the method of randomization of integrated problems of hydrodynamics offered by E.A. Novikov [36] and developed in [10]. For this purpose, we must introduce a probability measure on ensemble of realization of the initial conditions, which should be treated in this case as random functions.

The possibility established herein that a solution of the NS equation is existent is based on the fresh nonstationary analytical solution of the said equation that was said in the past to be unreachable [9, 13]. Following this way, it has been discovered that for the existence of the solution in an unbounded span of time it is just the viscosity that is required to be taken into account for this purpose. On the other hand, the issue on stability of the obtained solution should be treated on the basis of the available results which bear witness to a possibility of some destabilizing effects of the viscosity which may lead to a dissipative instability [37–40].

By this means, detected has been the mechanism of the appearance of the limitation in predictability and forecasting of a wind velocity field and impurity fields (affecting human health under the variable climatic factors of the environment) that can be realized, for example, with the numerical solution of the NS equation (for the divergent flows of compressible medium).

This mechanism is connected the truncation \( \lambda \), typical for the high wave
numbers or small scales that corresponds to entering of the external friction with the coefficient

\[ \mu = \frac{\nu}{\lambda^2}. \]

In this case, from the condition (5.3) it follows that only with selection of a sufficiently small scale of the truncation

\[ \lambda < \lambda_{\text{crit}} = \sqrt{\nu / \lambda} \]

(where the value \( \nu \) is computed in (3.11)) it is possible to avoid the explosive loss of the smoothness of the solution and the loss of predictability in a finite time \( t_0 \) even at the exactly defined initial data of the numerical forecasting based on the solution of the NS equation for compressible medium.

At the same time, actually the initial data are defined not accurately, but with a certain inevitable error. This may lead to breaking down the condition \( \lambda < \lambda_{\text{crit}} \) and loss of predictability in a finite time. In this regard, fascinating and intriguing is the relationship, as noted in [2], between the nonrandom randomness of the Sinai billiards, the problem of predictability based on the NS equation solution and another problem of relative longevity of biological species closely related by their initial physical and physiological parameters (raven and crow etc.) that has been known since the Sir Francis Bacon’s time.

Conflict of interest
None declared.

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

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Where the world of cardiology comes together
Relation of antistress and geroprotective effects of deuterium depleted water in aging female rats

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Abstract
The use of deuterium depleted water (DDW) in a dosing regimen of 25–30 ml per day for five weeks in aging female rats (20–22 months) contributed to the overall correction of age-related disorders of the adaptive status, estrous cycle regulation and nonspecific resistance, as well as the appearance of visually distinct signs of rejuvenation of the animals. The obtained results show the relation between the geroprotective effect of DDW and the development of the general nonspecific antistress adaptation reactions of calm and elevated activation that can serve as an experimental basis for the development of an effective method of geriatrics and prevention of cardiovascular diseases and degenerative processes in women in the peri- and postmenopausal period.

Keywords
Deuterium depleted water, Aging female rats, Estrous cycle, General nonspecific antistress adaptation reactions, Neuroendocrine regulation

Imprint

Introduction
Age-linked disorders of the neuroendocrine and immune regulation, as a rule, lead to a reduction in the nonspecific resistance of an organism and are responsible for development of various pathological states, which may include cardiovascular, degenerative and tumor-related diseases [1, 11, 21]. In addition, there are some specific sex-linked differences in the age-associated disorders, which manifest themselves as a faster decline in the reproductive function in the female organism in comparison to the male one, along with the existence of a certain relation between the hormonal function of the ovaries and the resistance of the female organism to cardiovascular and some other diseases [19, 28]. It has been demonstrated that, at the level of the entire organism, the key role in providing aging-retarding conditions should be assigned to a mechanism responsible for generation and changes of some discrete states in the organism, namely, some integral adaptation reactions of stress [20] and antistress [3, 4] in character. An accumulation and predominance of aging-related stress alterations provoke a gradual decline in the nonspecific resistance. In contrast, the development of stable reactions of the antistress type contributes to activation of CNS, the endocrine and immune systems, the energetic and peroxidation metabolism, i.e. the most important components governing an elevation of the organism resistance to unfavorable external and internal environment factors.

Progression of age-associated disorders depend on many of exogenous and endogenous factors, among them the peculiarities of the water condition profile in an organism that is of vital importance for biochemical processes and realization of effects produced by weak information actions of water due to the unique cluster structure of water and its metastability [18, 26]. In this case, it should be mentioned that known are some biotropic properties of water, which are determined by its actual isotope composition. It has been detected that even some slight changes in the relationship between the stable hydrogen isotope ratios may have a noticeable effect on the states of a living organism. By this means it has been found that water enriched with the deuterium is quite often the cause of some pathological changes in the
organism; in case when we deal with a shift in the water isotopic composition to light protium water, on the contrary, this type of water is capable of improving the functional state of a human or an animal [24, 25, 27]. A number of favorable effects produced by deuterium depleted water (DDW) on the conditions of various protection systems in the organism have been detected [7, 17, 23], up to and including pronounced triggering action by DDW on the mechanisms of the anti-tumor resistance [16, 22]. Evidence data obtained from epidemiological studies show that there are cases of extreme longevity for those individuals reported who drink original water supplied by some natural springs, differing from standard drinking water in a number of its properties, among which is deuterium depletion [15]. All this allows us to consider DDW use as a new way for correction of some homeostatic disorders associated with aging.

Our challenge was to carry out experimental studies addressing a corrective effect produced by DDW on the adaptation status, the state of the estrous cycle and the microflora composition on skin surfaces in outbred female Albino rats in their aging period.

Materials and methods
Our experimental studies were performed in the early spring period in 27 outbred Albino aging female rats aged 20–22 months, who had weights 290.7 ± 31.6 g, against 10 young female rates aged 8–10 months with a weight of 210.4 ± 31.6 g. All our experimental studies involving use of animals have been carried out in full compliance with the applicable international bioethics rules, guidelines and regulations [12]. The aging animals were divided into two groups: Group A and Group B, correspondingly. Group A included 13 rats who received DDW with a daily amount of 25–30 ml during 5 consecutive weeks. Group B covered 15 female rats who received only standard drinking water, the quality of which met the requirements specified by the relevant Russian National Standard GOST. DDW had a deuterium concentration three times lower than it was the case with regional standard-type natural water (150 ± 6 ppm) and showed no essential differences from the latter in its mineral analysis.

In order to assess effects induced by DDW on the adaptation status of the animals, in our experimental studies traced was dynamics of progression of general nonspecific adaptation reactions (GNARs) of the organism [3, 4]. Each type of GNARs, covering the reactions of acute stress and chronic stress as well as the antistress reactions of training, calm and elevated activation, was identified according to the Shilling's blood count data with the use of Giemsa – Romanovsky staining technique, with a 200 blood cell counting accuracy. In doing so, the percentage of lymphocytes in peripheral blood was taken as an identifier making possible to properly attribute each actually initiated reaction to the respective GNAR type. The corresponding leukogram patterns in the animals were identified first initially, prior to the experimental studies, and later, on a regular weekly basis, in the course of the experiment. Blood samples were taken from a rodent femoral vein located under the skin in the cellular tissue, throughout the medial surface, in the morning time before feeding. For the purpose of processing of the experimental data, utilized was our original Software Statistica 6.0, and the statistical analyses were completed in accordance with Student's t-test technique.

Cytological data on the functional status of the ovaries were obtained using vaginal smear reading. Upon flushing from the vaginal lining, smears were read with the Leica DM LS2 microscope two times a day, in the morning and in the evening, respectively. For that purpose, the following phases of the estrous cycle were traced: 1. Diestrus (D) phase which implies the functional rest and which is marked by the presence of leukocytes and mucus found in the smears; 2. Proestrus (P) phase recognized by the presence of polygonal, usually nucleated, epithelial cells, with excentrically located nuclei; 3. Estrus phase (O) when non-nucleated cornified squamous epithelial cells appear and form large clumps and sheets; 4. Metestrus phase (M), the day after estrus, exhibiting a mixed cell composition, when a mixture of cornified squamous epithelial cells and leukocytes predominates. Length of each phase or stage and their sequences within the estrous cycle were recognized that has made possible to evaluate periodicity of hormonal changes in the ovaries [2].

In order to assess the state of the nonspecific resistance of the organism, under administering DDW to aging female rats, applied has been the trivial assessment procedure by Klem-parksaya – Shalnova for the proper identification of autoflora species on the skin as current status testing for information [6]. To examine the actual nomenclature of the microorganisms...
sampled from rat tails with the agar replica test technique, the Korostyel medium consisting of meat-peptone agar with an addition of a 1,5 % Bromthymolblau alcohol solution and a 1 % mannit solution was used. The cultivated bacteria have been differentiate and recognized according to their ability to ferment mannit and change color of the colonies of Staphylococci both of pathogenic and non-pathogenic nature.

Results and discussion

Our analysis of leukocyte count data on peripheral blood in aging rates in the above mentioned Groups completed first before our experimental studies has revealed that the animals in 88,6 % of cases had low relative numbers of lymphocytes (30–45 %) at a rather high total amount of leukocytes in blood (see Table 1 below herein). Some cases of aneosinophilia were reported, too.

The said indices were in correspondence to the leukogram pattern typical for the symptom complex of stress. Moreover, they were statistically significantly different from the hematological characteristics in the female rats at a young age, whose lymphocyte percentage was 1.7 times greater as compared with the aging rats, with a lower total leukocyte count and with no cases of aneosinophilia.

Upon completion of the DDW treatment course, the animals in Group A demonstrated the normalized leukogram pattern. First it was applicable to the relative number of lymphocytes as the key index, showing the type of the adaptation reaction of the organism, which was higher by a factor of 1,5 in comparison with the initial state (see Table 1 below herein). The total count of leukocytes in blood became normal, too, and no aneosinophilia cases were observed. The peripheral blood leukogram changes in question made it possible to recognize the development of the integral reactions of the physiological classes in the Group A rats as follows: GNARs of training, calm and elevated activation. The hematological data obtained from the animals in Group B, who received standard drinking water, practically did not show any differences from their initial values: an elevated total count of leukocytes was recorded, and lower lymphocyte percentages were reported than those identified in the young animals. So, an analysis of developing GNARs of differing types within each Group and between the specified Groups has shown that the use of DDW instead of the standard drinking water has resulted in a substantial increase in the occurrence rate of the antistress reactions detected in Group A covering the aging female rats.

Table 2 below herein summarizes variability in the occurrence rate of different GNARs for a five week period in aging female rats of the Groups under examination. As may be seen from the Table, the occurrence rate of the stress reaction in Group A identified prior to the administration of DDW was comparable with that reported for Group B, and the occurrence rate of the antistress reactions of different types has varied. Upon DDW receiving, during the first week, reported were GNARs of the antistress types in the Group A rats only, and the same stable maintenance of the physiological reactions was recorded till the completion of the experimental studies. In the animals of Group B, in 35% of cases, in contrast thereto, observed was stabilization of the development of the stress reaction pattern, which was especially apparent by the end of the experiment. Differences of decisive importance between the aging animals belonging

<table>
<thead>
<tr>
<th>Blood cell types</th>
<th>Young female rats</th>
<th>Aging female rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial state</td>
<td>After DDW administration</td>
</tr>
<tr>
<td></td>
<td>Group A: activation</td>
<td>Group A: training</td>
</tr>
<tr>
<td>Total leukocyte count /mcL</td>
<td>7300±1200</td>
<td>17100±2900 1</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>75,5±4,5</td>
<td>44,0±2,94 1</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>1,0±0,13</td>
<td>0,5±0,11</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>27,5±3,5</td>
<td>42,0±2,7 1</td>
</tr>
</tbody>
</table>

Notes:

1 statistically significantly differing from the values in young female rats (p<0,001);
2 significantly differing from the values in aging female rats in their initial state (p<0,001).
Table 2. Relations of occurrence rates of different adaptation reactions in aging female rats receiving DDW (Group A) vs. those receiving standard drinking water (Group B)

<table>
<thead>
<tr>
<th>Types of adaptation reactions</th>
<th>Relation of occurrence rates of ARs of the same name (%) in aging animal groups under examination (A vs. B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initially</td>
</tr>
<tr>
<td>Stress</td>
<td>20,3/21,4</td>
</tr>
<tr>
<td>Training</td>
<td>44,1/40,8</td>
</tr>
<tr>
<td>Calm activation</td>
<td>20,6/20,6</td>
</tr>
<tr>
<td>Elevated activation</td>
<td>15,0/17,8</td>
</tr>
<tr>
<td>Intra-group relation between ARs: Antistress / Stress reaction in Group A</td>
<td>3,9</td>
</tr>
<tr>
<td>Intra-group relation between ARs: Antistress / Stress reaction in Group B</td>
<td>3,7</td>
</tr>
</tbody>
</table>

to different Groups were also found in the occurrence rates of the reactions of the same name of the antistress types. So, beginning with week 2 till week 5 of the experiment time, much more frequently (up to 3–7 times) observed were the reactions of the calm and elevated activation in Group A, which were considered to be the most favorable for the neuroendocrine regulation, against those seen in Group B, where and when the reaction of stress was accompanied by the antistress reaction of training.

The established inter- and intra-group relations between the antistress (AS) and stress (S) reactions have demonstrated the dominance of the antistress link within the entire structure of the adaptation reactions in the animals, who received DDW, and actually it has shown high effectiveness of the DDW action. As is known, the calm activation GNAR and the elevated activation GNAR are featured by higher percentages of lymphocytes in blood (for outbred rats 61–70 % and 71–80 %, correspondingly), in comparison with the stress GNAR and that of training (under 50 % and under 51–60 %, correspondingly). The above performed correlation & regression analysis of the relationship between the level of lymphocytes and the respective morphological, biochemical and hormonal indices of the functional state of the nervous, endocrine and immune systems in the organism has revealed that we deal with high values of the paired and multiple correlation coefficients as well the determination, which are decisive for production of a strong correlation between the key index and the multisystem attributes of an adaptation reaction [9, 10].

As is seen, the mechanism of development of the antistress calm and elevated activation GNARs has contributed to a favorable correction of the length of the estrous cycle stages in the rodents. The final data obtained in the Groups in question by the end of the experimental studies should be treated as evidence in support of the DDW effect on the organism for the aging female rates in Group A. As is indicated in Table 3, the estrous cycle length in the aging animals in Group B, who received standard drinking water, differed markedly from that recorded in the young animals in the reproduction age and was featured by a considerably reduced length of the proestrus and estrus stages (2–3 times) with a significantly increased length both of the metestrus phase (more than 3 times) and dioestrus (more than 1.5 times) stage. The DDW use for five consecutive weeks resulted in the statistically significant changes found in the estrous cycle that should be considered as evidence for the partial restoration of the reproductive function in the aging female rats in Group A. So, by the end of the experiment, the animals in Group A have demonstrated a substantial shortening of the length of the metestrus and dioestrus stages (1,5 and 1,8 times, respectively) and a lengthening of the proestrus stage, as compared with Group B, that has placed the said indices closer to those recorded for the young age rats (see Table 3 below herein).

When comparing the length of the individual stages in common within the estrous cycle over the entire period of observations, under developing of GNARs of various types, a clear-cut relationship between the integral changes and the hormonal fluctuations was also traced. It appeared as the restored length and sequence of the individual stages within the cycle that was primarily detected under formation of the stable reactions of activation under the DDW effect. As evidenced by the data given in Table 4, when supporting GNARs of the calm and elevated activation in the Group A rats, the length of each individual
Table 3. DDW administration effect on the length of individual stages of estrous cycle in aging female rats

<table>
<thead>
<tr>
<th>Animal Groups</th>
<th>Length of a separate stage of the estrous cycle (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Norms for young age</td>
<td>57 (55–57)</td>
</tr>
<tr>
<td>Aging female rats</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>91,1±7,0</td>
</tr>
<tr>
<td>Group A</td>
<td>51,2±5,4 ¹</td>
</tr>
</tbody>
</table>

Note: ¹ statistically significant differences from values in Group B, p < 0,01–0,05

stage of the cycle in common, considering a period of 30-35 days, was brought closer to the normal indicative values, that is to say, to those values identified in the young rat Group. So, the length of the diestrus stage in general in those cases decreased approximately by 50 hours in comparison to the same value in Group B, and it was found to be maximally close to the values detected in the young age animals. The duration of the proestrus stage in the Group A rats, with the development of GNAR of the calm and elevated activation, demonstrated no difference from the normal values. At the same time, in the animals in Group B, with the prevalence of GNAR of training, when and where the reaction of stress was often recorded, the length of the above mentioned stage was 3 times shorter than that reported for the young female rats.

The restoration of the estrus stage, which either has been absent in the initial state or exceeded by 1.6 times the limits of the stage range in young female rats, is of considerable importance for an evaluation of the gero-protective effect produced by DDW with the development of GNAR of calm and elevated activation. The duration of the metestrus stage in female rats in group A exceeded the norm, but was recorded to be statistically significantly shorter than that under the development of the training reaction. In cases of development of the reaction of the same name in animals in group B, the process of the estrous cycle normalization was moderately expressed only, but the indices of change of the phases and their length in common differed from those recorded under stress, which was characterized by profound disorders in the sexual function rhythmic activity in aging female rats in the reference group under examination.

Microscopic examination of vaginal smears in the aging female rats provided a means for visualizing the regulatory effect by DDW at the cell level. Figure 1 below herein exhibits vaginal smear readings obtained in the aging female rats who received DDW, where the cell composition corresponds to the normal cell types of the estrous cycle stages. Epithelial cells prevailed in the proestrus phase; squamous epithelial cells dominated in the estrus phase; mixed composition of cells (cornified squamous cells, epithelial cells, leukocytes) were dominant in the metestrus phase, and leucocytes were prevalent in the diestrus stage.

An interpretation of the obtained results from the standpoint of the estrous cycle neuroendocrine regulation

Table 4. Change in length of individual stages within the estrous cycle in general during the experiment period (in hours) in aging female rats with the development of different GNARs under DDW effect

<table>
<thead>
<tr>
<th>Stages of estrous cycle</th>
<th>Young female rats</th>
<th>Aging female rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td></td>
<td>GNAR of training and stress</td>
<td>GNAR of calm and elevated activation</td>
</tr>
<tr>
<td>Diestrus</td>
<td>346,6±7,2</td>
<td>389,4±42,2</td>
</tr>
<tr>
<td>Proestrus</td>
<td>71±2,4</td>
<td>24,1±1,7 ¹</td>
</tr>
<tr>
<td>Estrus</td>
<td>148±14,7</td>
<td>235,1±39,1 ¹</td>
</tr>
<tr>
<td>Metestrus</td>
<td>32,4±2,2</td>
<td>20,5±3,8 ¹</td>
</tr>
</tbody>
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Notes: ¹ statistically significantly differing from values in young rats (p<0,01)
² statistically significantly differing from values in aging rats (p<0,01)
in the context of the dominant integral reaction of activation, under the DDW effect, has demonstrated that the stimulation by estrogens, which are produced by ovaries and initiate the vaginal proliferative activity, determines also the cell composition. An indication thereof firstly are the implied DDW effects responsible for approaching the normal value of the proestrus stage, that indirectly confirms the fact of the activation of hypophysis follicle-stimulating hormone secretion. Secondly, despite the fact of the normalization of the estrus period, it has become apparent that we deal with a decrease in the metestrus period length with reference to the respective values in the aging female rats as an evidence of the corpus luteum shrink and inhibition of excessive luteinizing hormone secretion. And, thirdly, the noted normalization of the metestrus stage has shown there has been found the state of hormonal balance approaching.

The studies identifying the skin autoflora peculiarities in aging female rats have also revealed some differences attributed to the type of evolving GNARs by comparing two cases: that with DDW administration and another one with use of standard drinking water (see Table 5 below herein).

Thus, with the development of the stable calm and elevated activation reactions, under the DDW effect, observed has been a noticeable suppression of growth up to even complete disappearance of pathogenic staphylococcus with a negative mannit effect of the “yellow” colonies formation, while the “green” colonies with a positive mannit effect of nonpathogenic forms of staphylococcus remained. With the development of the training reaction, the “green” colonies significantly prevailed over the “yellow” ones. Under stress, in animals of Group B observed has been an increased pathogenicity in skin autoflora: against the background of suppression of the “green” colonies, a progressive growth in the “yellow” colonies of pathogenic staphylococcus has been detected. Hence, the dominant in Group A adaptation reactions of calm and elevated activation are the most efficient, when considering the antimicrobial resistance.

The antistress effect induced by the DDW administration led to an appearance of visually distinguishable signs of rejuvenation in the Group A animals. In the female rats, receiving DDW, a change in hair coat was recorded. Observed was replacement of a coarse stiff hair coat, yellowish toned, comprising multiple local areas characterized by varying levels of hair loss, by a white soft fur with a new thick undercoat; the eye sclera have brightened (see Figure 2), and the motion activity significantly higher in the animals under examination was also reported.

Thus, the obtained data demonstrate pronounced geroprotective DDW effect associated with DDW antistress action which has manifested in formation of stable GNAR of the calm and elevated activation, contributing to a considerable increase in nonspecific resistance and initiation of the restoration process in the aging female rats. It is obvious that the said effects take place due to such a specific property of DDW as its capability to activate the cell metabolism and elevate excitability of the neuroendocrine regulation centers [13, 14].

The data on the development of GNAR of the calm and increased activation under the DDW influence are in good agreement with the known findings in favor of the activating effect...
made by DDW on the CNS serotonergic structures [25], since the relationship between the given GNAR development and an increase in serotonin concentration in brain structures and blood formed elements had been established earlier [5]. This fact is of great significance due to an important role of stress-limiting serotonergic processes for the purpose of ischemic heart damage prevention and a reduction of cardiovascular disease risks [7] related to pathologies associated with aging.

The evidence of the correlation between mortality due to cardiovascular and degenerative diseases and a decline in the reproductive function in females during peri- and postmenopause reveal an additional aspect in the important role of properly maintaining the ovarian hormonal function to provide resistance of the female organism to damaging factors [28]. In this connection, the antistress and geroprotective DDW effects detected and traced in our studies is a matter of great interest.

Conclusions

The results obtained in our experimental studies bear witness that there is pronounced geroprotective effect produced by DDW in outbred aging female rats and that there exists the relation between this effect and the development of the general nonspecific antistress adaptation reactions of calm and elevated activation. The obtained evidence data provide unique insight into the effect exerted by DDW on mammalian organisms, and it may serve as an experimental foundation for development of an effective method suitable for use in geriatrics and prevention of cardiovascular diseases and degenerative processes in females during peri- and postmenopause.

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 authors read the ICMJE criteria for authorship and approved the final manuscript.

References

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 discords 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 circahoralian, 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 evolutionary 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.
Energy flow controls the levels of the functional activity and restoration of the bio-systems. Alternating priority principle of distribution of energy flows between processes with different parameters, 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, degradation 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 chronicdiagnostic 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 anabolism, 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 sapiens 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 immunity 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 definite 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 chronodiagnostic 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 ontogenesis, 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 temporally 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 of 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
cognitive disorders we detected desynchronoses of circahorlarian and circadian vegetative nervous status rhythms against the background of stable sympathicotonia [21]. Bio-controlled laser therapy in projections of frontal and temporal lobes of both hemispheres and in the areas of the internal carotid and vertebral arteries has successfully reduced sympathicotonia; the parameters of circahorlarian and circadian rhythms of R-R intervals on ECG and the rhythms of the vegetative nervous system status have been normalized; cognitive functions and sleep of the patients in question according to their neuropsychological have been improved.

21) As a result of feedback and adaptation to the external environment, the strategy of the efficiency begins prevailing over the active strategy that is just characteristic of aging of the bio-systems. A decline in the self-regulation reserves leads to an increase in the probability of damages, defects and a reduction of the possibility to eliminate them. In every organism, during aging, there is a certain organ appearing, which shows limiting stability of the entire organism as a system. The blood microcirculation rhythms in the affected limiting organ demonstrate most pronounced rhythm disturbances as compared to the other organs in the body. The most severe case of this sort of disorders in the biorhythms of the organs is carcinogenesis. The condition of being intact for the organism can be improved by detecting the limiting organ by detecting disorders in blood microcirculation spectrum rhythms and subsequently by restoring them due to harmonizing with the central blood flow rhythms.

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 circahorlarian 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 chronodiagnositics 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.

References:
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

Imprint


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-
ity of cosmonaut’s organism to adapt to the spaceflight environment and readiness to perform duties correctly and completely. Health definition in the WHO Charter as state of complete physical, mental, and social well being complies with the space medicine requirements and yet is not exhaustive. Evaluation of the health state of spacecrew members must proceed not from the philosophical, qualitative definition but from the specific, practical one that will open up possibilities of measurement and evaluation of the level of health [1–4].

Space medicine gave rise to a fundamentally new approach to health evaluation in light of the present-day theory of adaptation and the doctrine of homeostasis [5–7]. The essence of this approach is that health is considered to be a process of continuous adjustment of organism to its environment and the adaptive potential is the measure of health. Transition from health to disease is caused by a reduction of the adaptive potential, degradation of the ability to react adequately to social, labor, and usual everyday stresses. A large number of transitory or pre-nosological states develop in-between health and disease. Results of mass screening showed that 50 to 80 % of population have various prenosological states [8]. This means that the majority of people need not just medical or disease diagnostics but pre-nosology diagnostics, i.e. determination of degree of loss of adaptability or level of deviation from the norm. With space medicine, methods and approaches of pre-nosology diagnostics are among the most common and advancing instruments for evaluation of health level.

Evaluation of health level
In the turmoil of modern life most people are subjected, to one or another degree of emotional or physical stresses. This is particularly true for people dwelling in extreme climate, geographic and social environments. All these produce stresses. Low stress level is always good to organism as it stimulates the ability to adapt (adjust) to the continuously changing outer world. However, an excessive stress, permanent emotional pressure, depression, failures, heavy physical loads and inadequate rest lead to severe straining of the regulatory systems of organism, overstrain and eventual exaustion.

This classification was experimental substantioted in the first monograph on pre-nosology diagnostics published by V.P. Kaznacheev, R.M. Baevsky and A.P. Berseneva in 1981 [9]. With time the classification was elaborated further by space medicine and applied physiology. A 10-grade scale was proposed to evaluate four levels of health depending on the extent of regulatory systems straining [3].

Our concept of pre-nosology diagnostics places emphasis on the informational aspect of health on the ground that controlling mechanisms, i.e. informational or regulatory, are of primary importance for the optimal functioning of such complex biological system as human organism. Function of a living system is a behavior pattern that keeps integrity of structures and consists of successive levels of metabolism, energy and information exchange, and temporal organization (R.M. Baevsky, 1979, 2003, 2006). Irrespective of whether we consider a cell, organ or whole organism, their functioning can be described by a single algorithm that includes four stages:

1) renewal of structures with energy and matter expenditures;
2) generation and expenditure of energy by control commands;
3) reception, processing and transmission of command (signal) information for initiation of metabolism and energy exchange regulation;
4) temporal matching of structure, energy and information-level functioning.

Key principles of pre-nosology diagnostics
Adjustment or adaptation to a changed environment is attained at the cost of the functional resource or a certain “biosocial pay”. Every moment organism spends life resources and then renews them by, specifically, rest and sleep. Expenditure and renewal of the resources by organism and its individual systems is actually what the life process is. Adaptation, one of the fundamental properties of organized matter, is a result and means for resolution of internal and external contradictions of life. Organized matter exists and forms environments in cycles and intertransitions. "Pay" for adaptation that went beyond the limit of "biosocial budget" and demands extra efforts from organism causes breakage of the adaptation mechanism.

Fig. 1 shows the conceptual diagram of health measurement. From the diagram it is evident that homeostasis maintenance requires involvement of mechanisms responsible for mobilization of functional reserves, i.e. activation of relevant systems of regulation. Level of health or adaptive potential of organism are also dependent on individual characteristics of organism and environmental factors affecting its life.
The ability of adaptive mechanism to ensure stable adaptation to environment hinges on the functional reserve (FR) of organism. High functional reserve provides an adequate level of functioning (LF) of the main systems without increasing the degree of tension (DT). The dependence between FR, LF and DT can be expressed as a simple equation:

\[ \text{LF} = \text{FR} \cdot \text{DT}. \]

The equation shows that to retain adequate LF of organism or separate systems on the background of various stresses, DT must grow in sync with FR reduction. The equation should be regarded as a model describing the ratio of adaptive and homeostatic reactions of organism. The ratios of LF, DT and FR at different functional states can be quite diverse. The state of physiological norm can be observed against both the normal and increased level of functioning. At pre-nosological states, LF can be normal or high or reduced depending on FR. Premorbid states develop due to low FR and as a function of DT; they are characterized by either high or low LF.

Equation \( \text{LF} = \text{DT} \times \text{FR} \) is a base of the pre-nosological approach to health evaluation. The technology of pre-nosology investigations should involve calculation of all three components of the equation. However, the key position is occupied by the DT measurement. The main reason is that this index is the most dynamic indicator of adaptation level. Another argument for the choice is that DT is a key parameter in pre-nosology diagnostics, as it can be measured using a comparatively simple and proven method of heart rate variability analysis (HRV). It should be noted that the method was designed by space cardiologists and first applied in early orbital flights of animals and humans. HRV was tested in different disciplines of medicine and physiology and now is broadly applied in researches of autonomic regulation and stress level [10–13]. Finally, the third argument for choosing DT and giving priority to HRV is that they offer the opportunity to perform intimate evaluation of the functional state of organism leaning upon knowledge about the sequence in which levels and mechanisms of regulation are mobilized.

As a rule, in case of a pre-nosological state, level of functioning (LF) of the main systems (cardiovascular, respiratory, digestive, excretory) does not alter much. That is the reason why the traditional clinical measurements of pulse rate, blood pressure, expiratory volume etc. do not help recognize states in-between the norm and pathology. However, if homeostasis is provoked by challenging environment and DT remains high for a long period of time, there is a risk that organism will pass into a pre-nosological or even premorbid state. Besides, in addition to the traditional premorbid states we think it reasonable, along with early or initial pathological developments in organs and systems (pre-ulcerous, pre-hypertonic, etc.), to refer to premorbidity also such predecessors as overstrain and regulation depletion, manifested by non-specific signs of the general adaptation syndrome.

**Classification of the pre-nosological states**

State of the whole organism as a result of functional system activities is determined by the optimality of command signals, ability of control mechanisms to sustain equilibrium between organism and environment, or its adaptation. The adaptive function of organism requires energy and information and in this connection we may speculate on the "cost of adaptation" as a function of the degree of regulation straining and expenditure of the functional reserve. Adaptation-induced change in the level of functioning of a system or its components does not necessarily break homeostasis provided the regulatory mechanisms are not overstrained and the functional reserve is not depleted.
Overstrain and depletion are the causes for adaptation failure and disease. Pathological states as an aftermath of regulation disarrangement make grade four in the classification of pre-nosological states. A detail description of each of the four functional states is presented in table 1.

This classification was fairly widely accepted owing to the proposed analogy with the traffic lights. The green light gives the right to feel free and go the chosen way. In terms of health the green means that at the moment there are no serious deviations to care about. The yellow light signals to take a pause and look closely about before proceeding further. It means that some changes have occurred and that care must be taken to reestablish the normal health level. The red light alarms that it is time to visit the doctor for diagnostics and treatment. Already in 1980s, a roughly similar to the "traffic lights" classification was applied advantageously in mass pre-nosology examinations [8, 9, and 14]. The pre-nosology health evaluation campaigns were accepted by the broad public. For instance, factory workers took them much more seriously than the traditional prophylactic medical examinations aimed at detecting diseases. Quantification of the level of regulation strain is crucial for estimation of the reserve potential or adaptability of organism. Any stress causes the reaction of regulation straining and mobilization of the functional reserve which happens constantly. However, one and the same factor may strain regulation moderately in some people (working level of functional straining) and increase sharply the regulation strain in others. All depends on the functional reserve of organism, stamina, initial individual health level.

Transition from health to disease is instigated by overstrain, exhaustion and break of adaptation. The sooner we predict this turn of event, the higher will be chances to retain health. Thus, the problem comes down to finding ways how to measure the level of regulation strain in own organism to be able to control health. Pre-nosology monitoring is a practical step toward dynamic tracking of the regulation system functions, and detection of incipient signs of overstrain of organism, organs and systems. Instead of waiting for disease symptoms, the pre-nosology approach to evaluation of health, functional state of organism is aimed at detecting regulation changes and take timely appropriate actions for health improvement and prophylaxis.

### Table 1. Classification of the functional states in pre-nosology diagnostics

<table>
<thead>
<tr>
<th>No.</th>
<th>Functional state</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Physiological norm</td>
</tr>
<tr>
<td></td>
<td>Satisfactory adaptation to environment. Sufficient functional potential of organism. Homeostasis is maintained with minimal regulation straining</td>
</tr>
<tr>
<td>2</td>
<td>Pre-nosological states</td>
</tr>
<tr>
<td></td>
<td>Organism-environment equilibrium is maintained through mobilization of the functional reserve and, consequently, regulation straining. Adaptive potential of resting organism is lowered and adaptability to stresses is reduced. Homeostasis is achieved only by regulation straining</td>
</tr>
<tr>
<td>3</td>
<td>Pre-morbid states</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory adaptation. Low functional potential. Homeostasis only due to extreme regulation straining and mobilization of additional compensatory mechanisms</td>
</tr>
<tr>
<td>4</td>
<td>Failure (break) of adaptation mechanisms</td>
</tr>
<tr>
<td></td>
<td>Sharply reduced functional potential. Impaired homeostasis. Specific pathologic changes on organ and system levels</td>
</tr>
</tbody>
</table>

Pre-nosology diagnostics: Methodology

The theoretical developments above are objectified through methods and technologies of investigations. First of all, we should point it out that methodology and all the more technology of pre-nosology diagnostics may vary significantly with application areas in medicine and physiology. Much depends on purpose of investigations. Therefore, methodology and technology of pre-nosology diagnostics in preventive medicine may have little similarity with those in rehabilitative, sport, not to mention space medicine.

In context of purpose, the pre-nosological investigations can be divided into three groups:

1) pre-nosology diagnostics;
2) pre-nosology screening
3) pre-nosology monitoring

In a broad sense, pre-nosology diagnostics is interpreted as making a so-called pre-nosology diagnosis or, more exactly, evaluation of the functional state of organism within the norm-pathology interval, between health and disease. Classification of the states given above can and must be modified to fit the needs of various areas of medicine and physiology. Modifications do not imply revision of fundamental but rather practical aspects of adapting principles and terminology to the objectives of one or another field of application. For instance, medicine and physiology of labor are concerned with evaluation
of human ability to work; preventive medicine, with determination of the necessity and content of health improving and prophylactic measures, and urgency of visiting a doctor; rehabilitation medicine, with the progress of recovery from a disease. In all cases pre-nosology diagnostics serves to evaluate current functional state of organism, level of deviation from the norm and how close the deviation approaches to disease.

Pre-nosology screening is selection of people with functional states of organism that need to be improved, may not permit to work, require secondary care in medical institution etc. Public healthcare is short of these methods and technologies; instead, it has to handle perplexing medical and social issues using crude inaccurate. For example, working capacity examination relies on the nosological approach unsuitable for separation of groups of normal people with pronounced regulation strain; they are in the premorbid state though disease symptoms are still unapparent. Time must pass till break of adaptation when the need to limit workload will be obvious. Pre-nosology screening on this stage has received wide acceptance in preventive medicine, mass health examination, and medical flight certification. The first practical steps of pre-nosology diagnostics were made in pre-nosology screening. Effectiveness of the methodology was demonstrated in nationwide health examination campaigns conducted in the USSR in 1970-80s [8, 9]. Pre-nosology screening can be useful in different industries where it is important to identify employees with undesirably high levels of regulation strain, lowered functional reserve or risk of pathology.

Pre-nosology monitoring is a dynamic functional state check of essentially healthy people. In fact, this is a process of tracking the state of healthy human doing his job. The most illustrative example of pre-nosology monitoring is provided by space medicine that can be called the cradle of the prenosological approach. In the course of long-term space mission cosmonauts, rigorously selected healthy people, are regularly subjected to medical and physiological examinations. The reason is to see the trend and extent of shifts in the functional state of cosmonauts. If the functional state shifts toward pathology is paralleled by DT growth, intervention is urgent including release of workloads, change in diet or training program, prescription of prophylactic medication, etc. Pre-nosology monitoring can be beneficial to health check of shift personnel operating complex systems, evaluation of recovery from severe disease, functional state of sportsmen preparing for tournaments, etc.

Methodology and especially technology of pre-nosology diagnostics vary significantly with type of investigation. Methodology is generally understood as a basic scheme of investigation, stages and methods. Technology is specific procedures, details of investigation and description of instruments, methods of data processing and analysis. Technologies are often patented and licensed, as they provide a complete tangible or information result. We shall now consider methodology of pre-nosological investigations and outline some of the technologies from this standpoint.

Object of pre-nosology investigations is healthy people or sometimes patients recovering from diseases. The key criterion of choosing a contingent is a request to evaluate health but not to make diagnosis. This is a matter of principle, as we work in the field of prenosology. When we apply the pre-nosological approach to patients on the stage of recovery, we proceed from the assumption that even a sick organism possesses some store of adaptation potential and functional reserve to regain normal health state. In essence, treatment has the goal to mobilize the functional reserve of organism, to stimulate its adaptation potential. However, the point is that being unable to assess results of its effort the level to which health has regained (less straining of regulation systems, growth of the functional reserve), traditional medicine still uses the criteria of disease. Therefore, pre-nosology diagnostics helps traditional medicine to control health recovery using the arsenal of own methods to evaluate the progress from disease to health or from pathology to the norm. In all cases pre-nosological investigation is a process of recognition guided by a simple logical rule and sophisticated mathematical techniques. It is always noninvasive, comfortable and quick. These characteristics of the pre-nosological methodology are of fundamental importance because object of investigation is healthy human. As long as one is healthy and does not feel symptoms of disease, one is not mentally ready to any, even a very simple medical procedure.

Innumerable recreation centers and fitness clubs attract clients with the promise to improve quality of life and to raise mood by reducing diet, taking supplements to aid sleep or per-
forming exercises that will increase strength and elasticity of muscles. As a rule, all these do not imply sufficient monitoring or evaluation of the initial functional status of organism.

Healthy person must be motivated for a specific type of examination. Unfortunately, healthy lifestyle gets implanted very slowly. Some companies, private in particular, launch wellness programs for high-priced and qualified staff. Health of senior officers and generals has been standardized first in the US army and now in Russian army. In sport, health maintenance is a pivot for success. There are some though still few cohorts of people who regard pre-nosology investigations as important and indispensable. For others, comfort, noninvasiveness and short time of investigation are motivators for brooding on whether give preference to costly and time-consuming clinical examination which is effective only when there are symptoms of a disease or pre-nosological investigation that can delay disease.

We must not hold back an important principle of pre-nosology diagnostics which is use of data-intensive methods of investigation. This means that a very short and methodically simple investigation must generate massive and valuable information sufficient for stating conclusions about regulation activities, functional reserve and functioning of the vital body systems. The principle lays the ground for development of concrete technologies. An obvious example of how the principle works is a broad application of heart rate variability analysis in pre-nosological investigations. Another example is designing the method to evaluate level of the cardiovascular functioning by complex parameter FCI (functional change index) deduced from simple traditional measurements of pulse rate and blood pressure.

Pre-nosology diagnostics technologies are diverse and to a large degree dependent on type of pre-nosological investigation. In addition to the main indices of pre-nosology diagnostics (FL, DT, FR), consideration must be also given to the cause-and-effect factors such as environment, lifestyle and anamnesis. This explains the presence of questionnaires and socio-ecological survey among the pre-nosology diagnostics technologies. Flow chart of any technology can be divided into three parts, i.e. information collection (1); processing and analysis (2); data evaluation and conclusions (3). Algorithm of pre-nosology diagnostics implements the abstract theorems above in the form of conclusion concerning the functional state and adaptation potential of organism.

To begin with, we should note that information collection during pre-nosological investigations is arranged in a comfortable, quick and highly productive manner. In contrast to patients in hospitals and outpatient clinics, objects of pre-nosology diagnostics are, as a rule, healthy people. Their interest in this examination is driven, on the one hand, by the form and content of conclusions they receive and, on the other, simplicity and comfort of technologies. Mass examination, specifically, is often performed at production site during work time and, therefore, requires comfortable and time-efficient technologies.

Measurements of height, body weight, muscle strength and blood pressure usually take 2 to 3 minutes each; ECG recording for HRV analysis takes 5 minutes. Filling out the questionnaire also is not a problem. The questionnaire must contain no more than 15–20 questions with multiple choice answers. Information collection must utilize dedicated software tools as much as possible including databases storing individual files with results of measurements.

In the pre-nosology approach, the primary health criterion is level of adaptation potential of organism rather than presence or absence of diseases. The ability to withstand external stress factors and to maintain normal functioning of the vital body systems, as well as relative equilibrium with the environment is the main health indicator. Mechanisms compensating deviations developing in different systems underlie the enormous variety of adaptive reactions. Actively and continuously working regulation systems optimize interrelations between organism and affecting factors. In other words, deviations that traditional medicine qualifies as diseases and refers to appropriate nosological class, the for the pre-nosology approach are the reason for concern about the ability of organism to sustain balance with its environment. If the functional reserve is sufficient, organism does not need treatment but support of an adequate level of adaptation potential.

The pre-nosology diagnostics classification of the functional states by level of adaptation to environment makes it possible to distribute the total flow of people coming for mass medical examination into four categories depending on their need in medical aid. Medical investigations
are required only to those who have been referred to the category with broken adaptation and some people in premorbid state who have serious health complaints or face with sharply deteriorated environments. Mass pre-nosology investigations [9, 15-17] showed that no more than 20-30% really need medical diagnostics and treatment. Consequently, application of the pre-nosology approach in mass medical examinations would let more effective use of the healthcare strength and resources.

Pre-nosology diagnostics as a fundament for medicine in future

Practice of the pre-nosology investigations shows clearly that recognition and evaluation of functional states of organism in-between the norm and pathology require cutting-edge techniques and technologies. In this context, leadership still belongs to space medicine concentrated on enhancement of health evaluation methodology in long-duration orbital and exploration missions. It is natural that the present-day technologies are incomparably better than 30-40 years ago. In its turn, pre-nosology diagnostics has also made a leap forward. Now we discuss not so much recognition of functional states, as their probability, pathology risk estimation, and prognostication of a probable decline of the adaptation potential. The concepts of pre-nosology screening and pre-nosology monitoring have been reconsidered.

On the evidence gathered at the end of the last century, screening is focused on differentiation of pre-nosological and premorbid states as they require different health recommendations. This was supported by the results of examining bus drivers [18, 19] and pilots using hard- and software system Ecosan-2007, and data from project Mars-500 [20-28]. We succeeded in demonstrating a high correlation of the functional state of normal people with effecting factors (regional climate, working environment, psychophysiological parameters). Transition from prenosology to premorbidity and consequent growth of disease risks are accompanied by an increase in organism vulnerability to changed conditions. For example, seasonal rise in common cold incidence involves mostly people in premorbid and pre-nosology states due to low adaptation potential. In recent years, space medicine has been enriched with the concept of adaptation risk as a criterion of pathology probability [29, 30]. In light of this concept, pre-nosology monitoring is a dynamic estimation of individual adaptation risk aimed to reveal negative trends in health state and to predict possible pathologic developments.

Advancement of pre-nosology diagnostics is objective necessity, as it may build a bridge between the Western and Oriental models of medicine. The Russian healthcare system reproduces the so-called Western model, i.e. medicine is oriented at diagnostics and treatment of concrete diseases on the nosology principle. All types of pathology are related to specific organs and systems; medical specialties become more and more narrow. It is well known that Oriental medicine (Tibetan and Chinese in particular) sees human organism as a comprehensive whole. Its primary goal is to study health and ways to keep it. Different pains are considered to be health disorders that can be removed by various actions on whole organism, since a single organ pathology is linked with disorders on the level of whole organism.

In Russia and majority of the West countries doctor’s duty is, first and foremost, to diagnose correctly. This means precise location of a pathologic process and its characterization on the cell and even subcell levels. In doctors’ opinion, only precise diagnosis gives reason to prescribe treatment, typically drugs. They disregard the fact that the “aimed pharmacological blow” to the site of pathology impacts the entire organism and may cause an irreparable damage to healthy organs and systems.

Methods of pre-nosology diagnostics showed that no matter the treatment mode, it begins with mobilization of the functional reserve of organism (straining) and only afterwards, in a while, reaches local effects, provided a correct individual dosage and period of treatment. The reverse transition from disease to health is no less complicated. Sometime in future medicine will have technologies of assessing the therapy efficacy and conducting dynamic pre-nosology monitoring of rehabilitation.

Medicine of the future must be sure focused on maintaining health of healthy people. Methods and means of treating diseases will, of course be perfected; however, priority will be set on the energetic development of methods of health maintenance and improvement that could be integrated into the healthcare system. This is where the theoretical and practical knowledge of pre-nosology diagnostics will gain recognition and furtherance.

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

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After a long illness, on February 8, 2017 in Nottingham (United Kingdom) at the age of 83 years, famous English physicist, one of the developers of the magnetic resonance imaging (MRI), Nobel Prize winner in Physiology and Medicine in 2003, our journal's Editorial Board Member, Sir Peter Mansfield died.

The future Nobel laureate was born on October 9, 1933, in Lambeth, a central district of London. The war hindered him in receiving a systematic primary and secondary education, and at the age of 15 years he had to leave school and work as a printer’s assistant. He was fascinated by rocketry, and after several years of labor and military service, only at the age of 23, he attended Queen Mary College, University of London, Department of Physics. In 1959 Mansfield graduated from the College and three years later earned his PhD degree upon submission his NMR spectroscopy thesis. After two years of training in the United States, from 1964 until retirement in 1994, he worked as Professor at the University of Nottingham, where he continued his research as an Honorary Professor and the Chief of his own Company “General Vagnostic”. In 1962 he married Jean Margaret Kibble, who bore him two girls.

Sir Peter Mansfield is rightly considered “the father of MRI”. Despite the fact that the first Nobel Prize was awarded to F. Bloch and E. Purcell in 1952 for their NMR method, which was improved and called later MRI, and despite the fact that the first MRI scans of two thin water contained tubes were presented by Paul Lauterbur in 1973, P. Mansfield was a pioneer who was capable of obtaining really clear three-dimensional images of the body parts. In the same year he proposed to add a new electronic circuit to the existing MRI equipment to provide the faster imaging technology which made possible to produce images taking not many hours, but some fractions of a second! Mansfield improved the gradient field method, developed the mathematical procedure for the radio signal analysis that made possible developing of the fastest commercial 3D imaging technology (patents of 1977/78) and that has found its application in practice only 10 years later. The start of the revolution in medical diagnostics dictating the use of MRI is referred to the 1990s, and now MRI is on the way of the further expansion therein.

I was acquainted with Sir Peter Mansfield in 2004, when, upon my request, he sent me his biography, photos and Nobel Prize lecture. In 2011 he was greatly surprised when I asked him to join our new e-journal Cardiometry Editorial Board, however, after a long correspondence and communication between us in 2012 he accepted my offer: “And why not ... the MRI technology is used also for imaging the heart ...”.

His death is a great loss for the global science in general.

We remember Sir Peter Mansfield as a prominent scientist, a wonderful simple and kind man, a devoted father and grandfather. Our CARDIOMETRY Editorial team and I would like to extend our sincerest condolences to his family, colleagues, friends and relatives.

Professor V.M. Tyutyunnik
Heart rate variability analysis: physiological foundations and main methods

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Abstract
The article presents the main provisions of the methodology for the analysis of heart rate variability (HRV), which is now actively and widely implemented in many fields of medicine and applied physiology. This methodology was first developed in space medicine, where, already during the first manned spaceflights, there was a need in operative assessment of the person's reactions and abilities to maintain high performance and good level of health under different stress conditions.

The HRV analysis methodology is based on the measurement of a consecutive series of cardiac cycle durations, for which electrocardiography, rheocardiography, ballistic cardiography, etc., can be used. The resulting numerical series are subjected to mathematical analysis using statistical, spectral and other methods. The results are interpreted as medical and physiological criteria of the functional state of the organism.

Based on the mathematical model, a probabilistic approach to the prediction of pathological conditions was proposed. Indicators of the stress degree of regulatory systems and their functional reserve, which are calculated from the HRV analysis data, are used in the mathematical model of the functional states. In order to obtain the decision rules for the recognition of identified classes of functional states the stepwise discriminant analysis has been applied.

Equations of the discriminant function were obtained. This article examines in detail this new probabilistic approach to the HRV analysis and provides examples of its use for assessing the functional state of cosmonauts at various stages of long space flights.

Keywords
Heart rate variability, Space medicine, Stress, Discriminant analysis

Imprint

Introduction
Heart rate variability analysis (HRV) is a universally accepted methodology and technique of investigating and evaluating the functional state of organism and, specifically, components of the autonomic nervous system. At present, this is one of the most popular methods of functional diagnostics worldwide. In many respects it was initiated by the pioneering spirit of space medicine that worked up and implemented a number of complex indices to characterize functioning of the regulatory systems of organism [1]. On the first symposium on cardiac rhythm mathematical analysis in 1966 V.V. Parin presented a large report and noted that the source of this method was space cardiology where it had been first used to study circulation regulation during space flight.

Structure of heart rate as a diagnostic criterion was first applied in the USSR in 1960s. Originally, V.V. Parin and R.M. Baevsky proposed HRV as a method for evaluation of autonomous regulation and states of human organism in space flights [2].

"In the condition of microgravity, animals exhibited profound variations of cardiac contractions, depth and frequency of respiration. The considerable variability of the length of RR segments on the electrocardiogram was observed in Yu.A. Gagarin during his orbital flight. All these changes can be viewed as disorders in the feedback within the system of autonomic regulation where the brain is commander. This concept opens up the opportunity to investigate these phenomena experimentally with the help of electronic computing machines report titled "Heart rate as an indicator of neuroendocrine regulation" by academician V.V. Parin in co-authorship with R.M. Baevsky and G.A. Nikulina was presented at the 18th congress of the International Astronautic Federation in Beograd in 1967. In late 1960s, I.G. Nidekker and R.M. Baevsky proposed HRV as a method for evaluating periodic components of heart rate [3, 4].
Advances of space medicine in HRV analysis stimulated further development of the method. The first symposium on heart rate variability took place in 1966. In the USSR, investigations into HRV peaked in 1970s-80s. In Russia, interest to the HRV investigations decayed at the end of 1980s and beginning of 1990s but has revived in recent years.

Since 1970s, the number of HRV studies has increased sharply in Western Europe and the US. B.M. Sayers described rhythms present in changed HR [5]. In 1981 S.D. Akselrod et al. used power spectrum analysis of heart rate fluctuations to quantify cardiovascular parameters beat-to-beat [6–8]. Clinical advantages of HRV were accepted in 1965 after the observation made by Hon and Lee in their studies of intrauterine damages. They noticed that bad disturbances of fetal heart rate were preceded by changes in the HR structure [9–13].

HRV assimilation in cardiologic diagnostics was complicated because of the need for standards of measurement, physiological interpretation and clinical procedures. In 1996, the Task force of the European Society of Cardiology and American Society of stimulation and electrophysiology prepared and published guidelines 'Heart rate variability. Standards of measurement, physiological interpretation and clinical use'. In 2001, methodical recommendations on HRV analysis were published by a group of Russian investigators [14]. In the past 10–15 years these basic documents have been supplemented by more recent experimental and clinical findings and methodical approaches. The explosive development of microelectronics, hard- and software made it possible to design innovative, more refined HRV devices and techniques.

At present, thousands of papers on the subjects are published annually. HRV has gained footing in cardiology, surgery, physiology of labor and sport, experimental physiology. Particularly often HRV is used in stratification of the risks of cardiac and arrhythmic deaths in consequence of myocardium infarction (MI) and diagnostics of autonomic neuropathy in diabetic patients. It was established that HRV reduction increases significantly the risk of cardiovascular diseases. Physiological nature of cardio interval fluctuations is still far from clarification and causes many questions; that is why HRV remains essentially a research procedure but not a routine clinical tool [15].

Goal of this section in monograph "Devices and methods of space cardiology" is to propound the key principles of HRV methodology and new technologies that have been developed for the purpose of individual pre-nosology monitoring of space crews during long stay in microgravity. The technologies have been introduced in some areas of preventive medicine and applied physiology.

Physiological foundations of heart rate variability

The major information about the HR regulating is contained in the "ejection function" of interval duration. Sinus arrhythmia was discovered by Karl Ludvig in 1847. It reflects complex interactions of various loops of heart rate regulation. HRV is based on the theory that variability of RR duration or sinus rhythm frequency is controlled by the autonomic nervous system and catecholamines circulating in blood. Own or inherent frequency of the sinus node varies between 95 and 110 beats per a minute and is age-dependent [16]. Sympathetic influences increase pulsation rate, while parasympathetic, on the contrary, decrease. In the norm, resting heart rate is within the range of 60–70 beats/min which implies an obvious domination of parasympathetic influences on the sinus node. Rhythmic variations of the rate of pulses conducted via the vagus nerve are modulated by respiration rate and depth, which leads to RR changes known as sinus arrhythmia [17,18]. RR duration can also be affected by mental or physical activities and posture which reduce the average rate of pulses conducted via the vagus and, as stress grows, intensify the sympathetic nervous activity.

Literary data drive us to the conclusion that interval variability is largely neurogenic by nature, i.e. it is controlled by commands of different CNS levels to the segmental apparatus of the autonomic nervous system. Rhythm of cardiac contractions is a sensitive indicator of changes in nervous and humoral regulation. Due to nervous regulation HR is capable to react momentarily to changes in body demand in blood supply. Characteristics of interval variability carry information about functioning of the regulatory systems of organism [19–30].

However, as it was mentioned in the Introduction to this section, we still cannot tie up heart rate variability to frequency characteristics and underlying regulatory mechanisms. Some clarity has been reached only with regard of high-frequency HRV or respiratory waves associated with breathing movements and pointing
to vagus involvement in regulation. As for slow fluctuations, their origin remains unclear.

In the opinion of some authors, slow HR waves with the period of 7-20 seconds are associated with sympathetic (adrenergic) control of the autonomic nervous system [31-34]. The waves were first detected by Mayer et al. (1931) and this explains why they are called Mayer waves. Power of the 1st order slow waves describes activity of the vasomotor center. It is also believed that these variations reflect involvement of both parasympathetic and sympathetic regulation [35]. At the same time, the parasympathetic activity reveals itself indirectly through baroreflex regulation of the vascular tone [36]. Normally, sensitive receptors of the sinocarotid zone perceive changes in blood pressure. Afferent nervous pulses are transmitted to the vasomotor center in medulla oblongata where, following afferent synthesis (information processing and analysis), control signals (efferent nervous pulses) are sent to the vascular system. The process of vascular tone regulation with a feedback to vessels in smooth muscles is executed by the vasomotor center continuously.

Physiological correlates of power of 2nd order slow waves with a period of 20-70 seconds are still unknown and a subject of debate. Most of the authors hold it that the waves are linked with the sympathetic activity, and with influences of the cerebral ergotropic activity on subjacent structures. By and large, they characterize influences of higher autonomic centers on the cardiovascular subcortex center and can be viewed as a reliable marker of how tight is the link of autonomic (segmental) regulation with suprasegmental, including the pituitary-hypothalamic and cortical levels.

A two-loop model of heart rate regulation was proposed in 1968. It utilizes the cybernetic approach, i.e. the sinus node regulation is presented in the form of two interconnected loops – central and autonomic or controlling and controlled with feedward and feedbackward (Fig.1).

The sinus node, vagus nerves and their nuclei in medulla oblongata are working organs of the controlled (lower, autonomic) loop. Respiratory sinus arrhythmia is an indicator of the controlled loop activity; the respiratory system can be considered to be a feedback element within heart rate autonomic regulation. The controlling (higher, central) loop is characterized by various slow-wave components of heart rate. Its indicator is non-respiratory sinus arrhythmia. Feedforward between the controlling and control loops is implemented via nervous (mainly sympathetic) and humoral channels. Feedback is also implemented via these channels; however, an important role is played by afferent pulsation from cardiac and vascular baroreceptors, chemoreceptors, vast receptor areas in other tissues and organs. At rest, the controlled loop functions in the autonomic mode accompanied by marked respiratory arrhythmia. Respiratory waves grow high during sleep or under anaesthetic when the central effect on the autonomic loop weakens. Involvement of the central loop in heart rate control to support stressed organism slackens the respiratory component of sinus arrhythmia and intensifies the non-respiratory one. The general rule is that higher levels of control brake lower levels. Heart rate may respond to stresses in different ways. Provided regulation is optimal, control runs with minimal participation of higher levels or minimal centralization of control. Otherwise, activation of higher control levels will be necessary. The higher control level is activated, the longer periods of respective slow waves are. This appears as strengthening of the non-respiratory component of sinus arrhythmia and emergence of slow waves of increasingly greater orders.

On our own and literary data [37-40] we developed a model of neuroautonomic HR regulation. The model was built about the theory of R.M. Baevsky et al. supplemented with some inputs detailing the origin of cardio interval waves. Considering HR fluctuations as a result of activities of different CNS levels and HNS components, Kurinova E.V. maintains that frequency of HR waves or the chronotropic function of the heart is controlled at CNS levels, whereas wave amplitudes at all frequencies are dependent on both the sympathetic and parasympathetic HNS components, on whether their activities are balanced or one of the components prevails.

Main HRV methods and results evaluation

Quantitative evaluation of the nervous and humoral effects on the sinus node is made by calculating indices of RR variability. Methods of its description can be divided into time and frequency analyses [41-46].

Statistical methods are used for HRV quantitative evaluation within time periods under study. To this end, intervalogram is treated as a totality of sequential time intervals, i.e. RR intervals (Fig. 2).
Statistical characteristics of the cardio intervals dynamic sequence are: SDNN, CV, RMSSD, pNN50.

SDNN – is a cumulative index of RR variability over the period under study (NN – normal to normal series without extra systoles).

SDNN is expressed in milliseconds (ms). Normal SDNN values lie within the range of 40 to 80 ms. However, these values are age- and gender-dependent which must be taken into account during evaluation of the results of investigation.

SDNN rise and reduction can be caused as by autonomic regulation, so central (equally sympathetic and parasympathetic). In short records, as a rule, a SDNN rise points to activation of autonomic regulation, i.e. growth of the respiration effect on heart rate, typically observed in sleeping people.

SDNN reduction suggests activation of sympathetic regulation that inhibits the autonomic loop. Sharp SDNN reduction is a result of critical straining of regulatory systems and involvement of higher levels of control; consequently, the autonomic loop is almost completely inhibited. Similar physiological information can be learnt from the index of total power (TP). Specifics of the index is that it describes only periodic HR processes and does not contain the so-called fractal part, i.e. nonlinear and non-periodic components.

CV is a variation factor. It is very practical, as this is actually a normalized SDNN estimate, \( CV = \frac{SDNN}{M} \times 100\), where \( M \) is mean RR duration.

To describe fluctuations with cycles measured in seconds, two indices estimating difference between adjacent NN intervals are used: RMSSD and pNN50. They evaluate high-frequency NN variability due to the vagus modulation of sinus node frequency. RMSSD is a square root from the sum of squared differences of sequential NN pairs (normal RR intervals). RMSSD is an index of parasympathetic activity within the autonomic regulation and does not contain HR slow-wave components. It reflects the autonomic activity. The higher RMSSD, the more active parasympathetic regulation. Index normal values are within the range of 20–50 ms. Similar information can be obtained by pNN50 that shows in percent the number of differences greater than 50 ms.

NN50 is a number of pairs of sequential NN with difference greater than 50 milliseconds in all record; pNN50 (%) is percent of NN50 from the total number of sequential pairs of intervals differing in more than 50 seconds over the whole record time;

Geometric methods assess RR forms and distribution over the period of investigation. For the purpose, variation curve (histogram of interval distribution) is built and main characteristics are determined including Mo (mode), AMo (mode amplitude), MxDMn (variation range) (Fig. 3).
Mode is the most common interval value in a given dynamic series. In case of normal distribution and high process stationarity, Mo differs little from mathematical expectation (M).

AMo (mode amplitude) is a number of intervals corresponding to mode value in % to sample size.

Variation range (MxDMn) shows the degree of interval variativity in a given dynamic series. It is calculated from the difference of maximum (Mx) and minimum (Mn) intervals and, therefore, can be distorted by arrhythmias or artifacts.

Data of variation pulsimetry are used to calculate the widespread in Russia index of regulation straining or stress-index.

IS = AMo/2Mo* MxDMn.

Index of regulation strain (SI) characterizes the activity of sympathetic or central regulation. Activation of the central loop or sympathetic regulation during mental or physical stresses manifests itself by rhythm stabilization, decrease of the range of interval duration, and increase of the number of intervals with similar duration (AMo growth). Histogram form changes, i.e. it gets narrow and grows in height. In stressful situations and in the event of pathology, the diagram will have a narrow base and a sharp peak (excessive). Asymmetric diagram can be associated with a transitory process and impaired stability of process. Multimodal diagram is indicative of a non-sinus rhythm (extrasystole, ciliary arrhythmia).

Digitally it can be represented by the ratio of histogram height to width (see above). The parameter was termed the index of regulation strain (SI). Normal SI fluctuates within 80-150 conventional units. It is very sensitive to the sympathetic tone rise. A mild physical or emotional stress increases SI in 1.5-2 times. Strong stress increases SI in 5 to 10 times. In resting patients with permanently strained regulatory systems SI is equal to 400-600 conv.units. In resting patients afflicted with attacks of angina pectoris and cardiac infarction SI reaches 1000-1500 conventional units.

West-European and US investigators use triangular approximation of the interval distribution curve and calculate the so-called triangular index, i.e. the distribution density integral (overall number of intervals) referred to maximum distribution density (AMo). The index is abbreviated as TINN (triangular interpolation of NN intervals).

Another method to evaluate HRV is determination of spectral indices. The case in point is calculation of spectral power of NN fluctuations with the help of nonparametric (Fourier fast transform) and parametric (autoregression) techniques. Spectral methods are used to quantify frequency components of heart rate; they demonstrate graphically the ratios of different HR components representing specific regulation activities [47–52].

Spectral analysis in Fig. 4 estimates contributions of these or other periodic components to dynamic changes in RR duration. They can be [53]:

- high-frequency range (HF) representing largely the parasympathetic influence on heart rate;
- low frequency range (LF) characterizing generally the sympathetic nervous activity and its effects on heart rate;
- very low frequency range (VLF) conditioned, first and foremost, by the hormonal influence on heart rate.

Spectral analysis typically includes computation for each component of absolute total power within a range, mean power within a range, maximal harmonic and relative harmonic values in percent of total power (TP) (within all ranges). TP is a sum of power in the HF, LF and VLF ranges.

Vagal activity is a basic HF component. This is evident from absolute and relative (% of total power) values of respiratory wave power. Extent of autonomic regulation inhibition driven by the parasympathetic segment gives insight into the sympathetic nervous activity as one of the autonomic balance components.

As a rule, respiratory HF constitutes 15–25 % of total power. Percentage reduction to 8–10 % points to the au-
tonomic balance shift towards sympathetic dominance. If HF falls below 2–3 %, we may infer about a sharp sympathetic dominance. In this case, RMSSD and pNN50B also decrease drastically.

**Low-frequency power (slow waves of the 1st order or vasomotor waves, LF)** characterize the sympathetic nervous activity and, specifically, the vascular tone regulating system. Time for the vasomotor center to receive, process and transfer information varies from 7 to 20 seconds; typically, it is 10 to 12 seconds. This explains the appearance of waves with a frequency close to 0.1 Hz (10 s) which were termed vasomotor.

Transition from the supine to upright position leads to a considerable power rise within this range of HR fluctuations. The vasomotor center activity weakens with age; in senior people its effect virtually fades out. Instead of the 1st order slow waves, power grows in slow waves of the 2nd order. This means that blood pressure is controlled with participation of nonspecific mechanisms by activation of the sympathetic segment of the autonomic nervous system. In the norm, percentage of vasomotor waves in supine position varies between 15 and 35–40 %. Noteworthy is also the dominating frequency in the vasomotor range. Usually it is in the range of 10–12 seconds and its extension to 13–14 seconds may imply a lowered vasomotor activity or slowed baroreflex regulation.

**Very low frequency power (slow waves of the 2nd order).** Normally, relative VLF power is 15–35 %. Increase in percent suggests a more intensive sympathetic activity and suprasegmental regulation. Dedicated investigations of A.N. Fleishman (1999) demonstrated HRV significance in the VLF power range. His classification of HRV spectral components gives consideration to the ratio of HF, LF and VLF amplitudes and includes 6 classes of spectrogram. A.N. Fleishman also showed that VLF power is a sensitive indicator of metabolism regulation and a good representative of energy-deficient states well.

Besides, spectral methods are instrumental in determining the balance of sympathetic and parasympathetic influences and resulting autonomic nervous effects on heart rate [54, 55]. That is why practice took up various indices that reveal ratios of HR spectral components.

Spectral analysis allows calculation of the index of centralization \( IC = (HF+LF)/VLF \) and index of vago-sympathetic interaction LF/HF. In the norm, this index is equal to 0.5 – 2, while IC varies from 2 to 8.

In spectral power calculated for a 24-hour interval we may single out one more range (ULF) between 0.0033 Hz and 0.00003 Hz. Physiological correlates of this spectrum has not been established; however, some facts evidence that it is modulated by the renin-angiotensin system [53].

**Autocorrelation analysis** is used to explore heart rate as a stochastic process. The autocorrelation function is a diagram of correlation coefficients dynamics; data of this qualitative analysis makes it possible to judge about central influences on the cardiac autonomic system [56]. Computation and construction of the autocorrelation function of interval series has the goal to look into the internal structure of the series as a stochastic process (Fig. 5). The autocorrelation function is a diagram of correlation coefficients dynamics obtained by displacement of the series under study at one number relative to own series. Autocorellogram allows conclusions about hidden HR periodicity. Quantitative indices in the autocorellogram are \( C_1 \) – correlation coefficient after the initial displacement and \( C_0 \) – number of displacements resulting in the zero correlation coefficient.

**Correlation rhythmography (scatte-rography).** In essence, correlation rhythmography is graphic representation of sequential pairs of intervals (previous and successive) in a two-dimensional coordinate plane. R-Rn is plotted on the abscissa and R-Rn+1 is plotted on the ordinate. The diagram and the domain of acquired points (Poincare or Poincare-Lo-
rentz spots) are named the correlation rhythmogram or scatterogram (Fig. 6). This HRV technique falls in the category of nonlinear analysis and is particularly useful in cases when rare and sudden deviations (ectopic contractions and/or beat drop-outs) occur on the background of HR monotony. For arrhythmias when statistical and spectral HRV analyses are uninformative or unacceptable, it stands to reason to examine correlation rhythmograms. This technique enables evaluation of sympathetic nervous involvement in HR regulation. On scattergram constructed for healthy human the ellipse will be prolated along the bisector.

**Digital filtration.** Digital filtration has been proposed for rapid analysis of short ECG episodes (less than 5 minutes) and quantitative evaluation of HRV periodic components. There are several options of digital filtration as, for instance, moving averaging over a number of sequential intervals. First order slow waves are determined by averaging over 5 or 9 intervals. Second order slow waves are isolated by averaging over 23 or 25 intervals.

**Methods of nonlinear dynamics.** Multiple influences on HRV, including neurohumoral mechanisms of higher autonomic centers, are responsible for the nonlinear character of HRV changes that can be described with the help of special methods. In recent years this issue has been in the spotlight of investigators abroad and in Russia [57, 58]. Nonlinear properties of variability were described using the Poincare section, spectral clustering, attractor graphics, singular decomposition, Lyapunov exponent, Kolmogorov entropy etc. All these techniques are interesting only to researchers, as their application is limited. We should also mention the procedure of functional state evaluation based on the chaos theory embodied in device Vita-Ritm (Neirosoft, Ivanovo, Russia).

For investigators and clinicians of great importance is physiological and clinical interpretation of HRV data. However, at present there is no unanimity on the subject. The majority of publications hold more or less common clinical and physiological views on the main HRV parameters. Some of the indices have original and still debatable interpretation awaiting a more precise substantiation.

Difficulties with evaluation and interpretation of HRV data often stem from the fact that separate HRV parameters closely correlate with one another remaining relatively independent from others. As a result, there are three groups within which parameters correlate at \( r \geq 0.9 \). The first group consists of SDNN and total power (TP). The second group includes VLF and LF powers. The third group combines such indices as RMSSD, pNN50 and HF power. This ratio suggests that indices belonging to a group represent processes of common origin and can be, possibly, interchangeable [59].

For this reason, of particular significance is an HRV-based complex evaluation of the functional state of organism for functional diagnostics or nonspecific non-nosologic diagnostics. One of the approaches is computation of the index of regulation system activity (IRSA). The index is using a special algorithm comprising statistical indicators, data of histogram and interval spectral analysis calculated. IRSA allows differentiate levels of regulation straining and assess adaptive potential of organism. IRSA algorithm incorporates the next five criteria:

A. Total regulation effect – HR
B. Overall regulatory activity - standard deviation (SD) or total power (TP).
C. Autonomic balance – complex of indices: SI, RMSSD, HF, IC.
D. Vasomotor center control of vascular tone - power of 1st order slow waves (LF).
E. Activity of the cardiovascular subcortex nervous center or suprasegmental regulation – power of 2nd order slow waves (VLF).

IRSA values are expressed in numbers between 1 and 10. Different functional states can be diagnosed by dint of IRSA value analysis.
One more integrative indicator of regulation strain is the straining index (SI) that shows level of HR control centralization. Consistent SI growth not only points to alteration of HR regulation but also helps identify a variety of unfavorable states: compensated stress in case of a slight excess of normal values to functional disorders, and even damage of organs, first of all, the heart by the stress-fighting systems.

Recently, space medicine investigators have proposed a probabilistic approach to evaluation of the functional state of humans and level of adaptation risks based on the HRV data [60] and consisting of computation of integrative indices of the functional reserve and straining. The approach will be detailed in the chapter below.

It is important to compare data of investigations with normal values. The norm as a statistical population acquired through examination of a reference group of selected healthy people needs reconsideration to be applicable in HRV analysis. Since the subject of evaluation is not parameters of relatively stable homeostasis but rather changeable autonomic regulation, we maintain that it is proper to speak of the norm as a functional optimum [61].

It should be kept in mind that individual optimum of organism does not necessarily coincide with the average statistical norm, as similar adaptation reactions take on different patterns depending on conditions one lives in, and individual functional reserve. Space medicine has developed the concept of physiological norm and maintenance of a sufficient level of functional capabilities of organism [62, 63]. Homeostasis of the main systems is retained with minimal straining of regulation. Accordingly, for the most part, HRV parameters must not overstep the thresholds defined for specific age, gender, occupational and regional groups. This stipulation is best satisfied by thorough study of the HRV results (see below). There is also a concept of clinical norm applied to people who do not exhibit symptoms of a disease. However, it is common knowledge that the nosology approach consists primarily of evaluation of structural, metabolic or energy-metabolic shifts in organism and gives little consideration to the functioning of regulation systems. Apparently, the HRV-based norm concept calls for more scrupulous investigation.

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 authors read the ICMJE criteria for authorship and approved the final manuscript.

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Aneurysm left atrial appendage

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Abstract
Aneurysms of the atrial appendages are rare and extremely rare clinical entities. It can be confused with pericardial cyst, coronary artery aneurysm, left ventricular pseudo-aneurysm and partial or complete congenital absence of the pericardium. Usually clinically asymptomatic, diagnosed as incidental finding by the presence of heart murmur or cardiomegaly on chest radiograph, it can also manifest in the presence of supraventricular arrhythmias or systemic embolism. The treatment of this pathology makes aneurysmectomy. For 3-year preschool heart murmur and echocardiographic finding of insufficiency Mitral and aneurysmal dilation of the left atrial appendage it is presented.

Keywords
Aneurysm, Atrial appendage, Echocardiography, Cardiac murmur

Imprint
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Clinical case
Preschool female 3 years old, asymptomatic cardiovascular, who was heart murmur auscultation as incidental finding. When R1 single physical examination, breath holosystolic I / VI mitral area radiating to the armpit, physiological split S2, R3 and R4 not.

Chest X-ray

Figure 1.

ChestPA
ICT: 0.63. Right edge, with double contour image, vascular image in the left edge of cardiac silhouette.

Lateral left thorax
Retrocardiac space occupied in three thirds compressing the barium column due to growth of AI and VI.

Transthoracic echocardiography
1. aneurysmal dilation of the left atrial appendage.

Figure 2.

Figure 3. Parasternal long axis
Operative findings

Under Cardiopulmonary Bypass. Aneurysmal base level of the left atrium of approximately 8x6 cm dilation. Appendage of normal size and shape. Left atrial aneurysmectomy was performed to find healthy tissue resection 3 mm from the mouth of the left pulmonary veins and 4 mm mitral ring in the anterior segment, then placing an autologous pericardial patch.

With satisfactory evolution after surgery.

Discussion

Aneurysms of the atrial appendages are rare and extremely rare clinical entities. But there can be confused knowledge about the disease with other conditions such as pericardial cyst, coronary artery aneurysm, left ventricular pseudo-aneurysm and partial or complete congenital absence of the pericardium [1].

Historically in 1938, Semans and Taussig, reported the saccular dilation of the left atrium in a girl of 5 years with dextrocardia, without involving the appendage. In 1962, Parmley reported dilation of the left atrial appendage 2 children, a 11 year old patient who presented with atrial arrhythmia and two episodes of systemic embolism, and a second patient 7 years old, with an aneurysm of the atrial appendage left associated with a congenital anomaly of the left renal artery [2].

In 1963, Williams reported a case of dilatation of the wall of the left atrial appendage in a 27 years old. Subsequently they cited several articles which show the presence of aneurysmal dilation of the atrial appendage [3].

In 1999, Zhao and colleagues reported the case of a 27 year old with an aneurysm of the left atrial appendage, which was removed in 1996 without cardiopulmonary bypass, approached by lateral thoracotomy [2].

Among the etiologies of this pathology are mentioned which may be congenital or acquired causes, among the causes acquired history of chest or secondary trauma is a mitral valve disease and among congenital causes congenital dysplasia pectineus or muscle due to pericardial defects [3, 4]).

These congenital aneurysm of the left atrium may be extrapericardicos or intrapericardial. The extrapericardial type is associated with defects of the pericardium through which the atrial appendage or any portion of the left atrium hernia. Intrapericardial type is always associated with an intact pericardium [5].

Morphologically it can also be due to dysplasia pectineus bands or the presence of connection on the hand-set or weakness in the wall of the atrial appendage [4].

Clinically observed in patients with normal, asymptomatic phenotype, which are diagnosed as incidental finding by the presence of heart murmur during a physical examination, presence of cardiomegaly on chest radiograph, arrhythmias, usually supraventricular tachycardia, due to the significant expansion of the left atrium, dyspnea, symptoms of congestive heart failure or left chest pain. Other manifestations include the generation of systemic embolisms produced inside the dilated atrium [3, 6–8].

The diagnostic approach to this condition can be done in as first tool chest radiograph which is evidenced an increase in the upper left border of the cardiac silhouette as an incidental finding, echocardiography as initial study for the diagnosis of this disease, where evidence the presence of the aneurysmal portion, also studies Cardiac Magnetic resonance tomography or to define the image and discard if it is other clinical entities (see Figures 1–4) [4, 7, 9].

Treatment of this condition is surgical aneurysmectomy made with reconstruction of the atrium under extracorporeal circulation [10]. In other patients with arrhythmogenic foci Maze procedure is used. However arrhythmias in most patients tend to disappear in the immediate postoperative period. [4, 11, 12].

Figure 4. 3D reconstruction
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.

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References
Significance of fractal approach to scientific discovery in the context of interrelations between natural sciences and medicine

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Aims
The aim of the paper is to show the significance of the fractal approach to scientific discovery in the context of interrelations between the modern natural sciences and medicine in order to increase an efficiency of applications of most advanced medical devices.

Materials and methods
Herein used is the fractal approach as methodology and logics of scientific discovery as a fundamental component of scientific cognition that allows demonstrating an objective interrelation between modern natural sciences and medicine, first of all, cardiology. Also used are the methods for mathematical modeling of measuring and computing systems as methodology for biomedical signals studies.

Results
For the first time demonstrated is the role of fractal approach as methodology and logics of scientific discovery, which is the basis of the scientific cognition, that allows detecting the interrelations between the modern natural sciences and medicine, cardiology, in particular. For the first time denoted is an area of possibilities of applications of the methods for mathematical modeling of measuring and computing systems as a methodology for studying biomedical signals (electrocardiosignals).

Conclusions
The way out of the crisis in medicine is offered herein; prospects for overcoming the crisis are discussed in connection with the use of different methodologies such as tensor methodology, quantum mechanics, artificial intelligence, transdisciplinary research and others.

Keywords
Methodology, Logics, Fractal, Chaos, Dynamic system, Mathematical modeling, Natural science, Medicine, Biomedical signal, Electrocardiosignal, Medicine 3.0

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Introduction
At present, the world is developing rapidly due to a number of previously impossible scientific discoveries, the most significant of which have a great impact on the course of history and are able to radically change the world. Just the discoveries in natural sciences underlie the ever-changing world, when in the eyes of one generation almost all the technologies change, when new technologies allowing the humanity to make the transition to a new civilization arise [1]. These scientific discoveries make it possible to considerably influence all spheres of human and social life, including the sphere of medicine with its methods of treatment. Indeed, in 2012, a document was adopted by the UN plenary session, which outlined the following main challenges for the world community and the key health priorities in the near future: cardiovascular and oncological diseases, diabetes mellitus and chronic obstructive pulmonary diseases. The fundamental empirical fact that these diseases cause about 70 % (for cardiovascular diseases – 30 %) of all negative economic, social, moral and ethical consequences should also be mentioned.

One of the reasons for this situation is that modern doctors cannot master innovative high-tech diagnostics equipment designed by engineers on the basis of advanced achievements of fundamental science and the principles of analytical thinking. In this connection, there arises a problem of the proper understanding by doctors of the term "medicine" itself. In the new Webster Dictionary of English, the following definition of medicine is given: "medicine (medisin, Br. esp. medsin) n. any preparation or sub-
stance used in the treatment of disease; the science of the prevention and cure of disease and of health preservation; the branch of this science dealing with curative substances rather than with surgery, obstetrics etc.; the medical profession to take one’s medicine to submit stoically to punishment etc. that one deserves [fr. O.F. médecine]” [2]. From this definition it follows that medicine is both a science and a practical activity, but the existing socio-cultural situation in a number of developed countries in the West and Russia forces doctors to focus on the practical side of medicine. As a result, ignored is the scientific side of medicine based on the laws of nature, whose book is written in the language of fractal calculus, so that the existing situation discourages design & development of new medical equipment by practitioners, condemns practical medicine for stagnation in its development and inability of doctors to use fractal methodology and logics of scientific knowledge, especially in the field of scientific discovery. In fact, we face a crisis in practical medicine connected with the crisis of the medical education itself, in which, firstly, absent are an adequate methodology of scientific research, without which neither fundamental science nor modern business can do, and secondly, relevant courses adapted to various fields of medicine such as biophysics and biochemistry, allowing to identify the primary causes of pathology, and thirdly, proper mathematical methods of modeling and metrology. In view of all this, it becomes clear that, under the conditions of discoveries in the fundamental sciences and the ongoing technological revolution, the scientific medicine, using a range of methodologies of scientific research, is gaining more and more significance. The application of the fractal approach (fractal calculus that has grown in the framework of the synergetic paradigm) and the mathematical modeling of measuring and computing systems as methodological and logical bases for scientific research is widely spread in various areas of modern scientific knowledge and engineering expertise.

Materials and methods

Now, the attention of philosophers and methodologists of science is being focused on a number of fundamental changes taking place in various fields of science and technology, namely, development of the quantum information theory and design of quantum computers on its basis, the possibilities of genetic engineering, virtual reality, nanotechnology, neuroscience, artificial intelligence, computer psychotechnologies, robotics, and so on [3–6].

However, in the shadow of all these changes, essential for the further destiny of world civilization, silently going on in the natural sciences, engineering, economics, finance, medicine and other spheres of human activity, an advancement of the fractal paradigm takes place; sometimes this advancement is called the fractal revolution. It is known that in modern science, along with new information and communication technologies, used are the synergetic concepts and non-Markov paradigms, as well as the fractal calculus, which involve very unusual for a human, spatial and temporal, representations, but they allow describing a new level of complexity of the human world, environment and the human individual proper. It is just the fractal approach that reveals a considerable heuristic potential applied to the phenomenon of scientific discovery, when the old logics and methodology are already insufficient for its comprehension [7–10].

In fact, up to now, the logics (and methodology) of the scientific discovery has been comprehended within the framework of the classical, Aristotelian paradigm of the scientific cognition, a fine example of which can be found in the studies in the field of the scientific discovery logics by Mill, Peirce and Popper. From these studies it follows that the scientific discovery logics provides for the existence of the possibility of rationalizing the process of hypotheses generation with the help of modern intellectual computer systems such as DSM (John Stuart Mill), i.e. the systems which allow modeling the process of knowledge acquisition [11]. The DSM method for automatic generation of hypotheses is carried out by modern artificial intelligence systems by means of the Mill’s inductive methods. The given logics of the scientific discovery (in other terms, the acquisition of new knowledge) is a synthesis of such cognitive procedures as induction developed by Mill, analogical inference, abduction proposed by Peirce and deduction grounded by Popper as a mean of identifying a falsification. The value of the DSM method is supported by the fact that, within the functioning of artificial intelligence systems, the priority in the discovery logics should be given to the theory of truth as the correspondence to facts. However, nowadays, after the recent discovery that all objects and systems
from microworld to Metagalaxy show their fractional dimensionality, which is associated with a stochastic, nonlinear picture of the world (here we use the ideas and concepts of synergetics, adequate to the matter self-organization). The classical methods, methodology and logics of scientific discovery reveal their restrictions and limitations due to the fractal nature of the entire surrounding world. This highlights the fractal logics, methodology of scientific discovery and scientific cognition in the context of the stochastic model of the world in general.

In modern science, sociology, economics, technology and other spheres of human activity, fractal measurements connected with topology are used to solve a number of problems that turn out to be very successful in practice [12, 13]. In other words, here the concept of the fractal is one of the key categories in science as a whole; it follows from the empirical fact that the fractal language fixes such a fundamental property of real phenomena as self-similarity: small-scale structures repeat the form of large-scale ones. Thus, in case with a fiord or an electrocardiogram, the self-similarity consists in infinitely varying intricate curve patterns, and considering blood vessels in a human body, treating winter frosty patterns, or analyzing functioning of marketing, the self-similarity is displayed as infinitely variable complex branching.

A fractal is a nonlinear structure that preserves self-similarity (self-affinity) in unlimited scale change (thus, we see an example of mathematical idealization). Here we should notice that the key point is the retained property of nonlinearity. It is essential that a fractal has a fractional, irrational dimensionality in the limit, due to which it is a way to organize an interaction between spaces of different nature and dimensionality (neural networks, individuals and their interaction, etc. are also fractals). The peculiarity of the fractal is that it has neither beginning, nor middle, nor end, like the Leibnizian Monad, i.e. it is delocalized and has no boundaries.

The fractal is the core concept of synergetics, and it perfectly describes the self-organization of any system, models its self-unfolding; its properties are hardly perceived by our thinking. However, the fractal logics, operating with paradoxical logical objects, makes it possible to solve problems of thinking which cannot be solved within the framework of the existing logics [14]. Therefore, similar to the philosophy of cyberspace, the philosophy of communication and information, or the philosophy of information, which appeared for the philosophical comprehension of new information technologies in the West and China, the philosophy of the fractal world [15] is emerging, which acts as the methodology and logics of scientific research, including the scientific discovery.

From philosophical and methodological point of view, a rapidly developing mathematical discipline, the fractal and chaos in dynamic systems, which has applications in modern science [16], is of undoubted interest. It fits well into the modern stochastic, non-linear picture of the world (here the synergetic approach works), describing the systems of our hierarchical world, from the microworld to our Universe. A variety of dynamic chaos models and turbulence in water, atmosphere, human circulatory system and space, fluctuations in temperature and density of various systems of the surrounding world are fractal in nature, having a space of fractional dimensionality.

It is necessary to take into account the fact of complementary nature of the fractal approach and the linear one to describing the world, including the human being, which gives a possibility for a deeper understanding of their nature. Indeed, nowadays, a new concept of interference-wave coherence of large-scale structures of a distributed type in living nature has been put forward. One of such structures is a human body, the study of which at various levels is very effective through the use of the fractal and synergistic principles. Thus, the concept of a fractal description of the world comes from the integral relationship between a Man and Cosmos, i.e. the fractal approach is one of the methodological foundations of the interrelations between the natural sciences and medicine.

It is just the fractal approach as the logics and methodology that makes it possible to explain the fundamental nature discoveries made by Leningrad biologists and physicians during the famous Leningrad Blockade in the Second World War. In monograph "The Leningrad Blockade: discoveries in the field of biology and medicine" V. B. Simonenko and S.V. Malaev enumerate the discoveries, namely, high life potential of the human body; activation of natural mechanisms of viability in a significant part of human population under long-term extreme conditions; diseases of the nervous regulation of biological functions and their significance in the outcome of survival in the extreme
situation; dependence of severity and outcomes of alimentary dystrophy on psychoemotional status; dependence of severity and outcomes of atrophic process on the preservation of apoptosis regulation at the level of organism; a possibility of natural reduction in atherosclerotic lesions of the vascular wall; the key role of the nervous mechanisms in the pathogenesis of hypertensive disease” [17]. All these discoveries, which, due to the extreme conditions of the Blockade, were surprisingly revealed, because they remained hidden under the normal conditions of the organism vital activity, but manifested themselves on the verge of life and death. Under the normal conditions of the human body vital activity, biologists and doctors follow some rules of the classical formal logics. These rules are not applicable to the process of biomedical research of the human body viability in extreme situations; in this case, the fractal logics and methodology of scientific discovery demonstrate their adequacy.

The fact is that the fractal logics operates with paradoxical logical objects, the number of which also tends to infinity, and in its conceptual quality it appears as a feedback-based instrumental and socio-cultural means of the scientific discovery. In application to discoveries in the field of biology and medicine, made under the extremely unfavorable conditions of the Leningrad Blockade, it means that the human body fractal structures formed some specific structures and stable biochemical forms of living nature. Such stable structures and forms in the human body are, first of all, the brain and the kidneys that explain the reality of ”restoring the organism from the level of minimum life to a level quite sufficient for active life and procreation” [16, 17].

The methodological significance of the fractal approach in describing such a relationship is most pronounced expressed in the emergence of the so-called medicine 3.0, or health 3.0 as an adequate response to the crisis state actually of all modern western and eastern, traditional and academic medical models and practices. It is just this type of medicine that is characterized by, firstly, the human and socio-cultural dimension, secondly, the holistic approach when an individual is considered as the unity of all spiritual and psycho-physiological measurements, thirdly, the quantum mechanical interpretation of the body's resistance to the micro and macro levels of the existence (medicine is regarded as the quantum in this case), fourthly, the interpretation of a disease and health as different states of the body being a multi-layered, dynamic balanced system with properties of fractality, and fifthly, its existence is substantiated by the development of the modern exact natural sciences [18]. Just in the context of the general ideas and principles of medicine 3.0, research and development of new medical drugs and innovative medical equipment should be carefully and intensively analyzed.

Following this consideration, we should notice that an exemplary case is the Cardiocode device. This electrocardiograph was designed and developed on the basis of a fundamentally new paradigm of knowledge on the heart and blood vessels phase performance, including the developed in 1980 by G.M. Poyedintsev and O.K. Voronova theory of the elevated fluidity mode [19] of blood circulation. This mode differs from the laminar and turbulent modes of flow, although it has some areas of turbulence. This mode is the third of the known modes of fluid flow in nature, and the discovery of the latter has been simply impossible within the framework of the classical logics, but it can be adequately interpreted by the fractal logics. As a result, created has been a new fundamental science: cardiometry, which is based on its own laws, axiomatics and logics.

So, subsequently, the paradigm for cardiology requires solving the problem of the measuring accuracy of diagnostically relevant signals (electrocardiosignals). The given diagnostics problem is primarily “related to the metrology of measurement and recording of biomedical signals, as well as an assessment of the reliability of the criteria characterizing the functional parameter” [19].

Thus, we face a complex methodological problem associated with difficulties in measuring physiological parameters, when direct (invasive) and indirect (noninvasive) measurements are used, when salient features of any signal, including medical and biological one, are revealed by mathematical differentiation, when a great number of external factors and pathological processes interfere and produce their different effects thereon.

Nowadays, much attention should be paid to the theory of measuring and computing systems (MCS) as measuring instrumentation, which is based on the mathematical formalism of measurement reduction, which makes it possible to obtain the most accurate description of an unobservable system “measured object-environment” according to the measurement results.
obtained in the system “measured object-environment-measuring device” and not distorted by measurements (that is related to fractal methodology): “Another important consequence of the MCS theory is a new principle of measurements, according to which the characteristics of the measured object interacting with measuring component (MC) can be significantly distorted compared to their values inherent to the object in its natural state, not disturbed by measurement and interesting to researcher” [20].

If at the level of the measuring component all the processes obey physical laws with their known limitations and prohibitions like thermodynamics, diffraction, quantum, and other ones, then at the MCS level the situation is fundamentally different, since the computational component makes it possible to mathematically model and calculate what is directly unobservable. MCS is a fundamentally new class of measuring instrumentation, which allows designing ideal measuring equipment for scientific and practical research of an object in its natural state. It is just the MCS concept that is capable of supplying significant data, when applied in medicine, including studies of biomedical signals (among them electrocardiosignals as well).

Results and discussions

The obtained results show that the fractal approach has been used for the first time as a methodological and logical basis for the scientific discovery in the context of interconnections between the modern natural sciences and medicine, including cardiology. For the first time the application of the fractal methodology in the field of MCS to avoid distortions in biomedical signals (electrocardiosignals) has been proposed. These results demonstrate a good correlation with the fractal nature of the living and the fractality of channels in the human body.

One of the fractal nature features is that the fractal considered in the form of a point (in a cross-section) can be differentiated at a closer distance into one or another set of points, a cluster, each point of which can be again differentiated into a cluster and so on (Cantor dust is an example thereof). This type of the structural construction is referred to as the fractal-cluster architecture, expressing the self-similarity of a fractal and its geometry, with reflecting one or another level of dimensionality. If we add the principle of self-affinity and congruence of a fractal, then this fractal-cluster approach is fully capable of providing the proper methodological basis for describing the relationships between the modern natural sciences and medicine under development. In application to advanced cardiometry, which deals with the problem of how to eliminate distortions on electrocardiograms, the channel fractality considerations, covering the human body as a whole, should be regarded as a very productive approach. This approach is also applicable when using the MCS based electrocardiogram recording technologies that will provide distortion-free data sets indicating the true performance of the human cardiovascular system.

Conclusions

For the first time revealed is the significance of the fractal approach as a methodology and logics of the scientific cognition, where and when the key role is played by a scientific discovery, restoring the interrelations between the modern natural sciences and medicine under development, first of all cardiology. For the first time, on the basis of the fractal methodology and logics, a wide range of possibilities to apply mathematical modeling methods for measuring and computing systems as methodology for studying biomedical signals (electrocardiosignals) has been established. The first step on the way out of the current crisis in medicine has been made with the use of the fractal methodology and logics of the scientific discovery in the context of the interconnections between the modern sciences and medicine. Prospects for overcoming this crisis are linked to applications of a number of the fresh scientific methodologies: tensor methodology, quantum mechanics, quantum information theory, artificial intelligence, nanoscience, trans- or multidisciplinary, or research strategy and others.

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

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References

Correction of the functional state of female rats after unilateral ovariectomy using a succinate containing composition

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Abstract
Unilateral ovariectomy (UOE) of female rats caused an increase in duration of the non-reproductive period (NRP) – metestrus and diestrus phases, and shortening of the reproductive period (RP) – proestrus and estrus phases of the estrous cycle (a symptom of hormonal deficiency). Signs of stress persisted 5 weeks after UOE: reduction of the ratio of thymus weight to the weight of adrenal glands (T/A). A two-week course of the succinate-containing composition with added B vitamins (SCCV) administered to the control female rats and those upon UOE has increased the T/A ratio as compared to that of intact animals, which is an indication of “activation” according to Garkavi et al. [1] and restored the NRP/RP ratio. Cytobiochemical analysis found a significant increase in nitroblue tetrazolium reduction during succinate oxidation in lymphocytes according to reading of animal blood smears.

Keywords
Unilateral ovariectomy, Succinate containing composition, Estrous cycle, Stress, Cytobiochemical analysis

Introduction
Amber acid has been traditionally viewed as an intermediate of the tricarboxylic acid cycle in the energy metabolism. However, studies conducted in the last several decades revealed its new role as a signaling molecule that participates in functional regulations at the cellular level and that of the whole organism [2, 3]. These new views formed thanks to a discovery by He et al. [2] of ligand properties of small succinate concentrations (about 50 mkM) acting on the SUCNR1 receptor found in many animal tissues [2, 3]. Activation of the SUCNR1 receptor by the ligand stimulates release of calcium ions from intracellular depot, which leads to significant changes in the activity of cells, tissues, and the whole organism. Small succinate concentrations also inhibit prolyl hydroxylase – a molecule that promotes degradation of the labile subunit of the hypoxia inducible factor 1 (HIF1) [4]. As the result of HIF1 stabilization, formation of the functionally active HIF dimer takes place, and the adaptation to oxygen deficit begins by transcriptional activation of the genes responsible for angiogenesis, erythropoietin synthesis, genes encoding glucose carries and multienzyme glycolysis complex.

The new data on the regulatory role of succinate requires re-evaluation of the effects of succinate-based compositions (SBC) on the functional state of animals and humans, and actualizes the need to control effects of SBC on the organism as a whole. Here, we investigated effects of two versions of substrate composition – SBC and SBC enriched with vitamins (SBCV) – on the functional state of intact female rats and animals, which have undergone unilateral ovariectomy (UOE).

The SBC’s effects on the hormonal status of female rats after UOE were assessed by the estrous cycle phases. In order to quantify stress development and the effects of the SBC course on the stress, we relied on the classical description of stress by Selye [5]:
decrease in the thymus weight and concurrent hypertrophy of the adrenal cortex.

In order to assess the state of live organisms, we turned to the cytobiochemical (CBC) method developed by M. N. Kondrashova. The method allows one to measure the amount of nitro blue tetrazolium (NBT) converted to formazan during redox reactions that are stimulated by exogenous substrates [6] in the immobilized peripheral blood cells of specially-treated blood smears.

According to M. N. Kondrashova, the activation of succinate oxidation detected by the CBC method is reflective of the sympathicotonic changes in the body that lead to the mobilization of the energy metabolism. Because the CBC method uses enzymatic intermediates and inhibitors of the tricarboxylic acid cycle, which takes place in mitochondria, lymphocytes, having more mitochondria compared to other blood elements, are the main contributors to the formazan formation. NBT is a highly electrophilic molecule, and using it as an acceptor of reducing equivalents in the CBC test allows us to assess not only the levels of coupled electrons coming from the carries of the mitochondrial respiratory chain, but also to detect the presence of single electron leaks that occur during reactive oxygen species formation. According to the developers of the CBC method, the offered analysis of the mitochondrial reactions in lymphocytes can be informative and reflect hormonal and energy state of the body [6]. Specifically, in case with UOE, as with any stressful state, there is an increase in the blood levels of glucocorticoids that cause not only thymus degradation, but also degradation and suppression of the circulating lymphocytes’ function and significant modifications in energy metabolism, which can substantially change the entire spectrum of the NBT reactions.

The goal of the study was to analyze the effects made by SBC on the functional state of the animals, who have undergone unilateral ovariectomy, and to assess the potential of using the cytobiochemical method of reading of the peripheral blood smears to evaluate the respective changes in live organisms.

Materials and methods

The study was approved by the Commission on Bioethics and Humane Treatment of Animals at the Institute of Theoretical and Experimental Biophysics of Russian Academy of Sciences (Protocol No.14 dd.17 December, 2013).

The experimental studies were carried out in 43 fertile female rats (18 months old), S-D line, weighing 350–400 g. The animals were divided into 8 groups as follows: 1) intact control (INT), n = 5; 2) control after a course of SBC (SBC) n = 5; 3) control, after a course of vitamins B (VIT), n = 5; 4) control after a course of SBC with vitamins (SBCV), n = 5; 5) female rats upon unilateral ovariectomy (UOE), n = 5; 6) female rats, who received a 2-week course of SBC 3 weeks after UOE (UOE+SBC), n = 6; 7) female rats, who received a vitamin course after UOE (UOE +VIT), n = 6; and 8) female rats which received a vitamin-enriched SBC course after (UOE + SBCV), n = 6.

Unilateral ovariectomy was performed according to the generally accepted methodology [7]. Three weeks after UOE, SBC was administered in the amount of 34.4 mg per kg of animal body mass, perorally, once every 24 hours, for 2 weeks. The said dose is 6x of the human dose as per the Guidelines for testing new pharmacological compounds.

The succinate-based composition contained 50% ammonium succinate with the rest of the ingredients present in equal amounts: calcium disuccinate, magnesium disuccinate, sodium glutamate, and glycine. Vitamin composition contained vitamins B1, B2 and B6 in equal amounts and was administered perorally; it was 6x of the half daily prophylactic human dose, together or in combination with SBC.

The estrous cycle (EC) phases – proestrus, estrus, metestrus, and diestrus – were determined daily during the entire experiment and were based on the cytology of the vaginal smears, taken at 9:00 AM [8]. Fractions of round nucleated epithelial cells, irregularly shaped anuclear cornified cells, and leukocytes were calculated in the total cell pool.

Changes in the animals’ functional state were evaluated based on the integral parameter: ratio of thymus weight to adrenal glands weight (T/A). Thymus and adrenal glands were taken from decapitated animals and weighed to the 0.1 mg accuracy. An increase in the T/A ratio is an evidence of the increase in thymus mass, and thus points to the development of “activation” [1]. A decrease in the T/A ratio usually depends on the degradation of thymus and hypertrophy of the adrenal cortex and points to the development of stress [1, 5].

For the CBC analysis [6], blood smears were prepared using a special device in order to get replicable mono-
layer samples. The smears were dried and then fixed for exactly 30 sec in 60% acetone (in 10mM HEPES, pH 5.2 aqueous solution), then rinsed and dried. Fixed smears were incubated at 370 °C for 1 hour in a medium which contained 125 mM KCl, 10 mM HEPES (pH 7.2), and 1.22 mM NBT under oxidation of added potassium succinate. Potassium malonate was added to the incubation medium in order to inhibit succinate dehydrogenase (SDG).

A probe without substrates served as the control one; it allowed evaluation of the endogenous substrates (ES) contribution. After incubation with NBT, the smears were rinsed and a nuclear stain was added (0.5 % neutral red) for 8 min. Specific formazan color during NBT reaction was determined with a video camera built into the Leica DM1000 light microscope connected to PC. Intensity of formazan staining, normalized to the background levels of unstained cells, was expressed in arbitrary units (AU) calculated using BioImages program. 30 stained cells were evaluated in each smear. The following probes were used for the experimental studies: ES – oxidation of exogenous substrates, MAL – 5mM potassium malonate, SUC – 5mM potassium succinate.

Statistical analysis was applied to the collected data, with significance calculation utilizing Excel and OriginPro.

Results and discussion

Effects of partial ovariectomy and succinate-based compositions on the functional state of the animals

UOE produced distortions of the estrous cycle pattern in female rats.

Usually, to quantify changes in the estrous cycle, the changes in the lengths of each of the 4 phases are considered separately. However, in our case, evaluation of the statistical significance of the postoperative changes turned out to be overly complex because of the small samples of control and intact animals; the animals were included in the experiment at the same time, and it was almost impossible to get uniform groups of females with synchronized estrous cycle phases. Conducting the surgery and administering the substrate compositions during the same phase of the cycle in all animals would have significantly lengthened the study, and some
factors which are difficult to control would be at play: time and age trends, fluctuations in the weather and temperature conditions, food etc.

In order to get more homogenous data, which can be statistically analyzed, instead of comparing the length of each estrous cycle phase, we grouped the phases in pairs, separating non-reproductive and reproductive periods (NRP and RP), and used the ratio of the NRP to RP length as a quantitative parameter. NRP was made up of total lengths of metestrus and diestrus, RP – proestrus and estrus. The NRP/RP length ratio turned to be a significantly more uniform parameter.

Among the female rates in the 3 groups, which have not undergone UOE, the NRP/RP ratios were similar to those in the intact animals, regardless of which substrate composition was administered (left 4 columns in Figure 1 above herein).

UOE induced an increase in the NRP/RP ratio as the result of longer NRP and shorter RP. Such a change in the estrous cycle probably reflected insufficient estradiol production by the remaining ovary, although it is difficult to imagine that the potential of one ovary in fertile animals is not enough to adequately compensate consequences of UOE (5 weeks after the surgery) via hyperactivity and hypertrophy. Most likely, the cause of insufficient activity of the remaining ovary is due to the disruption of its functional control by the hypothalamus and the pituitary as a consequence of post-operative stress [5]. If this assumption is true, then the succinate-based substrate composition can be viewed as a potential corrector of estrous cycle; this was shown by Dilman et al [9] in the experiments using succinate and glutamate, and later supported by our team in the study evaluating possibility of correcting estrous phase ratios in female rats of post-reproductive age using SBC [10].

Indeed, administration of SBC to the rats, which have undergone UOE, significantly improved the situation: the NRP/RP ratio decreased to the levels observed in the control animals (Figure 1). Therefore, a SBC course stimulated compensatory hyperactivity of the remaining ovary. Noteworthy is the absence of a positive result after administration of the vitamin composition without SBC; the combination of vitamin and SBC (SBCV) successfully corrected the NRP/RP ratio (see Figure 1).

Thus, our assumption that unrealized potential of the remaining ovary may be due to the dysfunction in the control system (hypothalamus-pituitary-ovarian axis) that occurs under stress, when oscillation rhythm is disrupted and formation and secretion into the blood stream of follicle stimulating and luteinizing hormones are suppressed, can be considered substantiated. According to Selye [5], such disruptions may be consequenc es of an intense increase in the synthesis of adrenocorticotropic hormone that occurs under stress. This leads to the need to quantitatively evaluate degrees of developing stress caused by UOE and the effects of the substrate compositions on this process.

In order to detect the stress state in animals [5], instead of comparing decreases in the thymus mass and increases in adrenal mass separately, similarly to the estrous cycle phase analysis, we used a relative parameter: the ratio of thymus weight to ad-renal weight (T/A). This allowed to somewhat cope with heterogeneity in the samples in the groups, and to at least discover trends in the changes of the animals’ functional state (see Figure 2 above herein).

In the control experiments (no UOE), after 2 weeks of the SBC administration, compared to the intact group, a clear trend of an increased T/A ratio (+ 60 %) was observed. Combined actions of SBC and vitamins (SBCV) resulted in a significantly higher T/A ratio: by 236 % compared to the T/A ratio in the intact animals (p < 0.01).

An increase in the thymus weight was the main contributor to the increase of the T/A ratio; this clearly points to the development of the physiological “activation” state according to Garkavi et al [1]. The “activation” state is characterized by predominance of the adrenergic (sympathetic) regulation, a higher resistance to harmful external influences, mobilization of substrates, an increase in the glycogen deposition, and readiness of individuals to withstand stress, combined with the stimulation of the immune system [1].

On the contrary, a course of vitamins without SBC slightly decreased the T/A ratio (~ 27 %) in the intact animals. This trend toward a decrease of the T/A ratio can hardly be considered as a positive effect. Probably it should be attributed to vitamin overdose.

Five weeks after UOE, there was a trend toward a decrease in the T/A ratio (~ 40 %). We regarded the decrease as a remaining sign of post-operative stress, in accordance to Selye's views [5]. It is possible that this parameter would have been more pronounced if measured closer to the time of the surgery. A 2-week course
of SBCV that has started 3 weeks after UOE resulted in a sharp increase in the T/A ratio – by 350 % (p < 0.002) compared to the animals, which have undergone UOE, but have not received a SBC course. The increase in the T/A was so high that the T/A ratio in the UOE+SBCV group reached the same levels as those observed in the control group during “activation” state after the SBCV course (see Figure 2).

In fact, the SBCV course produced a marked anti-stress effect that resulted in the recovery of the T/A ratio and normalization of the regulation along the hypothalamus-pituitary-ovarian axis. The latter caused, as mentioned above, a compensatory activation of the hormonal production in the remaining ovary. As a result, the NPR/PR ratio of the estrous cycle in the operated animals that underwent a course of the SBCV dropped to the levels observed in the first 4 control groups of the animals who did not receive the surgery (Figure 1).

Cytobiochemical analysis of the effects of partial ovariectomy and the succinate-based composition treatment course

Based on the CBC analysis, in the control animals, who received a SBC course and who were not subjected to UOE, there was an increase in the intensity of NBT to formazan formation that occurred during the oxidation of added succinate (SUC, Figure 3). This is likely due to an increased activity of SDG [6]. The largest increase in the color intensity was observed with SUC probe after a course of SBCV (see Figure 3 above herein). A more intense succinate oxidation may reflect sympathetic effects of SBC [6]. At the same time, there was an increase in the color intensity of formazan with EC and MAL probes. This is usually due to an increase of the exogenous substrate pool in the cells, specifically, due to fatty acids mobilization. Unlike the decrease in substrate oxidation during the first half of the tricarboxylic acid cycle (isocitrate, α-ketoglutarate and succinate), oxidation of fatty acids is not blocked by malonate (inhibitor of SDG). However, without additional experiments we cannot determine a possible cause of non-responsive-ness of the NBT reaction to malonate. Along with the activation of endogenous fatty acids oxidation, an increase in the free-radical reactivity of NBT (as a result of SDG inhibition) may also take place.

The CBC analysis of the samples from partially ovariectomized animals did not reveal any significant differences between UOE, UOE+SBC, and UOE+VIT groups (Figure 4). In these three groups, the levels of NBT conversion (in the blood smears with immobilized lymphocytes) remained at the levels similar to those observed in
the intact animals (compare Figures 3 and 4). After UOE, only the course of vitamins in combination with SBC (SBCV group) resulted in significantly increased rates if the NBT reaction that occurred when added succinate was oxidized (SUC, see Figure 4 below herein).

Therefore, based on the three measurements – ratio of non-reproductive and reproductive estrous cycle period lengths, ratio of thymus and adrenal weights, and the quantitation of the NBT reaction that occurs during succinate oxidation – we determined that the most effective way to correct functional state of female rats with and without UOE is to use a relatively short course of succinate based composition enriched with vitamins (SBCV). The effect of SBCV can be described as an anti-stress effect. Noteworthy is the fact that a course of SBCV provided a complete compensatory activation of the remaining ovary, which was evidenced by a decrease of the non-reproductive to reproductive phases length ratio of the estrous cycle. The discovery that a SBCV course supports activity of the hormonal system was also apparent in the CBC analysis; there was a significant increase in the SDG activity: an increase in the formazan color formation that occurs when added succinate is oxidized.

Conclusions

1. A two week course of the succinate-based composition with vitamins resulted in a significant increase in the thymus to adrenal weight ratios in female rats; this points to the development of “activation” state: increased resistance to harmful stimuli and stressors.

2. Following unilateral ovariectomy, we observed changes in the estrous cycle phases: an increase in the length of the non-reproductive period and shortening of the reproductive period; this points to hormonal deficiency that typically occurs under stress.

3. A two-week course of the succinate-based composition with vitamins administered 3 weeks after partial ovariectomy resulted in the development of “activation” state and recovery of the estrous cycle.

4. The cytobiochemical analysis showed an increase in the nitro blue tetrazol reducing activity when probing with exogenous succinate and endogenous substrates during the development of “activation” state after a course of the succinate-based composition with vitamins in the control and UOE groups.

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

Study conception and design: Maevsky E.I. and Uchitel M.L. Acquisition of data: Vasilieva A.A., Simonova M.A., Grishina E.V. Organization and carrying out animal operations: Bairamov A.A. Analysis and interpretation of data, drafting of manuscript: Maevsky E.I. Critical revision: Uchitel M.L., Grishina E.V.

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Intermittent hypoxic training as an effective method of activation therapy

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Abstract
This article considers possibilities of achieving the most effective therapeutic effect of intermittent hypoxia training (IHT) by initiating an activation and training reaction. Thanks to IHT the body builds an anti-stress type adaptation which increases the body’s nonspecific resistance to the development of diseases. It works through a variable functional load which includes a mechanism for optimizing mitochondrial respiration and is a trigger for synchronizing the performance of the nervous, immune and hormonal systems. Some biochemical data presented in the article demonstrate the effects of moderate hypoxia. In addition, laboratory and hardware methods of diagnosing for the selection of individual IHT regimes are proposed. IHT is used to great effect in training of astronauts, pilots, athletes and in the treatment of diabetes mellitus, trophic ulcers, diseases of the cardiovascular system, the central nervous system and oncological disorders as well as for rejuvenation purposes.

Keywords
Intermittent hypoxia training, Activation therapy, Adaptation, Stress, Sport performance, Aging diseases, Lactic acid, Depression, Anorexia, Nitric oxide, Hypoxia inducible factor – 1 (HIF–1)

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human body to factors in aviation and space flights [21-23], to achieve maximum sports results [1] and increase the overall resistance of the body to adverse effects.

**Materials and methods**

Under clinical conditions, hypoxic training with alternating breathing of ambient air is most often encountered with a mixture of 10–14 % oxygen (O$_2$) and about 86–90 % nitrogen (N$_2$) at normal atmospheric pressure (through a mask for 3-5 minutes), 6–9 cycles, with pauses between cycles of 3–5 minutes (respiration air at sea level, i.e. 20.9 % O$_2$). The duration of the session is 45–90 minutes. Adaptation develops as a result of breathing a hypoxic gas mixture, in a discontinuous mode, which leads to the repeated shift, “swing”, of oxygen saturation in blood (SpO$_2$) from 100–94 % to 86–78 %. We are alternating tension and rest. The oxygen content in the inhaled air varies from 20.9 % (room air) to 10–14 % (through the mask). Rocking mode, “swing”, is the main key to successful treatment and training.

Youth is the flexibility in providing compliance with external influences. Old age and degenerative diseases are the rigidity in physiology and psychology. From our point of view, due to the "swing regime" of oxygen tension in the arterial blood and tissues, which we estimate by oxygen saturation, adaptive reactions develop. Monitoring and evaluation of efficacy shows that the greater the difference (amplitude) between SpO$_2$ tension (breathing with a hypoxic mixture) and SpO$_2$ of rest (20.9 % O$_2$) during the session, then the more effective the training. Of course, the limits of these oscillations are determined.

Oxygen gives life, oxygen takes it. Without oxygen cells die. With too much oxygen cells die even faster. Mitochondria determine a cell's choice between life and death. With a high energy consumption by the cell, i.e. with greater delivery of glucose and oxygen, the mitochondria do not work efficiently and generate more superoxide (O-2). Superoxide is one of the active forms of oxygen (reactive oxygen species further referred to as ROS). ROS, under conditions of cellular stress, trigger and intensify the sequence of reactions that ultimately leads to cell death. The metabolism of all eukaryotes is based on the reduction of oxygen to water (O$_2$ to H$_2$O). This reduction of O$_2$ to H$_2$O can occur only with the formation of reactive oxygen species (ROS). ROS as "the signal for life" occurs under low concentrations of H$_2$O$_2$. A superoxide radical stimulates the division of normal cells in various tissues. On the other hand, H$_2$O$_2$ ROS and other ROS trigger the mechanism of cell death, the transformation of normal cells into malignant cells.

Hypoxic training increases the stress-protein (caperone, shock protein) level in the cell [27]. There is an intensification of production and rejuvenation of mitochondria (a cell concentrator for the production of aerobic energy) and mitochondrial enzymes, which allows for more efficient use of oxygen for energy production and excellent enzymatic antioxidant protection.

Oxidative damage to mitochondrial DNA, mtDNA, is a recognized mechanism responsible for pathogenesis of aging in mammals. Progressive degradation of mitochondria underlies oxidative stress, which leads to an accumulation of molecular damage, genome instability, reduction of telomeres, metabolic disturbances, hormonal disorders and acceleration of glycosylation of proteins. Continuous renewal of mitochondria in somat-
ic cells can reduce oxidative stress, increase the efficiency of oxidative metabolism, slow down the aging process and prevent and/or retard the development of age-related pathologies. The natural mechanism of mitoptosis, discovered in the mammalian organism, promotes the continuous purification of the mitochondrial basin in the body from damaged, old mitochondria. This actively produces free radical oxidation Reactive Oxygen Species (ROS). ROS include oxygen ions, free radicals and peroxides both of inorganic and organic origin. Oscillations of oxygen delivery eliminate the destroyed mitochondria and stimulate mitoptosis, which is the key to longevity [28]. Mitoptosis facilitates purification of the mitochondrial basin thus ensuring the spread of unmutated mtDNA.

IHT improves blood circulation and oxygen delivery to tissues due to the efficient operation of the ATP-K + pump. It was discovered that the ATP-K channels of intact ventricular cardiomyocytes blocked by intracellular ATP under normoxic ambient conditions begin to open in 20–25 minutes under moderate hypoxia. The dynamics of this activity has a periodic/cyclical rhythm [29].

One of the most effective factors of the biochemical environment of the body is nitric oxide (NO). NO acts on the smooth muscle walls of the vessels relaxing them. Nitric oxide also promotes the inhibition of the proliferation of smooth muscle cells. There is a decreased aggregation of platelets, leukocytes and erythrocytes; and reduction of adhesion of leukocytes to the endothelium. Nitric oxide induces neurogenesis and angiogenesis. Vascular growth occurs only where there is smooth musculature. This fact is important for solving the problem of the use of IHT in patients with cancer. As known, the vessels of cancerous tumors do not have smooth muscle tissue lining them. The synthesis of nitric oxide (NO) and its accessibility activates the expression of other protective factors, including the following: heat shock proteins [30], antioxidants, prostaglandins of H-synthase [31]. An adaptation to hypoxia prevents both NO overproduction and NO deficiency, resulting in an improvement in blood pressure [10, 11, 33]. IHT optimizes concentrations of nitric oxide by stimulating its synthesis, and also limiting its overproduction [32]. Understanding the role of NO in the mechanisms of the adaptation to hypoxia will help to substantiate the program for the prevention and treatment of hypoxia or ischemic damage to organs and tissues. Hyperglycemia inhibits the formation of nitric oxide (NO) and weakens its effect. The lack of sufficient synthesis of NO under diabetes mellitus gives rise to a dysfunction of the endothelium, which in its turn leads to vasospasm, smooth muscle proliferation, activation/aggregation of platelets, and adhesion of leukocytes to the endothelium [34]. IHT is more effective when it is used for an organism under the conditions of normoglycemia or in a state of hunger. During and after fasting periods, sensitivity of receptors is increasing. Even morning fasts can play a positive role.

IHT improves oxygen delivery to tissues due to a change in hemoglobin, an increase in tissue affinity for oxygen. During IHT, hemoglobin binds to 2,3-DPG (2,3 diphosphoglycerate), which greatly facilitates the release of oxygen from hemoglobin into the tissue [35].

The uniqueness of hypoxic stimulation is that during IHT there is an improvement in blood circulation in that part of the body that is in the state of hypoxia. Affected or inflamed tissues and organs or parts of them have much lower pH, since they are in the state of hypoxia. IHT stimulates capillary dilation faster in tissues and organs where is much lower pH and an increased concentration of lactic acid (lactate) as compared to non-acidi-fied, healthy ones. Thus, blood circulation improves primarily in the affected tissues and organs, including the brain. Therefore, the uniqueness of IHT stimulation makes it possible to treat not only wounds, trophic ulcers, lung abscesses, but also degenerative brain diseases: epilepsy, complex partial seizures, hyperkinesis symptoms, phantom pain syndrome, anorexia nervosa, depression, Parkinson’s and Alzheimer’s diseases [32].

The therapeutic effect can be achieved by improving oxygen delivery to the subcortical structures and, first at all, the nuclei of the visual hillock (median center, ventrolateral nucleus), or, in other cases, has the protective and therapeutic effect in survival of nigral dopaminergic neurons and in substantia nigra and striatum. As mentioned above, nitric oxide (NO) production plays an important role, and it is stimulated in the brain by erythropoietin.

IHT as an activation method acts on the whole organism and undoubtedly has much more advantages in achieving a quick and lasting result in increasing the overall resistance of the organism than the methods of action of individual adaptogenes. The im-
The repeated destabilization seems to be an activator and a trainer expanding the reserves of adaptation.

The "swing" with oxygen suggests a repeated shift in the amount of ROS, which, apparently, play not the least role in repetitive destabilization and subsequent adaptation. The metabolic shift occurs due to repeated changing in oxygen transport and leads to improvement of all the biochemical chains of oxygen delivery to the cells. An adaptation is a re-setting of the body in a new mode of operation, more sensitive, suppler and more flexible.

The repeated destabilization seems to be an activator and a trainer expanding the reserves of adaptation.

What reactions can be observed in the patient's body immediately after IHT?

A positive response appears upon expiration of 15-30 minutes, the state of general calm manifests itself, often accompanied by relaxation and drowsiness, slowing down of breathing and heart rate. Some patients improve their color vision dramatically. Cheeks appear pink, limbs are warmed. After one or two sessions, sleep and mood improve. In some patients, long-term depression is cured. There is a comfortable feeling of relaxation in the stomach, "the lump in the throat or chest" often accompanies stress is gone. Digestion improves, and the nonspecific resistance of the body as a result of integral changes in the body increases.

Breathing gas mixtures with different oxygen content causes hypoxia of different levels and leads to various reactions by the body. A weak stimulus causes a training reaction, which leads to the accumulation of some substances (proteins, cells, tissues). A stronger stimulus induces the action of activation, which has some temporary destructive properties, but further leads to a more intensive synthesis of proteins and repair. A very strong stimulus initiates stress, which leads to a noticeable destruction and hinders the development of an adaptive response.

Strong, intense hypoxia, like other strong stimuli, causes stressful reactions of anxiety, resistance and oppression within 3 phases. Stressful reactions are accompanied by profound changes in the central nervous system, including the pituitary gland and its...
hypersecretion of ACTH, suppression of the activity of the thymic-lymphatic system, metabolic disorders and high energy expenditure. As the founder of stress Hans Selye said, "protecting the body from a strong stimulus is achieved at a high price – at the cost of breakage and high costs." Stress is the nonspecific basis of any pathological process.

IHT makes it possible to purposefully dose the strength of stimuli and the amplitude of fluctuations of the hypoxic mixture. The purpose of IHT is to cause the development of general nonspecific reactions, which correspond to the symptom complex of an integral nonspecific adaptation activation or training reaction described and studied by Rostov scientists. [44–47]. It is important to take into account the individual sensitivity and subjective sensations of the individual (sleep, appetite, motor activity, efficiency, emotional state) and compare them with objective indicators. One of these can be a morphological blood test that classifies the strength of the impact and identifies the archetype of the reaction (training, activation, or stress) [48]. Monitoring heart rate variability (HRV) and studying the thermography of the body, an electroencephalogram (EEG) before the session and after it, dynamics of SpO₂ and breath-holding time may be utilized as valuable indicators for the assessments of treatment efficacy.

The methods of controlled enhancement of adaptation or activation acting on the whole body undoubtedly have many more advantages in achieving a quick and lasting result than methods of uncontrolled, blind effect of individual adaptogens.

Conclusions
Nature demonstrates that there are certain resources which can have a powerful and quick effect on metabolism. They can kill or cure. Considering them, oxygen is among the strongest. Our aim is to design, develop and apply the most efficient IHT methodology to act as a natural trainer, regulator and activator for restoration and rejuvenation for the body and brain.

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 authors read the ICMJE criteria for authorship and approved the final manuscript.

Reference:


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