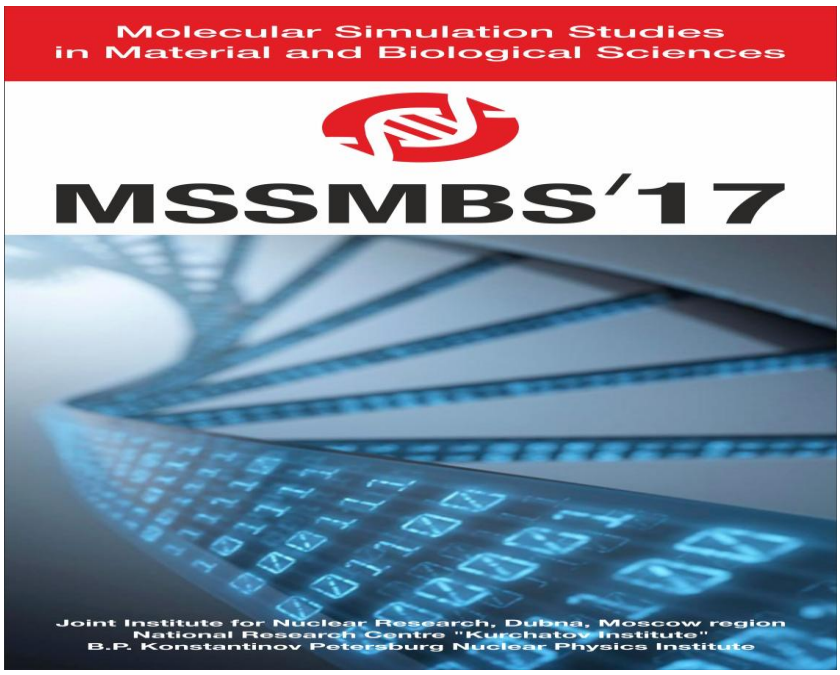
INTERNATIONAL SYMPOSIUM MSSMBS-2017 “Molecular Simulation Studies in Material and Biological Sciences”



Book of Abstracts

Petersburg Nuclear Physics Institute of the National Research Center "Kurchatov Institute" & Joint Institute for Nuclear Research, Dubna, Russia

INTERNATIONAL SYMPOSIUM MSSMBS-2017

“Molecular Simulation Studies in Material and Biological Sciences”

St.Petersburg, September 7 – 10, 2017

Book of Abstracts

Edited by
Kholmirzo T. Kholmurodov
and Andrey L. Konewega

St.Petersburg – 2017

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

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INTERNATIONAL SYMPOSIUM MSSMBS'17 "Molecular Simulation Studies in Material and Biological Sciences" (MSSMBS, 2017, St.Petersburg)
Book of the Abstracts of the INTERNATIONAL SYMPOSIUM MSSMBS'17 "Molecular Simulation Studies in Material and Biological Sciences" — St.Petersburg: Petersburg Nuclear Physics Institute (PNPI) of the National Research Center "Kurchatov Institute" (NRC "Kurchatov Institute"), Russian Federation, 2017. - 61 p.

ISBN

The MSSMBS-2017 symposium has appeared to provide an ideal opportunity to discuss the latest development and exchange technical ideas in the field of computational materials and biological sciences. This symposium is a 11th international symposium held in St.Petersburg, following the 10th one held in Khujand, Tajikistan in 2016. Especially, as organizers were planning, the MSSMBS-2017 would promote to establish the very close cooperation between young researchers that help to strengthen the future scientific cooperation between Russia, Japan, Tajikistan, USA, France, etc. In the framework of the MSSMBS the presentation talks and lectures would be given not only by leading Russian and Japanese scientists, but also by young researchers from Russia and Japan covering the following topics: the development of high performance computers and new theoretical methods; computational methods in modern materials and biological sciences, and so on. The contributions of young scientists are greatly welcome to make their bridges with Japanese and Russian colleagues and to promote a new branch of world science in the own country.

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МЕЖДУНАРОДНЫЙ СИМПОЗИУМ MSSMBS'17 "Молекулярно-динамическое моделирование по вычислительному материаловедению и биологическим наукам" (2017, Санкт-Петербург)

Сб. аннотаций МЕЖДУНАРОДНОГО СИМПОЗИУМА MSSMBS'17 " Молекулярно-динамическое моделирование по вычислительному материаловедению и биологическим наукам " ─ Санкт-Петербург: Отель Новый Петергоф, 2017. - 61 с.

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Международное рабочее совещание MSSMBS'17 " Молекулярно-динамическое моделирование по вычислительному материаловедению и биологическим наукам" является 11-м по счету международным совещанием в Санкт-Петербурге, Российской Федерации, после KSCMBS'16 "Худжандского Симпозиума по Вычислительному Материаловедению и Биологическим Наукам", организованным Худжандским Государственным Университетом (ХГУ) им. Академика Бободжона Гафурова, Худжанд, 2016, и посвященным проблемам молекулярного моделирования физических, химических и биологических систем. Наряду с организаторами настоящего совещания – Петербургским институтом ядерной физики имени Б.П. Константинова (ПИЯФ), Национальным исследовательским центром "Курчатовский институт" (НИЦ "Курчатовский институт", Гатчина) и Объединенным Институтом Ядерных Исследований (ОИЯИ) г.Дубна – в нем принимают участие многие исследовательские группы из России (Институт биоорганической химии им. академиков М.М. Шемякина и Ю.А. Овчинникова Российской академии наук, Московский государственный университет имени М.В. Ломоносова, Объединенный Институт Высоких Температур, РАН), Японии (Университеты Кейо, Нагоя, Васеда), а также ученые из США, Франции, Таджикистана, и т.д. Следует отметить, что в ОИЯИ, г.Дубна, Московской области подобные совещания (MSSMBS) проводились начиная с 2004 по 2014 годов.

Настоящее совещание MSSMBS'17 посвящено следующим проблемам современной науки:

- Методы и подходы компьютерного молекулярного моделирования.
- Молекулярно-динамическое (МД) и Монте-Карловское (МК) моделирования.
- Моделирование биологических молекул (РНК и ДНК, белков и ферментов с мутационными переходами и т.д.).
- Радиационная физика, влияние радиации на биосферу, физика твердого тела (физика конденсированного состояния).
- Физические и биохимические системы (газы, кристаллы, жидкости, полимеры, био-трибология и т.д.).
- Производство материалов и дизайн (ионно-примесные структуры, клатраты высокого давления, углеродные нанотрубки и т.д.).
- Создание лекарств в медицине (соединение одной молекулы к другой, ингибирующие действия ферментов и т.д.).
- Вычислительная физика, химия, биология и медицина.
- Графически ускоренная молекулярная динамика и связанная с ним техника.

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Keynote speakers:

- Yuko Okamoto (Nagoya University, Japan).
- Robert J. Woods (Complex Carbohydrate Research Center, University of Georgia, Athens, USA).
- Andrey L. Konewega (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
- Norbert Kucerka (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
- Tomobe Katsufumi (Keio University, Japan).
- Andrey S. Kuznetsov (National Research University Higher School of Economics, Russian Federation).
- Kholmirzo Kholmurodov (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
- Roman Efremov (National Research University Higher School of Economics, Moscow, Russian Federation).
- Mikhail Kiselev (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
- Jérôme Golebiowski, Pr. (University Nice Sophia Antipolis, Nice, France).
- Tomoyuki Yamamoto (Waseda University, Japan).
- Michael Petukhov (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
- Andrey Gurtovenko (Institute of Macromolecular Compounds, RAS, St.Petersburg, Russis)

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PREFACE

This is the Book of Abstracts of the International Symposium MSSMBS'17 "Molecular Simulation Studies in Material and Biological Sciences", which to be held in New Peterhof Hotel in St.Petersburg, Russian Federation, September 7 – 10, 2017.

The MSSMBS-2017 symposium has appeared to provide an ideal opportunity to discuss the latest development and exchange technical ideas in the field of computational materials and biological sciences. This symposium is a 11th international symposium held in Russia, Japan, Tajikistan, following the 10th one held in Khujand, a nothern ancient city of Tajikistan, in 2016. Especially, as organizers were planning, the MSSMBS-2017 would promote to establish the very close cooperation between young researchers that help to strengthen the future scientific cooperation between Russia, Japan, USA, France, Tajikistan, etc. In the framework of the MSSMBS the presentation talks and lectures would be given not only by leading Russian and Japanese scientists, but also by young researchers from Russia, Japan, Tajikistan, covering the following topics: the development of high performance computers and new theoretical methods; computational methods in modern materials and biological sciences, and so on. The contributions of young scientists are greatly welcome to make their bridges with Japanese, Russian, European, USA colleagues and to promote a new branch of world science in the own country.

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- Computational and computing physics, chemistry, biology and medicine
- GPU accelerated molecular dynamics & related techniques

The MSSMBS'17 workshop will be started and finished at New Peterhof Hotel of St.Petersburg in the old ancient historical city part. We will provide a broad discussion on computational materials and biological achievements along with the cultural exchanges, through the sightseeing of the modern and historical places of St.Petersburg and nearest regions.

Welcome to St.Petersburg, nothern capital of Russia!

Andrey L. Konewega and Kholmirzo T. Kholmurodov,

Co-Chairmen of the MSSMBS'17 Organizing Committee.

Generalized-ensemble algorithms for materials and biomolecular simulations

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Conventional Monte Carlo (MC) and molecular dynamics (MD) simulations in materials and biological sciences are greatly hampered by the multiple-minima problem, where the simulations tend to get trapped in some of huge 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 reviews, see, e.g., Refs. [1-5]). With these algorithms we can explore a wide range of the configurational space. The advantage of generalized-ensemble algorithms such as multicanonical algorithm (MUCA), simulated tempering (ST), and replica-exchange method (REM) lies in the fact that from only one simulation run, one can obtain various thermodynamic quantities as functions of temperature and other parameters of the system. Recently, new generalized-ensemble algorithms have been developed [6-10]. We have also given a general formalism for multidimensional MUCA, ST, and REM [11].

In this presentation, I will give the results of various applications of generalized-ensemble algorithms to materials and biological sciences. The first example is an application to pressure-induced protein denaturations [12]. The system is a protein ubiquitin. A new method, Pressure Simulated Tempering (PST) [6], was employed. A random walk in pressure space between 1 bar and 10,000 bar was realized. We have shown that at high pressure water molecules come into the protein and unfold it. In Fig. 1 we show snapshots at low pressure and at high pressure.

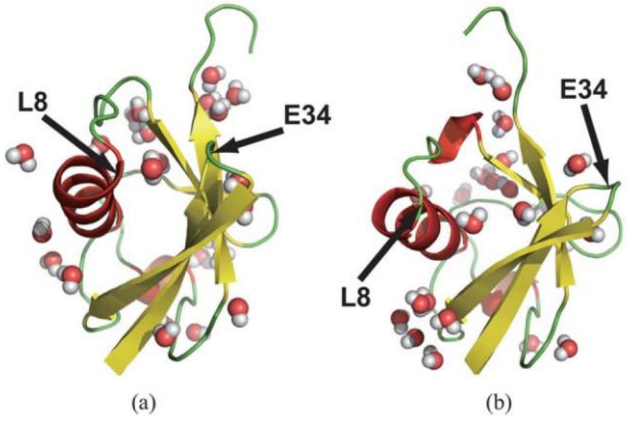

Fig. 1. Typical snapshots of ubiquitin at (a) low pressure and (b) high pressure.

The second example is a Replica-Exchange Umbrella Sampling (REUS) simulation [13] of phtalocyanin formation with quantum effects incorporated by Density Functional Tight Binding (DFTB). In Fig. 2 we show our proposed pathway of the formation of phtalocyanin and the other product.

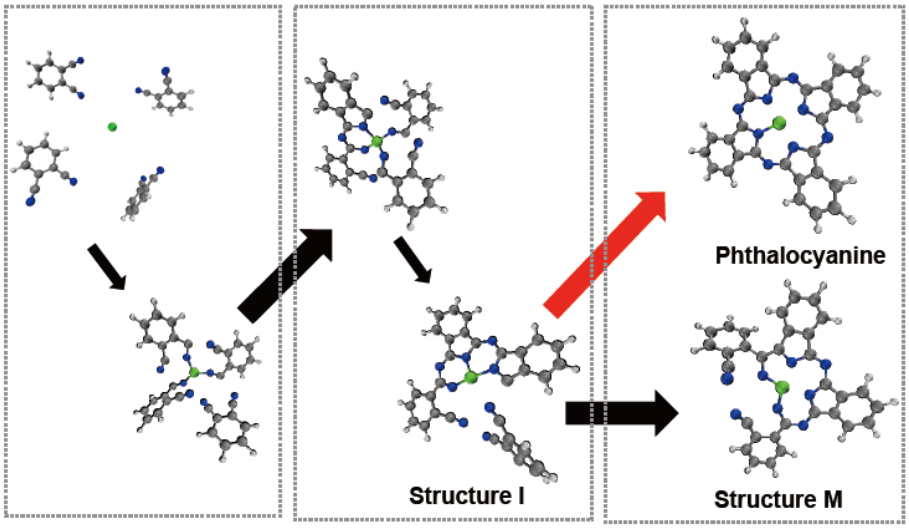

Fig. 2: Proposed pathway of phtalocyanine formation.

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INVESTIGATION OF NASCENT PEPTIDE EXIT TUNNEL BY MEANS OF MOLECULAR DYNAMICS SIMULATIONS

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The ribosome is a large ribonucleoprotein that synthesizes all cellular proteins according to the program delivered by mRNA. Nascent peptide chain goes out through the so-called nascent peptide exit tunnel (NPET), a channel composed predominantly from rRNA residues. NPET is also a target of many antibiotics and participates in the regulation of translation, selectively interacting with some peptides growing in NPET.

NPET, like the ribosome in general, is a dynamic system whose conformation reacts to ligand binding, the introduction of mutations or the modification of nucleotide residues, and changes during the translation process. Structural methods such as X-ray diffraction analysis and cryo-electron microscopy are not always able to propose adequate structural explanations of data describing ribosome functioning and its response to one or another effect. The efficient way to solve this problem is molecular dynamics (MD) simulations of the ribosome and its complexes with ligands [1]. In particular, using equilibrium MD and metadynamics we were able to model the structure of the phenylalanil derivative of the antibiotic tylosin (TylPhe) in the complex with the *E. coli* ribosome. TylPhe, in contrast to tylosin, is incapable to form a covalent bond with the walls of the NPET, but it is little more potent inhibitor of translation than tylosin, and binds to the ribosome only slightly weaker than one [2], whereas tylosin with the reduced aldehyde group is an extremely weak inhibitor of translation. It was found that the phenylalanine residue contained in TylPhe forms a stable stacking interaction with the C2610 base and a hydrogen bond with U1782 base while maintaining the conformation, position and intermolecular interactions of the tylosin part of the structure (Fig. 1).

One of the mechanisms of the bacterial ribosome resistance to antibiotics is the modification of rRNA bases. For example, 2,8-dimethylation of A2503 adenine which confers resistance to lincosamides, amphenicols, oxazolidinones, pleuromutilins and some macrolides. The wide spectrum of resistance caused by this modification suggests that the mechanism of its action is based on conformational rearrangements in the NPET, rather than a simple steric clash. Our calculations have proved this assumption: 2,8-dimethylated A2503 forms a strong stacking with the base A2059 differently than the constitutively 2-methylated A2503, that lead to conformational rearrangements, namely, stabilization of stacking interactions in the G2057-A2058-A2059-A2503 segment together with the destabilization of stacking interactions between A2503 and G2061 residues. These changes lead to a decrease in the stability of the hydrogen bonds that support conformations of the rRNA residues in the vicinity of A2503, lowering the affinity of the ribosome to the antibiotics of the groups listed above. 2,8-dimethylation of A2503 and the drug resistance provoked by it is an example of the sophisticated reaction of the ribosome to a small local effect.

An interesting example of the dynamic behavior of NPET is the interaction of chloramphenicol (CAM) with a bacterial ribosome. X-ray diffraction analysis of the CAM complex with empty ribosomes shows that this antibiotic interacts with the A2451 and C2452 bases of the peptidyl transferase (PT) centre [3]. However, biochemical experiments revealed

that CAM did not exclude the initiation of PT reactions and manifested selectivity in suppressing of the synthesis of certain peptide sequences [4] that contradict the X-ray structural data. Our simulations of the interaction of the CAM with the *E. coli* ribosome in the A,P-state enable us to suggest that the CAM forms stacking interactions with U2506 and Ψ2504 bases, entering between them, and hydrogen bonds with G2061 and Ψ2504 bases, while the dichloroacetyl fragment of CAM emerges into the lumen of the tunnel that was favored to its interaction with the nascent peptide chain (Fig. 2). Importantly, the nucleotide residues U2506 and Ψ2504 accept the optimal conformation for this interaction only during the elongation of the translation. Thus, the dynamic appearance of the antibiotic binding site that exists only in a certain functional state is possible in the ribosome. This supplements and extends the generally accepted idea of induced fit, according to which the binding of a ligand to a protein may cause conformational changes that align interacting groups in their correct orientation [5].

All simulations were performed on the Lomonosov supercomputer of the Moscow State University. GROMACS 5.1.4 and PLUMED 2.1 packages, parm99sb and GAFF force fields were used. Point charges were obtained by the RESP method using the molecular electrostatic potential, calculated by the Hartree-Fock method with a 6-31G* basis.

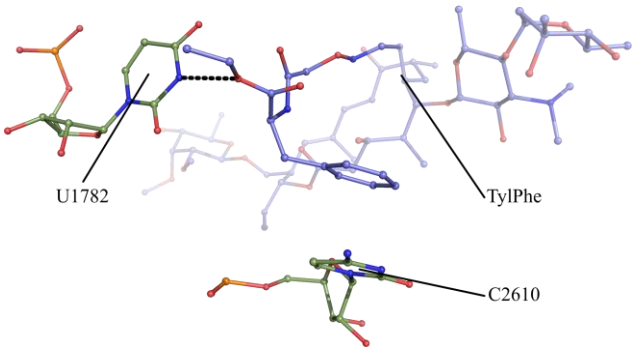

Fig. 1. Conformation of phenylalanyl substituent of TylPhe and its interaction with NPET walls. Hydrogen bond depicted by black dashes.

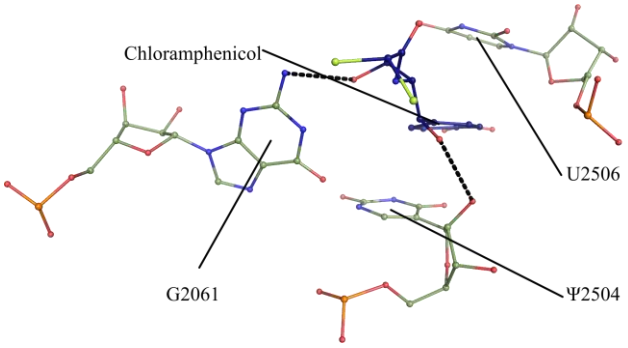

Fig. 2. Interaction of chloramphenicol with G2061, U2506 and Ψ2504 bases. Hydrogen bonds depicted by black dashes.

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DESIGN OF STABLE α-HELICAL PEPTIDES FOR BIOTECHNOLOGY AND MEDICINE

A.Yakimov[1,2], G. Pobegalov[2], I. Bakhlanova[1], M. Khodorkovskii[2], D. Baitin[1,2] and **M. Petukhov**[1,2]

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The α-helices are the most frequently occurring element of secondary structure in globular water-soluble proteins. α-Helices are often involved in protein interactions with other proteins, nucleic acids, and lipids of cell membranes and play a central role in thermal stability of proteins from thermophilic bacteria. That is why the highly stable α-helical peptides, used as highly active and specific inhibitors of protein-protein and other interactions have recently found more applications in biotechnology and medicine (1). However, it is known that sequences of α-helices from natural proteins generally are not enough conformationally stable and therefore cannot be used in many scientific and practical applications. To improve the conformational stability of the α-helical peptides and the thermostable proteins we developed **SEQOPT** (available at **http://mml.spbstu.ru/services/seqopt/**), a novel method for global sequence optimization capable to find amino acid sequences with possible maximum of stabilizing intramolecular interactions stability under given environmental conditions (temperature, pH, and ionic strength) (2,3).

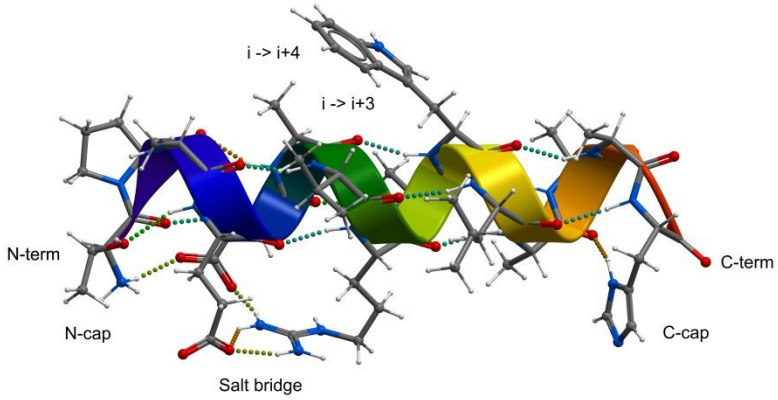

Figure 1. The structure and factors that influence the conformational stability of the α-helix in proteins and monomeric peptides

Short peptides are usually very mobile and do not have any specific conformation. **SEQOPT** radically change the distribution of α-helical segments maximizing the solution populations of long helical segments (Fig.2).

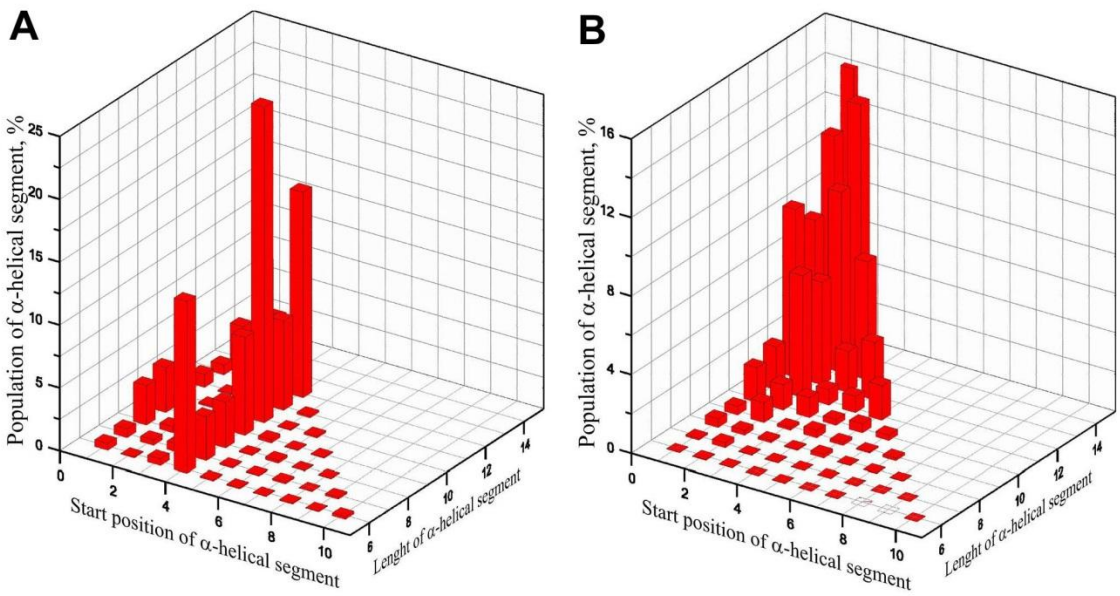

Figure 2. The distribution of populations of all possible segments in a short 13-aa residues peptide (according to AGADIR model (4,5)). A) C-terminal peptide from Ribonuclease A (ac-AETAAAKFLRAHA-nh2); B) peptide with an optimized sequence of the same length ac-DYMERWYRYYNEF-nh2

It is known that RecX protein, a natural RecA protein inhibitor, can completely disassemble RecA filaments at nanomolar concentrations that are two to three orders of magnitude lower than that of RecA protein. Based on the structure of RecX protein complex with the presynaptic RecA filament and **SEQOPT** calculations, we designed a short α-helical peptide that both inhibits RecA protein activities *in vitro* and blocks the bacterial SOS-response *in vivo* (6).

```
№aa    …-136-137-138-139-140-141-142-143-144-145-146-147-148-149-150-151-152-153-…
RecX   …-Val-Tyr-Ser-Glu-Lys-Val-Lys-Ile-Gln-Arg-Phe-Leu-Leu-Tyr-Arg-Gly-Tyr-Leu-…
4E1   Ac-Glu-Glu-Glu-Glu-Lys-Val-Lys-Ile-Leu-Arg-Tyr-Leu-Leu-Tyr-Arg-Leu-Ile-Tyr-NH2
```

Figure 3. The results of global optimization of the amino acid sequence of the α-helix protein RecX. RecX/#aa – the names and the position numbers of the RecX protein amino acid residues from *E.coli*. 4E1 – the peptide with optimized amino acid sequence. The amino acids that were fixed in the optimization are shown in red.

CD measurements showed that 4E1 peptide with optimized sequence indeed is highly stable α-helix (helix content (HC) ~ 80%) while RecX peptide from natural protein has HC~4% only. It is known that the bacterial RecA protein initiates the SOS-response only after the formation of their helical filament on ssDNA. Figure 4 shows that 4E1 peptide is capable to quickly disassemble the RecA filament *in vitro* as well as completely block bacterial SOS-response *in vivo*.

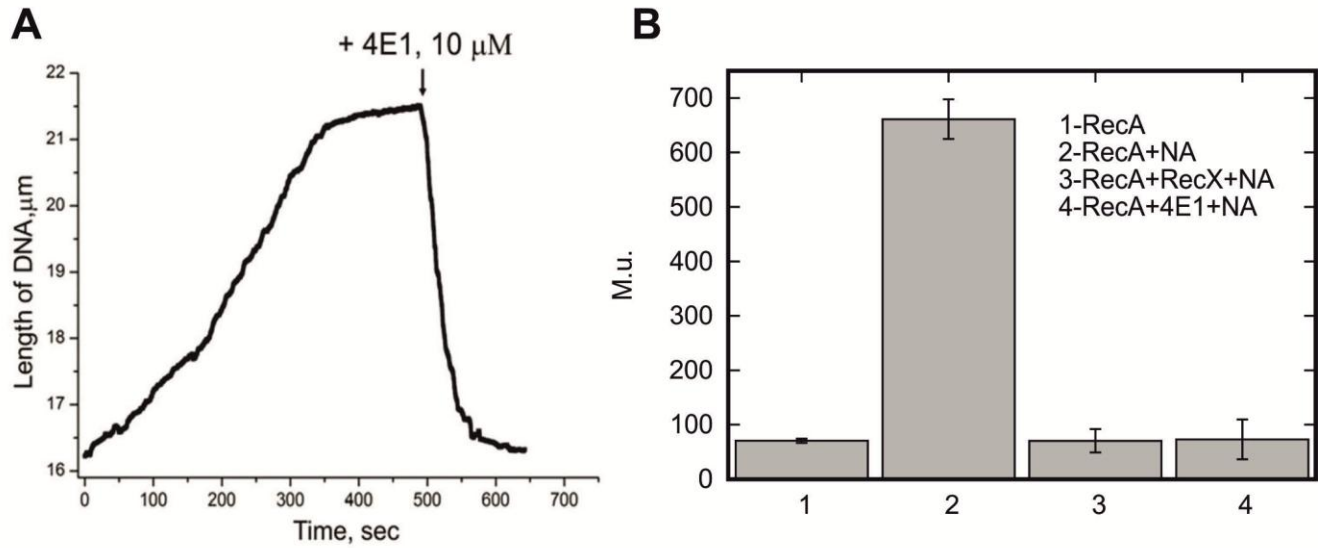

Figure 4. A) Dynamics of the DNA length during the assembly and disassembly of RecA-DNA filament by adding 4E1 peptide as observed in single molecule optical tweezer experiment. B) Effect of expression of RecX and 4E1 peptide on the magnitude of SOS-response in *E.coli* cells when exposed to nalidixic acid using Miller method.

Thus, these results indicates that α-helical 4E1 peptide with optimized amino acid sequence is not only an effective inhibitor of RecA protein *in vitro*, but also is capable to block bacterial SOS-response *in vivo* and thus a good candidate for the development of drugs to prevent the bacteria adaption to new antibiotics.

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Temperature-sensing receptor TRPV1: mechanism of gating as revealed by computation

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TRPV1 is a multi-modal receptor sensing heat, pH and capsaicin. This protein works as a nonselective cation channel activated by a wide variety of external and internal physical and chemical stimuli. Modulators of TRPV1 can potentially be used as analgesics, as well as regulators of the body temperature (anti-pyretic agents). Understanding at the molecular level structural and dynamic characteristics of the channel in its different functional states is an important factor for the development of new strategies of TRPV1 modulation in cell. The experimentally determined spatial structures of the rat TRPV1 channel are currently available both in its open and closed states. This makes TRPV1 a suitable target for computer-aided rational design of the new drugs prototypes. The aim of the current work is simulation of thermal activation/inactivation of the membrane bound receptor, determination of the factors important for its thermal sensitivity and delineation of a potential molecular mechanism of TRPV1 functioning.

To proceed with this, a number of long (up to 1 μs) atomistic molecular dynamics (MD) simulations of the membrane-embedded channel in its open and closed forms was carried out. We put emphasis on the analysis of temperature effects. It was shown that the structure of the channel in the open and closed states remains stable at T = 310 K. By contrast, increasing of the temperature to 325 K and further to 340 K leads to opening of the membrane pore, although its radius is still smaller than that in the experimentally determined structure in the open state. At 310 K, the channel can close in the presence of Ca^{2+} ions located in the central cavity of the pore. It was shown that the pore-lining surface of the channel is formed mainly by non-polar residues. Moreover, the observed transition from closed to open state is accompanied with growth of the solvent-exposed hydrophobic surface area. This can contribute to entropy increase upon the channel opening. Hence, one can speculate that heat, which activates the receptor, facilitates overcoming the entropic barrier. The simulation results show that molecular dynamics is an efficient tool to describe functionally meaningful atomic-scale properties of the membrane channels and delineate for them a number of important quantitative structure-function relationships.

Reference:

Chugunov A.O., Volynsky P.E., Krylov N.A., Nolde D.E., Efremov R.G. (2016). Temperature-sensitive gating of TRPV1 channel as probed by atomistic simulations of its trans- and juxtamembrane domains. Sci. Rep. 6, 33112; doi: 10.1038/srep33112.

Acknowledgements: This work was supported by Russian Foundation for Basic Research (16-04-00578) and RAS MCB Program. Access to computational resources of the Supercomputer Center “Polytechnical” at the Saint Petersburg Polytechnical University is greatly appreciated.

Molecular dynamics simulation of Rhodopsin and Opsin: Water transport through internal water pathways

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Rhodopsin is a light-driven G protein coupled receptor (GPCR) that mediates signal transduction in eyes and is located on the cell membrane in retina [1]. Rhodopsin is transmembrane 8 helixes frame protein with light-sensitive organic compound, called retinal [2]. When the dark-adapted rhodopsin absorbs light, 11-cis-retinal is isomerized to 11-trans-retinal within 200 fs, which is one of the fastest chemical reactions in the human body [3-5]. This state is called opsin. It is suggested that one of the intermediate states Meta II and opsin have one narrow pore on the cytoplasmic side, called solvent pore, which is important for intake and uptake and release of internal water molecules [6]; however, the precise pathways of water molecules between the cellular bulk and internal water molecules remain poorly understood.

In this study, we performed molecular dynamics simulation of rhodopsin, Meta II and opsin embedded in a POPC lipid bilayers to reveal water flux between the bulk and rhodopsin.

Using all-atom molecular dynamics simulations, we identified the solvent pore on cytoplasmic side in both the Meta II state and the Opsin (see Fig. 1). On the other hand, the solvent pore does not exist in the dark-adapted rhodopsin. In the solvent pore, there are two narrow gates which distinguish bulk, internal hydration sites and the retinal binding pocket. The pore also passes through the hydration sites adjacent to the conserved structural motif ”NPxxY”. The MD simulations also provided the dynamics of the water molecules in the solvent pore, which show that they do not diffuse in single file. The water molecules diffuse in the solvent pore through the well-known internal hydration sites by pushing, jumping or replacing a front water molecule. Moreover, water accessibility mapping and extracted trajectories of the water molecules reveals that some water molecules pass through other pathways located in a membrane bilayer including the ligand pores.

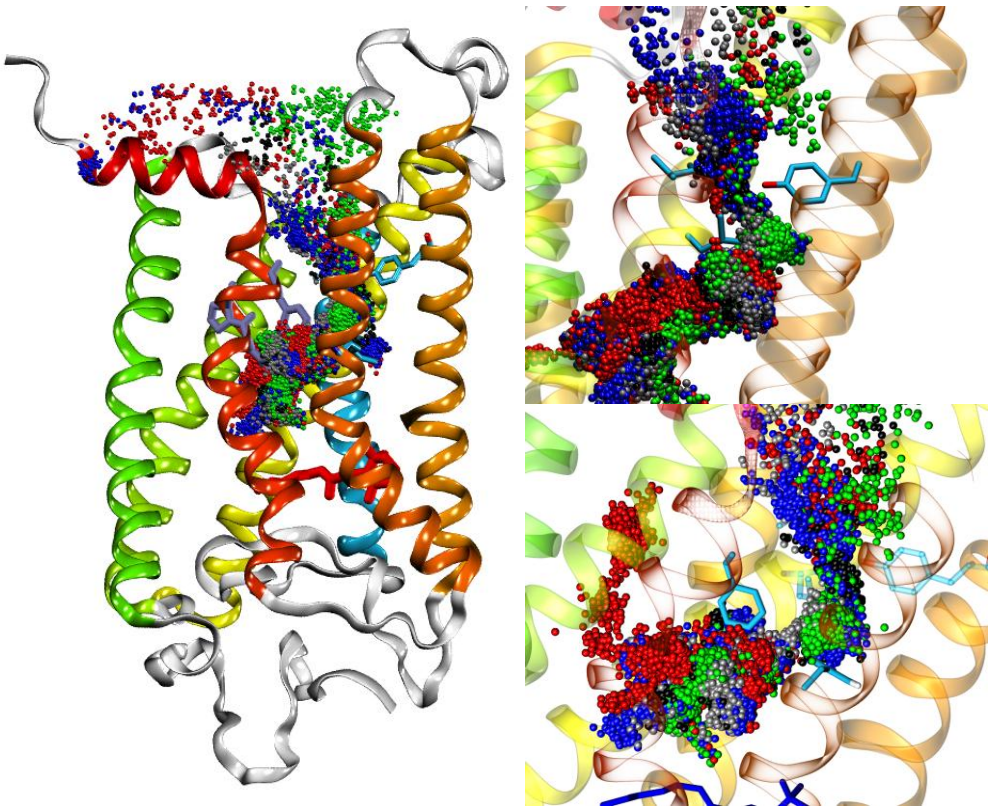

Figure 1. **Configuration of the solvent pore with ribbon representation of the Meta II structure.** Extracted 16 trajectories of water molecules that passed through the solvent pore are shown in different colors. The retinal is shown in orange VDW format. Right figures show close-up views of the first narrow region and the second region. Only five trajectories are shown. The first narrow region comprises L128, M257, and Y306, and the second narrow region comprises F261 and Y306.

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STRUCTURE AND FUNCTION OF HUMAN NEURAMINIDASE-1 REVISITED: A MOLECULAR MODELING STUDY

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Neuraminidase-1 is a lysosomal enzyme present in almost all vertebrate tissues having sialidase activity catalyzing the removal of terminal sialic acid residues from oligosaccharides comprising glycoproteins and glycolipids. The functioning of this sialidase in globular form is well described. Dysfunction of neuraminidase-1 is directly related to serious neurodegenerative genetic diseases, sialidosis, and galactosialidosis [1]. Recently, it was shown that neuraminidase-1 has a specific membrane-bound form with unknown structure. It is involved into the network of interactions of membrane proteins [2, 3]. The simple α-helix is a basic structural element of the most transmembrane (TM) protein domains. Dimerization or oligomerization of α-helical domains is a fundamental mechanism of protein-protein interactions in membrane. Lipid properties and amino acid sequence determine spatial structure and association strength of proteins. Thus, we focus on determination of possible helical TM segment in Neu1 structure [4].

The aim of this work was to examine the protein-protein and protein-lipid interactions of the previously predicted TM domain of neuraminidase-1 (TM peptide Neu1/TM2 with amino acid sequence DPELVDPVVAAGAVVTSSGIVFFSNPAHPEFR) using molecular dynamics (MD) simulations. First, the stability of this peptide in the hydrated lipid bilayer was tested. It was demonstrated that the central part of Neu1/TM2 forms a stable α-helix and its tilt angle with respect to the bilayer normal slightly fluctuates around the value of 15 degrees. To identify protein-induced lipid perturbations, average density was calculated around the embedded peptide. It was found that in the hydrophobic region there are several maxima corresponding to immobilized lipid acyl chains near the peptide surface (Fig. 1A) with lifetimes longer than 200 ns. To understand further the nature of these interactions, the lifetimes of contacts between peptide and lipids were estimated. It was shown that in the hydrophobic region there are no strong interactions of lipid acyl chains with lifetimes longer than 20 ns for individual lipids, whereas there are some stable contacts between the peptide's terminal polar and charged amino acids and lipid polar heads (Fig. 1B). Nevertheless, the integral picture is the opposite: terminal contacts are much more flexible corresponding to diffuse maxima on the average density map, and in the hydrophobic region there are fixed binding sites for lipid acyl chains that are highly occupied, but acyl chains substitute each other faster. Such a result is consistent with our previous findings for TM segment of glycophorin A [5]. It was not clearly understood if TM-peptide can form dimers or oligomers in native conditions, so we used the dimer prediction algorithm PREDDIMER [6] to generate possible dimeric conformations and then check their stability in MD simulations followed by the free energy calculations. We found two possible dimer structures, namely, "N-dimer", and "C-dimer". The second one is more energetically favorable (Fig. 1C), so we propose that neuraminidase-1 can form dimeric structures in membrane environment to compensate the rearrangement of its catalytic center structure during incorporation into membrane.

The results of this work show that native proteins are multi-function structures that interact with the environment and with each other, and we should go far beyond the principle "one protein – one function" to decipher the mechanisms of action of cell membrane systems.

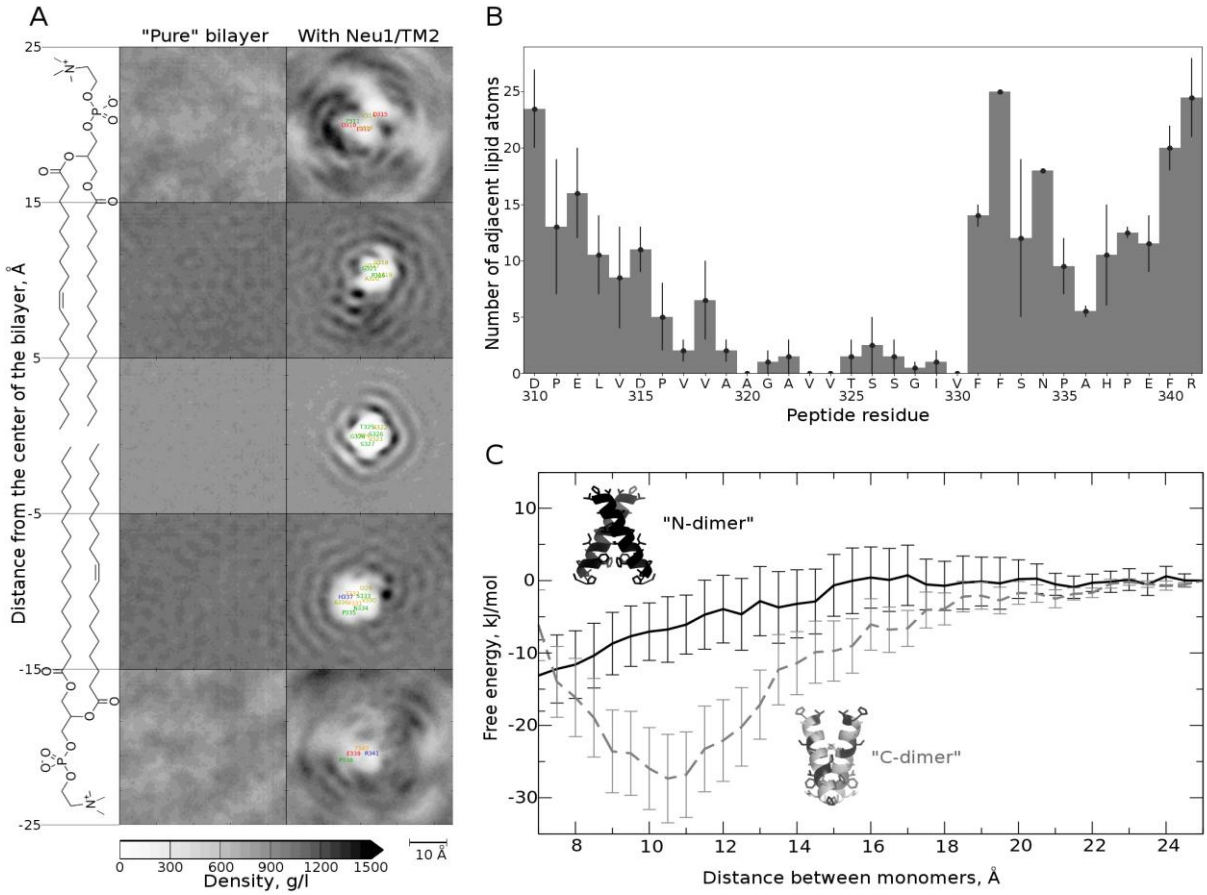

Fig. 1. A: Lipid density distribution in slices parallel to bilayer surface for "pure" palmitoyloleylphospatidylcholine and for the same bilayer containing Neu1/TM2 monomer. The data were averaged on 200-ns long MD trajectories. Darker areas correspond to higher lipid density, white circle on the right map corresponds to the peptide helix. Lipid chemical groups corresponding to each slice are shown on the left. Positions of the peptide Cα-atoms are marked. **B**: Average number of contacts (lipid atoms closer than 4 Å) with lifetime longer than 20 ns for each peptide residue. Errors were estimated based on 3 independent MD trajectories. **C**: dimerization free energy profiles calculated for two best dimer models of Neu1/TM2. Three-dimensional structures of the central parts are shown in cartoon representations near the lines.

This work was supported by the Russian Foundation for Basic Research (grant 16-04-00578), RAS Programme "Molecular and Cellular Biology", and the Russian Academic Excellence Project "Top 5-100". Computations were performed using facilities of the Supercomputer Center "Polytechnical" at the Saint-Petersburg Polytechnic University.

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PRINCIPLES OF MOLECULAR RECOGNITION IN CELL MEMBRANES: A COMPUTATIONAL VIEW.

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Molecular surfaces are the key players in processes of bimolecular recognition, interaction, and signaling. Nowadays, state of the art methods exist for visualizing molecule surface and surface distributed properties in three-dimensional space – the so-called "molecular portraits". However, such a visual information could only be analyzed by human eye and therefore prompt to be biased and onerous in case of biomacromolecules with a complex structural organization or for large sets of objects. This is especially true for such mesoscopic systems like cell membranes. Therefore, alternative (mostly computational) techniques operating with such "molecular portraits" are indispensable. Here, we present a number of original *in silico* methods to map and process multivariate surface properties of biomolecules and their assemblies – proteins, membranes, low molecular weight compounds, carbohydrates and their complexes. These techniques were shown to improve protein-ligand [1] and protein-protein [2] docking results. Also, a new protein surface topography (PST) method [3] is described. It permits pictorial visualization of the whole protein surface in terms of 2D "earth maps". PST can be used to delineate conformational changes between different states of molecules, perform group analysis, and reveal common patterns or dissimilarities. It is a useful tool to add to docking experiments, illustrating complementary features between ligand and receptor surfaces. The proposed original tools of detail mapping and graphical representation of biomolecular surfaces have been shown to be very efficient in analysis of atomistic details of the recognition processes in cell membranes – they allow easy monitoring of dynamic amphiphilic properties of lipid membranes (clustering phenomena, mosaicity of water-lipid interface, etc.), integral and peripheral proteins and peptides, membrane-anchored polysaccharides, and so on. Implementation of the "molecular portrait" technologies, along with complementary experimental and computational methods, is capable of rational design of new physiologically important compounds with predefined activities, including those involved in neurobiological processes [4].

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Acknowledgements

The work was supported by the Russian Foundation for Basic Research (16-04-00578) and RAS Programme "Molecular and Cellular Biology". Access to computational facilities of the Supercomputer Center "Polytechnical" at the St. Petersburg Polytechnic University is greatly appreciated.

COMPUTER DESIGN OF NANOSCALE PHENOMENA: EXPLORING NEW MATERIALS AND NEW DRUGS

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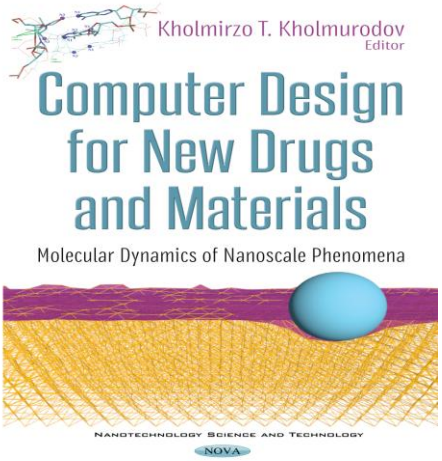
In the present report the author describe some of the own experiences on the computer molecular dynamics simulations in the modern chemical, biophysical and nanotechnological research fields, thereby outlining the scientific and educational cooperation established between the Dubna (JINR, Dubna State University) and several top research centers and universities of Japan (see: Appendices A and B). It is worth noting that computer molecular simulations (conventional classical and quantum molecular dynamics or hybrid of these approaches, Monte-Carlo and related techniques combined with the CPU/GPU accelerated hardwares and machines) for the exploring of the functional and structural properties of complex multiparticle systems play a fascinating role in fundamental physics, biochemical and life sciences. Having an increasingly significant impact on many applied industries, especially in modern biophysical and nanotechnological areas, molecular simulation provides a set of tools for predicting many functional properties of molecular systems. The chemical, pharmaceutical, materials and related industries - all share the computer molecular simulation methods. The molecular simulation studies cover different fields of either biological processes - protein folding and electron densities of DNA and proteins, or thin film formations and surface-cluster phenomena in nanoelectronics, synthetic copolymers and biopolymer design in biochemistry, so on.

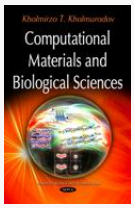
Practically all of the world's present supercomputers and many specially developed high performance computing clusters over the world are performing molecular simulations or are aimed on these needs. In this regard, scientists working closely in the above mentioned areas have been faced with several challenges due to peculiarities of simulation of large atomic/molecular systems, the huge data analysis and important visualization aspects. The parameters of present day MD-modeling could be roughly outlined as follows: (*a*) 10^5-10^6 atoms of the structure; (*b*) 5-500 ns simulation time scale; (*c*) 3-6 month picking up statistics. Some parameters of CPU to be as: (a) Intel Xeon CPU E5-2690; (b) memory: 128 GB; (c) 20 machines, etc. So far, even with moderate simulation parameters the analysis of the huge MD statistics look not a trivial task (only for one structure/function evaluation we have faced with multiple model calculation for the sake of comparative analysis, to be sure on conclusions and be capable on comparison with the experimental data, if to exist, or to confidently offer a predicting power of the MD - a highly appreciated nature of this method). For the huge data analysis and visualization purpose one have to mention some recently reported progress (http://www.riken.jp/en/pr/topics/2015/20151118_1/), where K computer in Japan takes first place again in Graph 500 supercomputer ranking, demonstrating the Japanese supercomputer's prowess in the area of data-intensive processing (high-performance computing, networking, storage and analysis) The computer used 82,944 of the K computer's 88,128 compute nodes to solve a breadth-first search of an extremely large graph of 1 trillion nodes and 16 trillion edges in 0.45 of a second. With this achievement it gained the top place again with a score of 38,621 gigaTEPS.

(*Ref*: gigaTEPS (traversed edges per second; gigaFLOPS (floating point operations per second, The number of traversed edges per second (TEPS) that can be performed by a supercomputer cluster is a measure of both the communications capabilities and computational power of the machine. http://www.graph500.org/specifications).

Appendix A

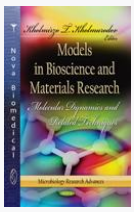


Appendix B



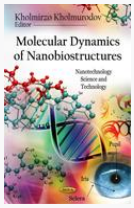
Computational Materials and Biological Sciences

Authors / Editors: Kholmirzo T. Kholmurodov (Leading Scientist, Frank Laboratory of Neutron Physics, Joint Institute of Nuclear Research, Dubna, Moscow Region, Russia)
Pub. Date: 2015



Models in Bioscience and Materials Research: Molecular Dynamics and Related Techniques

Authors / Editors: Kholmirzo T. Kholmurodov (Laboratory of Radiation Biology, Joint Institute for Nuclear Research, Moscow, Russia)
Pub. Date: 2013



Molecular Dynamics of Nanobiostructures

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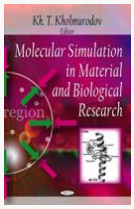

Molecular Simulation in Material and Biological Research

Authors / Editors: Kh. T. Kholmurodov (Center for Molecular Modeling, Joint Inst. for Nuclear Research, Moscow Region, Russia)
Pub. Date: 2009

Molecular Simulation Studies in Materials and Biological Sciences - International Workshop

Authors / Editors: Kholmirzo T. Kholmurodov (Joint Institute for Nuclear Research - Dubna, Russia)
Pub. Date: 2007

How Proteins Recognize Flexible Carbohydrates: The Roles of Affinity, Avidity, and Entropy

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Carbohydrate-protein interactions are critical for many aspects of normal cell and organismal development. However, the location of glycans on cell surfaces also exposes them to pathogens, many of which have evolved to infect the host by binding to specific glycans. Defining and quantifying the factors that affect the strength of carbohydrate-protein interactions is therefore important for understanding human biology, as well as guiding the development of therapeutic agents that seek to modulate such interactions.

Biophysical assays are often employed to characterize the affinity of carbohydrate-protein interactions, but such studies typically employ small oligosaccharides that are easy to produce, but are not necessarily representative of the biological glycan. In the natural environment there are many similar glycans that could act as receptors for a given protein, and thus avidity is inevitably an important additional component of binding. Furthermore, biologically-relevant glycans are typically larger and more flexible than the oligosaccharides employed in biophysical assays, resulting in a failure to define the critical role of conformational entropy.

Here we illustrate the power of computational methods such as molecular dynamics simulations to define the contributions to carbohydrate-protein binding from monomeric affinity, multimeric avidity, and conformational entropy.

Smelling in silico

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Chemoreception is the aptitude of living organisms to identify chemical compounds in their environment and to evaluate their concentration. Olfaction is initiated by a molecular interaction of chemicals called odorants with olfactory neurons located in the epithelium of the nasal cavity.

On the surface of the olfactory neurons, the activation of Olfactory Receptors, a class of protein belonging to the GPCR family and dedicated to transmit the signals to the brain, originates odor perception.

Computational approaches, either receptor or ligand-based are used to gain information on the mechanistic events underlying the perception of smells. Molecular dynamics simulations performed on homology models capture the dynamics of receptor activation while data-mining approaches allow the discovery of new ligands potentially useful for the flavor and fragrance industry.

ELECTRON-TRANSFER PROTEIN-PROTEIN COMPLEX FORMATION IN HIGER PLANTS AND CYANOBACTERIA

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Protein-protein interactions are of central importance for virtually every process in living matter. Simulation of protein association dynamics is crucial for understanding their functionality. In Brownian dynamics proteins are considered as rigid bodies subjected to electrostatic and random Brownian forces. This rough approximation is rather accurate when protein surfaces do not touch each other, and in combination with molecular dynamics used to simulate close contact of molecules this simulation technique provides complete reconstruction of protein-protein interaction over large temporal and spatial scales.

Brownian dynamics is not so computationally expensive as molecular dynamics, thus allowing exhaustive sampling of relative orientations of protein molecules approaching each other in a virtual reaction space. Long-range electrostatics is the major factor effecting molecule orientation on encounter. To gain some understanding of the role of electrostatic interactions at successive stages of protein-protein complex formation we need to detect and somehow describe intermediate metastable states on the association pathway. To do so we sample frames if electrostatic attraction energy between proteins is above some predefined threshold and analyze similarity of sampled structures in terms of root-mean-square deviation (RMSD) of their atomic positions in aligned to each other structures. Density based clustering technique [Khruschev et al., 2015] allows to find if all sampled structures constitute a single group, or they can be classified into several distinct clusters, and obtain characteristics of such groups (clusters).

We performed Brownian dynamics experiments (study of diffusional encounter of photosynthetic electron transport proteins) for two protein pairs: cytochrome f and plastocyanin from two species of cyanobacteria (Phormidium and Nostoc) and higher plants, and ferredoxin from *Chlamydomonas Reinhardtii* with Ferredoxin-$NADP^+$ reductase (FNR) from *Zea mays* and hydrogenase from *Chlamydomonas Reinhardtii*.

For cyanobacterial proteins plastocyanin and cytochrome f formation of structures with electrostatic attraction energy of 4kT or greater is a very rare event (k_{on} is less than 10^7 M^{-1} s^{-1}). Several electrostatically favorable binding modes were identified by density based clustering for cyanobacterial proteins. Namely, Phormidium plastocyanin always approaches cytochrome f far from its redox center (heme), thus electron transport is very unlikely in such orientations. So we can suppose that electrostatic interactions should not play any significant role in the formation of Phormidium plastocyanin-cytochrome f functionally active complex. This can be confirmed by the fact that experimentally obtained reaction rate for these proteins does not depend on solution ionic strength.On the contrary, Nostoc plastocyanin in most cases binds directly to the heme location in two predominant orientations (43% and 40% of all sampled structures). Copper atom is turned toward cytochrome f in all these structures, thus we conclude that electrostatic interactions facilitate the formation of final complex capable of electron transport. Indeed, in experiments we can see strong dependence of electron transfer rate on ionic strength.

In higher plants, formation of structures with attraction energy of 4kT or greater is much more frequent (k_{on} is above 10^9 M^{-1} s^{-1}). The structures constitute one uniformly dense group, in which plastocyanin is located in various orientations nearby the heme of cytochrome f. However, plastocyanin retains noticeable rotational freedom around its center of mass. We sampled protein orientations with even higher energy threshold of 8kT, and k_on still remained rather high (more than 10^7 M^{-1} s^{-1}), but two distinct groups of plastocyanin orientations were detected. In 57% of structures a flexible single-point joint is formed by oppositely charged areas of two proteins, thus allowing thermal motion to rotate plastocyanin molecule into electron-transfer-capable orientation without breaking electrostatic link. In remaining structures binding of plastocyanin is much more tight, and its

orientation suppresses electron transfer. We suppose that in higher plants the process of final complex

formation involves at least two stages: the first is diffusive entrapment of plastocyanin by cytochrome f, and the second is orientation adjustment in the transient complex.

For ferredoxin from *Chlamydomonas Reinhardtii* and FNR from *Zea mays* formation of structures with attraction energy of 6kT or greater is very frequent (k_{on} is above $2.8 \cdot 10^9$ M^{-1} s^{-1}). Three distinct groups of ferredoxin orientations were detected. The most of structures (96%) constitute one uniformly dense group (cluster), in which ferredoxin is located nearby FAD of FNR but its Fe-S cluster is turned away from the contact area (figure 1) but the distance between the cofactors is rather small (14.5 Å).

For hydrogenase and ferredoxin from *Chlamydomonas Reinhardtii* with attraction energy of 6kT or greater k_{on} is above $6 \cdot 10^8$ M^{-1} s^{-1}. Four distinct groups of ferredoxin orientations were detected. In all of them the proteins contact with each other in the same position (distance beetween protein centers of mass is 32.9 – 35.1 Å) but with varied distance between the cofactors from 17.7 and up to 25.5 Å. We suppose that the process of final complex formation for these two proteins is similar to that of plastocyanin-cytochrome f protein pair in higher plants.

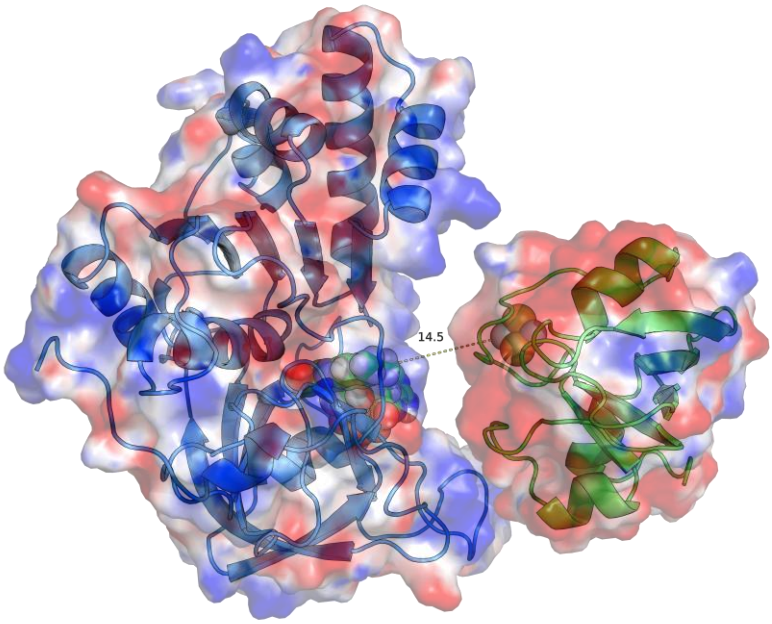

Figure 1. Central structure of the biggest cluster of ferredoxin (green) and Ferredoxin-$NADP^+$ reductase (blue) with electrostatic attraction energy 6kT or greater. Proteins are shown as secondary structures and surfaces colored from red to blue in accordance with the surface potential from -6.5 mV to 6.5 mV. Cofactors are shown as spheres and colored by elements, the minimal distance between them is shown.

This work is supported by Russian Foundation for Basic Research projects 15-04-08681, 15-07-08927 and 17-04-00676.

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New computational method to get D_2O/H_2O contrast from all-atom molecular dynamics trajectories for large biomacromolecular complexes

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Currently molecular modeling methods are widely used to study various biological systems. This raises the question of the verification of the obtained model using the existing experimental data. In the case of using small-angle neutron scattering methods, verification of the model raises the question about a way to take contrast variation information correctly into account.

A method to calculate SANS[1] and NSE[2] curves from MD trajectories was developed and implemented as analysis modules for molecular dynamics software package GROMACS. Previously other groups proposed methods to estimate contrast for small systems such as fatty-acids in organic non-polar solutions[3]. We extended method that was previously developed[1,2] to include D_2O/H_2O contrast estimation directly from molecular dynamics trajectories. Interesting that taking into account D/H exchanges in molecular model plays critical role in model data comparison with experiment, especially for systems containing carbohydrates, and for large biomacromolecular complexes.

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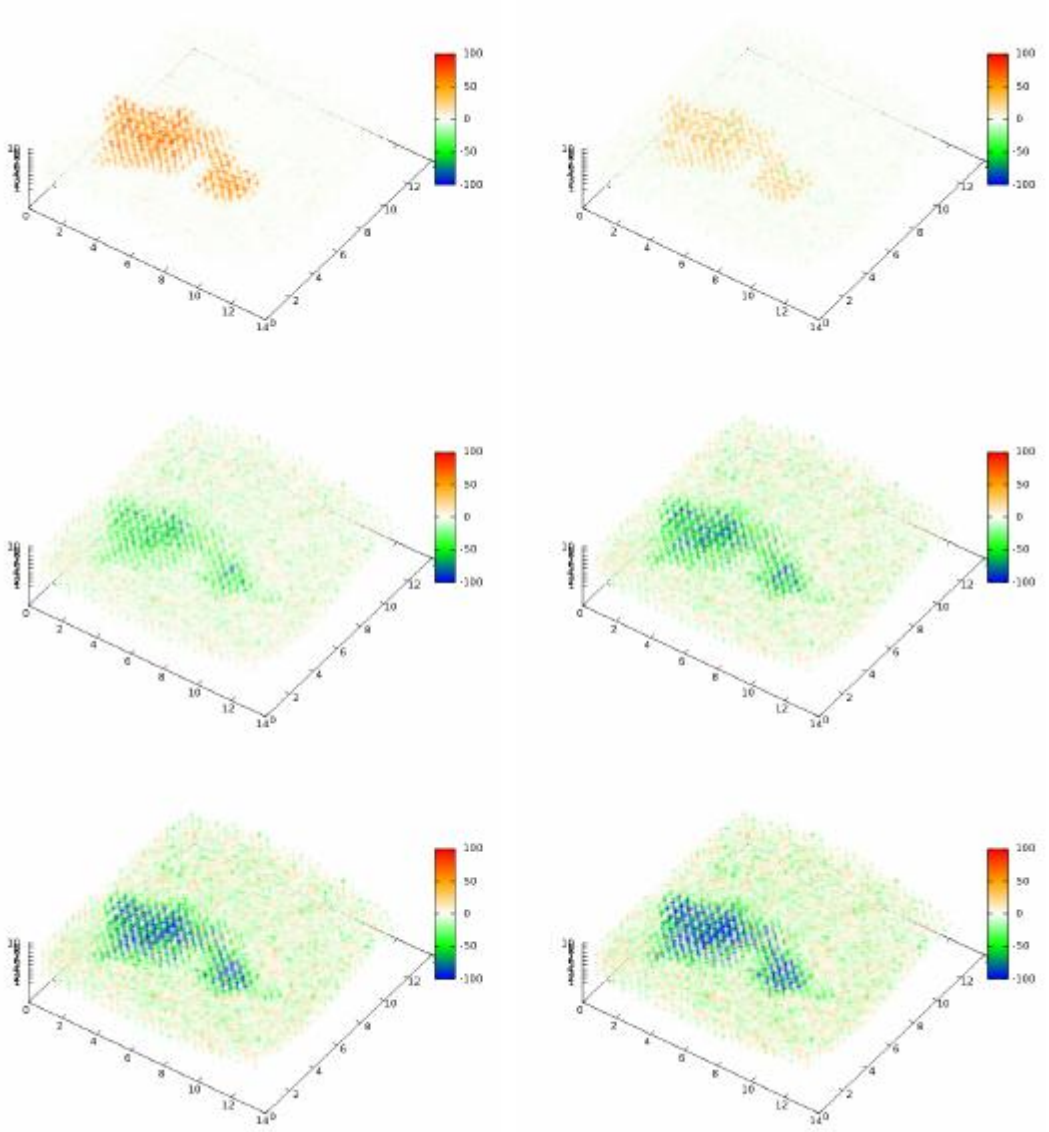

Figure 1: Scattering length density for glu-coamylase for different D2O/H2O contrast (0– top left, 0.235 – top right, 0.646 – middleleft, 0.794 – middle right, 0.992 – bottom left,0.998 – bottom right)

MOLECULAR DYNAMICS MODELING OF TRIAZAVIRINE ANTIAMYLOIDOGENIC ACTION MECHANISM

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Protein conformational changes play a significant role in disease such as amyloidoses. Amyloid-like fibrills are resistant to proteolytic enzymes and physico-chemical influences. We found that antiviral drug, triazavirine affects the model peptide (SI) amyloid-like fibrils formation, which was verified with transmissive electronic microscopy and small-angle neutron scattering [1]. Molecular dynamics simulations of triazavirine with SI peptide were performed [2]. According to our simulations, triazavirine is able to form linear supramolecular structures which can act as shields and prevent interactions between SI monomers (Figure 1). This model provides an adequate explanation of triazavirine's mechanism of action as it pertains to SI peptide fibril formation.

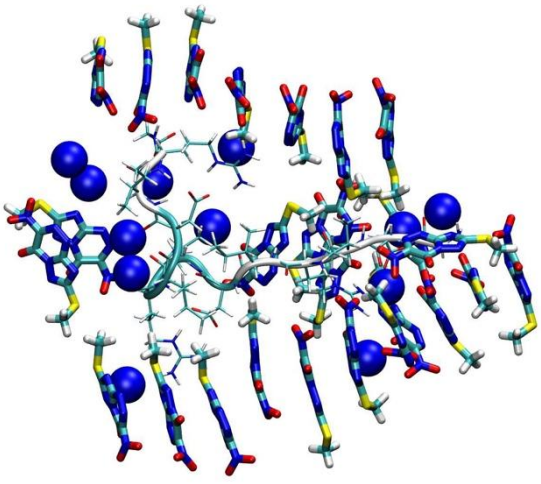

Figure 1 Rod-like TZV supramolecular complexes act as shields and prevent peptide-peptide interaction.

Acknowledgements

The authors wish to thank Dr. D. V. Lebedev (DMRB PNPI NRC KI) for the fruitful discussion of the experiments. This study was supported by the Russian Foundation for Basic Research, project no 14-24-01103 ofi_m.

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bioRxiv, 150664, 2017

XANES analysis for functional materials

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Functional materials have been often synthesized with doping technique, i.e., adding dilute extra elements in the host materials. For instance, the 3d-transition and rare-earth elements have been chosen as dopants for phosphor materials. In order to understand the mechanism of newly appeared functions in the functional materials synthesized with doping technique, it is essential to know the local environment of dopant in an atomic scale. However, it is very difficult to determine such local environment of dilute dopant. To overcome such difficulty, we have developed an analytical method using X-ray absorption near-edge structure (XANES) measurements and first-principles density functional theory (DFT) calculations, which have successfully determined local environments of dilute dopants in various kinds of functional materials [1-3].

In the present study, we will demonstrate the local environment analysis of various kinds of dopants, e.g., 3d-transition elements in optical materials such as those of Mn ions doped in $CaTiO_3$. As an example of our current studies, observed Mn-K XANES spectra of Mn doped $CaTiO_3$ is shown in Fig. 1 with the theoretical spectra calculated by the first-principles DFT calculations.

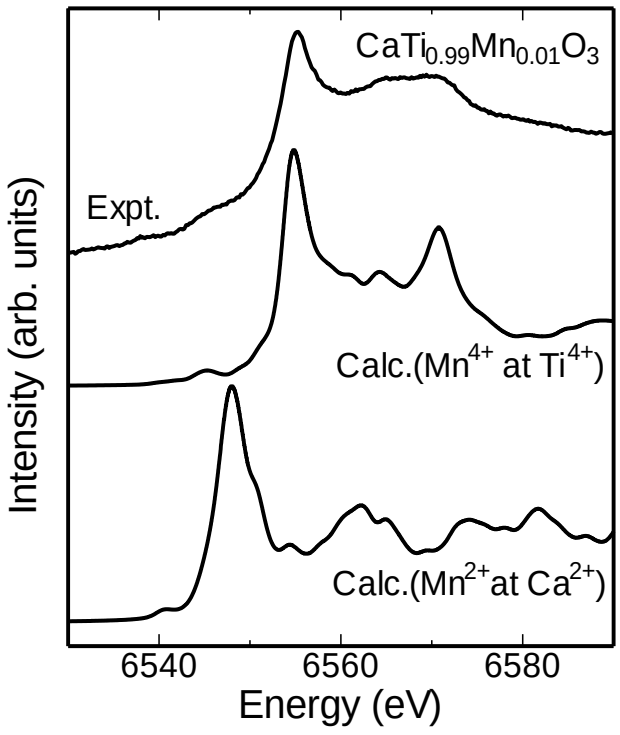

Fig.1 Comparison of Mn-K XANES spectra of Mn-doped $CaTiO_3$ between experiment and calculations

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DFT studies of the Mn-doped $CaSnO_3$, $CaZrO_3$, $SrTiO_3$ and $CaTiO_3$

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Studies on the Mn^{4+} activated red-emitting phosphors have been attracted a great attention in the past decades. Such interest has been mainly initiated by the possibilities of their application in different branches of technologies and applied sciences as lighting, holography, laser, and dosimetry, etc. [1]. It is worth mentioning that the diluted amount of Mn^{4+} multivalent ions in matrix materials plays a role of luminescent center.

The Mn^{4+} doped oxides have been extensively studied recently from the point of view of the morphologies, crystal structure, luminescence and other properties. The investigation of phosphors doped with Mn lies well within the framework the first-principles calculations as density functional theory (DFT). It is possible to know the local environment of the doped Mn ions in an atomic scale and the electronic structures of Mn-doped oxides with DFT.

The DFT methodology in the Kohn-Sham formulation [2] and its practical utilization by different approaches is extensively used for current electronic structure calculations of functional materials. In the DFT the exchange-correlation potential among the electrons is approximated by a functional of the electronic density; the studies proposed by Tran and Blaha have brought to a modification of the Becke and Johnson potential (mBJ) [3], which is more accurate for the band-gap estimation of a various kinds of the semiconductor materials than the conventional ones, such as local density approximation (LDA) and generalized gradient approximation (GGA).

In the present work, the DFT calculations for the understanding of electronic structure of Mn-doped perovskite structured oxides, $CaSnO_3$, $CaZrO_3$, $SrTiO_3$ and $CaTiO_3$, have been performed. The all-electron full-potential augmented plane wave plus local orbital (FP-APW+lo) method is employed with the mBJ potential as implemented in the WIEN2k code [4]. Some results are presented in Fig.1, which show the electronic density of states for the matrix materials $CaSnO_3$, $CaZrO_3$ and $SrTiO_3$. Calculated band gaps by generalized gradient approximation (GGA) and modification of the Becke and Johnson (mBJ) potentials are summarized in table 1.

Table.1. DFT calculations band gaps of $CaSnO_3$, $CaZrO_3$ and $SrTiO_3$ (a[5]; b[6]; c[7]).

System	Band gap - GGA calc. (eV)	Band gap - mBJ calc. (eV)	Experement
$CaSnO_3$	2.94	4.62	4.5[a]
$CaZrO_3$	4.16	5.23	5.7[b]
$SrTiO_3$	2.48	3.32	3.25[c]

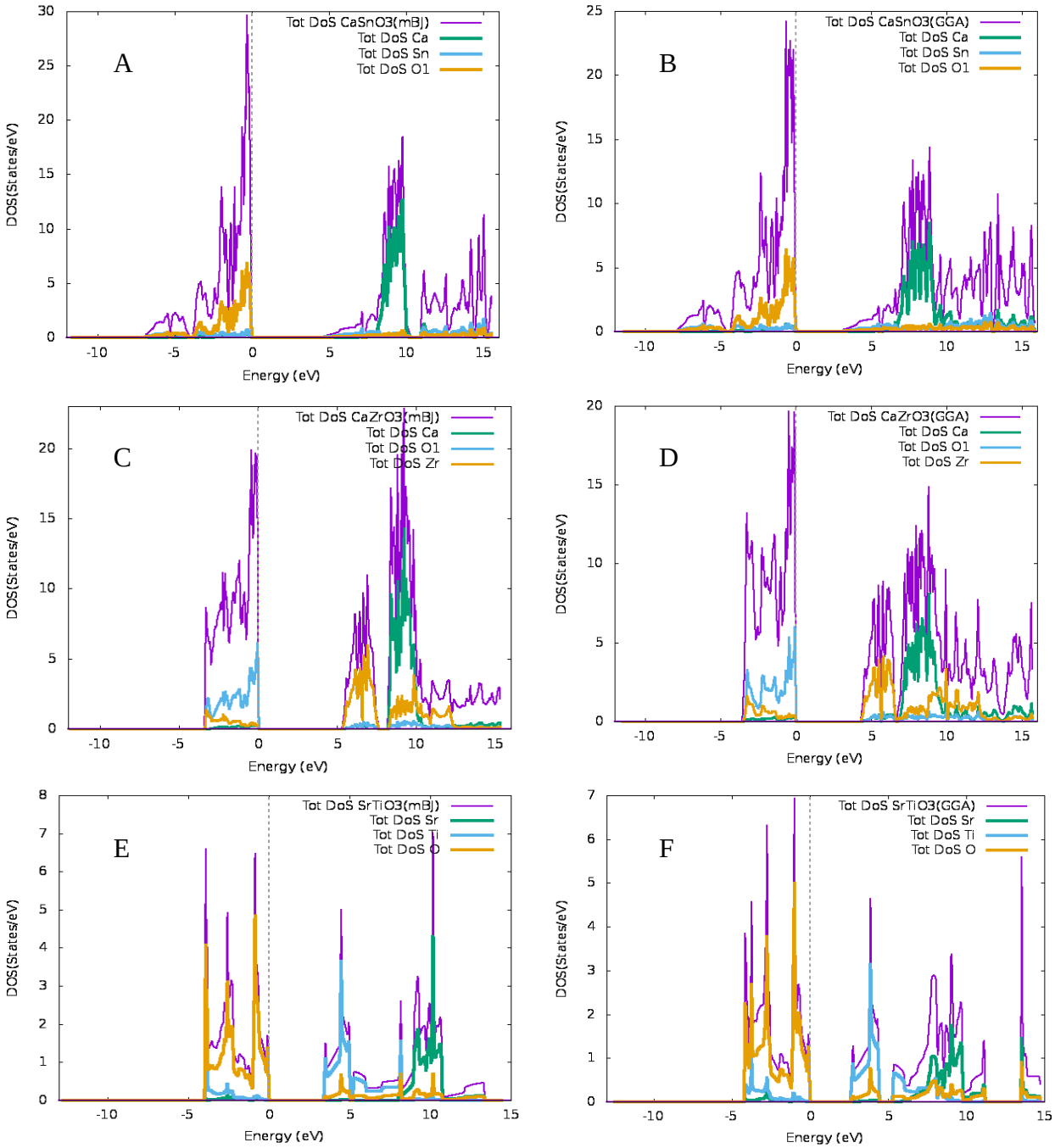

Figure 1. Density of states: A) $CaSnO_3$-mBJ; B) $CaSnO_3$-GGA; C) $CaZrO_3$-mBJ; D) $CaZrO_3$-GGA; E) $SrTiO_3$-mBJ; F) $SrTiO_3$-GGA.

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Peculiar Properties of Lipid Membranes by Neutron Diffraction

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Small-Angle Neutron Diffraction (SAND) has over the recent years proven to be a useful technique in structural biology, biophysics and materials science. Due to the intrinsic disorder present in biomimetic samples - a disorder possibly important for the proper function of biology systems - many membrane samples are far from being perfect crystals. In such cases, less than atomic resolution structures are best described by broad statistical distributions, rather than sharp delta functions typical of perfect crystals. This is especially true for the structure of non-crystalline biomaterials with a focus on the most important "soft" matter studied, namely the lipid membrane.

Our recent experimental data revealed several intriguing structural properties of biomimetic membranes that will be discussed. First, the membrane structure depends strongly on the chemical composition of its constituents. For example, cholesterol is known to increase the order of lipid hydrocarbon chains while increasing the stiffness of membrane. In the contrary, our previous experiments revealed the fluidizing effect of melatonin in neat lipid membranes [1]. We have extended our investigations recently by including transmembrane amyloid-beta (Ab) peptide in these model membranes to shed a light on the melatonin's potential role in preventing the development of Alzheimer's disease (AD). AD is a devastating neurodegenerative disease caused by the formation of senile plaques, primarily consisting of Ab peptides, while the crucial role in the process is imparted by the structural properties of membrane.

Although a complete understanding of the physicochemical processes taking place in biomembranes has yet to be established, an understanding of lipid bilayer structural changes as a result of different properties of environment outside and/or inside the membrane provides a foundation for better insights into the structure-function relationships that most certainly take place in more complicated biomembrane systems.

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COMPUTER MODELING OF DNA DELIVERY VECTORS

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Gene therapy, being one of the promising approaches to treat inherited and oncological diseases, is largely based on the introduction of the genetic material into target cells. To this end, a wide range of vectors has been used to facilitate the intracellular gene delivery. Here we employ the state-of-the-art computer simulations to explore nonviral DNA delivery vectors based on cationic polymers [1] as well as on lipid molecules (liposomes) [2,3]. The use of atomistic computational models made it possible to go beyond the resolution accessible by most experimental techniques and to gain an unprecedented molecular-level insight into the structure and dynamics of supramolecular complexes of DNA with the delivery agents considered. In particular, we demonstrate the existence of two distinct patterns of binding of DNA with linear cationic polymers; these patterns depend on the chemical structure of a polycation and can affect the transfection activity of the polymers [1]. As far as the liposome-based delivery vectors are concerned, our findings show that divalent calcium ions promote formation of complexes of DNA molecules with zwitterionic (neutral) phospholipid membranes [2,3]. Interestingly, calcium ions turn out to be crucial for stabilizing the DNA-lipid membrane complex as they bridge together phosphate groups of DNA and lipid molecules [2,3]. Overall, our computational results contribute considerably to a deeper understanding of molecular mechanisms behind functioning of DNA delivery systems and can serve as a basis for optimization of existing polycation- and liposome-based vectors.

Acknowledgments
The use of the computer cluster of the Institute of Macromolecular Compounds RAS and the Lomonosov supercomputer at the Moscow State University is gratefully acknowledged. This work was supported by the Russian Foundation of Basic Research through Grant 17-03-00446.

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EFFECT OF DESO ON STRUCTURE OF DMPC LIPID BILAYERS: MOLECULAR DYNAMICS SIMULATION STUDY

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The lipid bilayer is the structural basis of biological membranes which separate the cell interior from the surrounding environment and act as barriers between the inside and outside of a cell. The transport of the larger or charged molecules, such as ions, sugars, and amino acids, need active regulatory mechanisms for rapid attainment of osmotic balance across plasma membranes in response to rapid changes of various physical and/or chemical variables. The dimethyl sulfoxide (DMSO) – amphiphilic molecule consisting of a hydrophilic sulfoxide group (S═O) and two hydrophobic groups CH_3 – increase permeability across membranes [1]. It is a widely used cryoprotectant for biological cells and tissues. DMSO is also able to induce cell fusion [2] or cell differentiation [3]. Among the important biological and medical properties of DMSO should be noted anesthesia and anti-inflammation effects [4], antiviral and antibacterial activity, radioprotection abilities [5]. The molecular basis of DMSO-lipid interaction was investigated by Molecular Dynamic (MD) simulation [6-8].

In this work we present the first results of the MD study of the effect of the diethyl sulfoxide (DESO) on the lipid membrane structure. DESO is an amphiphilic molecule consisting of a hydrophilic sulfoxide group (S═O) and two hydrophobic groups CH_2-CH_3. DESO shows strong interaction with water, even stronger than that of DMSO [9]. The interactions of DESO and DMSO with the biological membranes are, probably, identical. By differential scanning calorimetry (DSC) method [10] a partial dehydration of the lipid bilayer of DMPC liposomes and simultaneous change in the structure of water at low concentrations of sulfoxides (20 wt %) was shown. The sulfoxides interact directly with the surface of the lipid membrane at high concentrations of DESO and DMSO ($\geq$ 40 wt %). Thus, it can be assumed that hydrophobic interactions play a crucial role in the intermembrane interaction in the presence of sulfoxides. The other important reason for investigation the molecular basis of DESO-lipid interaction is the fact that DESO less toxic than DMSO and glycerol, for example, for *E. coli* [11]. The investigation of the ability of DESO to act as an effective cryoprotectant on *E. coli* survival confirms that DESO, more than DMSO, is able to penetrate living tissues without causing significant damage [11].

MD simulations using GROMACS 5.0.4 [12] package were performed for four systems. A Model M0 was constructed from 128 DMPC lipid molecules (64 on each leaftlet) and 3800 water molecules. The initial topology was taken from literature [13,14]. Models M01 (Fig.1) and M02 were obtained by adding of 480 and 960 DESO molecules to initial system, respectively. And finally, the all water molecules were replaced by DESO molecules in Model M1. Modeling was carried out in three stages: i) minimization of the energy; ii) NVT and NPT equilibration of the system; and iii) MD calculations with the GROMOS96_53A6 force field and parameters of expansion taken from Berger lipids [15]. Simulation convergence was assessed using area per lipid, which suggested an equilibration time of about 50 ns. The production run continued for an additional 50 ns. Various structural and ordering parameters characterizing the DMPC lipid bilayers in the presence of different concentrations of DESO were investigated.

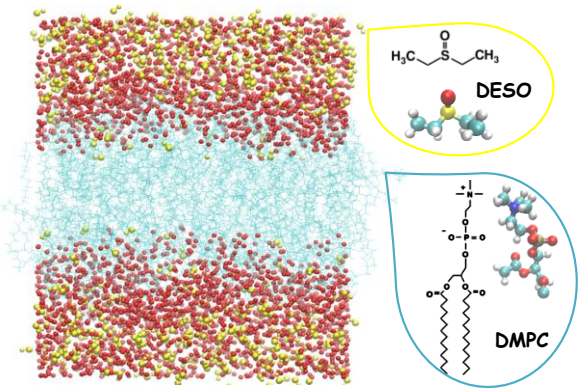

Figure 1. Snapshot of the dual DMPC lipid bilayer system M01 at 100 ns of simulation. The molecules of DESO are colored in yellow, water is in red and lipids are in cyan. The structures of DESO and DMPC molecules are presented.

The electron density profiles for DMPC lipid bilayer in DESO/D_2O at different DESO concentration (Fig.2) are showing the changes in the position of the head groups relative to the center of the lipid bilayer. Our results indicate that the DESO molecules (M01 and M02) penetrate deeply into the head group region of the lipid molecules. The few DESO molecules are located in the hydrophobic region and even in the center of the lipid bilayer when the all water molecules are replaced by DESO in liquid-crystal (LC) phase to the contrary to the gel phase. It is easy to understand taking in an account that the hydrogen-bonding becomes weaker with higher temperatures, and DESO prefers to interact with the bilayer tails. Thus, a hydrophobic effect has been observed at higher DESO concentration. The DESO molecule has a volume about 174 $Å^3$, and decreasing of the lipid area to 48 $Å^2$in LC phase for model M1 is not surprising.

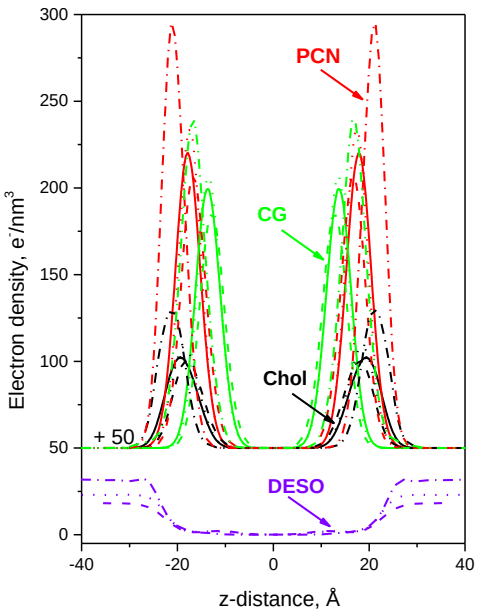

Figure 2. Electron density profiles for DMPC lipid bilayer in DESO/D_2O for M0 (solid), M01 (dash), M02 (dot) and M1(dash dot) models along the membrane normal in liquid-crystal phase

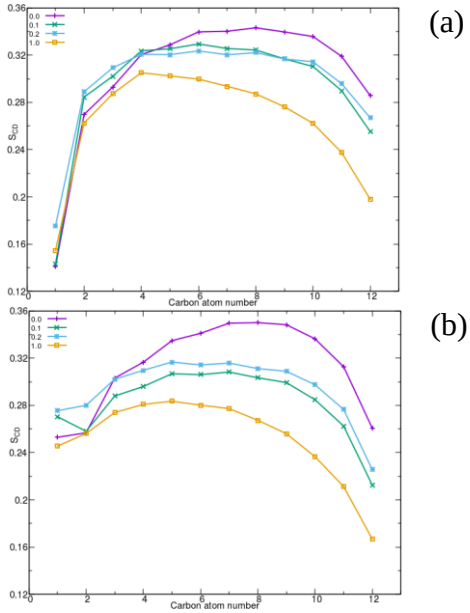

Figure 3. Deuterium-order parameter of (a) sn-2 chain and (b) sn-1 chain of a DMPC lipid versus DESO concentrations in liquid-crystal phase

The deuterium order parameter (SCD) measures the alignment of the phospholipid tails in the bilayer and gives valuable information regarding the structure of the bilayer. The order parameter profiles for a sn-2 and sn-1 chains of a DMPC lipid at various DESO concentrations are presented in Fig. 3 (a) and (b), respectively. It can be seen that the adding of DESO (M01 and M02) changed the ordering of tails compared to the ordering of tails in the DMPC bilayer in

the presence of pure water. And, finally, the increasing in the DESO fraction to 1.0 is causes a large decrease in the tail order parameter. This is a consequence of the large amount of DESO in the bilayer region, which also causes greater disorder among the tails. To the contrary, the increasing in the tail order parameter with rising of the DESO fraction has been observed in gel phase. This is due to the fact that the DESO (M1) does not penetrate into the tail region of the lipid bilayer in gel phase.

Acknowledgements: This research was supported by the JINR-UAIC Scientific Projects № 218_9 and № 219_36.

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NOTEBOOK

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SCIENTIFIC PROGRAM

September 7, Thursday

Arrival and Registration in New Peterhof Hotel, St.Petersburg, Russia

18^{00}-20^{00} **Welcome Party**

September 8, Friday (Hotel "New Peterhof", St.Petersburg)

09^{00} -09^{30} Registration in Hotel "New Peterhof" (cont.)

09^{30} -10^{00} **Opening ceremony. Welcoming by the Andrey L. Konewega** Petersburg Nuclear Physics Institute (PNPI) of the National Research Center "Kurchatov Institute" (NRC "Kurchatov Institute").

(Session I. Co-Chairs Kh. Kholmurodov & A. Shvetsov)

10^{00}-11^{00} **Yuko Okamoto** (Nagoya University, Japan).
"Generalized-ensemble algorithms for materials and biomolecular simulations"

11^{00}-11^{30} **Gennady Makarov** (South Ural State University, Chelyabinsk, Russia).
"Investigation of nascent peptide exit tunnel by means of molecular dynamics simulations"

11^{30}-12^{00} **Coffee Break**

(Session II. Co-Chairs Y. Okamoto & M. Kiselev)

12^{00}-12^{30} **Tomobe Katsufumi** (Keio University, Japan).
"Molecular dynamics simulation of Rhodopsin and Opsin: Water transport through internal water pathways"

12^{30}-13^{00} **Andrey S. Kuznetsov** (National Research University Higher School of Economics, Myasnitskaya ul.20, 101000 Moscow, Russia).
"Structure and Function of Human Neuraminidase-1 Revisited: a Molecular Modeling Study"

13^{00}-14^{00} **Lunch**

(Session III. Co-Chairs A. Kuznetsov & T. Katsufumi)

14^{00}-15^{00} **Robert J. Woods** (Complex Carbohydrate Research Center, University of Georgia, Athens, USA).
"How Proteins Recognize Flexible Carbohydrates: The Roles of Affinity, Avidity, and Entropy"

15^{00}-15^{30} **Anton O. Chugunov** (National Research University Higher School of Economics, Myasnitskaya ul.20, 101000 Moscow, Russia).
"Temperature-sensing receptor TRPV1: mechanism of gating as revealed by computation"

15^{30}-16^{00} **Michael Petukhov** (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
"DESIGN OF STABLE α-HELICAL PEPTIDES FOR BIOTECHNOLOGY AND MEDICINE"

16^{00}-16^{30} **Coffee Break**

(Session IV. Co-Chairs R. Woods & R. Efremov)

16^{30}-17^{30} **Dmitry Lebedev** (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
"Russian Science Mega-Project Neutron Source Reactor PIK"

17^{30}-18^{00} **Norbert Kucerka** (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
"Peculiar properties of lipid membranes by neutron diffraction"

18^{00}-18^{30} **Georgy Rychkov** (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
"Partially assembled nucleosome structures: full-atom molecular models and experimental data interpretation "

18^{30}-19^{00} **Kholmirzo Kholmurodov** (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
"Computer molecular dynamics of nanoscale phenomena: exploring new drugs and materials"

Closing of the 1st conference day

September 9, Saturday (Hotel "New Peterhof", St.Petersburg)

(Session V. Co-Chairs J. Golebiowski, Pr. & Kh. Kholmurodov)

09^{00}-10^{00} **Roman Efremov** (National Research University Higher School of Economics, Myasnitskaya ul.20, 101000 Moscow, Russia).
"Principles of molecular recognition in cell membranes: a computational view"

10^{00}-10^{30} **Mikhail Kiselev** (Frank Laboratory of Neutron Physics, JINR, Dubna, Russian Federation).
"SANS study of unilamellar DMPC vesicles: Fluctuation model of a lipid bilayer"

10^{30}-11^{00} **Coffee Break**

(**Session VI. Co-Chairs A. Chugunov & N. Kucerka**)

11^{00}-12^{00} **Jérôme Golebiowski, Pr.** (University Nice Sophia Antipolis, Nice, France).
"Smelling in silico"

12^{00}-12^{30} **Alexei Shvetsov** (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation).
"New computational method to get D2O/H2O contrast from all-atom molecular dynamics trajectories for large biomacromolecular complexes"

12^{30}-13^{00} **Eric Dushanov** (Laboratory of Radiation Biology, JINR, Dubna, Russian Federation).
"Cation-containing lipid membranes – experiment and md simulations"

13^{00}-14^{00} **Lunch**

(**Session VII. Co-Chairs A. Konewega & Kh. Kholmurodov**)

14^{00}-15^{00} **Tomoyuki Yamamoto** (Waseda University, Japan).
"XANES analysis for functional materials"

15^{00}-15^{30} **Mekhrdod Subhoni** (Physical Technical institute named after S. Umarov of Academy of Sciences of the Republic of Tajikistan).
"Experimental and DFT studies of the Mn-doped CaTiO3, CaZrO3, CaHfO3 and CaSnO3"

15^{30}-16^{00} **Andrey Gurtovenko** (Institute of Macromolecular Compounds, Russian Academy of Sciences, St.Petersburg, Russis).
"COMPUTER MODELING OF DNA DELIVERY VECTORS"

16^{00}-16^{30} **Vladimir Fedorov** (Biological Faculty, Moscow State University)
"ELECTRON-TRANSFER PROTEIN-PROTEIN COMPLEX FORMATION IN HIGER PLANTS AND CYANOBACTERIA "

16^{30}-17^{00} **Vladimir Egorov** (PNPI, NRC "Kurchatov Institute", St.Petersburg, Russian Federation)
"MOLECULAR DYNAMICS MODELING OF TRIAZAVIRINE ANTIAMYLOIDOGENIC ACTION MECHANISM"

17^{00}-17^{30} **Round table with Coffee Break. Symposium Closing.**

18^{00}-22^{30} **Social program** (excursion to be conducted in English with start and finish at the hotel New Peterhof)

September 10, Sunday (Hotel "New Peterhof", St.Petersburg)

Departure of the MSSMBS'17' delegates

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