

**3^d INTERNATIONAL
WORKSHOP MSSMBS'08
“Molecular Simulation
Studies in Material
and Biological Sciences”**

Book of Abstracts

Joint Institute for Nuclear Research

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WORKSHOP MSSMBS'08
“Molecular Simulation
Studies in Material
and Biological Sciences”**

Dubna, September 10-12, 2008

Book of Abstracts

**Edited by
Kholmirzo T.
Kholmurodov**

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3^d INTERNATIONAL WORKSHOP MSSMBS'08 "Molecular Simulation Studies in Material and Biological Sciences" (MSSMBS, 2008, Dubna)

Book of Abstr. of the 3^d INTERNATIONAL WORKSHOP MSSMBS'08 "Molecular Simulation Studies in Material and Biological Sciences" Dubna: JINR, 2008. -25 p.

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The series of MSSMBS "Molecular Simulation Studies in Material and Biological Sciences" meetings started in 2004, continued in 2006 and now comes to 2008, that are devoted to the molecular simulation problems of the physical and biological systems. MSSMBS is mostly contributed from the leading research groups of Japan and Russia (JINR, MSU named after M.V.Lomonosov), including participation from the European Institutes. MSSMBS'08 focuses on the different aspects of molecular simulation in material and biological research, on the computational and theoretical studies of atomic and molecular interactions, dynamics in between atoms, molecules, ions, clusters and surfaces, with emphasis on biomolecular protein simulation.

3^e МЕЖДУНАРОДНОЕ РАБОЧЕЕ СОВЕЩАНИЕ MSSMBS'08 "Молекулярно-динамическое моделирование в науках о веществе и биологии" (MSSMBS, 2008, Дубна)

Сб. аннот. 3^{го} МЕЖДУНАРОДНОГО РАБОЧЕГО СОВЕЩАНИЯ MSSMBS'08 "Молекулярно-динамическое моделирование в науках о веществе и биологии" Дубна: ОИЯИ, 2008. -25 p.

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Международное рабочее совещание MSSMBS'08 "Молекулярно-динамическое моделирование в науках о веществе и биологии" является третьим по счету международным совещанием посвященным проблемам молекулярного моделирования физических и биологических структур. Инициаторами проведения совещания, наряду с Объединенным Институтом Ядерных Исследований и Московским государственным университетом имени М.В.Ломоносова являются ведущие исследовательские центры Японии. Первое и второе совещания, MSSMBS'04 (2004) и MSSMBS'06 (2006), соответственно, также проходили в Объединенном Институте Ядерных Исследований. Заявленное совещание посвящено различным аспектам моделирования молекулярных систем, динамики взаимодействия атомов и молекул, кластеров и поверхностей, с особым уклоном на биомолекулярные белковые моделирования.

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Konstantin Shaitan (Moscow State University)
Victor Lakhno (IMPB, Puschino, Russia)
Kenji Yasuoka (Keio University, Japan)
Tatyana Feldman (Biochemical Physics Institute RAS)
Mikhail Avdeev (JINR, Frank Lab. Neutron Physics)
Roman Efremov (Institute of Bioorganic Chemistry RAS)
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PREFACE

A number of conferences in different countries are being devoted to the computer molecular simulations aimed for the physical and bio-molecular sciences. The current volume contains of the Book of Abstracts of the 3-d International Workshop MSSMBS'2008, "Molecular Simulation Studies in Material and Biological Sciences", which to be held in JINR, Dubna, on September 10-12, 2008. The series of the MSSMBS meetings started in 2004, continued in 2006 and now comes to 2008. The MSSMBS'2004 was the first international conference held in Russia, specially devoted to the methodological problems and applications of the art of molecular dynamics simulations in chemical physics and bio-molecular systems. The idea of the MSSMBS'2004 was first suggested by Prof. Kenji Yasuoka from Keio University of Japan, who is a leading expert of the molecular dynamics simulations in the physical and biochemical sciences. The MSSMBS is mostly contributed from the leading research groups of Japan and Russia, including participation from the European Institutes. The MSSMBS workshops to focus on the different aspects of molecular simulation in material and biological research, on the computational and theoretical studies of atomic and molecular interactions, dynamics in between atoms, molecules, ions, clusters and surfaces, with emphasis on bio-molecular protein simulation. The present meeting MSSMBS'08 deals in particular with:

- Protein modeling
- Drug design
- Simulation of liquids
- Liquid crystals, polymer systems
- Simulation of radiation-induced damages and mutations
- Quantum biophysics, electronic structure of macromolecules
- Parallel computing for the chemical physics and bio-molecular studies

The MSSMBS'08 workshop will be held in the International Conference Hall of JINR, Dubna, near Volga river - a beautiful place in Moscow region. We expect to provide a broad discussion on the radiobiological experiments and nuclear physics achievements of JINR, sightseeing of JINR basic experimental facilities and Dubna historical sites as well. The organization of the MSSMBS meetings has well fitted to the current research needs of the Joint Institute for Nuclear research (JINR). A special interest of the JINR, one of world leading nuclear centers, signifies an important bias in the global science from nuclear physics to life sciences. Taking into account the growing interest in computer molecular simulations, the modern computing capabilities and the breakthrough over world-wide scale, the molecular modeling becomes a challenging and useful tool in today bio- and nano-technological applications. The other side of this tendency is a capability of the nuclear measurement setups of JINR, say the NMR or experimental neutron source and beam spectral methods, to study the conformational aspects of the biological structures (proteins and related biochemical complexes).

The methods of computer molecular simulations (conventional or hybrid molecular dynamics (MD), Monte-Carlo, *ab initio* quantum-chemistry, etc.) of large molecular systems, first proposed more than 50 years ago with the invention of computers, have shown an outburst development in the last 5-10 years. With the creation of new parallel/vector supercomputers and special-purpose computational clusters the molecular simulation serves as a practical tool in the development of new materials and new drugs, performing the large-scale calculations on molecular complexes of hundreds thousands or multi-million particle systems. The molecular simulation techniques allows, for example, to explore directly the conformational changes and dynamical processes of DNA and proteins, to estimate the phase transition behavior of polymeric systems, to study the cluster-surface nanostructures in physical chemistry and biochemistry, so on.

Organization of the International Meeting in such dynamic area as computer molecular simulation is a great responsibility and a great challenge. In the one hand it gave the organizers a unique opportunity to promote the new scientific branch, the computer molecular simulations, within the framework of a traditionally nuclear experimental research center. On the other hand it gave the organizers an excellent opportunity for collecting a reach scientific experience through providing of a platform for leading research groups and scientists to meet and share their thoughts on the latest trends of art.

Welcome to Dubna!

Chairman of the MSSMBS Organizing Committee,

Kholmirzo T. Kholmurodov.

MOLECULAR MODELING IN CHEMISTRY OF LARGE MOLECULES

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We describe developments and applications of the hybrid quantum mechanical – molecular mechanical (QM/MM) method for modeling mechanisms of enzymatic reactions and properties of photoreceptor proteins. Chemical transformations in the active sites of enzymes or excitations in the chromophore binding pockets are described by quantum chemical approaches, while molecular mechanical (molecular dynamical) methods account for effects of protein matrices. In case of enzymatic reactions, the simulations aim to locate stationary points on the multidimensional potential energy surfaces of biomolecular systems referring to the configurations of reagents, products, intermediates, transition states, and to formulate conclusions on the mechanisms of chemical reactions occurring in protein environment by analyzing the computed minimum energy profiles along reaction coordinates. Initial geometry configurations of the enzyme-substrate complexes are constructed by the available crystal structure of relevant enzyme-inhibitor systems from the PDB archive.

Applications include a complete cycle of chemical transformations for the serine protease prototype reaction, the mechanism of serine-carboxyl peptidases, a novel class of enzymes active at low pH values, acetylcholinesterase catalysis for the hydrolysis reaction of the neurotransmitter acetylcholine. A special attention is paid to the enzymatic hydrolysis reactions of nucleoside triphosphates, including hydrolysis of adenosine triphosphate (ATP) by myosin and guanosine triphosphate (GTP) by human protein p21^{RAS} (RAS), by the protein complex RAS-GAP, and by EF-Tu. It is shown that in all cases the hydrolysis proceeds through the stage of the low-barrier cleavage of the P_γ-O_{βγ} bond of nucleoside triphosphate, separation of the metaphosphate moiety PO₃⁻ with a subsequent stage of proton transfers to complete formation of inorganic phosphate.

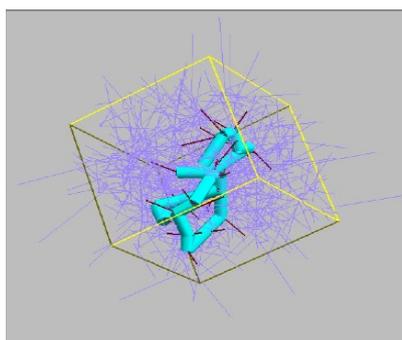
Another direction of the studies is modeling molecular dynamics of nano-size single molecule devices called ‘nanocars’.

Molecular simulations of polymers with primitive chain network model

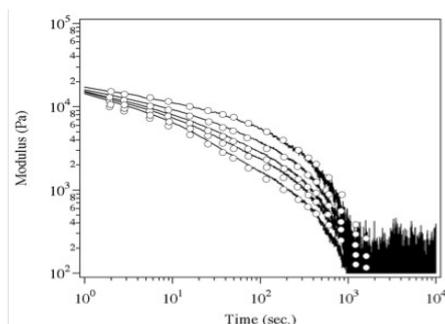
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Analysis and prediction of molecular level behavior of polymers are important for many fields in science and engineering due to the large degree of freedom in molecular design, which realizes variety of functions. Although molecular simulation is a promising tool to explore the effect of molecular structure, the conventional molecular simulations such as molecular dynamics is unpractical because of large molecular weight and long characteristic time of polymers. To overcome the practical and computational difficulty some coarse-grained ideas have been introduced for polymer simulations. Since it has been experimentally established that the most of polymers obey the universal behavior known as the scaling behavior both in statistics and dynamics, in the basic idea of the coarse-grained simulations inter-molecular interactions arising from two-body interaction potentials are regarded less important while intra-molecular forces according to the covalent bond along polymer backbone is the main source of material properties. A widely accepted and hence used simulation method is the Brownian dynamics simulations with bead-spring chains where each spring represents several carbon-carbon bonds on the polymer backbone. To achieve a higher level of coarse-graining we have been developing a method called primitive chain network simulations [1] where one element in the calculation corresponds to the entanglement molecular weight [2-6], which consists hundreds carbon atoms. In our method a network of chains having consecutive segments represents entangled polymer liquid. The chain segments are connected each other at the node of the network by sliplink standing for entanglement in between polymer chains. The dynamics of the polymer chain is described by the equation of motion for the network node, the kinetic equation of sliding transport of monomers assigned to the chain segment through the sliplink, and an algorithm to achieve entanglement and disentanglement around chain ends. It has been confirmed that the basic scaling behavior of linear polymers [1] are captured and that the viscoelasticity [2-8] can be quantitatively reproduced (see Figure 1 (b) for example). The method has been expanded to more complicated systems with long chain branching [8], blends [3], copolymers [10,11] and solid particles and quantitative assessment has been being performed.



(a)



(b)

Figure 1 (a) A typical snapshot of primitive chain network simulation. (b) Prediction of non-linear shear modulus (solid lines) compared with the experiment (open symbol) [12].

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Microbubbles: From Mechanical Stability to Hybrid Simulations

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Bubbles with size of micrometer or less, called "microbubbles", have become an attractive research target, partly because of recent technological progress of microbubble generations and partly in prospect of their fruitful applications, such as MEMS devices and biological treatments. However, experimental investigation of their physical properties is far behind the applications due to their size and fragileness. With various molecular simulation techniques, we are looking into their static and dynamic properties.

Mechanical Stability: The force balance concerning a spherical bubble of radius R is usually described by the Young-Laplace (Y-L) equation

$$P_{vap} = P_{liq} + \frac{2\mathcal{Y}}{R}, \quad (1)$$

where P_{vap} and P_{liq} are the pressure inside (vapor phase) and outside (liquid phase) of the bubble, respectively, and \mathcal{Y} is the surface tension. The question here arising is how far the Y-L equation is applicable to microbubbles and nanobubbles.

We carried out a series of molecular dynamics (MD) simulations of a tiny bubble in Lennard-Jones liquid (Fig. 1) to evaluate both P_{vap} and P_{liq} of a bubble with various sizes and found [1] that

- (i) The vapor density and the vapor pressure inside the bubble are independent of the bubble radius, equal to those of the saturated vapor in bulk equilibrium.
- (ii) The liquid surrounding the bubble is at a strongly stretched state, showing negative pressure.
- (iii) The surface tension is also little dependent on the bubble radius, and agrees with the surface tension of a planer interface, as shown in Fig. 2.

We conclude that nanobubbles observed under atmospheric pressure are either at some non-equilibrium state or containing impurity, such as non-condensable gas or surface adsorptions.

Initial Stage of Nucleate Boiling: We are interested in the very initial stage of nucleate boiling on ideally flat plate, where no bubble nuclei exist. Equation (1) predicts that infinitely large vapor pressure is required to create vapor nuclei under normal pressure conditions. We have carried out MD simulations (Fig. 3) to investigate how the initial vapor nucleus emerges.

Surface charge of microbubbles: Concerning the surface adsorption, it was reported that air bubbles intrinsically have negative electric charges in pure water. Although the origin of the charge is not fully understood, some researchers even think that the surface charge has various biophysical effects. We have observed microbubbles of diameter 10–100 μm under alternate electric field in electrolyte solutions. From their zigzag trajectories (Fig. 4), we estimated the surface charge and conclude that OH^- ions abound near the bubble surface.

This kind of ion adsorption can drastically change the mechanical stability and dynamics of microbubbles. Triboelectricity, or charge-up by friction, may explain the charge imbalance; we are investigating the process with molecular simulations.

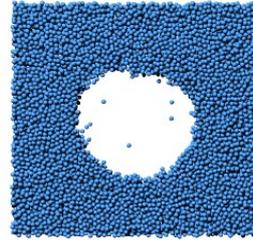


Fig. 1: Sectional view of a nanobubble in the simulation.

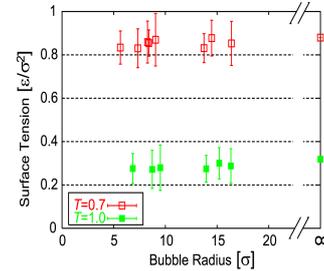


Fig. 2: Evaluated surface tension of a nanobubble [1].

MD-CFD Hybrid Simulation: A full MD simulation of bubble dynamics [2] is too demanding for computational resources. We have developed an MD-CFD hybrid simulation code [3, 4], targeting microbubbles, which rapidly shrinks, or collapses, under high pressure. The idea is simple. We divide the calculation space into two concentric spherical regions; the outer region, far from the bubble, is treated with CFD method, and the inner region containing the bubble is treated with MD method. The region boundary can smoothly move according to the pressure difference between the both regions. Figure 5 shows an example of non-spherical bubble collapse under planar shock wave. This kind of hybrid simulation can reveal the effect of various adsorbents.

The author is grateful to the collaborating students, K. Tanaka, S. Kawabe, S. Takamatsu, S. Kinouchi, and N. Ikemoto.

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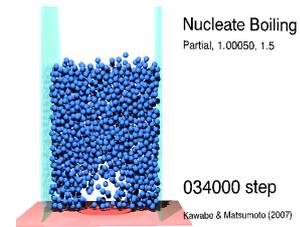


Fig. 3: Simulation of an initial stage of nuclear boiling.

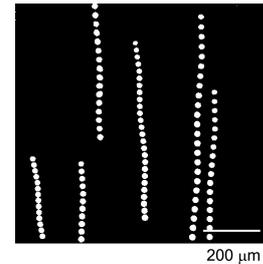


Fig. 4: Bubble trajectories in water under AC field.

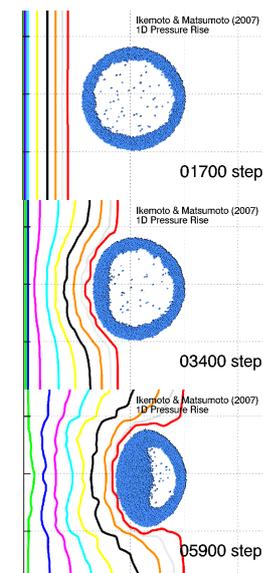


Fig. 5: Example of MD-CFD hybrid simulation of bubble collapse

Water exclusion mechanism of aquaporin-1 by Molecular Dynamics simulations

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Introduction Two-third of body weight is water molecules. The water molecule is essential for life beings. The total amounts of water molecule regulate accuracy at an organ or cell levels. Biological membrane separates the cell from outside environments. Most physiologists thought that there must be openings (pores or channels) in biological membranes to permit a flow of water, because the osmotic permeability of some epithelial cells was much too large to be accounted for by simple diffusion through the membrane. Because biological membranes are mainly made from hydrophobic molecules, it is difficult that water molecules pass through via biological membrane. Therefore, water pathway had been mystery until Dr. Peter Agre found aquaporin, known as water channel, in blood cell in 1992. Dr. Peter Agre was awarded the Nobel Prize in Chemistry for 2003 “for the discovery of water channels.”

Aquaporin family is known as a water channel and distributes in the whole body. There are 13 type of aquaporin (0 to 12) in human. Recent study indicates that aquaporin has a function not only water permeation, but also permeation of gas, alcohol, glycerol, and other molecules. And inhibitors of water permeation of aquaporin are known by biological study. But selective and inhibition mechanisms of aquaporin family has been unclear at an atomic level.

It is known that Hg^{2+} acts as a blocker of water permeation through aquaporin-1 (AQP1). However its mechanism is still unclear. Here, we executed molecular dynamics (MD) simulations of AQP1 with or without connecting Hg^{2+} to the Cys191 of AQP1 in order to clarify how Hg^{2+} inhibits AQP1 at an atomic level.

Method We constructed a model system of AQP1 tetramer in POPE bilayer system and obtained a standard structure of our study. To construct the model system, we used X-ray crystallographic structure of bovine AQP1 (PDB entry: 1J4N) [1]. The X-ray structure is published as a monomer, although AQP1 organizes as a tetramer both in the crystal and in living cell. We constructed AQP1 tetramer from AQP1 monomer and soaked it into POPE bilayer with two water layer of 20 Å. The system size is about $110 \times 110 \times 110 \text{ \AA}^3$. After 2.0 ns of equilibrium simulation, we obtained a standard structure. Additional 20 ns equilibrium simulation was executed to obtain control of our study. To clarify the exclusion mechanism of AQP1 by Hg^{2+} , mercury ions were connected to the sulfur atoms of Cys191 of AQP1 and MD simulations were executed.

All MD simulations were carried out at a constant number of molecules, a pressure of 1 atm, and a temperature of 310 K according to Berendsen's algorithm with a coupling time of 0.2 ps (NPT ensemble) after each system had been heated to 310 K over the first 100 ps. The time step was set at 1 fs. The bond lengths involving hydrogen atoms were constrained to equilibrium lengths using the SHAKE method. The parm99 and gaff parameters were used. The particle mesh Ewald (PME) method was used and direct space cutoff distance was set to 12 Å. The program package used for MD simulation was amber 8.

Results and discussion The averaged root mean squared deviation (RMSD) of each structure from a standard structure has been reached equilibrium state; the averaged value was about 3 Å. We obtained equilibrium structures of AQP1 tetramer with or without connecting Hg²⁺ to Cys191 (Hg-AQP1 or Free-AQP1) in POPE bilayer. The data were collected from equilibrium states. We found that the orientation near Cys191 of Hg-AQP1 was different from that of Free-AQP1. Water permeability of Hg-AQP1 was also smaller than that of Free-AQP1. We will propose the mechanisms of AQP1 inhibition by Hg atoms.

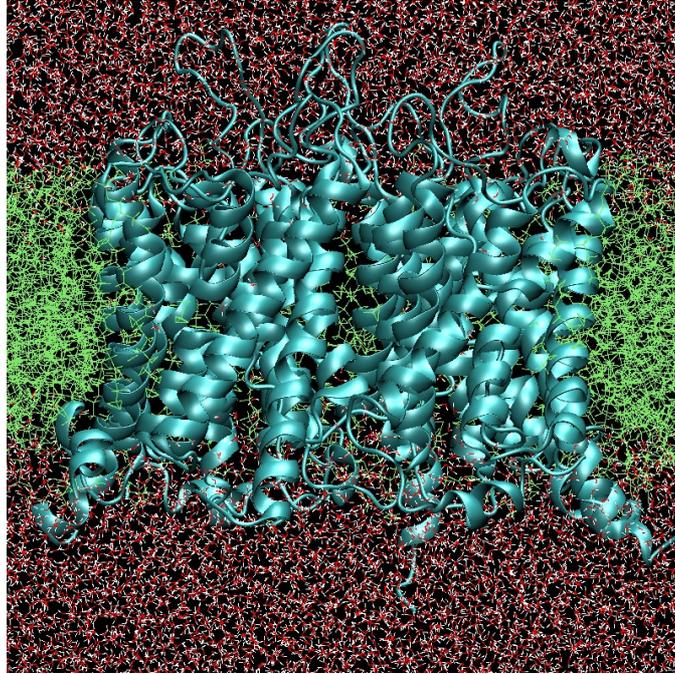


Figure 1: A snapshot of AQP1 embedded in POPE bilayer membrane.

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Computer Simulation Studies of Conformational Properties of Hydrocarbon Chains of Natural Lipids: from the Unperturbed State to Liquid-Crystalline Membranes

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Computer simulations of hydrocarbon chain molecules with *cis* double bonds have been carried out using Monte Carlo method. Such chains are of significant functional importance in natural membranes. Variations of all torsion angles of the chains were considered to be continuous from 0 to 360 deg. To calculate average characteristics, an importance sampling procedure was used for the efficient generation of chain conformations in the unperturbed state. The molecule-fixed coordinate system with the axes along principal axes of inertia of each molecule conformation was used. The method is applied to an investigation of the intramolecular C-C and C-H bond ordering characteristics, the bond orientation distribution functions with respect to the principal axis of inertia, and their temperature dependencies in 278 - 403 K region. A lower temperature sensitivity of not only the common geometric characteristics of polyunsaturated chains with methylene-interrupted *cis* double bonds in comparison with the saturated ones, but also that of local characteristics (i.e., of the shape of each bond orientation distribution function of the polyunsaturated chains) has been elucidated.

The characteristics of the unperturbed chains are compared with those obtained for the chains in hydrated homogeneous lipid bilayers (in the liquid-crystalline phase) constructed of saturated and unsaturated phosphatidylcholines, and with the available experimental data. In the homogeneous bilayers the order parameter characteristics of lipid hydrocarbon chains in the liquid region of the bilayer (somewhat remote from the membrane-water interface) are found to be qualitatively similar to those of single unperturbed hydrocarbon chains: the behavior of the acyl chains in this region is dominated by the intramolecular short-range interactions. Thus, the long-range interactions of the lipid segments in the liquid region of the bilayer and the interactions with atoms of the bilayer-water interface may be considered as a disturbance: the intermolecular interactions are largely used to orient the lipid molecules in the direction of the membrane normal. A close relationship between the physical characteristics and the structure of the chains is elucidated.

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Molecular dynamics study of biological membranes and lyotropic liquid crystals

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Taking into account that lyotropic liquid crystals and biomembranes study and research is widely spread and has very actual usage in nowadays science, particularly biomembranes investigations are important in fields of medicine, human healthcare, pharmaceuticals and lyotropic liquid crystals have wide range of applications in different areas of industry, such as pharmaceuticals, oil industry, food processing, cosmetics, paints, paper coatings, etc., we have started the molecular dynamics study of heterogeneous phospholipids bilayers like the membranes of human blood erythrocyte and lyotropic liquid crystals [1-4].

Lately, with the development of information technologies it has been possible to perform computer investigations of lyotropic liquid crystals and phospholipid membranes. For computational researches one of the most popular models for amphiphilic surfactants is the surfactant lamella (or bilayer) coated on water. As a model of lyotropic liquid crystal we have created high concentric aqueous solution of sodium pentadecylsulfonate (SPD) consisting of 512 SPD molecules and ~9000 water molecules and as a computational model of biomembrane we have created the human erythrocyte membrane consists of 5 types of phospholipids including also the cholesterol and as the membrane protein-Glicophorine A.

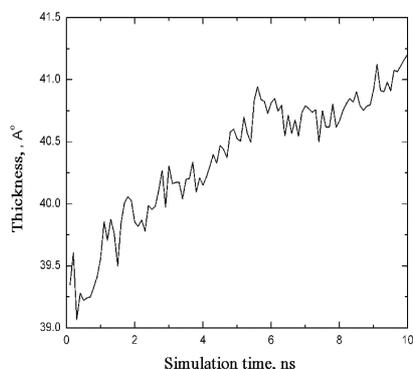


Fig. 1 Micelle thickness depending on simulation time

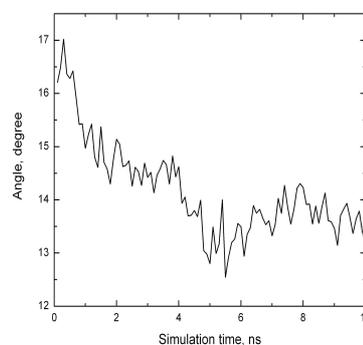


Fig. 2 Angle between alkyl tail and bilayer normal (Z-axis) depending on simulation time

The computational model of biomembrane bilayer (not counting Glicophorine A) contains 128 molecules of phospholipid such as 1-palmitoyl-2-oleoyl-3-phosphatidylethanolamine (POPE), 1-palmitoyl-2-oleoyl-3-phosphatidylcholine (POPC), 1-stearoyl-2-arachidyl-3-phosphatidylethanolamine (SAPE), 1-stearoyl-2-oleoyl-3-phosphatidylcholine (SOPC), and also cholesterol and ~4200 molecules of water. For erythrocyte membrane is mainly discussed the main properties of phospholipid bilayer and also the influence of cholesterol on the dynamoc structure of membrane.

We have done 10 ns of the parallel molecular dynamics simulation for SPD/water system and about 135 ns for erythrocyte membrane. For research is used NAMD code with CHARMM 27 all-atom force field, with 1fs time step. For biomembrane first of all it was performed about 130 ns MD simulation of bilayer without cholesterol after the simulation (5 ns) was continued in presence of cholesterol. Three-dimensional periodic boundary conditions were used and the temperature and pressure were fixed: T=300K and P=1 atm.

The simulation of SPD/water system was performed on "ArmCluster", using 30 processors the total CPU time was about 11,000 CPU/h and for the biomembrane 20 processors the total CPU time was about 65000 CPU/h.

Some structural parameters, like area per molecule on the surface of plane micelle (lamella), phospholipid bilayer, thickness of micelle and phospholipid bilayer, orientation of hydrocarbon chains of surfactant molecules in micelle and phospholipid and cholesterol molecules in hydrophobic core of bilayer, as well as the membrane and micelle surface roughness function have been calculated and compared with experimental data for both biomembrane and lyotropic liquid crystal.

After 10ns of run of SPD/ water system, as it is shown in fig.1 we see growth of micelle thickness and on the other hand as seen from fig.2 the angle between alkyl tail of SPD molecule to the normal of the bilayer surface, decreases. Taking account this two facts as well as visual picture we see similar to upright directed bent of hydrocarbon chains orientation, which assumed existence of new type (for the lyotropic liquid crystal) of phase (or intermediate phase) – anticlinic phase. Now we have done annealing of system, increasing the temperature up to T=410K and then decreasing it to the initial point to find out whether we reach in equilibrium.

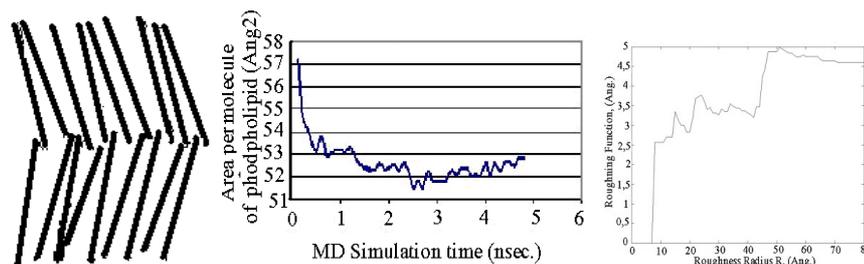


Fig.3 Anticlinic phase of lyotropic liquid crystal Fig.4 Area per molecule of phospholipid depending on simulation time Fig.5 Roughness function

As it is shown in fig.4 the value of area per molecule for phospholipid in biomembrane is quickly decreases from the moment of cholesterol integration into the bilayer, but in short period the fluctuation became very little, which shows the main property of cholesterol close packing of phospholipids molecules. Therefore was estimated the roughness function (see fig.5) which is computed as: $\xi(R) = \sqrt{\langle (z(r) - z(r+R))^2 \rangle}$, where the $z(r)$ and $z(r+R)$ are the z -axis coordinates of two oxygen and phosphor atoms in the same leaflet.

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DNA & NANOBIOELECTRONICS

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The paper gives a lecture of theoretical and practical approaches to the development of an element base of nanobioelectronics, i.e. DNA – based molecular wires and DNA - based electron logic elements and nanosensors. A general method for calculation of electron mobility in regular nucleotide sequences is presented.

The possibility of the development of an electronic biochip based on the idea of measuring the oligonucleotide conductance is considered. The operation principle of such a nanobiochip is based on the fact that the conductance of a single-stranded oligonucleotide changes if it hybridizes to the complementary chain.

The possibility of the development of the logic elements on the basis of a double-stranded oligonucleotide with control electrodes is considered. It is shown that suitable properties are offered by DNA duplexes where the interference pattern of electron waves determining the duplex conductance will lead to a logical table corresponding to basic logical element.

Using Special-Purpose and Video-Game Computers for Accelerating Molecular Dynamics Simulations

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Molecular Dynamics (MD) simulation is a powerful technique to investigate physical properties in an atomic level. However, one of the most severe problems of the MD simulation is the calculation cost for it. Parallel computers are often used for satisfying its request. Recently, using special-purpose or video-game computers is becoming promising approach to accelerate MD simulations because they are fast and often cost effective. They include an MDGRAPE-3 [1, 2] special-purpose computer by RIKEN, a PLAYSTATION 3 (PS3) [3] by SONY, and a GeForce Graphics Processing Unit (GPU) [4] by NVIDIA. A PS3 and a GPU have 179 and 518 Gflops peak performance for single precision operations, respectively. These speeds exceed the peak performance of the fastest CPUs for PCs. Moreover, the costs for them are only several hundreds of dollars.

We evaluated effective performance of these computers with N -body simulation, which gravity is the only interaction between particles. The MDGRAPE-3, PS3, and GPU are faster than a PC with a quad core CPU even with a highly tuned routine (see Table I). Moreover, their power consumption or size required for performing the simulation is much smaller than that of a PC. One of the important features of the PS3 and GPU is that they are very cost effective compared with a PC or an MDGRAPE-3. This fact showed us the possibility that video-game computers overtake a PC in the near future for MD simulations.

Similarly, we evaluated the effective performance of these computers with MD simulations. MD simulations usually require a little more accuracy than that of a single precision arithmetic operation. Therefore, the MDGRAPE-3 is the fastest because a PS3 or a GPU must perform additional operations to increase the accuracy by using single precision arithmetic units for many times. However, the cost performance of a PS3 and a GPU is still better than a PC or an MDGRAPE-3.

Table I. Comparison of effective speed, cost per speed, power consumption per speed, and size per speed for a PC with a Core 2 Quad Q6600 CPU, a PLAYSTATION 3, a PC with a GeForce 8800 GTX GPU, and a PC with an MDGRAPE-3 PCI-X card. Effective speeds were measured by the gravitational simulation with 65,536 particles.

System	Effective Speed (Peak Speed) (Gflops)	Cost/Speed (\$/Gflops)	Power/Speed (Watt/Gflops)	Size/Speed (liter/Gflops)
Core 2 Quad Q6600	72 [†] (77)	15.7	2.8	0.36
PLAYSTATION 3	157 (179)	2.8	1.3	0.06
GeForce8800GTX	443 (518)	4.0	0.9	0.06
MDGRAPE-3 CI-X	355 (380)	32.8	0.7	0.07

[†] Phantom-GRPAE code by K. Nitadori is used (<http://grape.mtk.nao.ac.jp/~nitadori/phantom/>)



Core2 Quad
(Intel)



PLAYSTATION 3
(SONY)



GeForce8800GTX
(NVIDIA)



MDGRAPE-3 PCI-X
(RIKEN)

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Phase transitions of Lennard-Jones fluid confined in slit pores

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Recently, a molecular confined system in nano-pore has been researched experimentally and theoretically, and the interesting phase which is not shown in bulk phase, was found [1]. The confined system is important for lubrication, adhesions, nanotribology and fabrication of nanomaterials. And also it is interested in understanding new physics that occurs due to finite-size effects and reduced dimensionality for science. Koga et al. exhibited using molecular dynamics simulation that water can freeze into various polymorphic phases of nanoice in carbon nanotubes [2]. Klein et al. confirmed experimentally that when the shear was applied to the parallel mica sheets confined polymer between them, there was an anomaly of the force perpendicular to the sheets [3]. It is very interesting that the effect of the confinement appears not only in complex systems like water and polymer but also in simple systems. Lennard-Jones (LJ) particles confined between parallel slit is one of the most important system for simulation. Self-diffusion coefficient of the confined LJ particle with the molecular dynamics method is reported [4]. Calculating crystal order of the confined LJ particle by the order parameter with Grand canonical MC simulation was also reported [5]. Though, an enough study was not done for the wide range of temperature, pressure and slit width. In this study we performed molecular dynamics simulation for wide-ranging conditions using confined LJ particle between parallel slit.

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Limit partial molar volume of mono-carboxylic acids in benzene by molecular dynamics simulation

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Limit thermodynamic molar characteristics of solutions contain information about hypothetical state of the solute molecules at infinite dissolution. Thus, the limit partial volume reflects compressibility of the structure packing of the solute molecule under the action of the solvent. In the given report this volume is determined by means of molecular dynamics simulation of the limit solutions. For this purpose the integral analysis of the found radial distribution functions is used. The method is applied for solutions of mono-carboxylic acids (non-saturated oleic and saturated stearic and myristic acids) in benzene, which are widely used in practice for stabilization of magnetic fluids (fine liquid dispersions of magnetic nanoparticles coated with surfactants). The found volume values are in agreement with experimental data (vibration densitometry, small-angle neutron scattering). The structure organization of the solvent at the molecule interface is compared for the acids with respect to their different stabilizing properties of magnetic fluids.

COMPUTATIONAL STUDY OF THE PRIMARY PHOTOPRODUCTS OF RHODOPSIN

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Rhodopsin (RHO) is light-sensitive visual pigment found in the rod cells. It consists of membrane protein opsin and chromophore 11-cis retinal (aldehyde of vitamin A). The chromophore is relatively firmly linked with opsin not only because of the formation of a protonated Schiff base of the retinal (PSBR) and Lys296 residue, but also because of the hydrophobic interactions of the β -ionone ring with hydrophobic residues of binding pocket of the protein. In addition, the PSBR is stabilized by glutamate residue counterion. All these interactions strongly affect the geometry of the chromophore and the reaction path of the retinal isomerization. Among the bleaching process the “primary process” can be defined as a formation of bathorhodopsin (BATHO). The latter is formed in picosecond time scale and can be stabilized at low temperatures. Recently the X-RAY structure of this photointermediate (PDB ID: 2G87) was reported in addition to electronic and vibrational spectra studied earlier.

We report the results of molecular modeling of the primary photoproducts in Rhodopsin performed at a high level of quantum-based theory. The calculations of equilibrium geometry configuration, vibrational and optical spectra for BATHO were carried out by using the mechanical embedding quantum mechanical - molecular mechanical (QM/MM) method as well as by using the effective fragment potential QM/MM method. The results of geometry optimization initiated by the model structure for the dark state of RHO are compared to the recently resolved X-ray crystal structure of BATHO. The estimates of excitation energies in quantum subsystems were performed by using an efficient version of the second-order multiconfigurational quasidegenerate perturbation theory employing construction of effective Hamiltonians of large dimensions, the so-called augmented version of MCQDPT2 (aug-MCQDPT2). This technique was employed earlier to calculate the S_0 - S_1 gap in Rhodopsin and PSBR in solution and gas phase to estimate so-called opsin shift (K.Bravaya, A.Bochenkova, A.Granovsky, A.Nemukhin, *J. Am. Chem. Soc.*, **2007**, 129, 13035). Detailed analysis of vibrational bands as computed in our work as well as observed experimentally was performed.

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First-Principles Molecular-Dynamics Investigation of Polymorphism in Liquids and Amorphous Materials

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The recent development of computational techniques has enabled us to perform molecular dynamics simulations with quantum mechanical description of interatomic forces, viz. first-principles molecular dynamics (FPMD) simulation. A variety of systems has been simulated by FPMD simulations, such as liquids, surfaces, clusters, and nanoscale materials. FPMD is of particular use to investigate structural phase transformations because electronic states significantly change in phase transitions, which are typically induced by temperature and/or pressure changes. Such pressure or temperature induced transformations can be handled by introducing a thermostat and barostat in FPMD calculation, which is called isothermal-isobaric (*NPT*) FPMD [1].

In this talk, I will briefly review *NPT* FPMD and will present its applications to polymorphism in liquids and amorphous materials (polyamorphism [2]). I particularly focus on polyamorphic transformations of amorphous Si (*a*-Si). It is well known that amorphous water (ice) exhibits, *at least*, two distinct forms: low-density amorphous (LDA) and high-density amorphous (HDA) forms [2]. Since *a*-Si under normal pressure contains a similar atomic configuration of water (*i.e.*, tetrahedral network), LDA-HDA transformations are also expected in *a*-Si.

A LDA form of Si (normal *a*-Si) was prepared by quenching a liquid Si at 0 GPa, and compression was performed on the LDA form. Around 12 GPa, a drastic structural change occurred and a HDA form of Si was obtained [3]. The resulting HDA Si has a distorted tetrahedral structure with an interstitial atom, which is an analogous structure of HDA water. Reverse transformation was also observed by decompression and heating as in the HDA-LDA transition of water. These findings indicate that Si and water share several common characteristics that should come from the directional bonding with an open tetrahedral structure.

The importance of open structure in polyamorphism will be further demonstrated by *NPT* FPMD simulations on a liquid-liquid transition of phosphorus [4]. Details of the polyamorphism in phosphorus will be discussed if time is allowed.

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BIOMEMBRANES AS PHARMACOLOGICAL TARGETS: INSIGHTS FROM COMPUTER SIMULATIONS.

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Cell membranes, along with their individual components like membrane-bound proteins, particular lipids or lipid bilayer itself, attract a growing attention as very perspective pharmacological targets. According to recent estimations, up to 70% of currently marketed drugs act on these targets. Rational design of new highly specific and selective compounds (drug prototypes) modulating activity of biomembranes, requires detailed information on their spatial structure and dynamics under different conditions. Because of experimental difficulties with structural characterization of biological membranes, computer simulations became an important alternative source of biologically relevant information for such supramolecular systems.

Here we present the results of structural/dynamic studies of membrane proteins (MPs) with diverse fold (α -helical, β -structural), mode of membrane binding, and biological activities, assessed *via* simulations with implicit and/or explicit theoretical models of membranes. Among the objects under study were antimicrobial and fusogenic peptides, cardiotoxins, GPCRs, artificial peptides targeting transmembrane helices of MPs, *etc.* [1-3]. A new computational approach was proposed to study behavior of MPs in different membrane-mimic media. The approach combines in a self-consistent manner Monte Carlo conformational search in implicit hydrophobic slabs, molecular dynamics in hydrated full-atom lipid bilayers and micelles, molecular hydrophobicity potential analysis, homology modeling, *etc.*

The predictive power of the computational protocols was proven *via* testing the modeling results against high-resolution experimental data. Based on the theoretical data, a number of MPps with “improved” biological activities were elaborated.

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PREDICTION OF SPATIAL STRUCTURE OF TRANSMEMBRANE HELICAL DIMERS USING COMPUTER SIMULATIONS.

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Motivation and Aim:

One of the most common elements of membrane proteins fold is alpha-helix intersecting the membrane (TMH). According to widespread theory of membrane protein folding TMH inserts into the membrane on the first stage of folding and the resultant protein fold obtained through the interactions of TMHs (practically as the rigid bodies) in the membrane. Thus providing information about such TMHs interactions and prediction the structures of their complexes cut a way to prediction of membrane protein structure, understanding of their work and direct design of membrane proteins with predefined structure/activity. Difficulties in research of membrane proteins by experimental techniques stimulate the development of computational approaches of membrane protein investigation.

The simplest system for optimization of computational algorithms and strategies of investigations is the dimer of TMH. In spite of its simplicity such system includes all outstanding characteristics encountered in more complex membrane proteins. Moreover, such systems have some biological activities – for instance receptor tyrosine kinases activate in answer to dimerization which in turn depends on interaction of their single TMH.

Methods and Algorithms: Prediction of a dimeric structure is based on a combination of computational techniques with different degree of approximation. The simplest approach is analysis of hydrophobic properties of TMS surface. Usually, this method produces several crude models of dimeric structure. More equilibrated models can be derived using Monte Carlo conformational search in implicit membrane. In addition to the structure of dimer, this approach also permits identification of the geometry of the dimer in membrane. And, finally, these models may be refined via molecular dynamics in explicit hydrated bilayer. The last two approaches can be easily adapted to parallel calculations, thus decreasing time cost of the computation. Combined application of these different approaches to analysis of TMS dimers provides relatively good models of dimeric structures.

Results: The aforementioned methods were applied for investigation of the spatial structure of some test dimers of TMS with experimentally determined structure (glycophorin A, bnip3). Comparison of the simulation results with experimental data permits delineation of advantages and disadvantages of different approaches. It should be noted that in each case the computational models were in a good agreement with the experimental ones. Then, simulations of dimers of TMS of biologically important RTK with unknown structure were carried out.

Conclusion: Good agreement of simulation results with the experimental information validates the proposed approach to prediction of spatial structure TMS dimers. This approach can be easily applied for structure prediction of any dimer (without difficulties connected with its experimental investigation). Finally, at least partially, these approaches may be elaborated for solution of more difficult problems, for instance, to development of the aforementioned medicines or prediction of more complex oligomers (bundle of helices, etc.)

Molecular simulation of visual pigment rhodopsin with E181K mutation associated with retinitis pigmentosa

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Autosomal dominant retinitis pigmentosa leads to the photoreceptor cell death and retina degeneration [1]. Approximately 25 % of this pathology are associated with rhodopsin gene mutation RP4(RHO)/Rhodopsin(3q) [2]. The amino acid substitution in the chromophore center during rhodopsin biosynthesis leads to the most distinctive clinical pathology of this inherited disease. The consequence of mutations like these is protein misfolding. As a result, formation of stable Schiff base linkage between 11-*cis*-retinal chromophore and amino acid residue Lys296 is impossible. Therefore, making of native visual pigments is injured, and pathological process of retina degeneration is initiated.

Using molecular simulation technique the process of 11-*cis*-retinal chromophore embedding into the chromophore center of opsin mutant form has been investigated. The comparative analysis of amino acid residues arrangement in the opsin chromophore center and its interaction with 11-*cis*-retinal as in the wild (native) as in the mutant opsins has been carried out. It was shown that there is no normal embedding of 11-*cis*-retinal as a chromophore into the chromophore center of opsin mutant form. As a result the impairment of conformation state of the opsin molecule takes place both in the chromophore center and in the cytoplasmic domain. As a result, the stable covalent linkage of 11-*cis*-retinal with protein part of rhodopsin molecule is not formed, and also the active site in the cytoplasmic domain of the protein that is responsible for binding of G-protein (so called, transducin) is not completely blocked.

Based on the molecular simulation data, the problem related to retinitis pigmentosa pathogenesis is discussed.

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JINR CICC in Computational Chemistry and Nanotechnology Problems: DL_P O L Y Performance for Different Communication Architectures

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This report compares the performance of the DL_POLY general-purpose molecular dynamics simulation package on the LIT JINR computing cluster CICC for various communication systems. The comparison of DL_POLY code involved two cluster architectures using Gigabit Ethernet and InfiniBand technologies respectively. The code performance tests include some comparison of the CICC cluster with the special-purpose computer MDGRAPE-3 developed at RIKEN for a high-speed acceleration of the MD (molecular dynamics) without fixed cutoff. The DL_POLY benchmark covers a set of typical MD system calculations detailed below.

The characteristics of the LIT CICC computing cluster are as follows:

	Cluster I	Cluster II
Processor	Intel 2xXeon 5150	Intel Xeon 5300
Clock rate	2660 MHz	3000 MHz
2L cache memory per CPU	4 MB	8 MB
Cores per CPU	2	4
CPUs per node	2	2
RAM per node	8 GB	8 GB
Operation system	Scientific Linux 4.5	Scientific Linux 4.5
Network Interface	Gigabit Ethernet	Gigabit Ethernet, Infiniti Band
Totals:		
Number of nodes	60	10
Number of CPUs	120	20
Number of cores	240	80
Amount of RAM	480 GB	80 GB
Peak performance	2553.6 GFlops	960 Gflops

THE DL_POLY BENCHMARK:

The benchmark summarized below is designed to reflect the typical range of simulations undertaken by the molecular dynamics. It includes 3 calculations carried out using the DL_POLY_2.17 molecular dynamics code, and includes the following functionality: [Benchmark 3: Simulation of valinomycin in 1223 water molecules (3837 atoms, 100 time steps); Benchmark 5: Dynamic Shell model MgCl₂ structure (768 atoms, 1280 sites, 1000 time steps); Benchmark 9: Simulation of a model membrane with 2 membrane chains, 202 solute molecules and 2746 solvent molecules (3148 atoms, 1000 time steps)]. Also it includes 3 calculations carried out using the DL_POLY_3.07 molecular dynamics code, and includes the following functionality: [Benchmark 1: Simulation of sodium chloride with Ewald sum (27000 ions); Benchmark 2: Simulation of sodium chloride with Ewald sum (216000 ions); Benchmark 4: DMPC in water (413896 atoms)].

In Fig. 1 we present the results of calculations with DL_POLY_3.07 molecular dynamics code on cluster I and II on comparison.

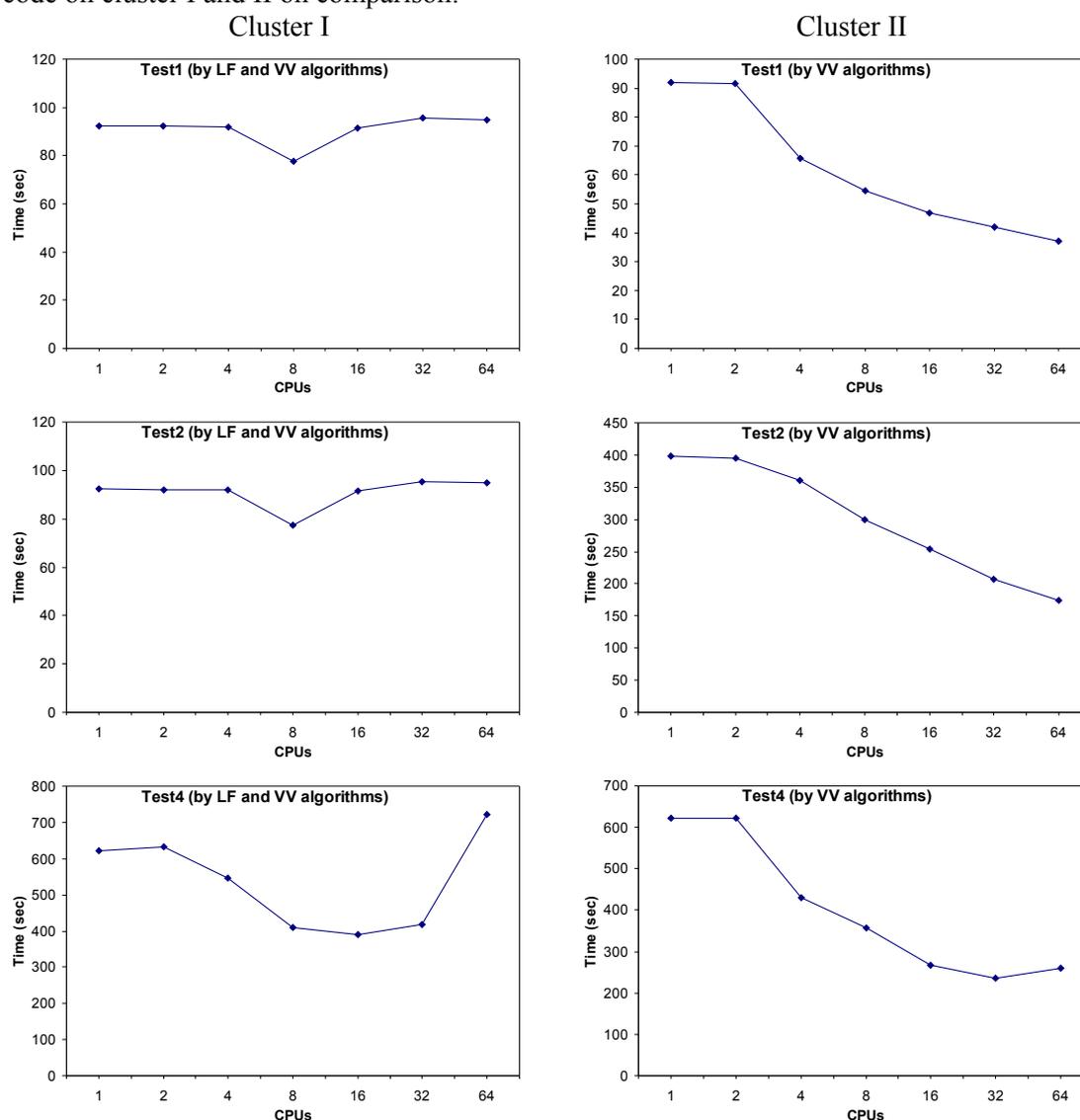


Fig. 1. Comparison results of calculations on cluster I and cluster II

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Self-organization and rational design of nanobiosystems

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Molecular modeling considers a specific and detailed treatment of all atom interactions and realizes this interaction through dynamic trajectories. This provides unique opportunities for unveiling the principles of self-organization of various molecular and supra-molecular structures at atomic level, the influence of variations in molecular structure on mechanical properties of nano-objects, the study of kinetics of mass transfer in complex micro-heterogeneous nanostructures, prognosis of functional activities of nano-devices.

Self-organization is in principle an inherent property of linear polymers with conformational mobility. Folding simulations of such structures revealed two main factors that determine this process. The first one is the geometrical factor, representing the monomer Van-der-Waals radius to chemical bond length ratio. Dependent on the magnitude of this parameter different “secondary” structures can be observed – helices, double helices etc. Introduction of side groups in the structure of a linear chain provides the capability of planar structure formation. The second factor is the energy one, which depends on the magnitude of non-valence interactions. This factor chooses the most stable conformation from a number of possible geometrical configurations. It should be stressed that the set of secondary structures that is found in such elementary systems is geometrically similar to the secondary structures of biopolymers. This is an evidence of the presence of some universe principles of self-organization and the possibility for using quasi-biological principles in nanotechnology (in the technology of atomistic precision).

Several examples of non-biological structures self-organization are considered: a device for the refolding of a polymer chain and poly-alanine adsorbed at a carbon nanotube. The force field of the nanotube prevents poly-alanine to form an alpha-helix, which it naturally tends to. On the other hand inside the nanotube the polymer has more atomic contacts which is energetically favorable. The interplay of these factors are realized in the self-assembly of a nano-syringe – entrance of poly-alanine in an alpha-helical conformation inside the nanotube. Possible applications of using nanotubes as targeted drug delivery containers are discussed.

Self-assembly of a super-helical molecular construction is discussed – the nano wires of spider web. Poly-alanine fragments of spider web under mechanical stretching are transformed into beta-threads. All-atom modeling of a stack of beta-threads reveals that a cascade of rather quick conformational transformations of the stack into super-helix takes place. A near ideal nano wire with outstanding specific rupture energy is obtained.

The functioning of systems of atomic precision is only possible if the detailed energy balance at all stages is maintained. The change in the details of nano-object's structure leading to the change in its energy plays a regulating role. By the example of a gramicidin ion channel the balance can be traced in details and clearly. The influence of ion channel interior on its selectivity and efficiency of membrane receptors (glycine, acetylcholine, serotonin receptors) is discussed. Possible modifications of ion channels for systematic changes of their properties are considered. The mechanism of collective conformation changes by the example of open/closed transition in ion channels is considered.

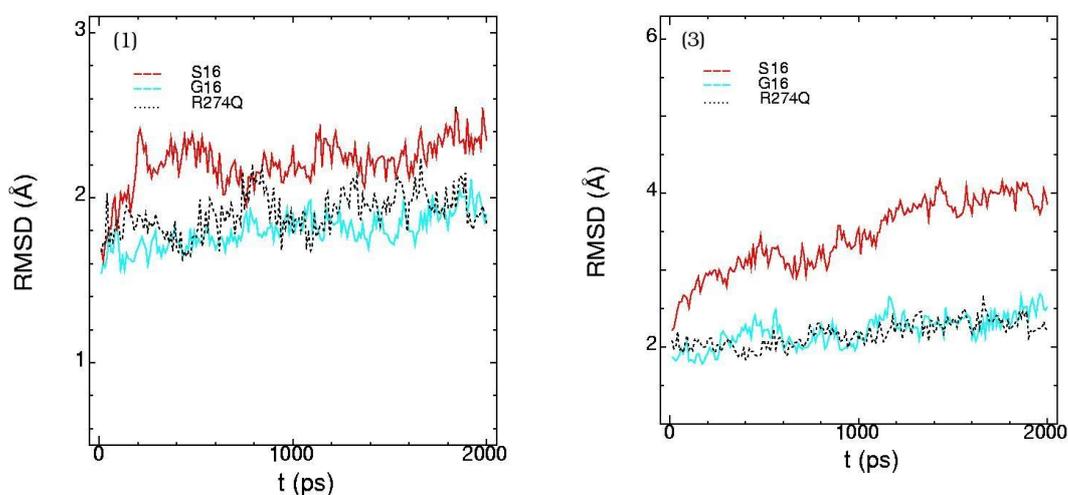
The issues of molecular transport in micro heterogeneous nanostructures are discussed by the example of biomembranes and the role of phospholipid heads as a selective permeability “filter” for different chemical compounds. Anisotropic kinetic characteristics of membranes are determined, which are quite hardly obtainable using experimental methods.

Comparison of 3D simulated of different allele forms of human kinase CDK2

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The crystal structures of the human CDK2/cyclin A complex has been solved [1]. We simulate the structure of wild type and mutant allele with a single substitution of glycine with serine in position 16 (G16S) in conservative G-rich loop [2]. It was shown that this substitution causes a serious modification in protein structure. In yeast such changes of homologous kinase CDC28 has serious pleiotropic biological effects [3, 4]. To investigate the significance of observed structural modifications we study structure of another mutant allele R274Q which in yeast has not biological effects at permissive temperature [3]. Comparison of simulated CDK2 structures of three allele show that root mean square deviation of kinase (Fig.1-1) and kinase+ cycline (Fig.1-3) don't change in last allele of kinase. Although the structures of T- (Fig.1-5) and G- (Fig.1-6) loops were modified. These results confirm the correlation between observed changes of kinase structure and biological effect.



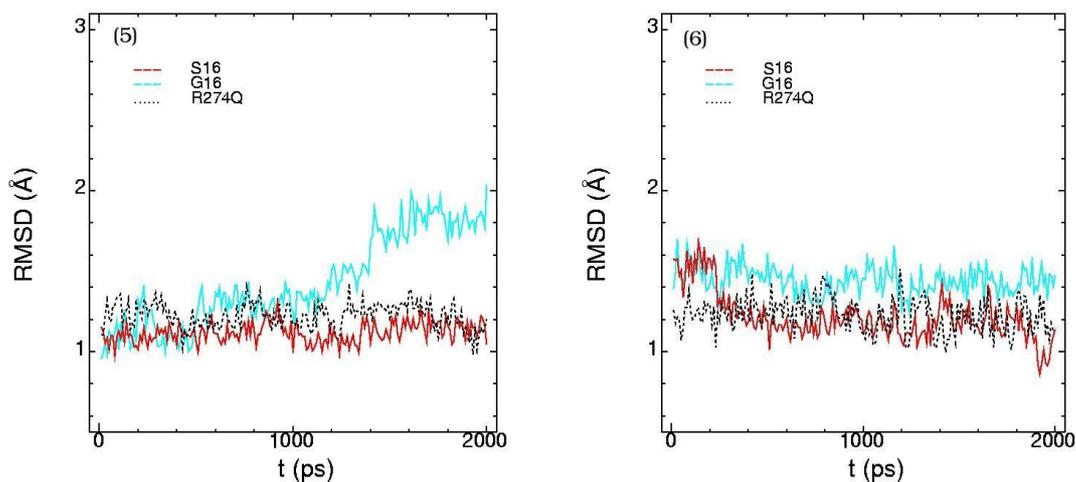


Fig. 1. Time dependence of configurations for different forms of kinase CDK2 – wild type (G16 R274) and mutant (G16S and R274Q).

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Minima Hopping, an efficient way to optimize geometry on the Potential Energy Surface and on the Free Energy Surface

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It is well-known that materials' mechanical properties are strongly dependent on the way their geometries have been optimized on the Potential Energy Surface. The study of shear band localization in Bulk Metallic Glasses (BMGs) is one example of this phenomenon. The shear band width depends clearly on the cooling rate which has been defined in order to decrease the control temperature during the simulated annealing procedure. Therefore, before studying mechanical properties, one has to find a well-cooled geometrical configuration. The global optimization (GO) is achieved by minimizing the potential energy in configuration space. I'll first present the concept and the flowchart of an adapted version of the so-called Minima Hopping (MH) method, which is an efficient way to avoid inconvenient features of Simulated Annealing methods. The second part will be devoted to numerical comparisons on metallic glasses of Minima Hopping and Simulated Annealing methods, performed within the EMT framework. I will show that Minima Hopping is an efficient way to optimize complex systems such as BMGs. In the third part, I'll introduce a version of Minima Hopping which involves calculations of forces with DFT methods the so-called Dual Minima Hopping (DMH) method.

On interaction of Au microparticles with pulse microwave radiation aimed to targeted application to tumor cells

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The new promising direction of targeted cancer therapy is the injection of metal micro or nano particles into the tumor tissue with consequent local microwave or laser heating see e.g [1]. In present contribution we study the physical mechanisms of Au microparticles (up to 1μm in size) with microwave 30GHz coherent radiation from the free electron maser operating at Joint Institute for Nuclear Research in Dubna. The maser is pumped by the electron induction accelerator with the beam energy 0.8 MeV, the beam current 250A and the pulse duration of 250ns. The setup gives the coherent microwave radiation at 30GHz with the peak power of 10-20MW. The biological objects (the human melanoma cells linked to Au microparticles by methylene blue molecules) are placed into the microwave beam focused up to 1.5-3 cm in diameter. The concentration of microparticles was about $2.44 \cdot 10^{11} \text{ cm}^{-3}$. The minimal size of the registered Au microparticles injected into melanoma cell was 0.2-0.3 μm, the average size 0.8-1.0μm. We have shown that in this range of sizes and frequencies the Mie theory [2] provides an adequate description for this experimental setting, with quantum effects of plasmon resonance being insignificant in this radiofrequency range for the radiation frequency being much lower than the electron plasma frequency for the metal.

$$\sigma_{ext}(\omega) = 9 \frac{\omega}{c} \varepsilon_m^{3/2} V_0 \frac{\varepsilon_2(\omega)}{[\varepsilon_1(\omega) + 2\varepsilon_m]^2 + \varepsilon_2(\omega)^2}$$

The above extinction cross-section of microwave radiation has been estimated for a spherical Au microparticles in dipole approximation using the methods of the metal cluster optics [3], with the metal heating described by classical electrodynamics and the Drude-Lorentz-Sommerfeld theory [4]. V_0 is the volume of microparticle and ε is the permittivity of surrounding media, which is set to the range of 1-20 in protein and aqueous media.

In real biological settings the Au microparticles are concentrated near the tumor cells; and therefore the electrodynamics of randomly distributed spherical particles describes the multiple wave scattering. The localized microwave heating of Au microparticles initiates the rapid bubble formation centered at Au clusters. Different mechanisms of microwave radiation effects on biological tissue with the admixture of Au particles are considered.

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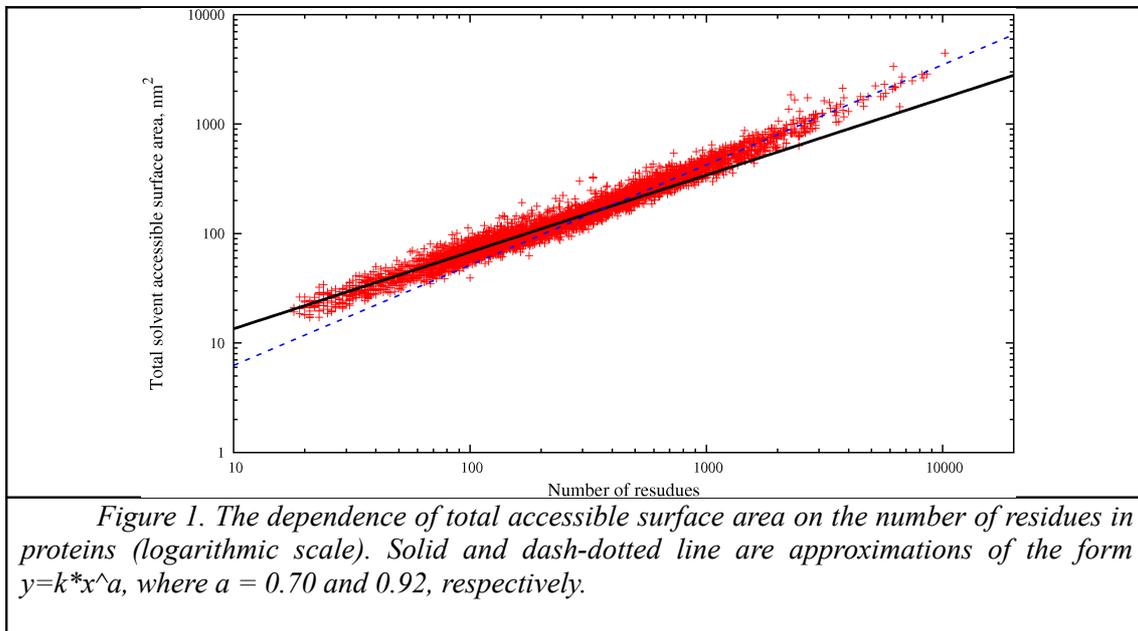
Solvent Accessibility of Amino Acids Residues in Globular Proteins and its Correlation with Hydrophobicity/Interfacial Activity of Amino Acids

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Water environment plays a key role in folding and stability of almost all protein structures. Hydrophobic interaction of apolar amino acids leading to formation of a molten globule is considered to be the main driving force of protein folding. Understanding the energetics of protein structure formation with respect to the distribution of different types of amino acid in the core or at the surface of the protein is beneficial for analyzing amino acid substitutions, stability of mutants, assessing ligand binding efficiency, designing de novo proteins etc.

In this study we analyze the solvent accessible surface of almost 6000 3-D protein structures resolved by X-RAY or NMR and obtained via the Protein Data Bank and compute the distribution of different types of amino acids with respect to their individual solvent accessibility. The surface is computed using the algorithm of Lee and Richards (1971) whereby a probe of given radius (1.4 Å) is rolled around the surface of the molecule, and the path traced out by its centre is the accessible surface. Surprisingly, as seen from Fig 1, the dependence of surface on the number of residues in protein chain doesn't follow the case of a simple 3-D sphere where the volume (V) to surface (S) ratio scales as $V/S \sim V^{2/3}$.



The protein surface has a “fractal like” behavior, and the volume to surface critical index is between 0.7 for smaller proteins to 0.92 for bigger ones. This corresponds to the situation where for bigger proteins the surface is almost proportional to the number of residues in protein.

As showed by Finkelstein et al. (1995) the occurrence of structural elements in proteins follows the quasi-Boltzmann statistics:

$$P \sim \exp(-F / kT_c), \quad (1)$$

where F - is the free energy of the element and T_c is some conformational temperature. This is in principle true for the distribution of amino acids between the inside of the protein and its exterior. Formula (1) suggests that there may be some set of apparent transfer free for residues from inside the protein globule to its exterior. In fact some correlations have been reported between the experimental transfer free energies of similar compounds from water to some less polar media and these apparent transfer free energies. The problem in question is what kind of solvent in these transfer experiments mostly resembles the interior of the protein.

In this study we use relative accessibilities of amino acid side chains in proteins to obtain apparent transfer free energies based on different criteria of residues classification as “exposed” or “buried”. These apparent energies are then compared with different experimental scales.

This thorough comparison enables us to make conclusions about different free energy terms contributing to formation of protein structure and description of mean interaction of amino acids in proteins with their local environment.

Computer simulation of zervamicin IIB action

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In present time investigation of antimicrobial peptides, which have activity against gram-positive bacteria's, some endo- and exoparasites and cancer cells, is very relevant. Research of these peptides represents a priority questions in biopharmacology. One of these peptides is zervamicin IIB, a member of the antibiotic peptaibol-family, is produced by fungi *Emericellopsis salmosynnemata*. It consists of 16 amino acids and contains a high proportion of helix-promoting α , α -dialkylated amino acids (Aib, α -aminoisobutyric acid; Iva, D-isovaline), an acetylated *N*-terminus and a *C*-terminal α -amino alcohol. The mechanism of action is still unclear, but it's suggested that the peptide interacts with the membrane of the target cell, several molecules form channel according to the barrel-stave model and increase ion permeability of the membrane.

Zervamicin dynamic was investigated in water and methanol surrounding to find out conformational changes in different solvents. Helical structure of zervamicin IIB was stable during 10 ns in both solvents and no conformational changes were observed, so it means that zervamicin IIB posses helical structure out of the membrane surface and it retains it's structure during embedding into the membrane. To determine amino acids residues important for molecular stability the number of zervamicin II mutants was investigated (Aib replaced by Gly in 7 and 9 positions). Computer research showed that replacement in 7 position didn't influence on the molecular stability, but zervamicin IIB with replacement in 9 position changed it's length in different solvents. So that the molecular length in water was 2,4 nm and in methanol – 1,6 nm. When Gly amino acid was added in 8 position, swivel motion of zervamicin II molecule appeared in methanol solvent, and molecule in water was as stable as native one.

Also interaction of zervamicin IIB with eucariote and procariote membranes was investigated. POPC lipid bilayer was chosen as model of eucariote membrane and POPG/POPE one -as model of procariote membrane. The orientation of zervamicin IIB relatively to the membrane surfaces was very different. It has better affinity with the procaryote membrane due to the negative charge of membrane surface.

With the aid of steered molecular dynamics (SMD) the zervamicin penetration into membrane was investigated. It was shown that zervamicin IIB inserted with its *N*-end. Insertion of peptide occurred in 3 steps, corresponding to broking hydrogen bonds between Gln , Hyp residues and lipid heads.

The 3 models of zervamicin channel consist of 4 (N4), 5 (N5) and 6 (N6) peptide molecules were suggested. The channel represents parallel bundle of helical peptides that line a cylindrical, electrolyte-filled pore. The dynamics of these 3 channels and water molecules in the channel pore were investigated. The ions penetration through the channel pore was simulated for the N5 channel. Gln residues were determined as the most important amino acids for the ion movement.

It is significant, that directed amino acid replacement, which can change molecular stability, is important not only for understanding action mechanism and role of each amino acid but also in pharmacology. So results of this work are directed to create new generation of antimicrobial peptides.

The work was supported by RF Federal Agency on Science and Innovation, Russian Foundation for Basic Research (project No. 07-04-01169), and The Foundation for Assistance to Small Innovative Enterprises (8080).

Unfolded bacteriorhodopsin become a phytohormone

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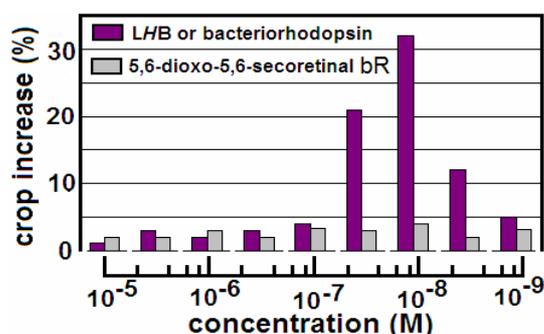
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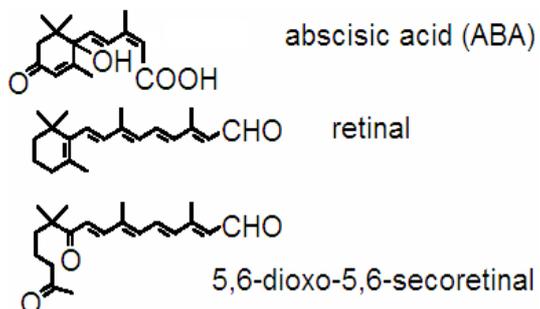
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Bacteriorhodopsin (bR) is a light-harvesting retinal-protein of an extremely halophilic archaeon *Halobacterium salinarum* naturally ordered in two-dimensional lattice referred as purple membrane (PM). This halobacteria is often used for a combination of genetic, bioinformatic, proteomic and transcriptomic researches. Some *H.salinarum* strains are interesting for biotechnological applied also. It was known that metabolites of *Halobacterium* act as a plants growth regulator [1, 2, 3]. Here we highlight a model for explanation of the plant-growth-promoting effect of lysate of *H.salinarum* biomass (LHB).



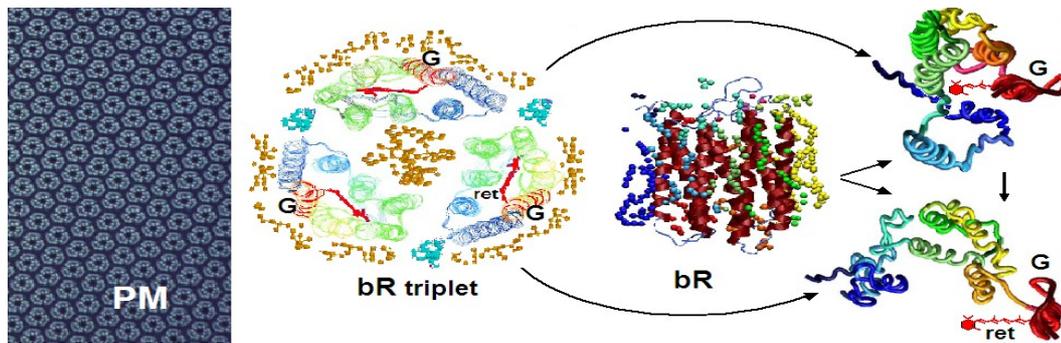
Biotests had been made for root growth and plants (*Brassica napus* var. *napus*, *Lactuca sativa* var. *Secalina*) respond on LHB solution and bR suspension in different concentration. It was surprising that the crop increase only within a narrow range of concentration as well LHB, as bR (Figure 1). There is no effect for plant growth and development when bR synthetic retinal moiety analog 5,6-dioxo-5,6-secoretinal bR (Figure 2) [4] had been used.

We suppose that the effect reported here can be explained by: – **i. high structural homology retinal** and phytohormone **abscisic acid (ABA)**, – **ii. “prolonged” stability of retinal pocket during unfolding bR** when lateral forces within the membrane eliminates in step-by-step dilution of suspensions in water.



chromophore the C₆-cycle and coupling alternation C=C and C–C bounds but less than in retinal moiety of bR (Figure 2).

Phytohormone ABA which in turn causes stomatal closure and induces the expression of drought stress-related genes [5]. Molecular analyses have demonstrated the existence of both ABA-dependent and ABA-independent regulatory systems in the transcriptional regulatory network under drought stress [6]. ABA is universally distributed within the plants kingdom and could be detected in the bacteria. The ABA molecule include as well as retinal



Bacteriorhodopsin was the first integral membrane protein to be unfolded and refolded *in vitro*, and has led the way in studies of 7TM transmembrane helical protein folding [7]. Most of the methods to probe helical membrane protein folding mechanisms were developed originally on bR, including kinetic, thermodynamic and mechanical approaches to monitor folding or unfolding. Despite their crucial importance for cellular life, little is known about the folding mechanisms of membrane proteins, not only chemically specific protein–protein and protein–lipid interactions.

High-resolution structural studies, in conjunction with detailed knowledge of the lipid composition, make the PM the best model for elucidating the forces that are responsible for the assembly and stability of integral membrane protein complexes.

Now we consider estimating the events succession of bR unfolding when molecules lose a lateral pressure because dilution in water. The fact that the crop increase and plants growth observed only in diluted PM reflects, the fact that only “naked” retinal is become available for ABA-receptors on plant objects (Figure 3). To choice the mechanism of corresponding bR unfolding it is necessary simulate the unfolding patterns of destroying regular structure of PM and trimeric bR.

It seems likely that bacteriorhodopsin represents the structure of the natural designed phytohormone (retinal) immobilized on a protein moiety of the molecule (bacterioopsin).

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MD simulations on mutant protein models (RecA, CDK, Rhodopsin proteins)

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The models and research topics studied through the MD (molecular-dynamics) approach have been performed within the joint collaboration projects as follow:

--MD analysis of the wild-type and mutant cyclin-dependent kinase (CDK) proteins [with N.Koltovaya, Group of Procarotes Genetics, LRB, JINR];

--MD simulations of the wild-type and mutant retinal proteins (rhodopsins) [with T.Feldman and Academician M.A.Ostrovsky, Inst. Bio.Chem.Phys, RAS & Photobiology sector LRB, JINR];

--MD simulations of RecA proteins and SOS Mutagenesis mechanism [with E.Krasavin, Group of Radiation Genetics and Radiobiology, LRB, JINR];

--MD simulations with special-purpose computers MDGRAPE-2 [with T.Narumi and K.Yasuoka; RIKEN & Keio University, JAPAN; 3 MDGRAPE-2 boards are granted to LRB JINR; pick performance 100 Tflops];

--MD simulations with special-purpose computers MDGRAPE-3 [with Y.Ohno, T.Narumi, G.Morimoto, M.Taiji; RIKEN-Yokohama Inst., JAPAN; 1 MDGRAPE-3 board is granted to LRB JINR; pick performance 1 Petaflops];

--MD simulations with RIKEN Super Combined Cluster [with T.Iitaka and T.Ebisuzaki; RIKEN, JAPAN; free computer time is provided by RSCC];

--High Performance Computing and MD simulations with LIT CICC computing cluster [with E.Dushanov, V.Korenkov, W.Smith (Daresbury Laboratory, UK)];

--MD simulations of mono-carboxylic acids in benzene solution [with M.Avdeev and I.Bodnarchuk; Laboratory of Neutron Physics, JINR].

Some recent study involves the MD to simulate the interaction of gold nanoparticles with the methylene blue and proteins. This study has to perform in the nearest perspective to investigate the physical and molecular mechanism of the interaction of nano- and micro-particles with biological objects. The new direction is aimed on targeted cancer therapy through the injection of metal micro or nano particles into the tumor tissue with consequent local microwave or laser heating operating at Joint Institute for Nuclear Research in Dubna. Molecular dynamics simulations have been performed to describe the interaction of methylene blue with gold nanoparticles. In Figs.1 and 2 the computer generated model of methylene blue chain and gold nanoparticles in surrounding water bath are presented.

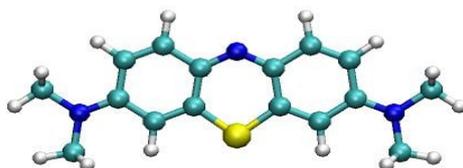


Fig.1. Snapshot of methylene blue structure

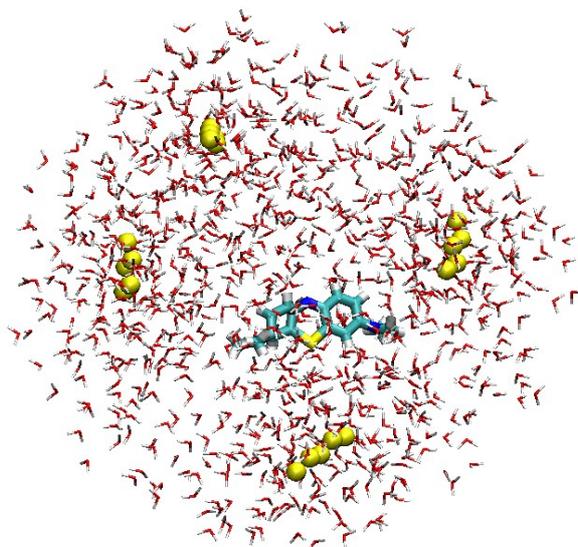


Fig.2. Computer model of methylene blue chain (center) interaction with gold nanoparticles (yellow balls) surrounded by water molecules (dynamic bonds)

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