**INTERNATIONAL SCIENTIFIC CONGRESS
IN THE MEMORY OF
PROF. L.A. BLUMENFELD
AND
PROF. S.E. SHNOLL**

HYBRID CONFERENCE 2021 ABSTRACTS

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Editor-in-chief

Prof. Dr. Vsevolod A. Tverdislov

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Trajectories of the movement of cytochrome c molecules nearby bc1 complex in mitochondrial crista – Brownian dynamics model

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Cytochrome C (cyC) transfers electrons in the mitochondrial respiratory chain between cytochrome bc1 (BC1) and IV membrane complexes. Using the ProKSim program [1], we constructed a model of the Brownian dynamics of diffusion of oxidized cyC (PDB ID 6FF5) in crista regions 300x300x120 Å containing reduced BC1 dimers (PDB ID 1BGY). The diffusion of cytC was simulated for 50 μs. The electrostatic forces of attraction between cyC and BC1 did not prevent cyC from escaping from BC1 but ensured frequent entry of cyC into electrostatically advantageous regions near BC1. Furthermore, it was found that cytC often passes along BC1 via the path connecting the sites of its binding with BC1 and with the IV respiratory complex in the respirasome (PDB ID 5GPN), determined by cryoelectron microscopy. Such a trajectory provides a faster electronic transport of cytC between BC1 and IV respiratory complex.

The research was carried out as part of the Scientific Project of the State Order of the Government of Russian Federation to Lomonosov Moscow State University No 121032500060-0.

1. Hrushev S.S. *et al.* 2013, DOI: 10.20537/2076-7633-2013-5-1-47-64

Entropy for biosystems at different scales of description

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The meaning of entropy is considered an essential characteristic of complexity for the organism as a whole and its parts down to the molecular level. Correlation of actions of various parts of the whole organism, intercellular interactions, control, and cooperativity at the micro-level leads to a complication of the structure and a decrease in statistical entropy. For a multicellular organism, the entropy is significantly less than the entropy for the same mass of a colony of unicellular organisms. Cooperativeness always reduces the system's entropy; a simple example of the binding of ligands to a macromolecule carrying two reaction centers shows how the entropy is consistent with the ambiguity of the result in the Bernoulli test scheme. A kinetic model of metabolism is proposed, which corresponds to Schrödinger's ideas about maintaining biosystems at the expense of "feeding on negentropy". The entropy of structural distributions during the aging of biosystems is determined. Particular attention is paid to the qualitative and quantitative relationship between the entropy of the system and the cooperativity of binding of ligands to macromolecules. The detected presence of minima and maxima in the dependence of entropy on the binding parameters can be interpreted as the possibility of the adsorption system to carry more or less information, respectively.

Self-organization and chaos in the model of the blood coagulation

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The mechanisms of self-organization of biological structures are currently among the least studied and understood. We know only two main mechanisms of self-organization:

1. Self-assembly according to the Lego principle. The system's individual elements are connected to each other due to the presence of particular complementary sites. The interaction of sites almost contacts. Websites begin to feel each other only at distances of several angstroms. Elements come into contact with each other through diffusion. This is how, for example, viral particles are collected. Such self-assembly is possible only at the molecular level.
2. Dissipative structures. Such structures arise in highly nonequilibrium systems called active media. The structures in these systems arise as a result of the loss of stability of the isotropic state. The characteristic distances at which individual parts of the system behave in a correlated manner reach tens of centimeters.

The ideas about which dissipative structures are possible and which are forbidden were formed by considering fairly simple examples of active media. In recent years, it has become clear that some of the prohibitions are not absolute and can be lifted in more complex active environments. In the course of the study of blood coagulation, we came to a model of an active environment, which allows the existence of almost any structure that was previously considered impossible. These examples will be discussed in the talk.

Biomechanics of the blood proteins and blood cells in computational models and real life

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Computer simulations are increasingly being used today to predict the dynamics of biological systems, test hypotheses, and deepen the understanding of the physical principles underlying biomechanics, hemodynamics, and biorheology. Due to the hierarchy and complexity of the studied biophysical phenomena, the main principles are consistency and multiscale. In models of the microvascular bed, it is necessary to take into account collisions of blood cells, and fluid dynamics, and conformational changes in proteins under the action of mechanical stresses and hydrodynamic forces. Our team has proposed a number of methods for three-dimensional computer modeling of hemodynamic phenomena in microvessels at levels from molecular to cellular. The report is devoted to biomechanical factors involved in the regulation of microvascular thrombosis: hydrodynamic forces acting on blood cells, their collisions and deformations, platelet aggregation, dynamics of blood proteins under the influence of mechanical and hydrodynamic stresses. Special attention is paid to selecting parameters and verifying mechanical models for cells and multimeric blood proteins in accordance with the experimental data known from the literature.

Study of regulatory processes in thylakoid membranes of algae *in vivo* based on the analysis of fluorescence, excited from microseconds to minutes

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To study the dynamics of dark-light transitions in thylakoid membranes of chloroplasts *in vivo*, the mechanisms of the processes are considered together with regulatory factors. Due to the flow of energy, the processes coordinated in the intervals of nano-, micro-, milliseconds ensure the redistribution of charges on the cofactors of photosystems 2 and 1, in the lumen, in the stroma of chloroplasts. When the sample adapts to light before reaching the hospital, regulatory connections are coordinated at time intervals that increase up to minutes. We measured the OJIPSMT fluorescence induction signals of *Scenedesmus* microalgae at times ranging from microseconds to ten minutes. The solar energy flux conversion stages were modeled by forming model subsystems - separately PS2 and thylakoid membrane (thylakoid model), including PS2 block. The capture of light energy, conjugate fluxes of charges (e⁻, protons, counterions), and energy losses was modeled without an explicit description of metabolic cycle reactions, and the conjugation of the thylakoid membrane subsystem with cycles of energy consumption stored in light reactions was defined as outflow reactions of NADPH → NADP and ATP → ADP.

Red blood cells actively contribute to blood coagulation and thrombus formation

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The talk describes the likely molecular mechanisms leading to the aggregation of human red blood cells (RBCs) under physiological conditions when prostaglandin E2 (PGE2) or lysophosphatidic acid (LPA) are released from activated platelets. In both cases, cation channels, especially the non-selective, voltage-dependent cation channel, are activated. This leads to an increase of the free intracellular Ca²⁺ concentration, resulting in the activation of the lipid scramblase, which mediates a movement of phosphatidylserine (PS) from the inner to the outer membrane leaflet. In addition, the increased Ca²⁺ concentration leads to the activation of the Gardos channel. Experiments suggesting this mechanism have been performed with fluorescence microscopy, flow cytometry as well as using single-cell force spectroscopy. The Ca²⁺-triggered RBC aggregation force has been identified to be close to 100 pN, a value large enough to play a significant role during thrombus formation or in pathological situations.

Effects of Melatonin and Glutathione on Oxidative Stress in Sperm

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The imbalance between the production of reactive oxygen species (ROS) and the cell's ability to neutralize them is called oxidative stress. In the sperm, this process can lead to lipid peroxidation, DNA fragmentation, changes in motility, and, as a result, infertility due to the incompleteness of the antioxidant system of the cell. Antioxidants can slow down or stop oxidative stress by engaging in redox reactions with ROS. Melatonin and glutathione are endogenous antioxidants that are present in human metabolism and have their own chain of reactions. From a practical point of view, the use of antioxidants to prevent oxidative stress in

sperm may provide better results in cryopreservation and in vitro fertilization. As a result of the experiment, it was found that Melatonin significantly reduces the degree of DNA fragmentation during the induction of oxidative stress. By spectrophotometry, the concentration of hydrogen peroxide during the induction of endogenous oxidative stress was determined, which was $CH2O2 = 6.3 \pm 0.5 \mu M$. Also, melatonin is not toxic and can be recommended as an effective antioxidant for working with cell cultures.

Alternative mechanisms of photochemotherapy

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Photochemotherapy (PCT) is a medical technique used in the treatment of cancer, fungal, bacterial and viral diseases, currently in the form of photodynamic therapy (PDT). A photosensitizer (PS) is introduced into the body, which accumulates in the diseased tissue. Irradiation with visible light transforms the accumulated PS into electronically excited states, which interact with molecular oxygen to form its active forms that destroy diseased cells. However, the energy of electronically excited states can also be spent through fluorescence and internal and intercombination conversions. This limits the effectiveness of PDT, stimulating the search for alternative pathways for PCT, using unexcited active particles, for example, free radicals (SR). Among SRs, an interesting radical $NO \cdot$ is involved in many vital processes, and in high concentrations causes cell death. The task is reduced to the search for PSs that release $NO \cdot$ under the action of light. Among the various classes of PSs, nitrofurantoin derivatives are attracting attention. A representative of this class, nitrofurantoin, used as a drug in urology, has demonstrated high photoactivity against a number of cancer cells and bacteria.

Nitrosonium cations as cytotoxic components of dinitrosyl iron complexes in living organisms

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The mechanism of formation of its dinitrosyl iron complexes (DNIC) in living organisms has been deciphered. The key feature of this mechanism is the disproportionation reaction - one-electron oxidation and reduction of nitrogen oxide molecules NO , pairwise bound with the ferrous ion. As a result of this reaction, a cytotoxic component of these complexes, the nitrosonium NO^+ cation, appears in the DNIC. DNICs of this kind are stable only in the presence of thiol-containing ligands that prevent hydrolysis of nitrosonium cations. The decomposition of these complexes, which ensures the release of nitrosonium cations from them and thereby their cytotoxic effect, is initiated either by superoxide ions or by exogenous iron chelators - dithiocarbamate derivatives. The cytotoxic effect of nitrosonium cations has been demonstrated in experiments on animal and bacterial cells, on malignant and non-malignant tumors in animals. There is reason to believe that the nitrosonium cations produced by DNIC are capable of blocking SARS-CoV-2019 infection by S-nitrosating the proteases of the virus host.

A metabolic trigger in rodent liver methionine metabolism

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Methionine is an essential amino acid that, except of protein synthesis, is needed for the synthesis of S-adenosylmethionine (AdoMet), the major biological methylating agent. An interesting feature of methionine metabolism in rodent liver is that AdoMet is produced by two isozymes of AdoMet synthetase, MATI and MATIII, one is inhibited by AdoMet, whereas the other is activated by it. To understand the regulation of methionine metabolism in rodent liver we constructed a mathematical model describing all enzymatic steps of this metabolism. Analysis of the model has shown that methionine metabolism can operate under two different modes. The first, associated with MATI, with low metabolic rate and low AdoMet concentration, serves predominantly to supply the cell with AdoMet and provides methionine recycling. The second one, associated with MATIII, with high metabolic rate and high AdoMet concentration, provides an avenue for disposal of excess methionine via transsulfuration pathway. The sharp switch between the two modes is triggered by methionine concentration and provides a mechanism for stabilization of methionine levels in blood over wide variations in dietary methionine intake. Investigation of methionine metabolism in murine hepatocytes at physiologically relevant conditions confirmed the sharp switch from low to high metabolic mode triggered by methionine concentration.

Spatial distribution of the autowave mechanism of the dual myogenic pacemaker of the tubular heart

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Similar signaling pathways are discussed that control the maturation and contractility of a rhythmically operating electromechanical pump found in chordates from tunicates *Tunicata* (*Ascidia*) to primates. The paper considers the structural and functional features and automatism of the tubular heart as a stage in the development of the 4-chambered heart of vertebrates in evolution. The experiments were carried out on an isolated spontaneously contracting heart of *S. rustica* at the Belomorsk Biological Station of Moscow State University named after M.V. Lomonosov. The simple (primitive) structure of the ascidian body is one of the convenient models for studying the early stages of the development of the function of the contractile organs and the heart, in particular. However, despite the simplicity of the compact genome, *Ascidia* has a number of similarities in development with vertebrate embryos: the nerve cord on the peritoneum, the tadpole stage, notochord, and the remnants of the tail. The heart of the ascidian is a U-shaped tube without valves, so the blood is pushed out in peristaltic waves. Myoepithelial cells with a diameter of 4-7 microns and a length of 15-20 microns are located along the wall of the pump in pairs to each other at an angle of 60° and form a dense spiral. During arousal, a gradual twisting of the heart tube is observed. This contributes to the

development of a pump force of about 78 mN in ascidians with a body length of 60-80 mm. The circulatory system of the ascidians is not closed, so the blood circulates in two opposite directions. This is done using a dual myogenic pacemaker mechanism located at the ends of the heart. Thus, the twisting of the pump tube and the formation of valves from the endothelium are necessary conditions for the formation of a multi-chambered heart for pumping fluid with nutrients, metabolic products and oxygen dissolved in it. The heart of the ascidian can be considered as a peristaltic pump with separate translational and rotational degrees of freedom included in the autowave mechanism of the functioning of the pump machine.

Tubulin microtubules as molecular motors

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Microtubules are polymers of tubulin protein that form a dynamic skeleton within all eukaryotic cells. Microtubules are highly non-equilibrium systems capable of cyclically switching between the phases of assembly and disassembly, expending the energy of hydrolysis of guanosine triphosphate (GTP). In addition, the ends of assembling and disassembling microtubules can develop significant pushing and pulling forces, performing useful mechanical work on the transport of intracellular goods, for example, chromosomes during cell division or membrane organelles such as cell nuclei, endoplasmic reticulum, etc. experimental and theoretical data that shed light on the mechanisms of operation of microtubules as molecular machines and briefly trace the history of the development of these concepts over the past 30-40 years.

Long-term fruitful cooperation between biophysicists of Moscow and Mongolian universities

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We congratulate the staff of the Department of Biophysics of the Physics Faculty of Moscow State University on the anniversary of our two highly respected professors, L.A. Blumenfeld and S.E. Shnol, founders of the Department of Biophysics of the Physics Faculty of Moscow State University.

I took a refresher course in 1972-1974 at your department. During this time, I attended courses of lectures by professors LA Blumenfeld and SE Shnoll "Problems of Biophysics" and "Biochemistry for Biophysicists", passed the candidate minimum examinations. During my internship at the Department of Biophysics of the Physics Faculty of Moscow State University under the guidance of Professor Blumenfeld and Associate Professor Kukushkin, I conducted research on the topic "Investigation of chromatic transitions in the leaves of higher plants" and in 1974 I defended my thesis for a candidate of physical and mathematical sciences. Since then, our friendly and close cooperation has begun.

In 1979, the Department of Biophysics was created at the Physics and Mathematics Faculty of the National University of Mongolia, which happened with the full support of the Chairs of Biophysics of the Physics Faculty and the Faculty of Biology of Moscow State University. As a result of our fruitful cooperation, an educational and research base was created at the Department of Biophysics of Mongolian University, hundreds of specialists were trained, several

fundamental and applied research in the field of biophysics was carried out. Furthermore, based on the results of our joint study, we have published more than 40 articles in foreign and domestic scientific journals, three Ph.D. and one doctoral dissertation have been defended.

We remember with gratitude the biophysicists of Moscow University, including L.A. Blumenfeld, G. N. Zatsepin, S. E. Shnol, V. A. Tvedislov, A. K. Kukushkin, E. K. Ruuge, S. V. Tulskey, M. K. Solentsev, A. N. Tikhonov, V. A. Karavaeva, S. P. Kuprina and others (Faculty of Physics), A. B. Rubina, O. R. Kols, S. I. Pogosyan, G. Yu. Riznichenko, A. V. Veselovsky, T V.V. Veselov, V.Z. Pashenko, D.N. Matorina, A.A. Churin and others (Faculty of Biology), who made a significant contribution to the development of our fruitful long-term cooperation.

May our cooperation last forever!

Nucleic acid aptamers – perspective receptors in biosensors for cancer diagnostics

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Nucleic acid aptamers are single stranded DNA or RNA that in a solution forming binding site specific for certain molecules, cells, viruses or bacteria. The aptamers are characterized by high specificity, which is comparable and even higher than those of antibodies. In contrast with antibodies the aptamers are more stable. They are developed *in vitro* by combinatorial chemistry using SELEX (Systematic evolution of ligands by exponential enrichment). Using the CELL SELEX, it has been possible to develop aptamers specific to cancer markers at the surface of the cells. The aptamers can be chemically modified by various ligands which increase their stability and allowing their immobilization at various surfaces, where serve as receptors in biosensors. This contribution represents overview of recent achievements in application of aptamers in development of biosensors for cancer diagnostics.

Boundary potential of lipid membranes - relationship with structure and biological significance

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Structural changes in the lipid matrix of biomembranes are reflected in the distribution of electric charges and dipoles at their boundaries or interfaces with the aqueous environment. The surface and dipole components of the electric potential at these boundaries are available for measurements on lipid models of membranes - liposomes, planar BLMs, and Langmuir monolayers - by methods of bioelectrochemistry. They make available the study of adsorption of inorganic ions, synthetic polycations, polypeptides and proteins, which is accompanied by changes of surface charge density, the state of hydrogen bonds and the orientation of dipole moments, as well as water exchange in the presence of a polymer layer on the membrane surface. By calorimetric, X-ray methods and molecular modeling, we have proved their participation in the regulation of the phospholipid phase state, which is essential for the conformational mobility of membrane proteins. In particular, the transition from the liquid expanded (LE) to the condensed (LC) state of anionic phosphatidylserine molecules, initiated by the adsorption of gadolinium cations, blocks mechanosensitive channels in cell membranes, and the binding of beryllium cations masks some signal molecules at the cell surface for calcium-dependent initial steps of apoptosis and thus leads to a serious beryllium disease.

Intellectual-sensor systems for life sciences

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A diagnostic system for analyzing the functional state of a person has been developed and investigated, which consists of two modules: sensor-electrochemical and computational information. The sensor module is represented by an array of electrochemical sensors. An information-computing module that carries out general management and displays the results obtained is represented by a mathematical model of statistical algorithms for processing and analyzing multidimensional data using machine learning technologies, pattern recognition, and visualization. A cluster analysis of the results of measurements of the diagnostic system was carried out using the methods of artificial neural networks in the form of self-organizing Kohonen maps and the method of principal components. The results of clustering of "digital images" of the functional state of the subjects by various ways confirmed the tendency of images to group. They made it possible to assess the stability and quality of the created cluster solution. The results make it likely to recommend the developed non-invasive sensory system as a hardware-software complex to support medical decision-making and an automated system for express diagnostics of a person's functional state.

Calorimetric and X-ray structural analysis of cryoprotective media

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Although the cryopreservation methods of biomaterial are actively developing for spermatozoa, the percentage of preservation of viability after freezing-thawing remains low: 40-60%. One of the leading causes of cell damage during cryopreservation is the formation of extra- and intracellular ice crystals. Therefore, the aim of the work was to study the influence of various components and conditions of freezing on the process of crystal formation in cryoprotective media. In the experiments, using the calorimetry method, the dependences of the heat capacity on temperature for basic solutions were obtained. It was shown that the addition of sucrose reduces the area of heterogeneous nucleation, which makes it possible to increase the survival rate of cells during cryopreservation in the studied media. With the help of X-ray diffraction analysis, more than 400 solutions for cryopreservation of cells, differing in the concentrations of the main components, and more than 30 types of alternative methods for freezing cells, differing in the location of cryotubes with samples during freezing and the rate of lowering the samples over nitrogen vapor were studied. As a result, two main methods of freezing were selected as the most effective in terms of the size of ice crystals formed in solutions.

The role of local gradients of chemokine CCL3 and follicular regulatory T cells in the control of B-cell immunity

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Gradients from various chemokines play a critical role in organizing cell migration in the body and coordinating intercellular interactions that determine the immune response to infections and vaccines. Antibody immune responses are triggered by B lymphocytes, as a result of their recognition of foreign antigens and interaction with T cells. Our *ex vivo* and *in vivo* studies, including in vivo 2-photon microscopy of the interaction of lymphocytes in the lymph nodes of mice, showed that the chemokine CCL3, produced by B lymphocytes, promotes their direct contacts with follicular regulatory T cells (Tfr) with the synergistic participation of two chemokine receptors to CCL3 on Tfr: CCR5 and CCR1. Tfr play a role both in the regulation of autoreactive B cells (and in the prevention of autoimmune diseases) and in the maturation of B cell affinity in germinal centers. Our studies indicate the important role of CCL3 production by B cells for their interaction with Tfr and optimal control and affinity of B cellular immune response *in vivo*.

Condensed DNA architecture in the E. coli nucleoid

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The 3D architecture of the genome determines the function of the cell. The study of DNA condensation in a cell is also important for understanding the mechanisms of bacterial survival. For medicine, ordered DNA condensation ensures the resistance of pathogenic bacteria to antibiotics. Under the stress of starvation, bacteria, in contrast to actively growing bacteria, use a non-volatile mechanism to maintain order and protect vital structures (DNA), as in inanimate nature. The study of the structure of DNA in the nucleoid of the bacterium *Escherichia coli* was carried out using diffraction of synchrotron radiation and transmission electron microscopy (TEM). The experimental results made it possible to visualize the structures of the lower hierarchical level of DNA compaction in the nucleoid of resting cells. For the first time, a series of diffraction experiments carried out indicates the presence of a periodic ordered organization of DNA in all studied bacteria. TEM made it possible to extract finer visual information about the type of DNA condensation in the nucleoid of the bacterium *Escherichia coli*. Intracellular nanocrystalline, liquid crystal and folded nucleosome-like DNA structures were found. A folded nucleosome-like structure was observed for the first time; it is the result of multiple folding of long DNA molecules around the Dps protein and its associates.

Analysis of the applicability of regression models to describe the oxygenation of hemoglobin

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A review of the most well-known models describing the binding of hemoglobin to oxygen is given. An approach is proposed that allows, on the basis of formal criteria, to find the optimal mathematical and physical models of cooperative binding of oxygen by hemoglobin. Using the methods of regression and cluster analysis on the basis of experimental data on the dissociation of oxyhemoglobin, a comparison was made of the main models of oxygenation, which are based on power-law and exponential dependences. It was shown that the models of Eder, Bernard and Hill, corresponding to power functions, have an advantage in describing oxygen binding by hemoglobin compared to models corresponding to exponential functions. It has been found that the sequential four-stage Koshland-Nemethy-Filmer model, which corresponds to the Eder equation, best describes the experimental data. The approach proposed in this work in assessing the efficiency of approximation of the oxyhemoglobin dissociation curve can also be used to solve problems similar in their formulation, i.e. testing mathematical models that have physical meaning. This makes it possible, in our opinion, to increase the efficiency of the search for the most promising options in the development of modern molecular models, as well as the verification of templates, models and schemes existing in the studied area.

Impact of weak forces on biological systems

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The study of weak effects was one of the topics of the Physical Biochemistry Laboratory, headed by S.E. Shnol. This problem arises when trying to explain the effects of the impact of low concentrations and physical factors of low intensity on biological and model objects. The phenomenon of a stimulating effect of various chemical compounds in small doses on the functioning of living organisms was explained by the stimulating effect of stress-causing substances, but still insufficient for the manifestation of harmful consequences, and was called hormesis. A stimulatory effect of a similar nature was found for ionizing radiation and was called radiation hormesis. Later, a wider range of concentrations of active biologically active substances was investigated for various functions of simple model systems, where the concept of hormesis loses its meaning. The uniformity of the response of different model systems in the form of a non-monotonic polymodal dependence of the measured parameters on the concentration of the active reagent in the range of low and ultra-low concentrations indicates the common cause of these effects, which is water. Experimental results are presented that confirm the decisive role of water in the effects of weak influences on biological and model systems..

Self-organized criticality management at the edge of stability and chaos

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The features of the regimes and their physical properties in the region close to the bifurcation points in systems with self-organized criticality are considered. It is shown that a regime is possible when a system with self-organized criticality operates in an instability region without leaving this region. This mode is called work on the edge of stability or chaos. It is shown that the indicated regimes near the bifurcation point in a number of cases can be considered as threshold synchronization of nonlinear relaxation self-oscillating systems. In this case, the system acquires a number of remarkable properties. Its sensitivity to external signals is significantly increased (it can be increased up to millions of times or more), the selectivity is significantly increased (it can be increased up to a thousand times or more). These modes are called bifurcation resonances. The system becomes remarkably easy to control. It is shown that for the stability of the operating mode in an unstable region near the bifurcation point, it is necessary that, as the amplitude of the unstable regime increases, nonlinear negative feedback arises, which will stabilize the unstable regime and turn it into a stable one. This situation occurs in most biological systems and living organisms.

Examples of the implementation of operating modes in an unstable region of systems with self-organized criticality in biology, brain, radio electronics, and technology are considered. Examples of the work of physiological sensory systems, in which the generation of powerful impulse flows occurs from very weak receptor potentials, are considered. Examples of the realization of unconditioned reflexes formed at the spinal level and conditioned reflexes formed in the brain are considered. To study the modes near the bifurcation point, we used a mathematical model of synchronization of relaxation self-oscillations based on the modified axiomatic Wiener-Rosenbluth model and the properties of uniform almost periodic functions. The operating modes of systems with self-organized criticality in the unstable region before bifurcation with entry into the unstable region after the bifurcation, but in the presence of return mechanisms have been established.

Biomechanical factors regulating the dynamics of thrombus formation

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One of the most common pathologies associated with the work of the hemostasis system is arterial thrombosis - the formation of a large clot (thrombus) in the lumen of the damaged artery. The formation of an arterial thrombus is a physiologically unique process: within a time period of the order of minutes, a large macroscopic structure with a size of the order of millimeters appears in the lumen of the vessel. This process occurs under conditions of rapid arterial blood flow. It is essentially determined by the interaction between platelets - small cellular fragments and critical participants in the vascular-platelet link of hemostasis. In the case of a normal hemostatic response, the dynamics of a thrombus have a three-phase nature: the stage of growth of the platelet aggregate is followed by a phase of reduction in its size and subsequent stabilization. Moreover, the final size of the thrombus is only a tiny part of the vessel lumen without affecting the blood flow rate. The mechanisms responsible for the observed dynamics of a thrombus, as well as the relationship between changes in the size of an arterial thrombus and its spatial heterogeneity, remain the subject of research. To study the key factors that regulate

the dynamics of thrombus formation, animal models of arterial thrombosis, in vitro systems, and computer modeling are actively used today. The computer model of thrombosis developed at the Department of Biophysics made it possible to describe the dynamics of the outer layers of an arterial thrombus. It was shown that the plasticity of the thrombus membrane can be provided by the stochastic nature of the primary interactions between platelets through the GPIIb receptors and the von Willebrand factor.

Acidosis and the effect of Verigo-Bohr in the pathogenesis of COVID-19

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A number of mechanisms linking the damaging factors of COVID-19 with acidosis have been considered, and the existence of positive feedbacks between the development of hypoxia and acidosis has been shown. In the early stages of the disease, inflammation, difficulty in gas exchange, thrombosis and other damage to the body bring the onset of acidosis closer. In accordance with the Verigo-Bohr effect, a decrease in blood pH leads to a decrease in saturation, which contributes to the further development of acidosis and leads to a deterioration in the patient's condition. A decrease in pH can also cause conformational changes in the S-protein of the virus and lead to a decrease in the affinity and avidity of antibodies.

Redox regulation of Na, K-ATPase

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Na, K-ATPase creates a transmembrane gradient of K^+ and Na^+ , which is necessary for the viability and functioning of animal cells. Inhibition of Na, K-ATPase during hypoxia and oxidative stress is one of the fastest and most critical events for cell viability. It was found that the functioning of Na, K-ATPase depends on the redox (redox) status of cells and is regulated by redox-dependent modifications of the thiol groups of the enzyme. Glutathionylation (addition of glutathione) of certain cysteine residues of the catalytic α -subunit of Na, K-ATPase leads to its inhibition and underlies a decrease in the activity of Na, K-ATPase during hypoxia. The cause of inhibition is a violation of the binding of adenine nucleotides by glutathionylated protein. Short-term inhibition of Na, K-ATPase plays an important role in cell adaptation, preventing the depletion of the ATP pool. When the redox conditions return to normal, the enzyme is deglutathionylated and its activity restored. In addition to the transport function of Na, K-ATPase acts as a receptor for cardiotonic steroids, which is also redox-sensitive. The reason is the violation of the interface of interaction between Src-kinase and Na, K-ATPase due to glutathionylation of Na, K-ATPase. Changes in the receptor function of Na, K-ATPase under hypoxic conditions must be taken into account when considering the effect of cardiotonic steroids on cells and tissues.

Multi-nuclear MRI imaging

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New approaches to MRI on nuclei heavier than the proton are considered. An additional goal of Larmor-tuned MRI imaging of heavy nuclei is to detect proton-free tissues and drugs within the body in vivo. First of all, it was required to know where the fluorine-containing drugs are located - the blood substitute Perftoran introduced into the bloodstream, contrasting gases filling the airways in MRI pulmonology, etc. A similar problem arises when ^{23}Na , ^{13}C , ^{31}P , ^2H and other nuclei are detected in living tissues and introduced into the body medicines. It is especially important to know the content of ^{23}Na atoms in the body, which affect the level of blood pressure, the occurrence of diabetes and kidney pathologies. It is also of interest to obtain a hyperpolarized state of ^{129}Xe , ^{83}Kr , ^3He , ^{13}C , ^{29}Si nuclei capable of amplifying MRI signals by 4-5 orders of magnitude and providing high-contrast MRI images in real time.

This work was supported by RFBR grants 19-29-10015, 20-52-10004, Russian Science Foundation 21-75-10038 and the Interdisciplinary Scientific and Educational School of Moscow State University "Photonic and Quantum Technologies. Digital Medicine".

Nucleic acid physics from the discovery of the double helix to the present day

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As a result of millions of years of biological evolution, a surprisingly expedient structure of the substance of heredity, DNA, arose. This most important molecule of life, a biopolymer of a relatively simple chemical structure, provides storage, reproduction, implementation and evolutionary changes in the genetic information of all living organisms. The implementation of these functions by a DNA molecule is ensured by its unique molecular structure, which combines almost flat and rigid subunits (bases) with conformationally flexible ones (sugar-phosphate backbone), which allows the formation of various spatial structures. The talk will examine the change in ideas about the structure and functioning of DNA since the discovery of the double helix by Watson and Crick to the present day. The physical foundations and patterns of the formation of spatial structures of DNA with Watson-Crick nucleoside pairs, the dependence of conformations and conformational preferences of the polynucleotide chain regions on the base sequence will be discussed.

Repositioning of the drugs in the COVID-19 pandemic using *in silico* and *in vitro* approaches

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Repositioning of the drugs - identifying new indications for drugs approved for medical use - is a natural prompt response to SARS-CoV-2 / COVID-19 coronavirus infection. Remdesivir, Favipiravir and Umifenovir, which initially had other indications, were approved for emergency use in COVID-19. To search for new pharmacological effects in known drugs, *in silico* studies (molecular modeling, machine learning, network pharmacology) and *in vitro* (biochemical and cellular test systems) are carried out. Several large-scale studies are devoted to *in vitro*

screening for one or several targets from 1400 to 12000 drugs, which made it possible to select a number of "hits" for repositioning. In many cases, the results obtained for specific drugs in various experiments do not agree with each other due to the lack of standardization of test systems and generally accepted comparison drugs. To select the most promising candidates for repositioning for COVID-19 therapy, an analysis of all available information obtained in silico, in vitro and in vivo is required. The possibilities and limitations of drug repositioning in the SARS-CoV-2 pandemic and actions to reduce the danger of new biogenic threats in the future are discussed.

Capabilities of the laser-optical methods in detecting changes in the microoroeological properties of blood in socially significant diseases

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Methods based on the use of diffuse elastic, quasi-elastic and Raman scattering of light and diffractometry, optical tweezers, flow cytometry, fluorescence microscopy and capillaroscopy, enhanced by digital image processing, are widely used to measure a number of parameters characterizing the microrheological properties of blood, which determine its fluidity and its fulfillment of its main functions both in normal conditions and in the presence of many diseases. The report will present the results of applying these methods to identify changes in microrheological parameters, namely: indices of erythrocyte deformability, aggregation of erythrocytes and platelets, strength of aggregates and forces of interaction between them and others characteristic of diseases such as hypertension and diabetes, as well as for research biophysical mechanisms of interaction of cells with blood plasma proteins. This work was supported by the RFBR grant No. 19-52-51015.

Carotenoids protect photosynthetic organisms from singlet oxygen. But not always

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According to the generally accepted point of view, one of the most important functions of carotenoids (Car) in photosynthesis is to quench the triplet states of the main pigments, chlorophylls and bacteriochlorophylls, and thereby suppress the formation of a chemically active singlet-excited state of oxygen. We found, however, that in a wide range of purple photosynthetic bacteria, photoexcitation of Car leads, on the contrary, to the generation of 1O_2 and the oxidation of the main pigments. The study of this effect by the EPR method of high temporal resolution showed that in this case, in the process of singlet-triplet fission of excitation, triplet states of carotenoids are formed, $^1Car^* + Car \rightarrow 3Car + 3Car$. The generation of singlet oxygen occurs as a result of the interaction of these states with atmospheric oxygen only for carotenoids with a sufficiently short ($n < 10$) system of conjugated double bonds.

Scientific origins of Lev Alexandrovich Blumenfeld

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Lev Aleksandrovich Blumenfeld belongs to the scientific school of the outstanding physicist and chemist Ya.K. Syrkin. The role of Yakov Kivovich Syrkin in the development of domestic science remains underestimated and is associated not only with the development of theoretical chemistry, but also with the introduction of new physical phenomena and measurement methods based on them into the practice of chemical research. On behalf of J.K. Syrkin's name is inseparable from his student, co-author and like-minded person M.E. Dyatkina, who shared with him not only the contribution to science and education, but also the tragic opportunity to become a symbol of true science in the era of persecution against it. L.A. Blumenfeld in all respects was one of the most prominent representatives of the scientific school of J.K. Syrkin and M.E. Dyatkina, who continued their scientific and ethical traditions.

Conformational dynamics of the von Willebrand factor

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The ability to conformational transitions is a key property of biopolymer macromolecules, which largely determines their functions. An important role is played by conformational changes in biopolymers that occur under the conditions of a moving solvent flow. Recently, the role of the conformational dynamics of von Willebrand factor (VWF) in the activation of thrombus formation has been actively studied. The report discusses the description of the conformational dynamics of VWF under the action of increased shear stresses. It was found that, under the action of shear stresses, the globular structure of the VWF macromolecule can be transformed into a threadlike one. A dependence is obtained linking the value of the critical shear stress with the length of the VWF macromolecule. It is shown that under the action of unsteady shear stresses, the description of the conformational dynamics of VWF is essentially determined by the value of the cumulative shear stress. The dependence of the critical value of the cumulative shear stress on the degree of multimeric VWF is obtained. State diagrams are built.

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Microlens optical microscopy of nanometer resolution

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The resolution of modern conventional optical microscopes is limited by the diffraction limit. To increase it, as well as to overcome this limitation, it is proposed to use microlenses. Microlens - an optical lens that allows you to get an image by "capturing" light waves in the near field, reflected from an object. Located between the sample and the microscope objective, the microlens is an optical amplifier that increases the resolution of the microscope.

The prospects for the use of optical microscopes with microlenses lie in the achievement of new possibilities for obtaining images of bacteria, viruses, DNA and biomacromolecules with a detailed study of their morphology in real time.

To observe biological objects in air and in liquids, it was proposed to combine optical microscopy with scanning probe microscopy: this gives rise to a unique opportunity to detect viral particles by an optical method in a large field and to study it in detail using various versions of probe microscopy.

The study was carried out with the financial support of the Russian Foundation for Basic Research and the Royal Society of London, project No. 21-58-10005.

Variation of the geometry of the sugar-phosphate backbone of DNA in DNA-protein complexes: analysis of experimental data

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In the context of the development of coarse-grained DNA models, [DOI: 10.1021 / acs.jcim.1c00506] comparison (by PDB) of the geometry of the sugar-phosphate backbone of DNA during binding to proteins, in crystalline form and in solutions was carried out. The "orthogonal" coarse-grained degrees of freedom, analogous to the principal degrees of freedom of the skeleton (pseudorotational angle τ_0 and angles ε / ζ), are determined. When DNA binds to proteins, a change in one of the angles C3'C1'N * or C4'C3'P (2) occurs at a constant (as a rule, canonical) value of the other angle - exactly as for the pair τ_0 and $(\zeta - \varepsilon)$... Noncanonical conformations of the angles τ_0 and ε / ζ are found mainly in transcription complexes, polymerases, and endonucleases. Most of the statistical characteristics of the distribution of lengths and angles on the DNA backbone turned out to be the same for the sample of X-ray and cryo-electron microscopy data, with the exception of the histogram of the angle τ_0 . A possible explanation for this difference has been proposed. Artifacts on the histogram of ε / ζ angles in a sample of NMR data for DNA in solution appear due to the use of imprecise protocols for obtaining the structure of a molecule from a set of measured distances. The work was carried out on the topic of the state assignment of the Federal Research Center of Chemical Physics RAS 0082-2019-0005.

The binary response of membrane potential on pulsed UV excitation in photosynthetic cells

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When studying the effect of UV-B radiation on the plasma membrane of cells of aquatic plants, a rapid and reversible depolarization of the MP was found. At the beginning of exposure to UV radiation on leaf cells rapid and reversible depolarization occurs, followed by a slow phase of depolarization. The spectrum of action of the fast UV response lies in the range of 300 - 330 nm, and of the slow phase - in the range of 280 - 300 nm. In a series of UV exposures, pulsed with duration of 15 s with dark interval of 3 min there was observed binary responses of MP. The depth of depolarization is greater in the first and the following odd impulses than in the

second and the following even impulses in series. It is concluded that the H^+ -extrusion complex of the plasma membranes of plant cells actually consists of two types of interconnected electronic H^+ -pumps: the redox H^+ -pump and the H^+ -pump of the H^+ -ATPase enzyme complex.

Magnetic and gold nanoparticles in living systems and for living systems

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Various living systems contain biogenic nano-phase magnetic structures formed as a result of biogenic processes of biomineralization, which play an important physiological role (provide orientation in the Earth's magnetic field), and can also be a biomarker of certain pathologies. Biogenic magnetic nanoparticles (mainly magnetic single-domain iron oxides), first discovered by L.A. Blumenfeld and colleagues in unicellular cultures and in DNA preparations (the so-called broad EPR signal lines), are currently found in a wide variety of living organisms from bacteria and plants to insects, fish, birds and animals, including humans, in which their presence correlates with neurodegenerative pathologies. Even the search for traces of life on Mars consisted in the search for magnetite nanoparticles, which are inextricably linked with life processes. Nano-phase gold can also be generated by living systems and is formed during biomineralization processes as a result of the biogenic recovery of Au (III).

Currently, magnetic and gold nanoparticles and functional nanosystems based on them, due to their unique physicochemical properties, are popular research objects in several fundamental and applied fields of science. Given a certain "biogenicity" and the corresponding low toxicity, it is nanoparticles of magnetic iron oxides and nanoparticles of metallic gold that are of great interest for modern and promising biomedical applications, including highly effective diagnostic tools and new technologies of drug therapy based on controlled Spatio-temporal conjugation of drug delivery and activation processes. Drugs in local target areas of the body. This communication describes our approach to solving the problem of controlled, targeted drug delivery in living systems, based on the principles of biomimetics and using the most biocompatible and non-toxic functional materials found in living systems (lipids, amphiphilic molecules, polymers, magnetite, and metallic gold nanoparticles), as well as the safest external control physical effects that provide remote control of the permeability of nanocomposite vesicles - non-thermal effects of magnetic fields, as well as for ultrashort electrical impulses that cause the effect of selective electroporation of nanocomposite liposome membranes.

Revealing the toxic effect of heavy metals on plant organisms using machine learning methods

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Heavy metals are common pollutants that pose a serious threat to living organisms. One of the main targets for heavy metals in plant and algal cells in the photosynthetic apparatus (PSA). For a quick assessment of PSA activity, the method of fluorescence induction of chlorophyll a is widely used - measurement of the fluorescence intensity (the so-called OJIP curve). The

possibility of using machine learning methods (classifier of the "random forest" type, neural network models, methods of cluster analysis) to automate the detection of the toxic effect of heavy metals based on fluorescent data has been investigated. As input data for the classifiers, we used both the readings of the induction curves directly obtained from the measuring devices and the parameters of the JIP test calculated from them. It is shown that for all types of studied classifiers, the best overall accuracy (88–90%) was obtained for samples of natural phytoplankton; for pea seedlings, the overall accuracy was lower (67% –78%). Based on this, it seems promising to create automatic stations for continuous monitoring of the functional state of natural phytoplankton based on the data on the fluorescence induction of chlorophyll a.

The research was carried out within the framework of the scientific project of the state assignment of Moscow State University No. 121032500060-0 with partial support of the Russian Science Foundation grant No. 20-64-46018 (Pskov State University) and the RFBR grant No. 20-04-00465.

The physical basis of biological computation in the works of Lev Blumenfeld

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Lev Blumenfeld (1921-2002) made a significant contribution to understanding the operation of biological macromolecules. He developed a concept according to which the conformational relaxation of macromolecular systems acting as macroscopic oscillators represents an elementary action of bioenergetic processes. In this action, the fast quantum effect is followed by a slow conformational transition during which the energy is not dissipated but remains stored in a stable entangled coherent state for a total lifetime long enough for work to be performed. He successfully applied this theory to enzymatic catalysis and explained its exceptional precision and specificity. We will show the importance of this understanding for the description of information transfer and computation performed by Cell Molecular Computer as suggested by Efim Liberman. In fact, Lev Blumenfeld substantiated the physical basis of informational processes in biological systems and should be considered as one of the founders of the concept of biological computation.

Neuronal membrane contamination hypothesis, epilepsy and the ketogenic diet

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In the light of new data, Altrup's hypothesis on the contamination of neuronal membranes in epilepsy is considered. This hypothesis links the paroxysmal depolarization observed during epileptic activity with the pacemaker potential of a single neuron. The physicochemical characteristics of the membrane, fluidity, and contamination affect its ability to conduct impulses and recharge. The previously proposed methods of treating epilepsy based on the ketogenic diet and their possible explanations in connection with the Altrup hypothesis are discussed. Among the possible mechanisms of action of the ketogenic diet, the antiepileptic effect of ketone bodies, the role of increased glutathione synthesis, and the impact of polyunsaturated

fatty acids and cholesterol included in the diet are emphasized. These three mechanisms lead to the regulation of the fluidity and other biophysical properties of the lipid bilayer, as well as to the decontamination of the membrane from amphiphilic impurities, following Altrup's hypothesis.

The S.E. Shnoll effect: 70 years later

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From 1951 until the end of S.E. Schnoll studied fluctuations in measured quantities - the scatter of measurement data - in processes of a different nature, from biochemical reactions to radioactive decay. He developed a special method for time series analysis using inconsistent sample histograms. The main content of the discovered effect is that the shapes of this kind of histograms for fluctuations of measured quantities in processes of any nature are not random. Analysis of the results of many years of research led S.E. Shnoll to conclude that changes in the shape of histograms are determined by cosmophysical factors, such as changes in the characteristics of the gravitational field during the movement of the Earth, associated with the fractal structure and anisotropy of space-time. The report considers the previously proposed interpretations of changes in the shapes of histograms, other approaches to identifying hidden patterns in time series and their interpretation, proposed modifications of experiments to study time series of different nature. The report's main goal is to draw the attention of students, graduate students, and young researchers to the remarkable discoveries of S.E. Shnoll and unresolved problems in this area.

Biophysical principles in the treatment and prevention of ovarian hyperstimulation syndrome

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One of the serious, life-threatening complications of hormonal stimulation during *in vitro* fertilization (IVF) is ovarian hyperstimulation syndrome (OHSS). There is no generally accepted understanding of the onset and development of OHSS in the literature. Existing models of OHSS pathophysiology do not allow preventing the occurrence of OHSS and developing an effective therapy for it. The aim of this work was to develop a new pathophysiological model of the onset and development of OHSS, which made it possible to: 1) explain the need for the injection of the hCG trigger to trigger OHSS; 2) explain the accumulation of fluid in the abdominal cavity (ascites) in OHSS; 3) predict an effective strategy for the prevention and non-symptomatic treatment of OHSS.

Analysis of the literature data allowed us to make the assumption that the central role in the development of OHSS is played by such a biophysical parameter as the transmembrane potential of ovarian cells. As a result, a completely new model of the emergence and development of OHSS was developed, which linked together all the literature data on OHSS and made it possible to propose a new strategy for the emergence and development of OHSS, based on the stabilization of the transmembrane potential of cells. The proposed strategy for the therapy and prevention of OHSS has been tested in more than 10,000 IVF patients and has been shown to be effective.