MOLECULAR SIMULATION STUDIES IN MATERIAL AND BIOLOGICAL SCIENCES

4th Japan–Russia International Workshop MSSMBS'10

Book of Abstracts

Joint Institute for Nuclear Research

MOLECULAR SIMULATION STUDIES IN MATERIAL AND BIOLOGICAL SCIENCES

4th Japan–Russia International Workshop MSSMBS'10

Dubna, September 26–29, 2010

Book of Abstracts

Edited by *Kholmirzo T. Kholmurodov*

УДК 51-7, 538.91-97, 577, 51-72:530, 51-72:541.1
ББК 22.183, 22.36, 28.07, 28.707
М79

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М79 **Molecular** Simulation Studies in Material and Biological Sciences: Book of Abstracts of the 4th Japan–Russia International Workshop MSSMBS'10 (Dubna, September 26–29, 2010). — Dubna: JINR, 2010 — 62 p.
ISBN 978-5-9530-0256-1

The series of meetings «Molecular Simulation Studies in Material and Biological Sciences» (MSSMBS) started in 2004, 2006, 2008, and 2010. The meetings are focused on different aspects of molecular simulation of physical, chemical and biological systems. The current subjects of MSSMBS'10 are the following: novel MD simulation techniques & methods; hybrid computational approaches: DFT, QM/MM, MD, MD/CFD; new computing & communication architectures; general- & special-purpose MD machines; video game computers for accelerating MD; simulation of biomacromolecules; protein & DNA modeling; simulation of radiation-induced mutations; simulation of crystal & polymer systems; quantum biophysics and electronic structure of macromolecules.

Молекулярно-динамическое моделирование в науках о веществе и биологии: Сборник аннотаций 4-го Российско-японского международного рабочего совещания «MSSMBS'10» (Дубна, 26–29 сентября 2010 г.). — Дубна: ОИЯИ, 2010. — 62 с.
ISBN 978-5-9530-0256-1

Международное рабочее совещание MSSMBS'10 «Молекулярно-динамическое моделирование в науках о веществе и биологии» является четвертым по счету международным совещанием, посвященным проблемам молекулярного моделирования физических, химических и биологических структур. Первое, второе и третье совещания (2004, 2006, 2008) также проходили в Объединенном институте ядерных исследований. Совещание MSSMBS'10 посвящено следующим проблемам: новейшие методы и техники МД-моделирования; гибридные вычислительные подходы: DFT, QM/MM, MD, MD/CFD; современные вычислительные и коммуникационные архитектуры; МД-машины многоцелевого и специализированного назначения; видеоигровые компьютеры для ускорения МД; моделирование биомакромолекул; моделирование белков и ДНК; моделирование радиационно-индуцированных мутаций; моделирование кристаллов и полимерных систем; квантовая биофизика, электронная структура макромолекул.

УДК 51-7, 538.91-97, 577, 51-72:530, 51-72:541.1
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ISBN 978-5-9530-0256-1

Keynote speakers:

- Tomoyuki Yamamoto (Waseda University, Japan)
- Roman Efremov (Institute of Bioorganic Chemistry, RAS)
- Aram Shahinyan (Institute of Applied Problems, NAS, Armenia)
- Kenji Yasuoka (Keio University, Japan)
- Victor Lakhno (IMPB, Puschino, Russia)
- Leonid Chernozatonskii (Biochemical Physics Institute, RAS)
- Julia Novakovskaya (Moscow State University)
- Yuko Okamoto (Nagoya Univeristy, Japan)
- Alexander Nemukhin (Moscow State University)
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PREFACE

This is the Book of Abstracts of the 4th Japan – Russia International Workshop MSSMBS'2010, "Molecular Simulation Studies in Material and Biological Sciences", which to be held in JINR, Dubna, on September 26 – 29, 2010.

The series of the MSSMBS meetings started in 2004, continued in 2006, 2008, and is now to be held in 2010. The MSSMBS'2004 was the first international conference held in Russia that was focused on methodological problems and applications of the art of molecular dynamics simulations in physical, chemical and biological systems. The MSSMBS is mostly contributed by leading research groups of Japan and Russia and is also participated by European Institutes. The subjects of the MSSMBS workshops include different aspects of molecular simulation in material science and biological research; computational and theoretical studies of atomic and molecular interactions; dynamics between atoms, molecules, ions, clusters and surfaces; modern high-performance computing facilities; and simulation techniques and methods applied for studying molecular systems and structures.

The scope of the MSSMBS'10 meeting includes, in particular, the following topics:

- Novel MD simulation techniques & methods
- Hybrid computational approaches: DFT, QM/MM, MD, MD/CFD
- Novel computing & communication architectures
- General- & special-purpose MD machines
- Video-game computers for accelerating MD
- Simulation of biomacromolecules
- Protein & DNA modelling
- Simulation of radiation-induced mutations
- Simulation of crystal & polymer systems
- Quantum biophysics, electronic structure of macromolecules

The MSSMBS'10 workshop will start at the International Conference Hall, Dubna, and then will be continued and finished at the Chemical Faculty of Moscow State University. We are going to provide a broad discussion on JINR's radiobiological and nuclear physics achievements of JINR's basic experimental facilities and Dubna locality, too.

Welcome to Dubna!

Kholmirzo T. Kholmurodov,

Chairman of the MSSMBS Organizing Committee.

Molecular Dynamics Studies on the Conformational State of the Chromophore Group (11-*cis* Retinal) in Rhodopsin Media

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Rhodopsin protein is a typical member of the G-protein-coupled receptor (GPCR) family. Among a wide variety of the GPCRs, it is the only receptor for which a tertiary structure is known. Thus, rhodopsin represents as an excellent model to investigate the main properties and function of these receptors. In Fig.1, our simulation results on the dynamic behavior of the binding pocket (with 11-*cis* retinal) in the beta-ionone ring region are presented. We have observed that beta-ionone ring began to rotate at the temporal point of 0.4 ns (after 400 000 steps) from the start of the simulation run. The beta-ionone ring turns approximately 65° around the polyene chain axis to. To estimate the "twisting degree" of different parts of chromophore retinal, we have calculated the rotational torsion angles of all methyl groups C16-C20 within the 3-ns dynamical changes (Fig.1, middle diagram). We consider the retinal rearrangement process, as observed in Fig.1, to bea chromophore "adaptation" inside the chromophore binding pocket.

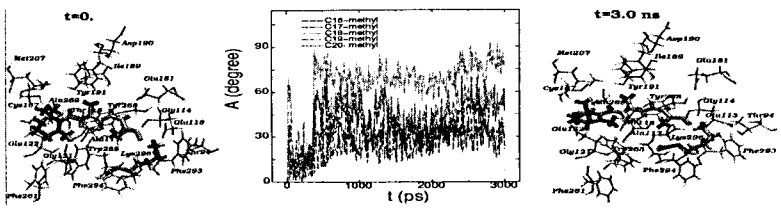

Fig. 1. Molecular dynamics of 11-*cis*-retinal in the chromophore center of a rhodopsin molecule at physiological temperature (T=300 K); (middle) torsional rotation angles of five methyl groups (C16-C20) in 11-*cis*-retinal of rhodopsin with time.

The details of dynamical changes have been analyzed for the amino acid residues of alpha-helix H-VI, which is located in a close neighborhood to 11-*cis* retinal. As is

known, alpha helix H-VI plays a stabilizing role in keeping the rhodopsin molecule in its inactive state [2].

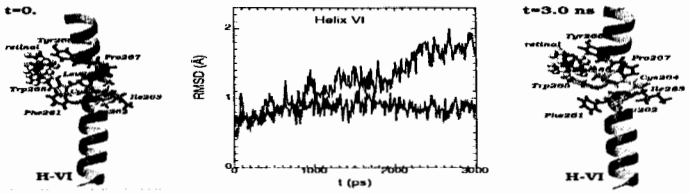

Fig. 2. The dynamics of alpha-helix H-VI and amino acid residues surrounding the 11-cis-retinal chromophore for the initial (t=0) and final (t=3 ns) states.

We have found (Fig.2) that the distance between H-VI and 11-*cis* retinal decreases with time. Helix H-VI approaches the chromophore retinal by approximately 1 Å. It should be noted that the simulation results agree with experimental observations [2].

Next, we have modeled *ab initio* quantum chemical configurations at t=0 and 3 ns as displayed above and estimated the absorption maxima in the initial and final states at 549 and 559 nm, respectively. Hence, the conformational changes in rhodopsin observed by molecular dynamics simulation over 3 ns must be accompanied by a 10-nm red shift in its optical absorption spectrum. A configuration interaction assessment of the effect of β-ionone ring rotation relative to the polyene chain in the nearest protein environment has shown that the excitation energy for such a "twisted" configuration will be lower than for the initial state when the chromophore ring and chain are coplanar; this is reflected in a 10-nm red shift of the absorption maximum [1]. Such structural changes may be important for the light-induced isomerization of 11-cis retinal in rhodopsin and may explain why this photochemical reaction is so much faster and more efficient in the visual pigment than in solution.

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Multiscale simulation of nematic liquid crystals

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Liquid crystals attract more attention as softmatter because of its character in the middle of crystals and liquids. They have both order of crystals and flowability of liquids. Liquid crystalline phases are classified depending on the orientational order of molecules and the positions of the center of mass, such as nematic phase and smectic phase. Nematic liquid crystals, which have only orientational order of molecules and no order of positions, are most industrially used. To study behaviors of nematic liquid crystals, orientation of molecules and its time variation are very important. So, molecular dynamics (MD) simulation is effective solution to research nematic liquid crystals. In this study, we performed MD simulation of 5CB (4-pentyl-4'-cyanobiphenyl, we present in Fig. 1) nematic liquid crystal.

However, MD simulations of liquid crystals have fatal difficulty of large computational costs. For example, to simulate liquid crystal phase transition from liquid phase of 512 5CB system, it takes about a month by using 2-chips MDGRAPE-3 [1,2].

To solve this difficulty, we developed multiscale MD simulation of nematic liquid crystals by using both atomistic model and coarse-grained model.

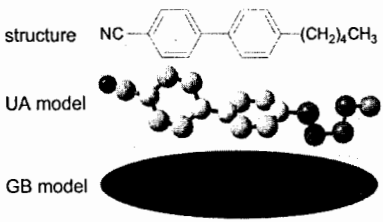

Fig. 1 Structure and calculational models of 5CB.

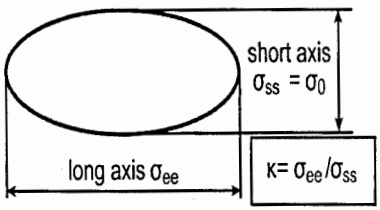

Fig. 2 Gay-Berne parameters we renewed in this study.

We used OPLS-UA (UA) model as atomistic model, and Gay-Berne (GB) model [3] as coarse-grained model (Fig. 1). Time integration in this multiscale simulation is only on the simulation of GB model. We used UA model only for renewing parameters of GB model. GB parameters, which were renewed in the simulation, are σ_0 and κ in Fig. 2. These GB parameters determine the shape of molecule and have much effect on phase diagram of GB particle [4]. To renew GB parameters, we used principle of equipartition. By using this method, we simulated phase transition of 5CB from liquid phase to liquid crystalline phase and from liquid crystalline phase to crystalline phase.

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[4] J. T. Brown and M. P. Allen, *Phis. Rev. E*, **57**, 6685, 1998.

Local environment analysis of dilute dopant in functional materials by using the synchrotron radiation and the first principles calculation

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Doping additional elements into the materials, i.e., doping technique, is often used, especially in semiconducting materials, to give additional properties to the materials, e.g. electronic, magnetic and optical properties. In order to understand the mechanism of appearance of new properties by doping and to design new materials with desired properties by the doping technique, it is essential to know the local environment of dopants on an atomic scale. There are some experimental methods to investigate the local environment of dopants. Among these methods, X-ray absorption near edge structure (XANES) is one of the most powerful methods, which enables us to determine the local environment of dopant at an ultra-dilute concentration level [1]. Conventional analytical method of XANES is based on a fingerprint type method, in which the experimental XANES spectrum of interest is compared with the experimental spectra of reference materials. However, it is difficult to determine the local environment of dopant by such an experimental fingerprint type method. To overcome this difficulty, a lot of attempts to reproduce the experimental XANES profiles by theoretical calculations have been made. If quantitative agreement can be obtained between experimental and calculated XANES spectra, we can get the theoretical fingerprints. For these theoretical XANES calculations, various kinds of calculating methods, i.e., the molecular orbital method, band-structure method and multiple scattering method, were employed. However, the theoretical spectra do not always reproduce the experimental spectra satisfactorily. There are several factors contributing to the poor agreement. One of the most typical reasons is improper treatment of the interaction between a core hole and an excited electron, i.e. the core-hole effect. Proper inclusion of the core-hole effect is mandatory for reproducing experimental spectra by theoretical calculations.

Recently, we have reported quantitative reproductions of experimental XANES from many different kinds of crystals [2, 3] by the first-principles band-structure calculations within the density functional theory (DFT) using the orthogonalized linear combination of atomic orbitals (OLCAO) method and the full-potential augmented plane wave plus local orbitals (APW+lo) method. In these calculations, the core hole was directly included in the self-consistent calculations. Interaction among core holes was minimized using supercells. Thereby the core-hole effect was included within the framework of the one-electron approximation.

In the present study, the local environment analysis of dopants in four kinds of functional ceramic materials, i.e., (1) dilute magnetic semiconductor (Mn and Fe-codoped In_2O_3), (2) phosphor (Pr-doped $SrTiO_3$ and $CaTiO_3$, Pr- and Ga-codoped $SrTiO_3$), (3) electrolyte of a solid fuel cell (Y-doped CeO_2) and (4) bioceramics (Zn-doped □-TCP), are carried out by XANES analysis with the aid of first-principles calculations. For these target subjects denoted above by (1)–(4), Mn-K and Fe-K, Pr-L_3 and Ga-K, Y-L_3 and Zn-K XANES were investigated here, respectively. Ga-K XANES analysis of Ga-doped SrTiO3 is shown in Fig .1 as an example of the present studies.

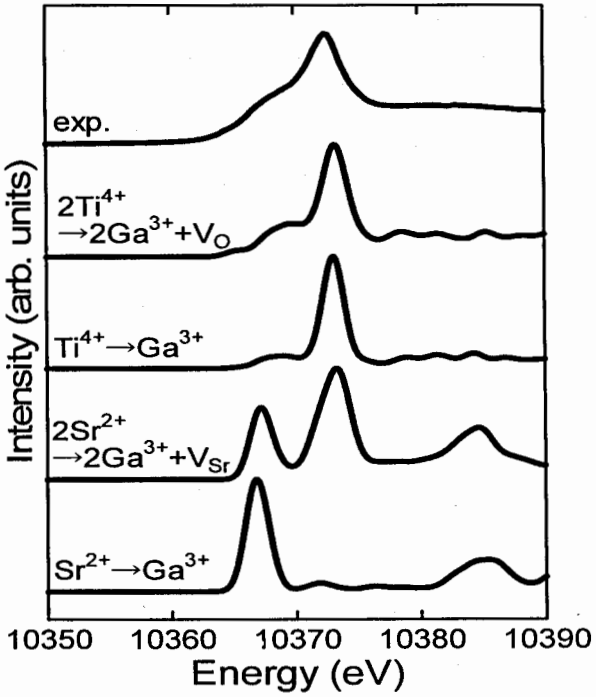

Fig. 1 Comparison of Ga-K XANES spectra of Ga-doped $SrTiO_3$ between experiment and calculations.

References:

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LATERAL HETEROGENEITY AS AN INTRINSIC PROPERTY OF HYDRATED LIPID BILAYERS: A MOLECULAR DYNAMICS STUDY

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Studies of lateral heterogeneity in cell membranes are important since they help to understand the physical origin of lipid domains and rafts. The simplest membrane mimics are hydrated bilayers composed of saturated and unsaturated lipids. While their atomic structural details resist easy experimental characterization, important insight can be gained *via* computer modeling [1, 2]. We present the results of all-atom molecular dynamics simulations for a series of fluid one- and two-component hydrated lipid bilayers composed of phosphatidylcholines with saturated (dipalmitoyl-phosphatidylcholine, DPPC) and mono-unsaturated (dioleoyl-phosphati-dylcholine, DOPC) acyl chains slightly differing in length (16 and 18 carbon atoms, respectively). The following conclusions can be drawn:

1) Lateral arrangement of lipids (according to both, geometrical and hydrophobic properties) in all studied systems is not random. Instead, it reveals occurrence of small (most often, 3 lipids) clusters on the surface. Clustering seems to be a feature inherent in the lipid bilayers near the equilibrium state. 2) Lateral heterogeneity is even more pronounced deep in the bilayer – in the hydrophobic core of the membrane (in the region of C=C bonds of DOPC), although not near the termini of acyl chains. Toward the surface, the mosaic-like 2D distribution of lipids becomes much "fuzzy". 3) In mixed bilayers, the clusters are formed both, by alike and unlike lipids. One-component clusters appear only at high concentrations (above 40-50%) of this type of lipid. 4) The observed microheterogeneity picture is highly dynamic – lipid molecules enter and leave clusters with the characteristic lifetimes about 1 ns. 5) Clustering determines to a large extent the structural, dynamic, and hydrophobic properties of bilayers, like area per lipid molecule, bilayer thickness, order parameters of acyl chains, parameters of the mosaic hydrophobicity patterns on the lipid-water interface (Fig. 1), hydration degree of lipid heads, and so forth. 6) Addition of even small (~10%) amount of DPPC to the DOPC bilayer strongly affects the physico-chemical characteristics of the entire system, while the opposite is not true. By other words, in the two-component system, one (DPPC) may be considered as an "order-preferring" agent, which efficiently modulates behavior of the second one (DOPC).

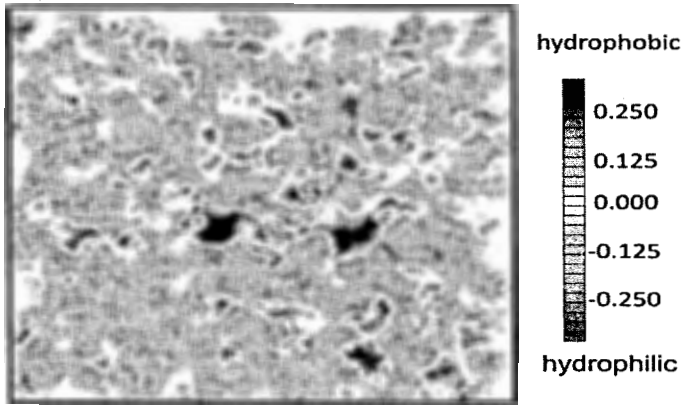

Fig. 1. Hydrophobic/hydrophilic organization of the surface of DOPC/DPPC (50:50) bilayer. In-plane view of the solvent-accessible surface area of the model bilayer (2D-map of the molecular hydrophobicity potential, MHP [3]). MHP values (in octanol-water *logP* units) are calculated in each point of the surface. The map is given for one of the bilayer leaflets. Coloring scheme is shown in the right.

To summarize, bilayer properties are tuned in a wide range by the chemical nature and relative content of lipids. The impact that the micro-heterogeneity may have on formation of lateral domains in response to external signals is discussed. Understanding of such effects creates a basis for rational design of artificial membranes with predefined properties.

This work was supported by the Russian Foundation for Basic Research and by the RAS Programmes (MCB and "Basic fundamental research of nanotechnologies and nanomaterials").

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Density-functional-based molecular-dynamics simulations of disordered materials

Fuyuki Shimojo,[1] Satoshi Ohmura,[1] Rajiv K. Kalia,[2] Aiichiro Nakano,[2] and Priya Vashishta[2]

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We have implemented several schemes of large-scale molecular-dynamics (MD) simulations on massively parallel computers, in which interatomic forces are computed quantum mechanically in the framework of the density functional theory (DFT), and applied them to high temperature phenomena with chemical reactions.

Hydrogen production by metal particles in water could provide a renewable energy cycle, if its reaction kinetics is accelerated. The DFT-based MD simulations have been carried out to investigate processes of the hydrogen production from water by a cluster (or superatom) consisting of a magic number of aluminum atoms, Al_n (for instance, n = 12 or 17) [1]. In a low activation-barrier mechanism found in the simulations (Fig. 1), a pair of Lewis acid and base sites on the Al_n surface preferentially catalyzes hydrogen production. This reaction is immensely assisted by rapid proton transport in water via a chain of hydrogen-bond switching events similar to the Grotthuss mechanism, which converts hydroxide ions to water molecules at the Lewis-acid sites and supplies hydrogen atoms at the Lewis-base sites.

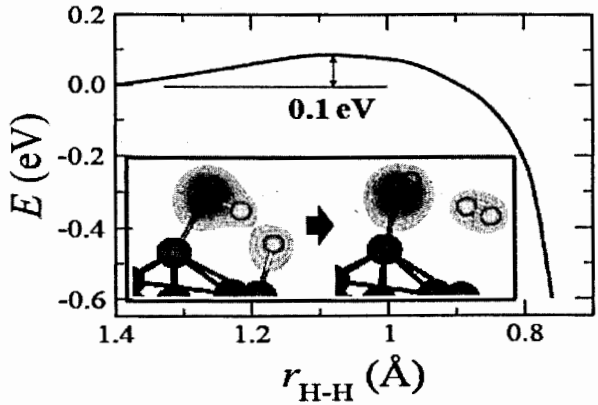

Fig. 1. Energy profile along the reaction path of molecular hydrogen production, Al-OH_2 + Al-H → Al-OH + Al + H_2, as a function of the distance between the two hydrogen atoms that form a hydrogen molecule, obtained by nudged elastic band calculations. The distribution of the electron density larger than 0.05 a.u. is shown by contour surfaces.

Synthetic supermolecules such as π-conjugated light-harvesting dendrimers efficiently harvest energy from sunlight. The electronic excitation energy is rapidly transferred from peripheral antennas to photochemical reaction cores, the atomistic mechanisms of which remains elusive. MD simulation incorporating nonadiabatic electronic transitions [2] reveals the key role of thermal molecular motions that significantly accelerate the energy transport based on the Dexter mechanism.

Rapid reaction of a molten metal with an oxide is key to understanding fast reactions in nanothermite composites. The thermite reaction at an Al/Fe_2O_3 interface has been investigated [3] by a linear-scaling DFT-based MD simulation using a divide-and-conquer (DC) scheme. In this scheme, electronic wave functions are represented on a real-space grid, which is augmented with a coarse multigrid to accelerate the convergence of iterative solutions and with adaptive fine grids around atoms to accurately calculate ionic pseudopotentials [4]. Spatial decomposition is employed to implement the hierarchical-grid DC-DFT algorithm on massively parallel computers. The simulations show that mass diffusion and reaction rate at the interface are enhanced by a concerted metal-oxygen flip mechanism, which leads to two-stage reactions. The redox reaction to form iron metal and Al_2O_3 initiates with a rapid formation of Al-O bonds at the interface within 1 ps, followed by the propagation of the combustion front.

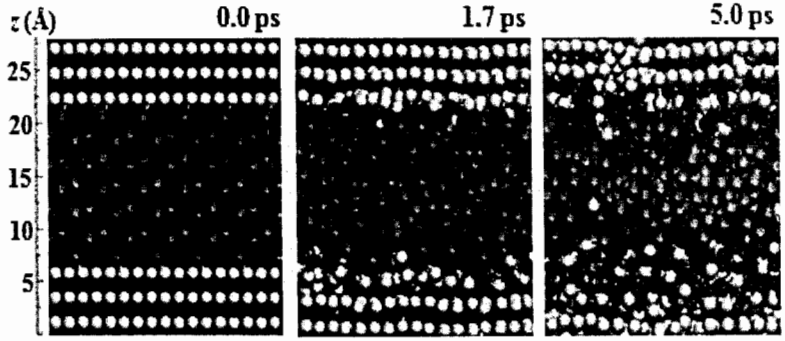

Fig. 2. Snapshots of the atomic configuration obtained by the DC-DFT-based MD simulations of thermite reaction at an Al/Fe_2O_3 interface.

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Molecular dynamics study of the human red blood cell membrane

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We have performed an 80 ns molecular dynamics (MD) simulation of the asymmetric membrane of human red blood cells (erythrocytes) and investigated its dynamic properties.
For membrane modeling, we created a patch of phospholipid bilayer using the phospholipid composition of human red blood cell membrane known from experiments [1]. The model also consists of cholesterol molecules and the transmembrane part of the Glicophorin A protein [2]. The final system was solvated (using TIP3 model water molecules [3]) with 33 molecules of water per phospholipid polar head for the full hydration of the system. At the starting point of MD simulation, the membrane size was 10.5 x 9 x 9 nm3 with 57640 atoms.

Presented below are the simulation details of the system.

Pressure (1 atm) and temperature (310 K) were controlled using the Langevin dynamics method for a thermostat and the Langevin piston method for a barostat [5]. The integration time step was 2 ps. For electrostatic iteractions, the Particle Mesh Ewalds (PME) method was used [6]; for Van der Waals interactions, the cutoff radius was 12–14 Å. For MD simulation, NAMD software was used; it was installed on an ArmCluster (a 3.06 GHz processor and 2 Gb RAM on each node), which is part of an ArmGrid system. Myrinet interconnections between nodes were used.

The free energy of the system was minimized to provide the thermodynamic equilibrium of the membrane model.

The thickness of the membrane in the equilibrium state is 51–52 Å. It is shown that some phospholipid molecules are arranged tighter in the inner layer of the membrane than in the outer layer but at the same time the average area per phospholipids molecules is almost the same in both layers of the erythrocyte membrane model.

A detailed investigation of the orientation of cholesterol molecules in the phospholipid bilayer and membrane surface roughness was performed. Fig. 1 represents the cholesterol molecules density dependence along the normal (the z axis) to the membrane surface. It is seen in the figure that cholesterol molecules are mainly localized in the hydrophobic part of the membrane – more precisely, below the polar heads of phospholipid molecules.

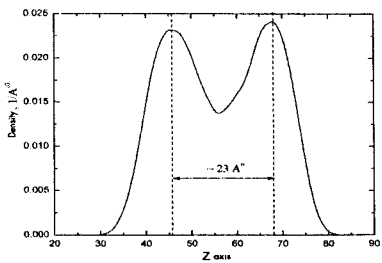

Fig. 1. Cholesterol density in the human red blood cells asymmetric membrane.

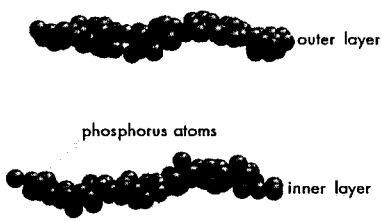

Fig. 2. Molecular structure of the surface of the inner and outer layers of the asymmetric membrane of human red

As the cholesterol molecules are mainly localized in the hydrophobic volume of the phospholipid bilayer surrounded with hydrocarbon chains of phospholipid molecules, it can be assumed that they contribute to more rigid packing of phospholipid molecules in the erythrocyte asymmetric membrane.

Figure 2 represents the molecular structure of the erythrocyte membrane surfaces. It is shown that in spite of the asymmetric character of the membrane, the undulations of the inner and outer layers of the membrane are almost the same.

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DNA nanobioelectronics – possible solutions

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Development of nanobiological devices such as biosensors and electron biochips, which are devices for detecting and analysis of various biological objects, is based on the use of biological molecules, as for instance, proteins, DNA and RNA. The field of application of biosensors and biochips is very wide – from the problems of proteomics and genome decoding to the use in medical diagnostics, drug designing and in biotechnology as a whole [1].

One of the fast-paced investigations concerned with DNA/RNA analysis is development of DNA-biochips technology. Since the time when first DNA-chips were constructed [2], they have evolved into a powerful investigation tool for the study of living systems. The overwhelming majority of DNA-biochips are optical ones. In recent years, however, more and more attention is given to electron biochips in which changes in the electric current are measured which are caused by the presence of the biomacromolecule being detected [3]. This attention is associated with enormous potentialities promised by their use – miniature size (up to nanometer scale), short time required for biomacromolecule detection, lack of the need for the use of markers , etc.

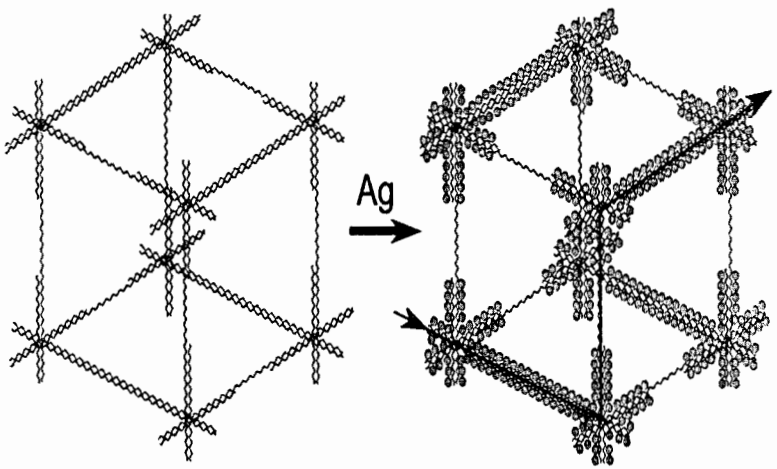

Fig. Double strand DNA fragments represent M-DNA.

In the report we propose that for creation of biochips use can be made of a self-assembly technology of DNA-based nanostructures, such as cubic lattices (Fig.1). The principle of operation of biochips for medical diagnostics is based on identification of pathogens with the help of special oligonucleotide samples which are present in the genome

of an organism being studied in a unique form. The choice of appropriate samples is preceeded by a computer calculation aimed at the selection of a suitable variant of a nucleotide sequence. In the proposed DNA-based biochip whose realization is based on the self-assembly principle, it is essential that preliminary computational experiments on supercomputers should be performed for selection of appropriate nucleotide sequences which will be components of the biochip. In this case numerous factors such as composition of salt in the solvent, melting temperature of hybridized chains, and other factors influencing the hybridization should be taken into account.

The work was done with the support by the RFBR (projects №№ 09-07-12073 ofi-m; 10-07-00112

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MINING OF STRUCTURAL REGULARITIES IN TRANSMEMBRANE DOMAINS OF PROTEINS: ADVANTAGE FOR STRUCTURE PREDICTION

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Integral membrane proteins (MPs) are the core of the cell machinery for transmembrane (TM) signaling, perception of various stimuli, transport and other vital functions — therefore making up a considerable part of pharmaceutical targets. TM-domains of MPs transduce biological signals into the cell — *via* conformational switch in G–protein-coupled receptors (GPCRs) structure upon ligands binding, or phosphorylation of cytoplasmic domain of receptor tyrosine kinases (RTKs) that follows dimerization, or in some other way. Given the difficulties related to experimental structural characterization of the most novel MPs, computational structure prediction may be of substantial help for pharmaceutical industry and structure-based design of new drugs — e.g., high-affine GPCR ligands or antitumor inhibitors of RTK dimerization.

In consideration of constantly (though rather slow) growing body of structural data on TM-domains, it's becoming possible to take into account peculiarities of MPs organization for prediction of TM-domains 3D-structure. Here, we propose a method for evaluation of "packing quality" of polypeptide chain in TM-domain. This approach (the "Membrane Score") mines for structural regularities that are observed in experimentally solved TM-domains: structural preferences of aminoacid residues to predefined "classes of membrane–protein environment" are derived from non-redundant database of available MPs structures, thus permitting assessment of 3D-model feasibility (Chugunov *et al.*, 2007).

The "membrane score" method proved itself useful for identification of close-to-native structures among massive sets of native-like and erroneous models: 7-TM proteins like rhodopsin and bacteriorhodopsins, non-covalent TM-dimers like glycophorin A and BNIP3, and others. Other capabilities are inherent in this method: detection of alignment errors, optimal choice of template for modeling, coarse-grained optimization of models. Furthermore, the membrane score may assist in construction of sequence alignments between low-homology targets — such as GPCR A and B subfamilies, for latter of which there's no complete structures available so far.

As a part of a project for design an exclusively selective inflammation inhibitor that should act through engineered VIP receptor (VIPR1), a structural model of TM-domain of this receptor was constructed, and also mutagenesis study was performed (Chugunov *et al.*, 2010). The results suggest that residues important for VIP binding and/or receptor activation — R^{188}(TM2)–Q^{380}(TM7)–N^{229}(TM3) — line up, and this proximity is further confirmed by cooperative and anti-cooperative activation effects that appear in double mutants built from reciprocal residue exchanges (see Figure).

To conclude, consideration of MPs distinctive features is prerequisite for successful modeling of TM-domains structures which may be of help in the drug-design process. The "membrane score" method, especially if accompanied by efficient conformational sampling strategies, will supply industry with realistic models of TM-domains of membrane proteins.

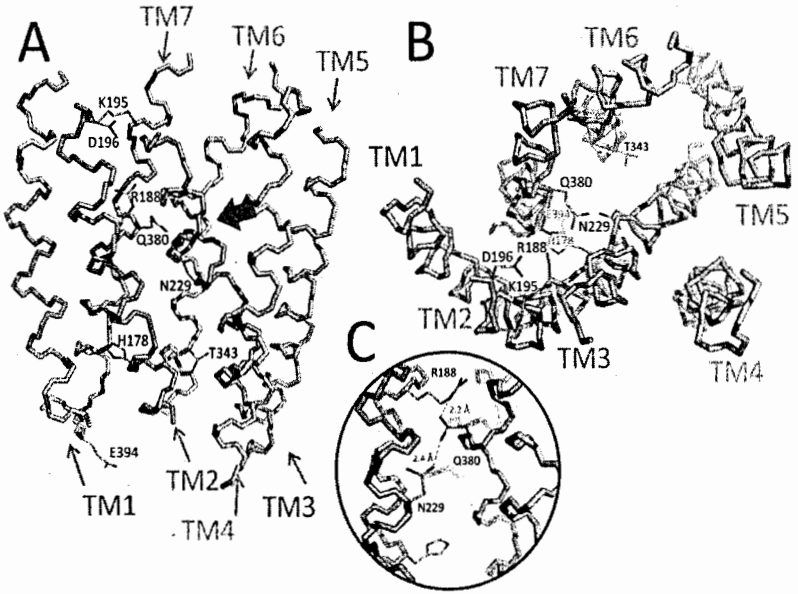

Figure: 3D model of the TM-domain of VIPR1 receptor. (A) Side view. (B) Top view (from the extracellular space). (C) Zoomed view of the mutated region (the view direction is shown by the arrow in *A*). Residues that were shown to be important form a chain, stabilized with h-bonds: R^{188} in TM2–Q^{380} in TM7–N^{229} in TM3 (Chugunov *et al.*, 2010).

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Mechanisms of Atomic Diffusion in Covalent liquids: *ab initio* Molecular-Dynamics Study

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Dynamic properties of covalent liquids under pressure are very interesting because of their unexpected pressure dependence. Diffusion coefficients of atoms have maximum under pressure in some covalent liquids [1,2]. In addition for a number of covalent liquids, such as SiO_2, GeO2, silicates and germanates, abnormal pressure dependence of the viscosity has been observed, i.e. the viscosity significantly drops with increasing pressure [3,4,5]. These anomalous behaviors of dynamic properties are considered to be related to the atomic diffusion in the liquids under pressure. It is, therefore, of particular interest to explore the pressure dependence of the microscopic diffusion mechanism in covalent liquids. In this study, the atomic dynamics in covalent liquids (GeO_2 and $SrGeO_3$) under pressure is investigated by *ab initio* molecular-dynamics simulations, in which the electronic states are calculated using the projector-augmented-wave method within the framework of density functional theory. To clarify the mechanism of atomic diffusion, we investigate the time evolution of the bonding nature by utilizing the population analysis. The bond-overlap populations, which give a semi quantitative estimate of the strength of the covalent like bonding between atoms, are calculated as a function of time.

The simulations show that non-bridging oxygens (NBO) are needed for the atomic diffusion in both liquid GeO_2 and liquid $SrGeO_3$ at ambient pressure. In liquid GeO_2, each O atom is normally bonded to two Ge atoms, and Ge atoms are fourfold coordinated to O atoms. In this liquid, overcoordinated atoms (fivefold-coordinated Ge, and threefold-coordinated O) are always involved with the atomic diffusion accompanied by the formation of NBO. On the other hand, in liquid $SrGeO_3$, almost one third of O atoms bridge two Ge atoms, and the rest of O atom is bonded to only one Ge, when the pressure is low. Therefore, the rearrangement of covalent bonds is possible without generating the over coordinated atoms as shown in Fig.1, where bridging oxygen (BO) O1 changes to NBO by breaking the O1-Ge2 covalent bond. In Fig. 1(a), Ge1 and Ge2 are fourfold-coordinated to O atoms and O1 is twofold-coordinated to Ge atoms. As shown in Fig. 1(b), O1 changes from BO to NBO and the oxygen coordination around Ge2 changes from four to three because the O1-Ge2 bond is broken.

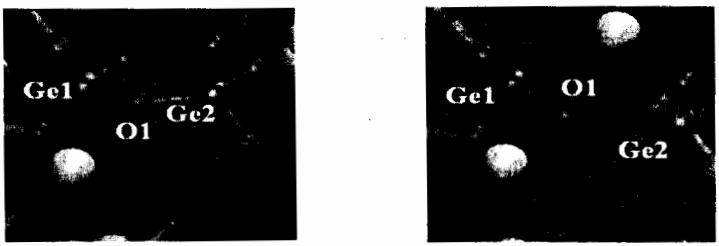

Fig. 1(a,b): Diffusion process in liquid $SrGeO_3$ at ambient pressure

When the pressure increases, the different diffusion mechanism appears only in liquid GeO_2. In this atomic diffusion mechanism, NBO doesn't appear as shown in Fig.2, where Ge3-O2 and Ge4-O3 bonds break and Ge3-O3 and Ge4-O2 bonds are formed through threefold-coordinated

O atoms. In Fig. 2(a), both Ge atoms (Ge3 and Ge4), and O atoms (O2 and O3) displayed are fourfold- and twofold- coordinated, respectively, to hetero atoms, i.e., there is no bond defect. As shown in Fig. 2(b), four atoms (Ge3, Ge4, O2 and O3) are over coordinated because Ge3-O3 and Ge4-O2 bonds are formed. Since the over coordination is energetically unstable, the covalent bonds around the threefold-coordinated O2 and O3 are broken. All atoms recover from over coordination (Fig. 2(c)).

We discuss the relation between the pressure dependence of the diffusion coefficient and the microscopic-diffusion mechanisms.

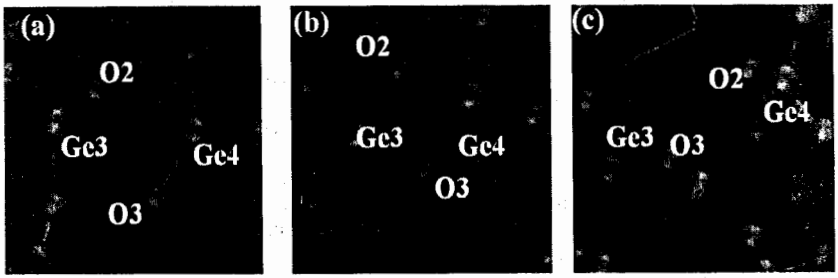

Fig. 2(a,b,c): Diffusion process in liquid GeO_2 under high pressure.

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Digital fundus images morphing for automatic detection of threshold norma→pathology of retina

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Exciting development in image processing relevant to ophthalmology over the past 10 years includes the progress being made towards developing automated diagnostic systems for clinically significant retina pathology and disease. Progress has been made in the identification of the retinal vasculature and the more common pathological features, such as small aneurysms, exudates and age-related macular degeneration [1-3]. If detected early, treatments can preserve vision and significantly reduce debilitating blindness. However, the lack of screening and the shortage of ophthalmologists limits the available ocular health care. Currently, there is an increasing interest for setting up medical systems that can screen a large number of people and increase the relevance of using image processing in teleophthalmology (eHealth) as an aid in clinical decision-making to large rural-based communities [4]. This requires tools and indicators to develop a guidebook for the purpose.

For the first time we use digital fundus images morphing techniques to create computer-generated imagery (CGI) of none existing fundus images (Figure 1).

Norma . . . i . . . pathology of cotton wool spots

Figure1. Morphing digital fundus images of healthy retina to pathological retinal image of cotton wool spots as example.

Morphing is a special effect in motion pictures that changes (or morphs) one image into another through a seamless transition. CGI was used for morphing digital fundus images of healthy retina to pathological one what allows us to create of intermediate images that correspond to initial stage of pathological changes and that would not be feasible using any other technology. The quantitative measurements of retinal vascular topography of none existing fundus images are validated by expert-ophthalmologists classifying the normal and pathological retinal images and then using for creation computer-based developed sophisticated retina coefficients of retina (CR) (Figure 2) on the basis of circumferences "mask" [5]. Morphing digital fundus images of healthy retina to healthy one used as control for CR definition.

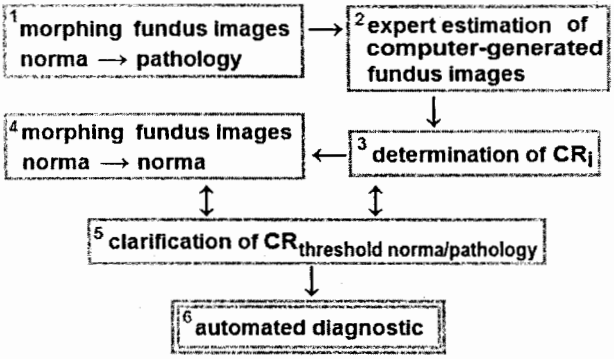

Figure 2. Principal algorithm of automatic diagnostic system for retina pathology

In conclusion, we present a technique for detection of initial stage of pathological changes of a network of blood vessels and zones of detail ophthalmology analysis in a retina (such as microaneurysms, hemorrhages, hard exudates, druses, cotton wool spots or venous loops) by computer-based analysis of digital images.

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Generalized-ensemble simulations in protein science

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Conventional molecular simulations are greatly hampered by the multiple-minima problem, where the simulations tend to get trapped in some of astronomically large number of local-minimum-energy states. In order to overcome this difficulty, we have been advocating the uses of generalized-ensemble algorithms which are based on non-Boltzmann weight factors (for a review, see, e.g., Ref. [1] and for our recent algorithm developments and applications, see, e.g., Refs. [2-6]). With these algorithms we can explore a wide range of the conformational space. The advantage of generalized-ensemble algorithms such as multicanonical algorithm and replica-exchange method lies in the fact that from only one simulation run, one can obtain various thermodynamic quantities as functions of temperature. In this talk, I will present the latest results of various applications of generalized-ensemble simulations in protein science.

Compared to globular proteins, the three-dimensional structures of membrane proteins are very difficult to determine. Figure 1 shows typical snapshots from a replica-exchange Monte Carlo simulation of the seven transmembrane helicies of bacteriorhodopsin [3]. We found that seven local-minimum-energy states exist at low temperatures and that a native-like structure is included as one of the seven states.

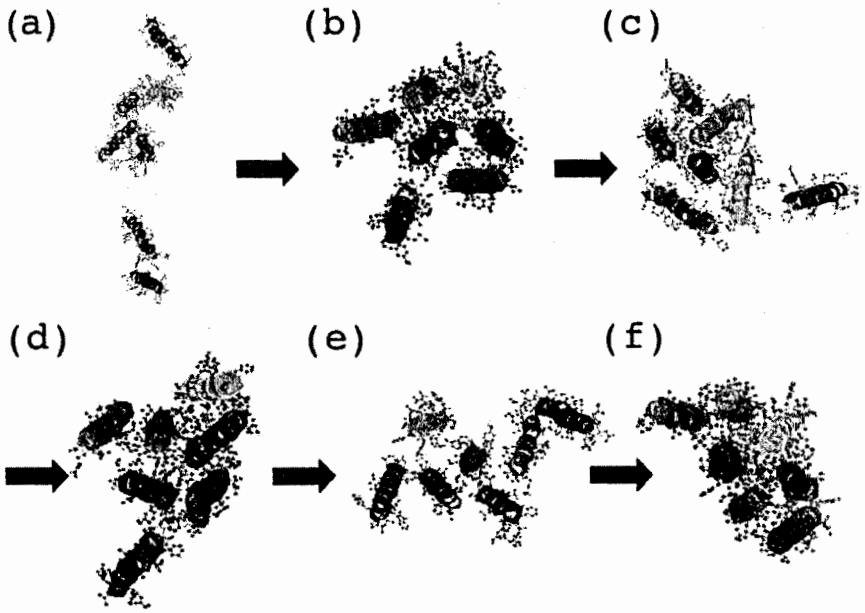

Fig. 1. Typical snapshots from a replica-exchange simulation of the seven transmembrane helices of bacteriorhodopsin.

We have also succeeded in the folding of a small protein, chicken villin headpiece subdomain [6]. The number of amino acids is 36. The protein was soaked in a sphere of 3513 water molecules. The initial conformation was prepared from a simulation with implicit solvent, which was started from a fully extended conformation. We have performed two independent multicanonical replica-exchange molecular dynamics simulations of length of about 1 micro seconds. The number of replicas was eight. During these simulations, we observed at least five independent folding events into the native structure. In Fig. 2, we show a couple of native-like conformations that were obtained during the simulations. They are indeed quite similar to the native conformation. We have also shown that among the three native alpha-helices, the one closest to the C-terminus is formed first. As far as we know, this is the first time that a single simulation run with explicit solvent observed more than one folding events.

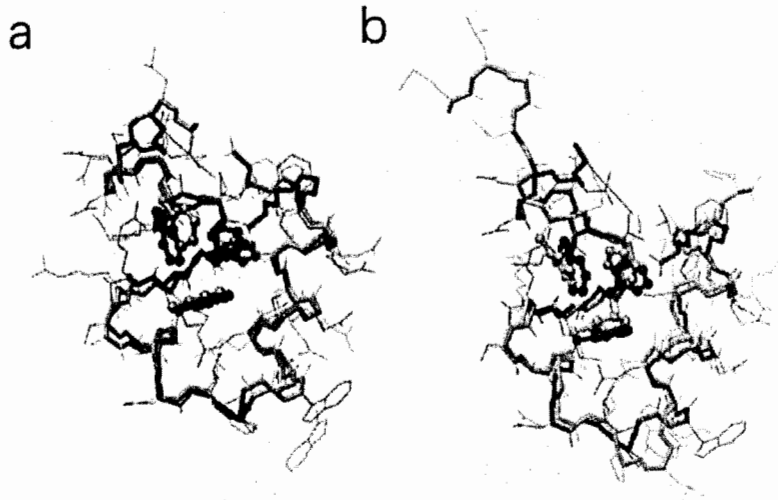

Fig. 2. Two of the closest structures obtained from multicanonical replica-excchange method. (a) RMSD is 1.1 angstroms for the main chain from residue 2 to residue 35, (b) RMSD is 1.2 angstroms for the main chain from residue 9 to residue 32. Yellow chains are the conformations from the simulation, and blue and green chains are the native conformation.

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Modeling structure and spectra of photoreceptor proteins

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Accurate characterization of electronically excited states and vibrational spectra in large molecular systems as in photoreceptor proteins is a key step in establishing mechanisms of light-induced biophysical processes. We describe developments and applications of modern tools of molecular modeling including the molecular dynamics, quantum chemistry and hybrid quantum mechanical – molecular mechanical (QM/MM) methods for modeling mechanisms of action of photoreceptor proteins. Chemical transformations including changes in hydrogen bonding networks in the chromophore binding pockets are described by quantum chemical approaches. while molecular mechanical (molecular dynamical) methods account for effects of protein matrices. Initial geometry configurations of the enzyme-substrate complexes are constructed by the available crystal structure of relevant systems from the PDB archive. Fig.1 gives an illustration of the QM/MM based modeling properties of the photoreceptors taking the flavin chromophore containing protein AppA as a representative example.

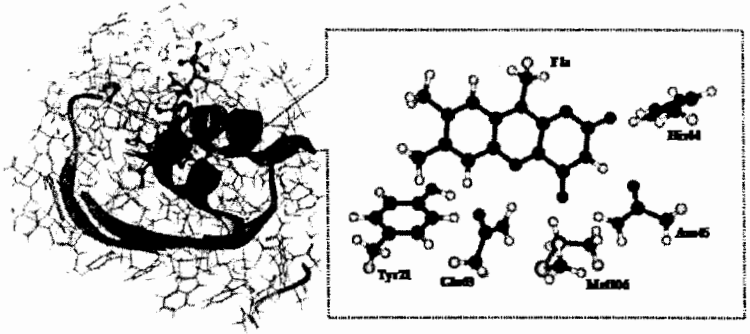

Fig.1. Left: a general view on the model protein system mimicking the AppA protein in the dark state; right: a molecular cluster (QM-subsystem) selected for quantum chemical calculations of electronic excitations. Hydrogen atoms distinguished in the QM-part by light blue color are the link atoms in QM/MM geometry optimizations.

Flavin containing proteins constitute an important class of biological photoreceptors cycling between the dark-adapted and light-induced functional states. Focusing mostly on the ground electronic state structures that might occur in early events near the dark-adapted species we performed molecular dynamics (MD) simulations initiated from the corresponding atomic coordinates in the crystal structure PDBid: 2IYG followed by the QM/MM geometry optimizations for a fairly large molecular model from the representative MD snapshots. The high level *ab initio* quantum chemistry calculations of the absorption bands in the chromophore

containing molecular cluster finalized simulations. We report occurrence of several conformations of the model protein system, which can be characterized by the intermediate red shifted optical bands.
Other applications include simulations of properties of the Green Fluorescent Protein (GFP) and of its chromophore in different environments, and the GFP-like red-fluorescent proteins.

Acknowledgement:

These works are partly supported by the grant from the Russian Foundation for Basic Research (Project No. 10-03-00139) and from the grant MK-64815.2010.4.

ATOMISTIC THEORY OF NUCLEATION IN SOLIDS AND LIQUIDS

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A review is presented of the universal atomistic approach to treat diverse nucleation phenomena in solids and liquids. Molecular dynamics (MD) method is used to define spinodal (boundary of stability of the given phase) positions on the phase diagram and investigate homogeneous nucleation in metastable states adjacent to the spinodals, and an approach to the calculation of the lifetime distributions of metastable states is developed in [1,2]. The approach is based on the stochastic properties of MD and allows one to study nucleation as a stochastic phenomenon.

The idea is that one MD run gives a value of the particular lifetime τ for a given initial configuration in the phase space. Then averaging should be performed over the ensemble of initial configurations which are equivalent to each other macroscopically [1-3]. To prepare such an ensemble of microscopic configurations one should fix the macroscopic conditions that determine the degree of metastability, e.g. the values of temperature and density. Then MD trajectories calculated from each of the initial conditions of the ensemble give us the set of the lifetime values. Their lifetimes are short enough to be within the computational capabilities. The averaging over lifetimes results in a mean value $<\tau>$ which is specific for the given degree of metastability and the volume studied. The set of lifetime values obtained forms an exponential distribution as if the metastable phase decay goes as a Poisson random process with the same value of $<\tau>$. The value of $<\tau>$ determines the homogeneous nucleation rate.

The approach is applied to the calculation of the rate of homogeneous nucleation for such processes as transition of a superheated crystal into liquid [1-4], cavitation in stretched liquids [4-6], void formation in stretched crystals [7], homogeneous nucleation of dislocations in metals under shear stress [8], nucleation phenomena at crystallization [9]. The embedded atom method model for interatomic interactions is used for metals. Simple liquids are studied within Lennard-Jones model.

The results obtained for the nucleation rates of the diverse processes are compared to the classic nucleation theory predictions for the ranges of pressures and temperatures studied by MD. Different approximations used in the classic nucleation theory are tested. Both agreement and quantitative and qualitative disagreements between the classic nucleation theory estimates and the MD results are found.

The substantial advantage of the MD approach is the possibility to study microscopic mechanisms and kinetics of nucleation at the atomistic level. It is important in particular for such processes as void formation in stretched crystals, crystallization and nucleation of dislocations. It turns out that the microscopic mechanisms and elementary processes of nucleation are strongly dependent on the ranges of pressures and temperatures as well as on material microstructure (grain boundaries, dislocation subsystem, nanosize pores and inclusions etc).

The MD results can be used as a base for the multi-scale approaches to study such macroscopical phenomena as shock wave loading and rarefaction waves in solids, the spall strength of liquids, monocrystalline and polycrystalline metals. Comparisons with experimental data available are presented.

This work is partially supported by the grant 09-08-12161-ofi-m of the Russian Foundation for Basic Research, grants of RAS Programs of Basic Research № 2 (coordinator ac. Fortov V.E.). № 13 (coordinator ac. Savin G.I.), № 14 (coordinator ac. Zhuravlev Yu.I.).

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APPLICATIONS OF SURFACE HYDROPHOBICITY ANALYSIS FOR PEPTIDES, PROTEINS AND MEMBRANES

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Most important features of bimolecules are represented by their surfaces, which contain patterns for intermolecular interactions. The distribution of different physical-chemical properties on the molecular surface (e.g. net charge, hydrophobic/hydrophilic properties) also characterizes propensity for a molecule to reside at most likely environment (hydrophilic phase, membrane, etc). Molecular hydrophobicity potential approach can be efficiently used to assess numerically the spatial "hydrophobicity" of the molecular surface [1]. Application of such a method in many cases leads to better understanding of organization and the function of biomolecules. For instance, lipid membranes posses mosaic hydrophobic/hydrophilic surface, which plays important role during binding of different membrane-active agents [2]. Hence detailed analysis of the surface of antimicrobial peptides (most of them are membrane-active molecules) allows performing efficient design of their mutants with the predefined spectrum of biological activity [3]. For globular proteins we found that "hydrophobicity" of the surface correlates to thermodynamic properties of the molecule (e.g. conformational entropy). Moreover, efficient algorithms of prediction of protein-protein complexes (e.g. transmembrane dimers of bitopic membrane proteins) can be based on such a surface analysis.

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Nanostructure of the Model Stratum Corneum Membranes

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The stratum corneum (SC) represents the outermost layer of the mammalian skin (Fig. 1) and serves as the main skin barrier. The superficial layer consists of dead cells, the corneocytes, filled with the protein keratin. The corneocytes are further embedded in a matrix of multilamellar organized lipid membranes. The lipid matrix SC is the major diffusion-rate limiting pathway, as most of the drugs applied topically pass the SC through the multilamellar organized lipids as shown in Fig. 2 as intercellular route. The knowledge and comprehension of the nanostructure and the relative properties of the SC on the molecular level, in particular of the SC lipid matrix is essential for the understanding of drug penetration through the SC as well as for the development of new dermal drug delivery systems.

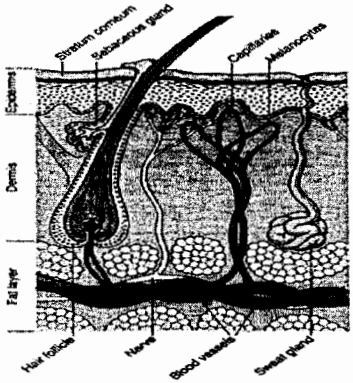

Fig.1. Structure of the mammalian skin

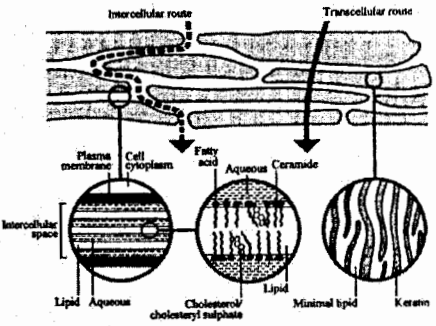

Fig.2. Structure of the stratum corneum and possible route for drug diffusion.

Neutron and X-ray diffraction from multilamellar model stratum corneum (SC) membranes have been used to provide the information on the internal nanostructure and hydration of the lipid bilayer [1-3]. The main distinguishing feature of model SC membranes based on ceramide [AP] is the extremely small intermembrane space (1 Å) as shown in Fig. 3. The role of the fully extended (FE) conformation of ceramide [AP] molecules in the organization of the nanostructure of the lipid matrix is discussed. The FE conformation gives rise to extremely strong intermembrane attractions (armature reinforcement), which tighten the adjacent bilayers to form a steric contact as shown in Fig. 4.

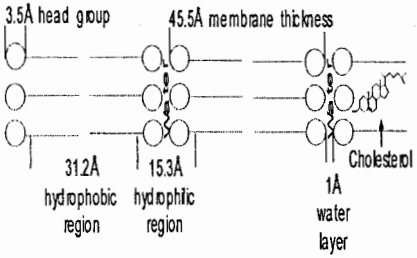

Fig. 3. Nanostructure and hydration of the model SC membrane derived from neutron diffraction experiment.

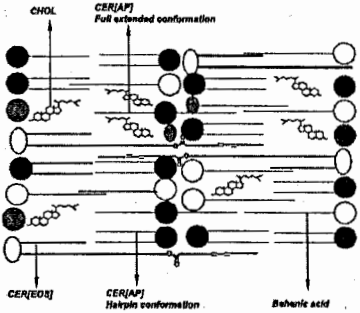

Fig. 4. Molecular organization of the SC model membrane derived from neutron diffraction experiment.

We present last results about nanostructure of the model SC membranes obtained from neutron and X-ray diffraction experiments:

- Basic membrane nanostructure
- Possible conformations of ceramide [AP] molecules in the basic nanostructure
- Arrangements of long chain ceramides and fatty acids in the bilayers
- Conditions for the formation of the long periodicity phase.

The arrangement of the ceramide [AP] molecules in the lipid matrix and the conformation of these molecules (fully extended or hairpin) are important questions for the interpretation of experimental results and further development of the theory of SC structure and drug diffusion through the skin.

First application of the molecular dynamic simulations for stratum corneum lipid mixtures was done recently [4]. Molecular dynamic simulations of our model SC lipid membranes could be useful for more deeply understanding the membrane nanostructure and molecular organization.

The work was supported by Russian Foundation for Basic Research, grant 10-04-91330.

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Empirical account of molecular electrostatic interactions through atomic charges

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Electrostatic interactions play a crucial role at different levels of organization of matter in the nature both living and inanimate. Intermolecular interactions comprise an important level determining most physico-chemical properties of compounds as well as their biological activity. Despite several techniques had been proposed to account for the electrostatic intermolecular interactions, the Coulomb term with atomic charges has gained the most widespread acceptance in routine molecular modeling (e.g. force fields, scoring functions, QSAR/QSPR, chemoinformatics). The reasons thereof are clear interpretation, relative ease of charges computation and the fastest but still correct estimation of interactions, which is particularly important for large, biologically relevant systems simulation.

Among a vast pool of schemes proposed so far for atomic charge generation, those based on empirical rules have certain benefits provided adequate underlying theory is chosen and the model's empirical parameters have been optimized so that resulting charges reproduce molecular electrostatic potential (MEP) calculated quantum chemically.

As exemplified by one of our empirical charge schemes [1] based on Dynamic Electronegativity Relaxation (DENR) principle [2], which generates topologically symmetric charges, we explain current achievements in the field and outline the future development guidelines. The latter includes proper account of formally charged fragments and molecules, enhanced description of electrostatics around relatively heavy elements of the periodic table, effects of anisotropy of electrostatic potential, polarization of molecular charge distribution in external fields, adequate description at distances close to atoms (near van der Waals radii), proper intermolecular charge transfer and judicious calibration of empirical parameters of the methods.

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Stochastic simulation of base excision repair in *Escherichia coli* bacterial cells

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The detailed mathematical modeling of repair processes taking place in living cells after exposure to the damaging factors of the physical and chemical nature is an important approach to determine the mechanisms of the induced mutation process. The most common DNA lesion caused by most of the damaging factors is a modification of nitrous bases, which can be removed by the mechanism of base excision repair (BER) [1]. Data available in the modern literature allow a mathematical description of the BER mechanism, which could be used to analyze in detail the interconnection between the processes being realized.

In this research, a stochastic approach-based [2] model is developed that describes the key processes of the excision repair of the damaged bases of the 8-oxoguanine (8-oxoG) type in *Escherichia coli* bacterial cells. This repair involves formamidopyrine-DNA-glycosilase (the Fpg protein), which has several types of activity.

The model describes the base excision repair (BER) processes such as the transformation of modified bases into apurinic/apyrimidinic (AP) sites, β-δ-elimination, 5'-terminal deoxyribose phosphate excision from a pre-incised AP site, and DNA polymerase I and DNA ligase activity. This model, which takes account of the stochastic nature of the biochemical reactions, has allowed predicting the kinetics of the key BER enzymes and intermediate DNA states. Simulation results are in a good agreement with experimental *in vitro* data [3] which characterize the early stages of the repair process involving the Fpg protein (Fig. 1).

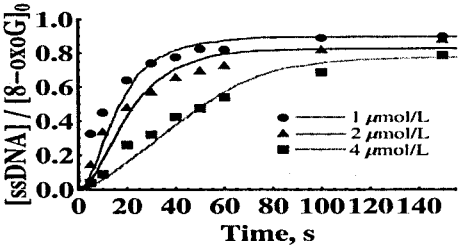

Fig. 1. The kinetics of Fpg-dependent 8-oxoG removal in comparison with experimental data [3]. Calculated and experimental data are presented for three different initial concentrations of 8-oxoG.

In this research, a quantitative estimation is performed of the kinetics of the following intermediate DNA states: [8-oxoG • Fpg], [AP site • Fpg], [3'-nicked site • Fpg], [5'-nicked site • Fpg], [ssDNA • Pol I], and [filled gap • DNA ligase], as well as repair enzymes: [Fpg], [Pol I], and [DNA ligase] (Fig. 2).

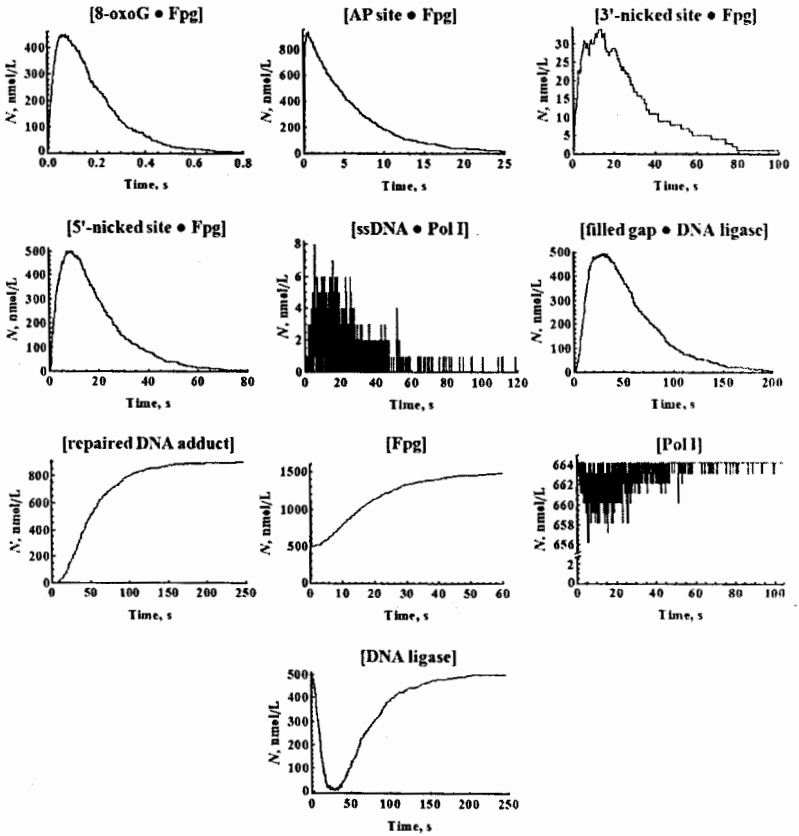

Fig. 2. The kinetics of the basic DNA states and repair enzymes during *E. coli* BER. The concentration of 8-oxoG is 1μmol/L. *N* is the concentration of the complex.

Here, a special case is shown of using the developed model to describe 8-oxoG repair involving bifunctional DNA glycosylase. It also seems to be promising to describe, based on the developed model, *E. coli* BER in the general case, which involves other DNA glycosylases, including monofunctional DNA glycosylases, when some of activities described here are realized by additional repair enzymes.

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PREDICTION AND CHARACTERIZATION OF TRANSMEMBRANE HELICAL DIMERS USING COMPUTER SIMULATIONS TECHNIQUES

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Interactions of membrane proteins play a very important role in cell life. Many of membrane proteins (MP) accomplish their function in a complex of several subunits. Often, protein-protein association have a regulatory function. Thus, understanding on the atomic level the driving forces of membrane protein association is crucial for deciphering of their mechanisms of action. One of the most common elements of membrane proteins fold is an alpha-helix intersecting the membrane (transmembrane helix, TMH). So, it is rational to start the solution of MP's association from the simplest case – namely from dimerization of isolated TMH. In spite of its simplicity, such a system includes all important characteristics encountered in more complex MPs. Moreover, interaction of individual TMH has a serious biological impact – for instance, receptor tyrosine kinases are activated in answer to dimerization, which in turn depends on association of their single TMH. Therefore, delineation of molecular mechanisms of such processes will facilitate prediction of membrane protein structure and make possible design of membrane proteins with predefined structure/activity.

As for the dimerization of TMH, the two main questions appear: (1) How does the dimeric structure look like and (2) what are the determinants of the dimerization? Partial answer on these questions can be provided by experimental methods (although they are resource and labour- demanding). Alternative approach consists in using of molecular modeling techniques. In this work TMH dimerization is studied via computer simulations. In the first part of the work, different approaches to prediction of dimeric spatial structure are described. Strengths and weaknesses of the methods and choice of the optimal computational strategy are discussed. Applications of the methods are illustrated in studies of several biologically relevant dimers. The second part of work is devoted to ranging of the predicted structural models through the calculations of free energy of dimerization. In addition to selection of the 'native-like' structure, this approach permits qualitative assessment of the molecular determinants responsible for the dimerization. Combination of the presented methods provides novel information about interaction of TMH and opens up new opportunities to design of TMH with predefined dimerization ability.

Molecular dynamics studies on functional and structural properties of a vitally important CDK kinase protein

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The Group of the Radiation Genetics of Lower Eukaryotes at the Laboratory of Radiation Biology (LRB) studies the genetic control of yeast cell radiosensitivity. Modeling the structure of the yeast CDC28 kinase and human homologous CDK2 kinase, which is conducted jointly with the Computer Modeling Sector of the LRB, presents a promising field of research. In collaboration with the Institute of Molecular Genetics (the Russian Academy of Sciences), mutations were isolated and genes were determined which participate in the regulation of radiosensitivity and genetic stability. Among them, the *CDC28, NET1,* and *HFI1* genes, which encode the components of the enzymatic complexes (modifying chemically the substrate proteins), turned out to be the most important. These complexes participate in essential cellular processes. A pleiotropic manifestation of mutations was experimentally observed in the gene of the key regulator of the cell cycle progression of the cyclin-dependent protein kinase *CDC28.* These mutations disturb the cell cycle progression, repair, and checkpoint control, and, as a consequence, they lead to higher radiosensitivity and increased mutagenesis [1]. Research on the pleiotropic manifestations of the yeast *cdc28* mutations is topical, because disorder in the functioning of a homologous kinase in human cells results in their malignant transformation.

The analysis of the protein structure allows genetic research to be added by understanding which kinds of structure changes lead to specific mutations and why the protein functions less efficiently. Besides, as it is rather difficult to obtain and study mutant forms of a human kinase, it is possible to use the homologous yeast kinase as a model. An analysis of the crystal structures of the catalytic subunits of kinases showed that they have a similar structure (Fig. 1).

Fig. 1. A model of the CDK2 kinase and cyclin A. The positions are shown of the amino acid residues G16 in the G loop of the small lobe, R274 in the large lobe, and T160 in the T loop of the large lobe of kinase

The crystal structure of the human CDK2 kinase is well studied and used as a model of kinases, including the yeast CDC28 kinase. CDK2 consists of one polypeptide chain (298 amino acids), which forms a compact structure packed into two lobes: the N-terminal (res. 1–85), which is folded into a β-list that consists of five anti-parallel β-strands (β1– β5) and the only large coil (α_1), and the larger C-terminal one (res. 86–298), which consists mainly of α-coils. The catalytic activity of the ferment consists in the transfer of the phosphate group from an ATP molecule to the protein substrate. The kinase site of ATP binding is localized in the deep cleft between the lobes. The kinase is active when it is bound with specific proteins: so-called cyclins. A cyclin, as it is interacting with both lobes of CDK2, gets bound with one of the sides of the catalytic cleft. The CDK2 catalytic subunit has a domain near its amino end (the α_1 coil), which is known as the

PSTAIRE motif (res. 45–56: CDK2; res. 52–58: CDC28). Mutations in this section disturb cyclin binding. The T loop (res. 152–170: CDK2), which blocks the entrance to the catalytic cleft in the non-active monomer form of the kinase, is also bound with the cyclin. This interaction is weaker than PSTAIRE but is necessary to stabilize the complex. The full activation of CDK usually requires two events: the kinase binding with cyclins followed by phosphorylation (T160 in CDK2 and T169 in CDC28). The catalytic residues and the T loop of CDK2 undergo strong conformational changes as a result of the kinase binding with a cyclin and T160 phosphorylation in the T loop. These changes are responsible for a 40,000-fold increase in kinase activity. The kinase is activated as a result of conformational changes in the PSTAIRE coil, which lead to a shift in the active residues simultaneously with a significant advancement of the T loop opening the catalytic cleft.

In our research, amino acid substitutions have been used that have pleiotropic manifestations in *cdc28-srm* [Gly20Ser] and *cdc28-13* [Arg283Gln] yeast cells. The *cdc28-srm* mutation consists in replacing the third glycine in the conservative sequence GxGxxG in the so-called G-rich loop in the small domain of the kinase subunit and is located against the T loop of the large domain of the kinase subunit. The *cdc28-srm* mutation is localized in the large domain of the kinase and is held away from the site of kinase interaction with a cyclin and ATP. Despite the established importance, the role of the G and T loops is poorly studied.

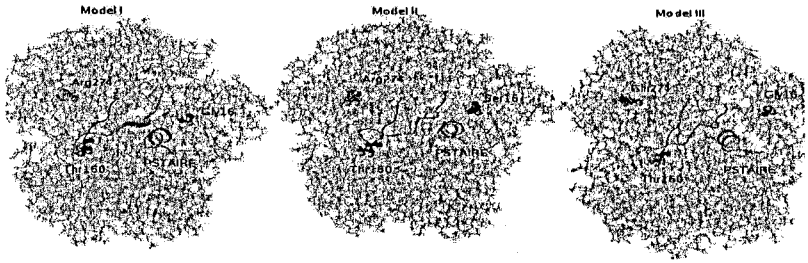

Fig. 2. The structure of the native (model I) and mutant (models II and III) kinase forms

In molecular dynamics (MD) modeling of the human CDK2 kinase structure (the native protein: model I) with substitutions for the respective amino acids: CDK2-Gly16Ser (a mutant protein: model II) and CDK-Arg284Gln (a mutant protein: model III) – the nanosecond dynamics was studied of the CDK2/cyclin A/ATP complex progression. Fig. 2 shows important structure elements of a stabilized kinase in its native and mutant forms. The obtained MD-results indicate that mutations disturb the local structure around the T loop. In the remote C-terminal area, the Arg284→Gln284 mutation has a more pronounced effect and leads to the loosening of the CDK2 kinase structure and an increase in the distance between the G and T loops [2, 3].

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Influence of super high doses of gas ion implantation into multilayered nanostructures on grain grows and gas bubble lattice formation and its radiation stability

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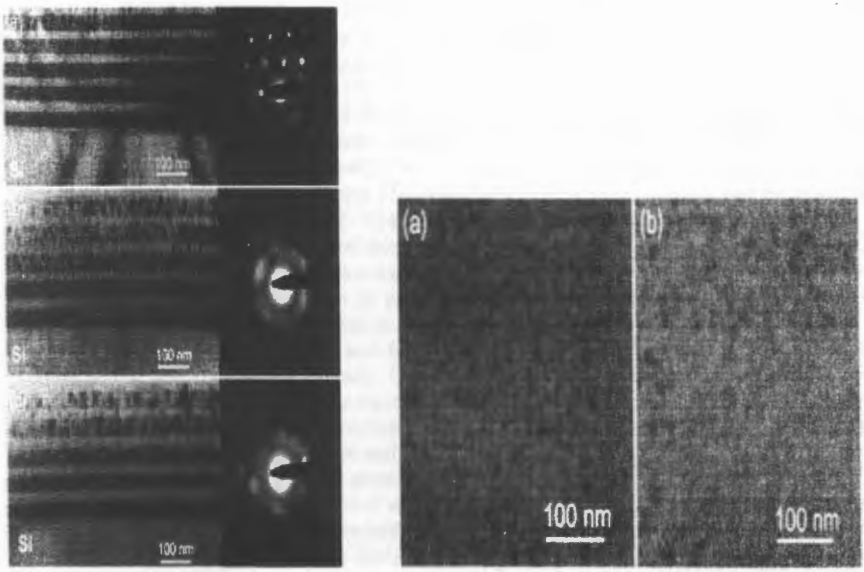
High-strength nanolayered structures (AlN/TiN)×5/Si are interesting as radiation protective materials due to a large number of interfaces that act as obstacles to slips and sinks of radiation-induced defects. So far, only multilayers of immiscible metals, such as Cu/Nb, W/Ni, Cu/W or Mo/Cu were investigated. First ever reports on the ion irradiation stability of metal-nitride multilayers were published by the author of this presentation in [1, 2]. Results presented here are a first ever report on the ion irradiation stability of metal-nitride multilayers (AlN/TiN)×5/Si under low-energy heavy ion irradiation. High-resolution transmission (XTEM) electron microscopic images of these multilayered structures are presented in Fig.1 (see [1], [2] and references in it).



a) b) c)

Fig.1. Cross-section TEM analysis of 5×(AlN/TiN)/Si implanted with ^{40}Ar. (a) – unirradiated (as-deposited); (b) – ion fluence is $2{,}0\times10^{16}$ ion/cm^2; (c) – ion fluence is $4{,}0\times10^{16}$ ion/cm^2.

Thermal spike model calculations for thermal processes in (AlN/TiN)×5/Si multilayered structures under irradiation by low-energy heavy ions were carried out, and estimations of possible melting and recrystallization processes and phase transitions under low-energy heavy ion irradiation were made (see [3] and references in it).

The discussions of gas bubble lattice formation or absence of such processes under the implantation of various gas ions like $^{1}H^{+}$, $^{2}D^{+}$ and ^{4}He with an energy of 25 keV during fluence intervals of about a few times of 10^{18} ions/cm^{2} are carried out. The first experimental results are presented too.

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Modeling small water-based clusters as a source of information about some characteristics of nanoscale systems

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Recently, the number of works devoted to the investigation of clusters has increased in an avalanche. The matter is that clusters are interesting subjects of gas-phase chemistry and physics and, at the same time, may be considered as precursors of nano-scale objects, whose properties can be guessed based on the known properties of the clusters of diverse sizes and especially their dependence on the cluster size. It is especially interesting in the case of ionization and fragmentation energies, which should regularly change with the change in the cluster size.

When clarifying the energetic trends people often use power functional approximations of the experimental values. Such dependences may have even no physical grounds, which makes the predictions based on them fruitless. Just two opposite examples can be given. In the case of individual water cluster anions, the excess electron density distribution is typically nearly spherical and localized in the center of a water cluster, so that a spherical charge placed in a cavity inside a dielectric can serve as a reasonable model. Then, the vertical electron detachment energy I_v should be inversely proportional to the thickness of the spherical layer around the charge, i.e., to the number of water molecules comprised (n): $I_v \propto n^{-1/3}$. A dependence of this kind provided a good approximation of the vertical electron detachment energies of water cluster anions formed in a molecular beam [1].

An example of another kind is the attempt of approximating the ionization energies of water clusters involving foreign anions (such as Cl^-, Br^-, I^-, or SO_4^{2-}) using dependences of the following general kind: $I_v = a + b(n+\delta)^{-p}$, where δ is an effective volume estimate of the solvated anions, and p is a variable parameter [2]. Although the effective volumes can be found from quantum chemical calculations of $X(H_2O)_n$ clusters and may be relatively reasonable, the exponential factors have no physical meaning. Furthermore, the confidence levels of these and simple $I_v = a + bn^{-1/3}$ dependences constructed for the systems are very close, which (in the absence of a physical model) gives no ground for selecting any of them as more reliable. One cannot expect to face a better situation in the case of other polyatomic solute particle anions.

The solution of the problem was found in a thorough analysis of the quantum states of the initial anions and the product clusters. Quantum mechanical and dynamic simulations provide the necessary information about the electronic-nuclear states of molecular water clusters, either individual or involving foreign X particles (atoms, ions, or molecules), that forms the basis for developing a theoretical approach of estimating probabilities and energies of the ionization and electron localization in water-based systems of an arbitrary size.

As model structure fragments of water, molecular clusters of various sizes are considered, which is founded by the data of classical dynamic simulations. Analysis of the electronic states of neutral and charged $(H_2O)_n$ and $X(H_2O)_n$ clusters revealed that, starting from n=6, the total electron density of the cluster can be represented by a superposition of the electron densities of separate water molecules and an X fragment, each of which can be approximated by a one-center (or multicenter in the case of some X particles) expansion in spherical functions. Accordingly, construction of one- or multicenter expansion of the differential electron density $\Delta\rho$ (the difference between the electron density distribution functions of $X(H_2O)_n^-$ and $X(H_2O)_n$ systems) is theoretically founded. On a condition that the size of the $\Delta\rho$ localization region does not noticeably change with an increase in the n number of water molecules (this is the case of the

most of stable $X(H_2O)_n^-$ systems), a general integral expression for the excess electron binding energy is derived; and substituting the results of numerical $\Delta\rho$ expansions of particular systems provides the dependences of $A = B_\infty + \sum_{l=0}^{p} B_l (n+\delta)^{-(l+1)/3}$ kind, where δ is the proportionality factor between the effective volumes of X particle and water molecule (determined from the analysis of the stationary points of the electron density distribution function); and only those terms are involved in the sum, for which l values ($l \in \mathbf{Z}$, $l \geq 0$) correspond to the functions, whose weights are the largest in the $\Delta\rho$ expansion. B_∞ and all B_l coefficients can be determined by fitting in either nonempirically calculated or experimentally measured ionization energies of small clusters (with n up to 20 or 30).

The possibility of extrapolating the constructed dependences to an infinite size of systems (that meet a number of conditions) is theoretically proven, which enables one to estimate the ionization energy of larger systems up to macroscopic ones based on the data obtained for small clusters of the same nature.

The work was partly financially supported by the Russian Foundation for Basic Research, project no. 08-03-01042.

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MOLECULAR DYNAMICS SIMULATIONS ON THE EFFECT OF THE PRO32THR MUTATION FOR HUMAN INOSINE TRIPHOSPHATASE

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The current progress in computer molecular modeling technologies allows performing a rapid structural analysis of small but physiologically important protein or enzyme molecules. Computer simulation and X-ray or NMR protein crystal structure data allow building relevant protein equilibrium structures that are relaxed in a water solvent and at the physiological and room temperatures.

We have investigated the structure of human inosine triphosphatase (ITPA) on the basis of crystal structure data (1, 2). ITPase activity prevents accumulation of the IMP and dITP nucleotides, which can be incorporated into RNA and DNA, posing a risk for mutagenesis. ITPA deficiency is not linked to pathology in the affected individuals, but perturbed ITP levels may be harmful under circumstances such as cellular stress, an increase in a human sensitivity to drugs, chemotherapies of cancer tumors, or in transplant procedures. We have focused on the structural effect of Pro32Thr which is detected in all ethnic groups, mostly in Asian (11–19%) and rarely in Central and South American (1–2%) ones.

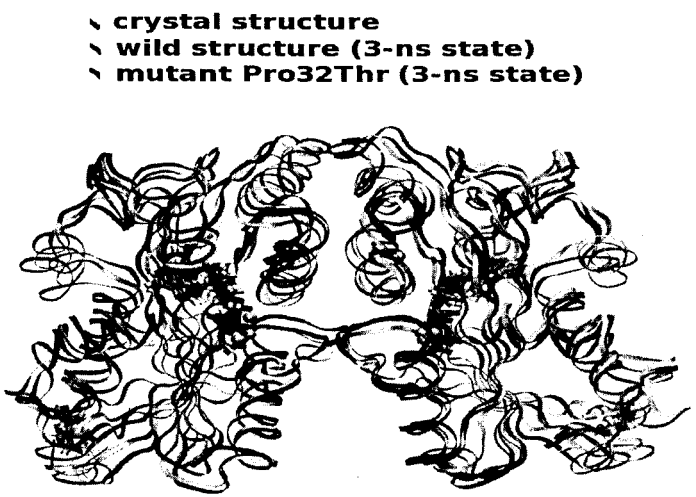

Fig. 1. A snapshot of three models of hITPA structure are shown. Superposition of the crystal (wild-type), relaxed at room temperature equilibrium (wild-type) and mutant (Pro32Thr) are presented. The positions are displayed for the two ITPA subunits (left and right) along with the amino acid residues Pro32Thr (В какой субъединице замена?) and two ITP nucleotides binding with ITPA subunits.

Human ITPA is a homodimer whose catalytic activity is actuated by Mg^{2+} ions. The nucleotide (ITP) is bound in the cleft between the (upper) dimerization lobe and (lower) N-terminal lobe of the enzyme. Molecular dynamics (MD) simulations of the structure properties of hITPA have been performed for 3-ns conformational changes (Fig.1). We try to establish the

structural difference between the ITPA models in the crystal and liquid (MD) native forms, and between the liquid native (wild-type) and mutant (Pro32Thr) heterozygote forms. In the mutant form, one subunit had a mutation. The effect of the induced Pro32Thr mutation is evaluated, and structural measurement results on distance peculiarities between the ITPA subunits and amino acid exchange point are presented, which are calculated within the framework of three models.

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Some aspects of the trans-membrane transport of alkaline ions

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Investigating interactions between alkaline metal ions or atoms and water can shed light on the mechanism underlying the functioning of parts of biological systems, particularly, the trans-membrane transport of ions in sodium and potassium channels. The following hypothesis dominates in most of the investigations devoted to trans-membrane transport of alkaline ions: before entering the channel, an ion looses its solvation shell and moves through the channel interacting with water molecules and functional groups of a polypeptide chain of the protein. A simple model of such a channel wherein hydrophilic functional groups involve a proton bound to either oxygen or nitrogen is a network of hydrogen-bonded water molecules rolled up to form a cylinder.

Using nonempirical approaches, we studied a set of model systems, which are neutral and positively charged $Na(H_2O)_m$ clusters imitating fragments of ion channels, where a sodium atom or cation is surrounded with water molecules forming a shorter or larger part of the molecular cylinder. Two states of the clusters, namely neutral and positively charged, were considered, since the peculiarities of polypeptide chains may lead to the appearance of local charges in the systems; and the negative charge close to the alkaline metal cation provides the electron density distribution similar to that typical of a neutral $Na(H_2O)_m$ cluster. Such situation may be important in the case of the pH-controlled channels.

It is obvious that the electrostatic field (a membrane potential) plays an important role in the process of ion transport through any kind of channels. However the majority of researchers ignore the effect of the electric field, though it seems quite natural that the field determines the energetics and mechanism of the process. Therefore, a special attention in our studies was paid to the effect produced by the external electric field.

As was found, clusters with the surface location of a sodium atom are more stable compared to those where the atom is located inside the cluster, and there is a high potential energy barrier on the reaction path corresponding to the inclusion of the atom in an existing water cluster, since the process involves the breakage of at least three hydrogen bonds between water molecules, whose energy is much larger than that of the appeared weak Na...O bonds.

In order to find out which kind of the local configuration of water molecules can be favorable for the inclusion of a sodium atom in the cluster, i.e., for its entering the channel mouth, diverse configurations of small system involving four to six water molecules arranged at different distances from each other were considered. When a sodium atom is initially placed near a molecular ring, it just slightly shifts to find itself over the ring plane, producing no perturbation of the ring itself. When the initial structure is composed of two non-bonded water oligomers, the atom can build in between them.

By contrast, a sodium cation is inclined to build in the existing hydrogen-bond networks of water clusters, which is clearly illustrated by $Na^+(H_2O)_{19}$ system, where the ion was initially placed close to the surface of the completely hydrogen-bonded cluster. Sodium was built in the cluster having initiated its noticeable reorganization with the breakage of several hydrogen bonds. The reason for that is as follows: the bond energy between the cation and a water molecule is nearly thrice as large as that of a hydrogen bond between water molecules. In the final structure, sodium has a neighborhood typical of stable $Na^+(H_2O)_n$ clusters with the inner localization of sodium. This means that sodium cation has no obvious obstacles for building in a hydrogen-bond network of any configuration.

At an electric field intensity of 0.005 au ($2.57 \cdot 10^7$ V/cm), sodium begins to exit from small solvation shells composed of four to six water molecules by 300 fs, and during the preceding period, the solvation shell moves aside the cation chiefly preserving its original configuration. The sole change consisted in the reorientation of oscillating water dipoles along the intensity vector of the applied field. At the higher field intensity, the molecules not only reorient along the field vector, but also move aside from each other, facilitating the transfer of the cation in the direction determined by the field and its exit to the cluster surface.

In the case of a cylindrical water cluster composed of 18 molecules, inside which a sodium ion was placed, the first stage of a similar dynamic evolution consisted in the reorientation of water molecules along the field vector in about 100 fs, which repeated the structure reorganization typical of small molecular rings and produced not only the additional field determined by water dipoles, but also provided a larger inner radius of the water channel.

Stationary analysis of the potential energy surface of $Na(H_2O)_{18}$ and $Na^+(H_2O)_{18}$ systems along the expected coordinate of the sodium exit from the cylindrical water cluster showed that the process has a high potential energy barrier, but is exothermal; and the migration of sodium inside such channel is barrier-free. The reverse process of the inclusion of sodium in the existing water cluster under the effect of the properly directed external electric field was found to be barrierless even on a non-optimal path on the potential energy surface. In the case of the atom, the barrier was about 1.36 eV.

Thus, the process of sodium transport through a membrane should be affected by two factors, namely the membrane potential and the pH of environment. The latter one makes the system more similar to either cation of neutral sodium atom surrounded with water molecules, which strongly affects the inclination of the particle to enter and exit the channel. The former one provides a certain orientation of the free OH groups inside the channel and certain distances between them (a certain radius of the channel), which affects the mobility of sodium inside the channel.

The work was financially supported by the Russian Foundation for Basic Research, project no. 08-03-01042.

Mechanical properties of graphene ribbon – carbon nanotube nanostructures

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Since their discovery graphene-carbon nanotube (CNT) composite structures are attracted attention due to their remarkable mechanical and electronic properties. Various nanodevices based on carbon nanotube or graphene were proposed such as ultrasensitive sensor, emitter and hydrogen storage devices. In recent years different composites were synthesized which includes carbon nanotubes or graphene nanoribbons or both of them [1-4]. Methods of preparing films with carbon nanotubes and graphene are similar, they include aqua dispersion of components, chemical deposition, mixing and drying with increased temperature. It was shown that the presence of carbon nanotube or graphene in composite makes better properties of latter [5, 6]. Films containing carbon nanotubes and graphenes were investigated. It was shown that they have unusual mechanical and electronic properties.

In this work, we have been explored covalently bound structures from graphene and nanotubes. The structures were designed by connection of edge atoms of graphene nanoribbons with atoms of the nanotube. Here, as a sample of compounds, the (12,0) zigzag nanotubes with covalently bounded zigzag graphene nanoribbons (ZGNR): with two (CNT/2ZGNR, Fig. 1a), four (CNT/4ZGNR, Fig. 1b) and six (CNT/6ZGNR, Fig. 1c) ZGNR.

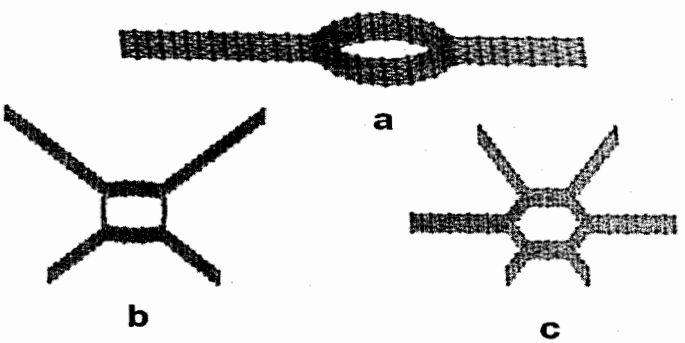

Fig. 1. The structure of zigzag graphene nanoribbons and (12,0) carbon nanotube composite: (a) two-leafed CNT/2ZGNR, (b) four-leafed (propeller shape) CNT/4ZGNR, and (c) six-leafed CNT/6ZGNR.

All of these compounds was appear energetically favorable. They possess better elastical properties that carbon nanotube. For instance, Young's modulus of the CNT is equal to 1.34 TPa. The calculated moduli of CNT/2ZGNR, CNT/4ZGNR and CNT/6ZGNR structures are equal to 2.77 TPa, 2.83 TPa and 3.04 TPa respectively.

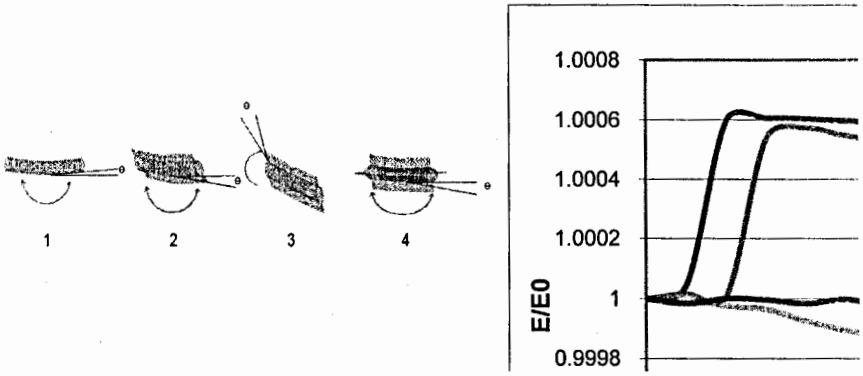

Fig. 2. – Energy of bend. Angle of bend showed in picture. 1 – NT(12,0), 2,3, - NT/2ZGNR, 4 - NT/4ZGNR.

We have been study behavior of these stucture for twisting and bending. They possess more rigidity that single nanotube because they have sp^3 bonding on junction between carbon nanotube and graphene.

We suppose that these structures can be applied in the field of chemical-physics nanodevice elements as mechanically strong conductive nanowires, memory cells, nano-mixers and so on. Using of studied structures in polymers instead of ordinary CNT looks a new promising direction in composite material development due to their extraordinary physical properties.

This work has been carried out under the financial support of Russian Foundation for Basic Research (project no.08-02-01096a) Russian Academy of Science, Program no.21

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Srtucture and mechanic properties of chiral Si-nanowires

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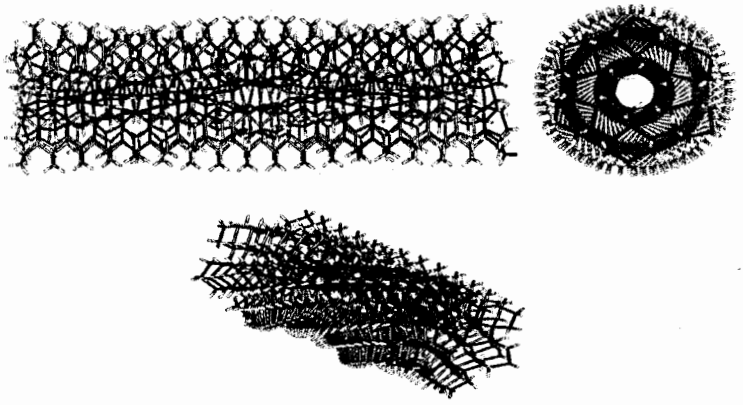
Two types of chiral Si-nanowires were discussed in this work. They are formed on hexagonal (Fig.1) and pentagonal (Fig.2) bases.

(a)

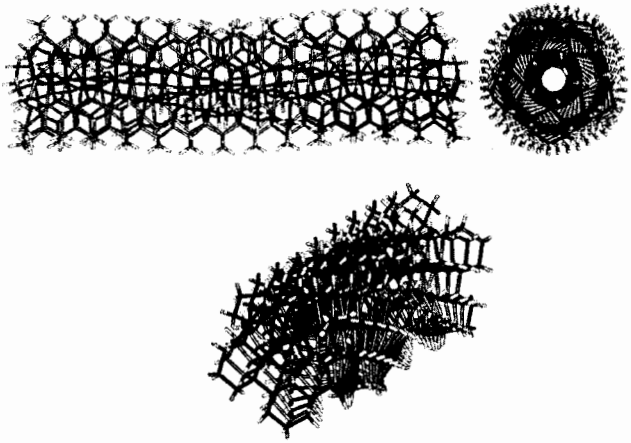


№	r (Å)	E	E (эВ)
0	53.52	0	0
1	53.12	0.0074738	0.0701395
2	52.72	0.0149477	0.28612393
3	52.32	0.0224215	0.62008818
4	51.92	0.0298954	1.1190665
5	51.52	0.0373692	1.7059569
6	51.12	0.044843	2.36688867
7	50.72	0.0523169	3.08741217
8	50.32	0.0597907	3.86326808
9	49.92	0.0672646	4.69050341
10	49.52	0.0747384	5.56537226
11	49.12	0.0822123	6.48427737

(b) (c)

Fig.1. Structure of chiral Si-nanowire based on hexagon corn: views of along and perpendicular NW axis, and its isomeric view (a). Table of deformation energy (E) changing via deformation (ε)/ The №0 is NW without loading.

Structures are formed by Si atoms in sp^3-hybridization. But structures are deformed from ideal one because of channel formation. Surface of nanowires are passivated by hydrogen.



№	r (Å)	E	E (эВ)
0	42.3	0	0
1	41.9	0.0094563	0.14642115
2	41.5	0.0189125	0.59991905
3	41.1	0.0283688	1.33370958
4	40.7	0.0378251	2.24018226
5	40.3	0.0472813	3.30860438
6	39.9	0.0567376	4.52757641
7	39.5	0.0661939	5.88561247
8	39.1	0.0756501	7.37013121
9	38.7	0.0851064	8.97180643
10	38.3	0.0945626	10.6809808

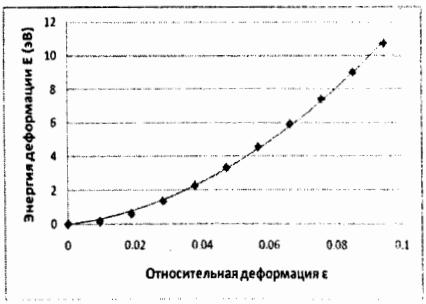


Fig.2. Structure of chiral Si-nanowire based on pentagon corn: Views of along and perpendicular NW axis, and its isomeric view (a). Table of deformation energy (E) changing via deformation (ε)/ The №0 is NW without loading.

We examined its deformation and calculate Young's modulus which were found as 27,9 GPa for nanowire with hexagonal base and 49,6 GPa for nanowire with pentagonal base. This value of Young's modulus could be compared with such parameters for mono-crystal Si-nanowires.

This work has been carried out under the financial support of Russian Foundation for Basic Research (project no. 08-02-01096a) Russian Academy of Science, Program no. 21.

Molecular dynamics simulation of water adsorbed on ice nucleation protein

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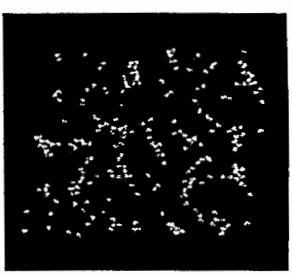
An ice nucleation protein induces a phase transition of liquid water to ice in an air. A specific hydrophilic surface of the protein may have an influence on the network of hydrogen bonds touching on the protein. However, microscopic characteristics of the ice nucleation protein and behavior of water molecules on it have not been clarified.

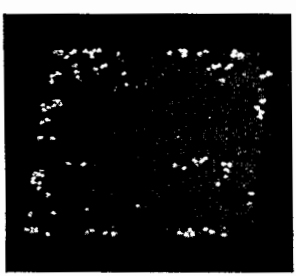
There are some studies for the protein/water system. A function of a protein may depend on the interaction of water and protein. Oleinikova A. et al [1] performed the molecular dynamics simulation of the percolation transition of water on the surface of lysozyme. They found that the formation of a spanning 2D water network on a single rigid protein molecule was described by adapting the cluster analysis of conventional percolation. They also specified the ratio of the area of hydrophilic residues covered with water molecules.

In this study we carried out the molecular dynamics simulations about various quasi-two dimensional densities of water molecules on the ice nucleation protein and analyzed the differences of the dynamics between them. We adapted *inaZ* [2] as a model of the ice nucleation protein. We fixed the motion of *inaZ* for all simulations. First, water molecules were equilibrated at T = 300 K in the system of the liquid state interacting with the protein. Then, we eliminated some water molecules at random to make initial configurations of various densities. Finally, we did the main simulations.

Fig. 1 shows water clusters surfaced on the ice nucleation protein at different densities. It was found that the percolation transition threshold of the water cluster was confirmed. But slants of the percolation probability and the finite cluster size nearby the threshold did not diverge. Those results differ from the case of the universal percolation theory or the ones of the weak coupled *inaZ* arbitrarily. It was also interesting to compare with other proteins [1] or materials.



(a) $C^* = 2.0 / nm^2$



(b) $C^* = 8.0 / nm^2$

Fig. 1: Snapshots of water clusters at a high and low concentration on *inaZ*. C^* is the ratio of the number of water molecules to the surface area of *inaZ*. White spheres are atoms of non-spanning clusters. Red spheres are ones of spanning clusters. Over a density of water molecules, spanning clusters emerge.

Fig. 2 shows the root mean square deviation of water molecules in the case of the percolating and non-percolating. It was suggested that the behavior of the water molecules in the low density

oscillate around same places. In other words, there were some differences between the movement of spanning clusters and the one of the non-spanning clusters. These consequences were the first insights of the molecular dynamics of water molecules adsorbed on the ice nucleation protein unlike bulk.

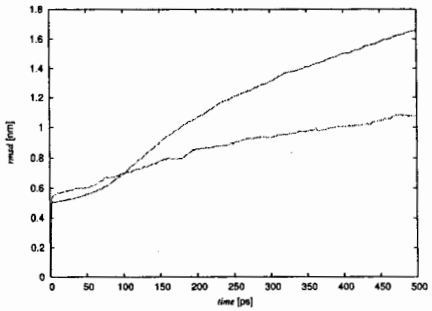


Fig. 2: Root mean square deviation of the water molecule from the initial configuration. The bottom line is the low concentration (Fig. 1 (a)) and the upper line is the high concentration (Fig. 1 (b)). The temperature is the same in both cases.

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Molecular modeling simulations in SKIF-GRID supercomputing project

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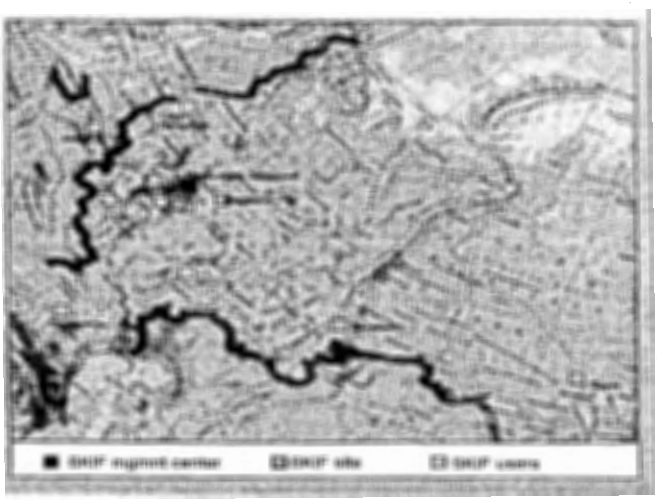
High-performance computer simulations of molecular properties play an important role in modern computation chemistry. SKIF –GRID is a joint effort of Russia and Belarus to advance high-performance and distributed computing. Important part of the project is dedicated to pilot applications of new machines and grid systems, including computational chemistry.

The Chemistry department project under SKIF-GRID framework is dedicated to the problem-solving environment for molecular simulations in the federation of SKIF-GRID supercomputers. The SKIF-GRID grid system now includes several supercomputing centers across Russia and Belarus supercomputing center in United Institute of Informatics Problems, with total theoretical performance around 100 trillion operations per second.



The SKIF-GRID middleware is based on UNICORE open-source software. The middleware enables uniforms access to all supercomputers across network, as well as provides global storage and workflow engine services.

The environment includes:

1. Classical molecular simulation packages (NAMD)
2. Quantum chemistry services (primarily, PC GAMESS primarily)

We have also characterized performance and scalability of quantum chemistry codes on several SKIF machines.

Molecular dynamics simulation and theoretical analysis of the interaction of CNT with carbon disulphide solvent

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Carbon nanotubes (CNTs) exhibit unique electrical and chemical properties. They are of great importance for material research, microelectronic applications, and organic chemistry. Depending on their chemical structure, CNTs can be used as an alternative to organic or inorganic semiconductors, as well as conductors [1, 2].

The aim of the present paper is to simulate the dynamic and structural properties of CNT interacting with carbon disulphide CS_2 solvent in terms of the influence of the van der Waals forces. The molecular dynamic simulation of a CNT interaction with CS_2 solvent has already been performed in the conditions of an NPT ensemble with the Berendsen thermostat, see [3], where the formation of self-assembling layered structure around a CNT was found. Here, we do some theoretical analysis of structure formation under the simplifying assumption of axial symmetry and using the thin-wall approximation of the CNT potential.

The interaction of atoms with a CNT has already been studied by the molecular dynamics method [3] using the homogeneous thin wall potential inside the CNT, which is yielded by integrating the van der Waals potential. The present approach is different from the ones known to us in that we study the self-organization of solvent molecules not inside the nanotube, but *in the outer region of the nanotube*. This makes the analytic equation for the thin wall potential [4] inappropriate and requires special numeric and analytic studies.

In the case of complex solvents like carbon disulphide CS_2 studied by the MD method [2, 3], it is problematic to integrate the full tensor interaction potential, which depends on the orientation of the CS_2 molecules with respect to the CNT. So, the optimal way is to study the interaction by MD with an exact potential for both C – C and C – CS_2 interactions. The results of the simulation are presented in [3]. Simulations performed for different atomic concentrations show the formation of stable self-assembled structures like the one in Fig.1.

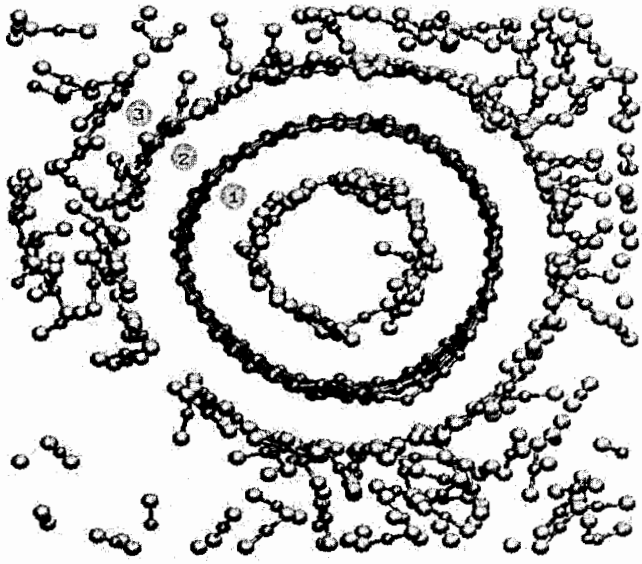

Fig. 1. A snapshot of the stationary state obtained by MD simulations at t=80 ps. A high-density phase is displayed (the number of solvent molecules is equal to that of the CNT).

In the equilibrium state, the maximum of the particle distribution should correspond to the minimum of the effective potential acting on the particles. This corresponds to the Boltzmann distribution function exp(-U(x)/T). In our case, the potential U(x) in the outer region of the CNT is expressed in terms of the elliptic functions of the ratio of the geometric mean to the arithmetic mean radii between the thin wall and the test particle. In our MD simulations, we used Lennard – Jones potentials (the 12-6 and 10-4 types) for the set of parameters.

The corrections to the Boltzmann solution obtained under the assumption of axial symmetry and taking into account the secondary Boltzmann effects in the first layer lead to the second layer structure, which is distant from the first layer by approximately one width of the Lennard – Jones potential. This is observed both in MD simulations and the 1d stationary integral equation for the density function.

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Molecular Dynamics Studies on the Structure of Onco-Proteins P53: Correlation between the Wild-Type and Radioresistant Mutant Systems

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p53 (53 kilodalton (kDa) protein, also known as **protein 53** or **tumor protein 53**) is activated either to induce a cell cycle arrest to allow repair and survival of the cell or apoptosis to discard the damaged cell. **p53** tumor suppressor protein is involved in preventing cancer and plays central role in conserving genomic stability by preventing genome mutation. When activated **p53** binds DNA and activates expression of several genes including WAF1/CIP1 encoding for p21. p21 (WAF1) binds to the G1-S/CDK (CDK2) and S/CDK complexes (molecules important for the G1/S transition in the cell cycle) inhibiting their activity.

Single amino acid substitutions (mutations) in the **p53** structure causes deactivation of the **p53** protein which result in cancer [1]. Usually most mutations (95% of all known tumor mutations) occur in the DNA-binding domain (DBD) of the **p53** protein. Thus, an oncohenic form of **p53** is predominantly a full-length **p53** protein with a single amino acid substitution in the DBD. Most of these mutations destroy the ability of the protein to bind to its target DNA sequences, and thus prevents transcriptional activation of these genes. It is worth noting that tumors with inactive **p53** mutants are aggressive and often resistant to ionizing radiation and chemotherapy.

The aim of the present paper is to study the molecular mechanism of **p53** (dimer structure) and DNA binding based on MD (molecular dynamics) simulation method. Apart from the previous MD study [2] we have investigated the correlation effects between the human (entry 1TSR in PDB; Fig.1: left) and mouse (entry 3EXJ in PDB; Fig.1: right) **p53** proteins under the same environment (water solvent) and simulation conditions (temperature, ensemble, pressure).

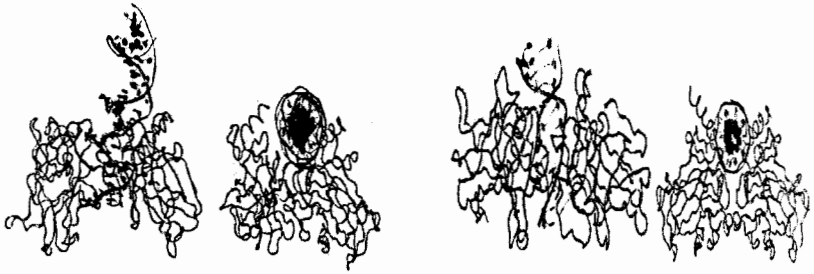

Fig. 1. The side and top views of p53 human (left: PDB entry file 1TSR) and mouse (right: PDB entry file 3EXJ) proteins are shown. For each p53 protein structure two chains (A and B) symmetrically surround the related DNA sequence located in the central domain.

For both human and mouse **p53** structures we have examined the effect of Arg273→His (R273H) mutation on the p53–DNA binding domain. Totally we have performed 16 model calculations (periodic PME-NPT; periodic PME-NVT; non-periodic cutoff) on four p53 relevant structures (human p53: wild-type and mutant; mouse p53: wild-type and mutant), to compare the conformational changes between the **p53** relaxed structures and the original 3D structures.

For the p53-DBD interactions three arginines (R248, R273, R280), one serine (S241) and one alanine (A276) are responsible for DNA binding. We have calculated the positional changes of all five amino acid residues which are related to the direct p53-DNA contact. In Fig.2 the MD distance diagrams are presented for the R248 - DNA(DG13) interaction during 3-ns dynamical changes of the human **p53** protein (chain B). In Fig.2(A) the left diagram displays the R248 – DNA(DG13) distance for the p53 wild-type and right diagram – for the p53 mutant (R273H) proteins. From the comparison of distance diagrams in Fig.2 it is seen that the induced mutation R273H has to essentially perturb the conformation and to effect the DNA contact. A similar behavior we have observed for the mouse p53 protein (Fig.2, diagrams B). In Fig.2(B) the R248 – DNA(DC16) interaction during 3-ns dynamical changes are shown for the mouse **p53** protein (chain A). The diagrams B of Fig.3 present the R248 – DNA(DC16) contact for the mouse p53 wild-type and mutant (R273H) proteins. The comparison of distance distributions in Figs.2(A) and 2(B) are straightforward.

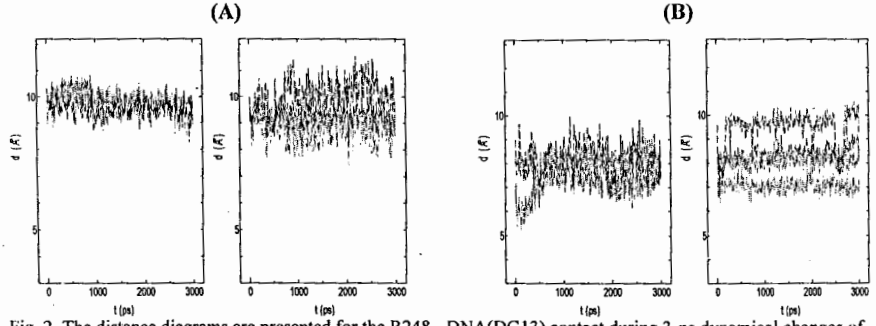

Fig. 2. The distance diagrams are presented for the R248 - DNA(DG13) contact during 3-ns dynamical changes of the human p53 protein (chain B). Left diagrams (A) are for the human p53 wild-type and mutant (R273H) proteins; right diagrams (B) are for the mouse p53 wild-type and mutant (R273H) proteins, respectively.

In summary the structural correlation effects between the **p53** human (PDB: 1TSR) and mouse (PDB: 3EXJ) proteins show the essential perturbation induced by the R273R mutation on DNA contact domain. The results seem to be in a good agreement with the experiment [3], where the R273H mutation has shown to simply remove the DNA contact [3].

Acknowledgments: The MD simulations have been performed using computing facilities, software and clusters at CICC (JINR, Russia), RICC (RIKEN, Japan), RIKEN-Yokohama (MDGARPE-3), Yasuoka Laboratory (Keio University, Japan). We thank Prof. Toshiaki Iitaka (CAL RIKEN) for the help in getting access to the software and hardware of the RIKEN computing cluster RICC.

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AB INITIO MODELS OF ELECTRON SUBSYSTEM RESPONSE ON EXTERNAL PERTURBATIONS IN MOLECULES, LIQUIDS AND SOLIDS

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The description of many atomic systems with the consideration of electron component evolution is required for the relaxation models for the nonequilibrium states formed as the results of radiation interaction with matter and fast nonadiabatic perturbations. From the point of view of the balance between quantitative accuracy of real materials description and computational complexity, the electron density functional theory (DFT) can be distinguished as a tool of choice among the hierarchy of approximation to the exact solution of the problem of many electron dynamics. Although the existing DFT based methods for excited states description require further study and improvements they allow constructing models for the study of electron-ion relaxation in condensed matter that is illustrated in this talk using three examples.

The quantum molecular dynamics is used with the semiclassical method of the Tully switchers to describe the surface hoping between hypersurfaces of two different states. The model of the radiationless nonadiabatic relaxation of photoexcited states of N-methylformamidi molecule C2H5NO is developed. Calculations of relaxation dynamics are performed.

An approach for coupling of the classical and quantum molecular-dynamics models of the electrolyte-graphite systems is developed. The models of alkaline and organic electrolytes were built. The calculations of the electrical double layer capacity and diffusion properties of the electrolytes at various conditions are performed. The guidelines are proposed for the modifications of the porous graphite structure for increasing of the energy and power properties of supercapacitors.

The finite temperature density functional theory approach is deployed for description of the fcc LiF crystal in a two-temperature warm dense matter state with hot electrons and cold lattice that is formed after ultrafast energy deposition. The lattice stability and the interatomic bonding at elevated electronic temperatures are studied. The excitation of the electronic subsystem at temperatures Te ~ 3eV results in the loss of mechanical stability of the fcc LiF lattice that is manifested as an appearance of the soft acoustic phonon mode and should probably lead to non-thermal melting. The corresponding redistribution of the electronic density implies that the originally strongly ionic interatomic interaction becomes more of covalent character with the rise of electronic temperature.

Graphene-graphane mixing nanostructures: hydrogen functionalization of graphene, properties and applications

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Undoubtedly work on graphene is at present mostly about fundamental research [1]. But the interest is also growing for potential applications The main idea is to organize integral electronic scheme based on the one graphene sheet using its fictionalization by non-carbon atoms transforming sp^2-hybridized C-atoms to the sp^3 C-atoms, for example, using chemi-adsorbed H-atoms [2-4]. Recently we have considered quasi-2D superlattices and electronic waveguides based on graphene lined by chemically bounded hydrogen atom lines or nanopeaces [2,4-6]. We have observed that the small amount of adsorbed H-atoms can drastically semimetal graphene opening gap (tranformed it to semiconductor [3]. band gaps oscillate with increasing of SL period and vanish in infinite limit (pure, semimetal graphene). Here we consider also quasi-1D SLs and quantum dots based on graphene nanoribbons lined by chemically bounded hydrogen atoms.

We have observed that the structures - composites based on graphene and graphane parts may systematized as two different areas of electronic behavior during transition from graphene to graphane under step by step adsorption of H-atoms by different ways of H-atom filling up - Fig.1 [5].

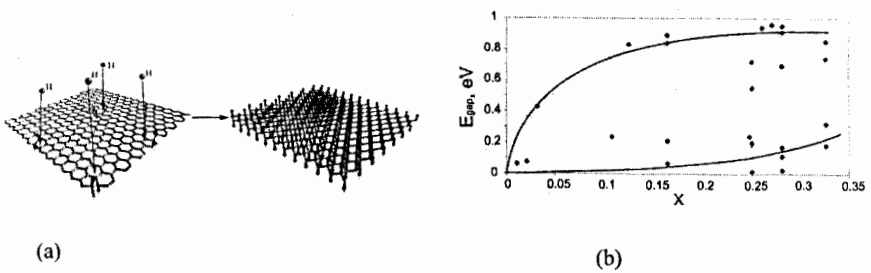

Fig.1. Scheme of graphene filling by chemically adsorbed H-atoms up to graphane – (a): two types of electronic gap behavior with different step by step H-atom filling up (CH_x) of areas shown on the left (a) structure [5].

We have constructed quasi-random stricture of graphane organized from three possible graphene-like configurations – Fig.2 [6]. This structure demonstrates decreased lattice parameter, while at the same time preserving the overall trigonal symmetry of graphane sheet, and suggests that the unexpectedly small lattice parameter values of the materials [2] may result from in-layer conformational disorder.

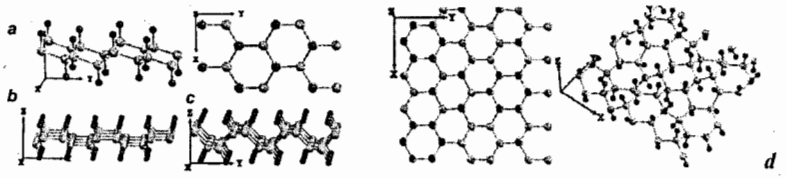

Fig.2. Three possible conformations of graphane: (*a*) "chear", (*b*) "bed", (*c*) "gauche-chair " (C-atoms - yellow, H-atoms -- blow) -- (a), and quasi- random stricture of graphane organized from these configurations -- (*d*).

Elastic properties of the structures based on chemically bound graphene layers covered by hydrogen have been considered also.

The possible applications of described C-CH_x structures in nanoelectronics (nanowires, transistors, switchers, rectificators), as sensors, as mechanical elements (vibrators, springs, membranes, cantilever diamane tips) and optical elements. The new technique, which involves "writing" electrically conducting nanowires onto graphane using a heated atomic force microscope tip, could be ideal for making flexible nanoelectronic devices.

This work has been carried out under the financial support of Russian Foundation for Basic Research (project no. 08-02-01096a) Russian Academy of Science, Program no. 21.

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Научное издание

MOLECULAR SIMULATION STUDIES IN MATERIAL AND BIOLOGICAL SCIENCES
4th Japan–Russia International Workshop
MSSMBS'10

Book of Abstracts

МОЛЕКУЛЯРНО-ДИНАМИЧЕСКОЕ МОДЕЛИРОВАНИЕ В НАУКАХ О ВЕЩЕСТВЕ И БИОЛОГИИ
4-е Российско-японское международное рабочее совещание «MSSMBS'10»

Сборник аннотаций

Ответственный за подготовку сборника к печати *Х. Т. Холмуродов.*

Сборник отпечатан методом прямого репродуцирования
с оригиналов, предоставленных оргкомитетом.

E19-2010-88

Подписано в печать 6.08.2010.
Формат 60 × 90/16. Бумага офсетная. Печать офсетная.
Усл. печ. л. 3,75. Уч.-изд. л. 6,24. Тираж 80 экз. Заказ № 57048.

Издательский отдел Объединенного института ядерных исследований
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