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Moscow, September 21–22, 2014

Book of Abstracts

Edited by
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- Roman Efremov (Institute of Bioorganic Chemistry, Moscow)
- Mitsuhiro Matsumoto (Kyoto University, Japan)
- Ilya Kovalenko (Moscow State University, Russia)
- Kenji Yasuoka (Keio University, Japan)
- Catherine Etchebest (University Paris-Diderot, France)
- Tomoyuki Yamamoto (Waseda University, Japan)
- Anton Chugunov (Institute of Bioorganic Chemistry, Moscow)
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PREFACE

The MSSMBS-2014 workshop has appeared to provide an ideal opportunity to discuss the latest developments and exchange fundamental and technical ideas in the field of computational material and biological sciences. Especially, as Organizers were planning, the MSSMBS-2014 would promote establishing very close cooperation between young researchers that helps to strengthen future scientific relationships between Russia and Japan. In the framework of the MSSMBS-2014, 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 techniques in modern material and biological sciences, and so on. The contributions of Russian young scientists are greatly welcome to make their bridges with Japanese and Russian colleagues for the future joint research and cooperation.

The research topics to be covered at MSSMBS-2014 are the following:

- Computational methods and techniques;
- Molecular dynamics (MD) simulations;
- First-principles calculations;
- Novel quantum mechanical methods (DFT, QM/MM, hybrid, etc.);
- GPU accelerated molecular dynamics;
- Molecular dynamics simulations of protein folding;
- Mutation transition effects in protein structures;
- MD and Monte Carlo simulations of radiation-induced mutations;
- Chemical and nanostructure design (crystal, liquid and polymer systems);
- General- & special-purpose MD machines;
- Modern communication architecture;

The MSSMBS-2014 workshop will be hosted by M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences (IBCh RAS) in the capital city Moscow. We will provide a broad discussion on development and application of computational approaches in material and biological sciences.

Welcome to IBCh, RAS, Moscow!

Kholmirzo T. Kholmurodov, Roman G. Efremov

Co-Chairmen of the MSSMBS-2014 Organizing Committee.

DRUG DESIGN BY GENERALIZED-ENSEMBLE 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 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 reviews, see, e.g., Refs. [1-4]). 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, we have given a general formalism for multidimensional MUCA, ST, and REM [5].

In this presentation, I will give the results of various applications of generalized-ensemble algorithms to materials and biological sciences. The first example is a proton transfer calculation that includes quantum effects [6]. The system is a malon aldehyde in water solvent (71 water molecules). A new method, Simulated Tempering Umbrella Sampling (STUS) [6], was implemented to the program CP2K, which is based on density functional theory, and a STUS simulation was performed for 200 ps. In Fig. 1 we show the potential of mean force for this proton transfer process. The results are in accord with other previous calculations.

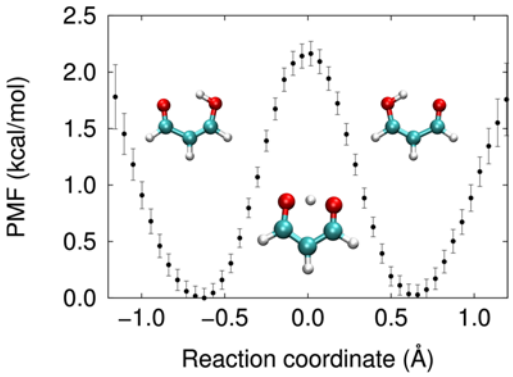

Fig. 1 Potential of mean force for proton transfer in malon aldehyde.

The second example is the docking simulations of ligands to target proteins [7-11]. We have applied Replica-Exchange Umbrella Sampling (REUS) to five test cases. In Fig. 2 we compare the conformations from experiments and our REUS results.

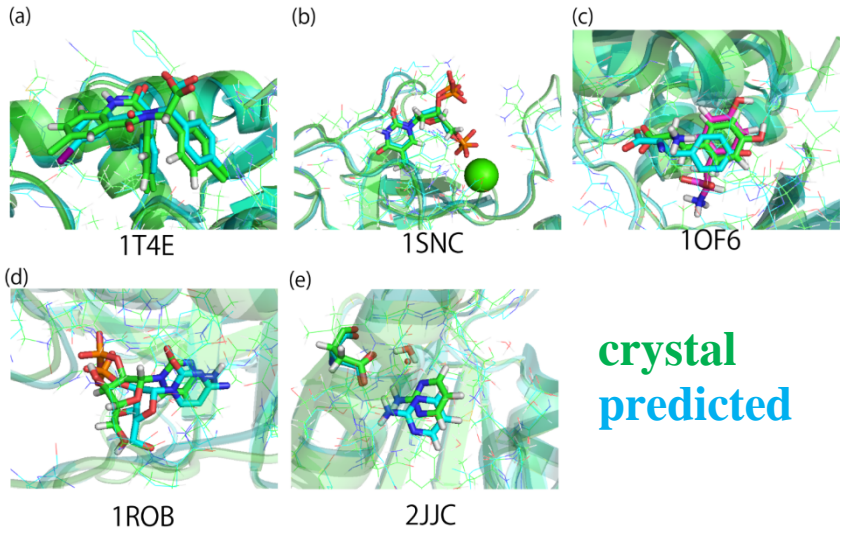

Fig. 2: Comparisons of docked conformations of ligands to target proteins.

They are in good agreement for all the five cases, while a popular docking program *GOLD* fails in two out of five cases.

References:

[1] U.H.E. Hansmann and Y. Okamoto, *Curr. Opin. Struct. Biol.*, **9**, 177-183 (1999).
[2] A. Mitsutake, Y. Sugita, and Y. Okamoto, *Biopolymers,* **60**, 96-123 (2001).
[3] H. Kokubo, T. Tanaka, and Y. Okamoto, in *Advances in Protein Chemistry and Structural Biology*, Vol. 92, T. Karabencheva-Christova (ed.) (Academic Press, Burlington, 2013) pp. 63-91.
[4] T. Yoda, Y. Sugita, and Y. Okamoto, in *Protein Conformational Dynamics, Advances in Experimental Medicine and Biology*, Vol. 805, K.-L. Han, Xin Zhang, and M.-J. Yang (eds.) (Springer, Berlin, 2014) pp. 1-27.
[5] A. Mitsutake and Y. Okamoto, *Journal of Chemical Physics* **130**, 214105 (14 pages) (2009).
[6] Y. Mori and Y. Okamoto, *Physical Review E.* **87**, 023301 (4 pages) (2013).
[7] Y. Okamoto, T. Tanaka, and H. Kokubo, *Journal of Computer-Aided Molecular Design,* **24**, 699-712 (2010).
[8] H. Kokubo, T. Tanaka, and Y. Okamoto, *Journal of Computational Chemistry,* **32**, 2810-2821 (2011).
[9] H. Kokubo, T. Tanaka, and Y. Okamoto, *Journal of Chemical Theory and Computation,* **9**, 4660-4671 (2013).
[10] H. Kokubo, T. Tanaka, and Y. Okamoto, *Journal of Computational Chemistry,* **34**, 2601-2614 (2013).
[11] Y. Okamoto, H. Kokubo, and T. Tanaka, *Journal of Chemical Theory and Computation,* **10** (2014), in press.

TOPOGRAPHY OF MOLECULAR SURFACES - A NEW COMPUTATIONAL TOOL TO STUDY STRUCTURE-ACTIVITY RELATIONSHIPS FOR PROTEINS AND BIOMEMBRANES

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Hydrophobic interactions play a key role in the folding and maintenance of the three-dimensional structure of proteins, as well as in the binding of ligands (e.g., drugs) to protein targets. Therefore, quantitative assessment of spatial hydrophobic (lipophilic) properties of these molecules is indispensable for the development of efficient computational methods in drug design. One possible solution to the problem lies in application of a concept of the 3-dimensional molecular hydrophobicity potential (MHP). The formalism of MHP utilizes a set of atomic physicochemical parameters evaluated from octanol-water partition coefficients (*log P*) of numerous chemical compounds. It permits detailed assessment of the hydrophobic and/or hydrophilic properties of various parts of molecules and may be useful in analysis of protein-protein and protein-ligand interactions.

This study surveys recent applications of MHP–based techniques to a number of biologically relevant tasks (1-3). Among them are: (i) Detailed assessment of hydrophobic/hydrophilic organization of proteins; (ii) Application of this data to the modeling of structure, dynamics, and function of globular and membrane proteins, membrane-active peptides, *etc*. (iii) Employment of the MHP-based criteria in docking simulations for ligands binding to receptors.

It is demonstrated that the application of the MHP-based techniques in combination with other molecular modeling tools (e.g., Monte Carlo and molecular dynamics simulations, docking, etc.) permits significant improvement to the standard computational approaches, provides additional important insights into the intimate molecular mechanisms driving protein assembling in water and in biological membranes, and helps in the computer-aided drug discovery process. One recent application of the MHP technique is related to mapping of protein surfaces according to their hydrophobicity. To proceed with this, a new method to create 2D spherical projection maps of entire protein surfaces and manipulate with them — protein surface topography (PST) – was developed. Representing complex molecular surfaces as regular arrays of data permits vivid visualization and thoughtful analysis of surface properties. PST may find a use to easily portray conformational transitions, analyze proteins' properties and their dynamic behavior, improve docking performance, carry out group analysis, and reveal common patterns and dissimilarities in molecular surfaces of related bioactive peptides. We suggest that PST is a beneficial approach for structure—function studies for bioactive peptides and small proteins.

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References:

[1] Efremov R.G. et al., *Curr. Med. Chem.,* **14**, 393 (2007).
[2] Chugunov A.O. et al., *J. Biol. Chem.,* **88,** 19014 (2013).
[3] Koromyslova A.D. et al., *J. Chem. Inf. Mod.,* **54,** 1189 (2014).

LUBRICATION MECHANISM IN JOINTS
— ROLE OF BIOPOLYMERS —

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Joints in animal body move very smoothly under high load or with low relative velocity, owing to articular cartilages covering each tip of the bones [1]. The articular cartilage is a complex tissue of extracellular matrix, which is a composite of collagen fibers, proteoglycan, and hyaluronic acid. With this complicated structure, the dynamic friction coefficient between two articular cartilage plates was found to be as small as 0.002-0.020. The mechanism of such low friction has long been discussed in order to develop better joint replacements, such as fluid pressurization mediated lubrication [2] and boundary lubrication due to biopolymers [3]. We focus on the role of proteoglycan, which is glycosylated protein, forming aggregation and being entwined with collagen networks. Since this is a typical polymer brush system, we carried out molecular dynamics simulations of polymer brush under shear to examine the role of biopolymers in lubrication of articular cartilages [4].

A typical simulation system is shown in Fig.1. We slide two plates (walls) each other, on which a given number of polymers are grafted. Periodic boundary conditions are imposed for horizontal directions. We adopt a coarse-grained polymer model of the Grest-Kremer type [5]; each polymer, corresponding to a proteoglycan molecule, consists of N particles (beads) of point mass m connected with a spring. Four types of forces are exerted on each bead; (1) Harmonic spring force between connected beads, (2) Lennard-Jones (12-6) potential force between all bead pairs, (3) Soft repulsive force from the walls, and (4) Hydrodynamic interaction between each bead and its surrounding "medium" (synovial liquid). For the term (4), a simple Langevin equation is assumed:

$$\vec{F}_{liq} = -\gamma(\vec{v} - \vec{v}_0) + \vec{F}_r \tag{1}$$

where the first term is the friction proportional to the velocity difference, the second the random force with a white noise character. The velocity of surrounding liquid $\vec{v}_0$ is modeled to have linear dependence on the local packing fraction.

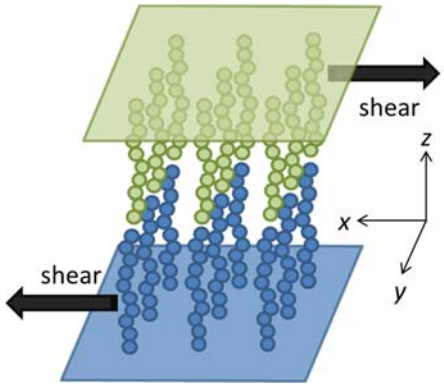

Fig. 1: Schematic view of simulation system.

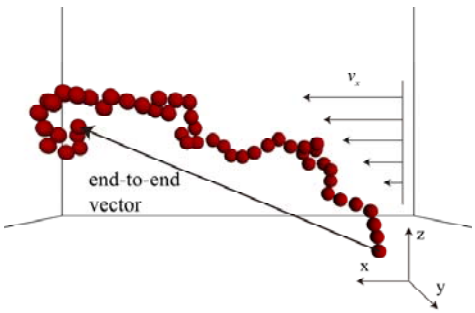

Fig. 2: Typical configuration of single polymer under steady shear of 2 s^{-1}.

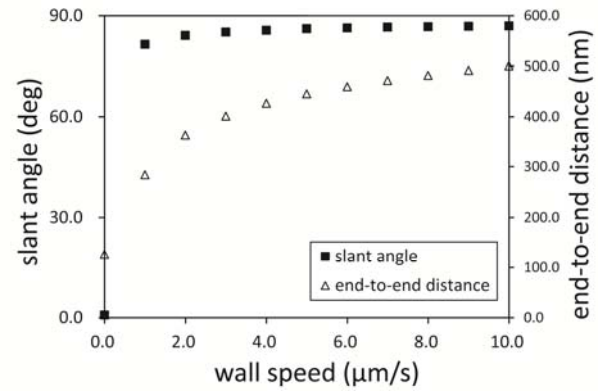

Fig. 3: Polymer deformation.

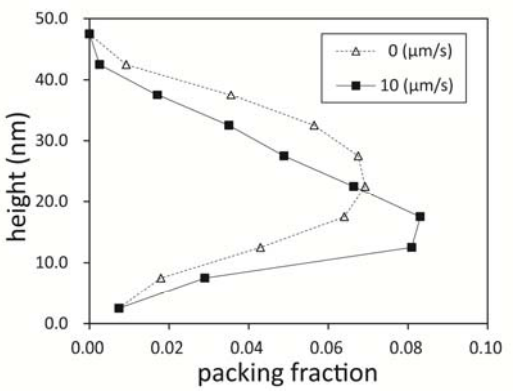

Fig. 4: Change local packing.

Typical behaviors of the model polymer under shear flow are shown in Fig. 3; the model is so flexible that a weak shear of $\approx 4\ s^{-1}$ (wall speed 1.0 μm/s) causes large elongation and strong orientation. As the deformation proceeds, the local density (packing fraction) of beads changes from the equilibrium one, as shown in Fig.4; the fraction peak shifts to the wall, due to the orientation.

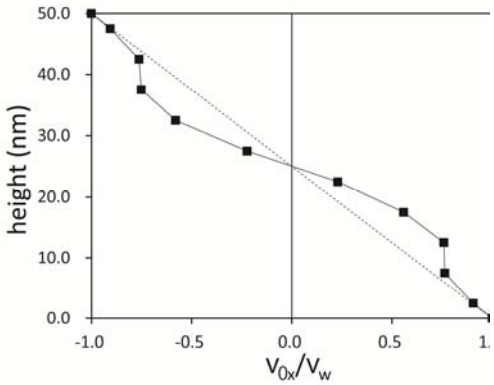

Fig. 5: Change of local fluid velocity.

Forces on the sliding wall by the grafted polymers were evaluated as a function of shear rate. While the parallel component $f_{//}$ increases proportionally to the shear rate, the normal one $f_{\perp}$ decreases. When we assume a typical value for the graft density of articular cartilage in vivo as 10^9 molecules/cm^2, $f_{//}$ has an order of 100 Pa; $f_{//} \sim 500$ Pa is reported with AFM experiments [6]. Synovial fluid exerts shear stress on the wall as well. Shown in Fig. 5 is the obtained fluid velocity in comparison with the Couette flow. Due to the increase of bead packing fraction near the wall, the velocity gradient near the wall is drastically reduced, which causes the large reduction of shear stress on the wall. Since the polymer force and the fluid shear stress have a similar order, we conclude that this shear stress reduction is important in the lubrication mechanism.

References:

[1] D. Dowson, *Faraday Discuss.*, **156,** 9-30 (2012).

[2] G.W. Greene, A. Olszewska, M. Osterberg, H. Zhu, R. Horn, *Soft Matter*, **10,** 374-382 (2014).

[3] J. Klein, *Polymers Adv. Tech.*, **23,** 729-735 (2012).

[4] M. Ide and M. Matsumoto, *Molecular Simulation,* in press.

[5] M. Murat and G. S. Grest, *Macromolecules*, **22,** 4054-4059 (1989).

[6] L. Han, D. Dean, C. Ortiz and A. J. Grodzinsky, *Biophys. J.*, **92,** 1384-1398 (2006).

PROTEIN-PROTEIN INTERACTION IN PHOTOSYNTHETIC ELECTRON TRANSFER CHAIN: COMPUTER SIMULATION

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Plastocyanin (Pc) is a small copper containing protein which transfers electrons in the chloroplast thylakoid lumen from cytochrome f (Cyt f) in the cytochrome bf complex to photooxidized P700 in photosystem I (PSI), fig. 1. Since PSI complexes are distributed in a thylakoid membrane heterogeneously, Pc molecules are assumed to diffuse over long distances in the luminal space of chloroplasts, shuttling electrons between granal and stromal areas of a thylakoid membrane.

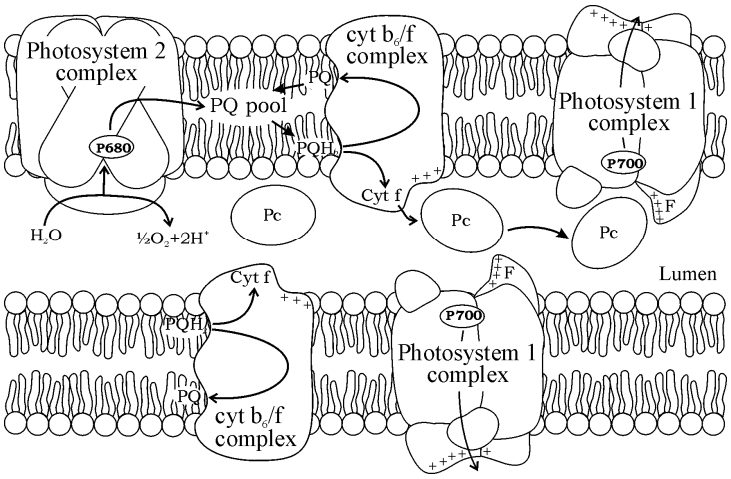

Fig. 1. Outline of electron transport (arrows) in chloroplast thylakoid lumen: two thylakoid membranes with PSI, PSII and cytochrome bf complex, and plastocyanin in the luminal space.

We present a Brownian dynamics (BD) computer model of limited diffusion of protein Pc and its interaction with transmembrane protein complexes photosystem 1 and cytochrome bf in the narrow chloroplast thylakoid lumen. The model is multiparticle, it considers many Pc molecules that compete to form complexes with numerous PSI and Cyt bf complexes embedded in the photosynthetic membranes. In addition to the possibilities of conventional BD method, our approach gives the possibility to simulate interactions of many protein molecules proceeding in a cell simultaneously and obtain in computer simulations the time curves to compare them with experimental time curves.

The model takes into account the geometry of the luminal space packed with many protein molecules and considers electrostatic interactions of plastocyanin with its reaction partners in the thylakoid membrane. The simulation area consists of two thylakoid membranes with the luminal space between them (fig. 2). On the lateral plane the simulation area is presented as a rectangle divided by the granal and stromal parts. The computer model includes 3D diffusion of Pc in the narrow thylakoid lumen and reactions of Pc with PSI and Cyt bf: protein-protein transient complex formation, electron transfer inside the transient complexes, and complex dissociation.

In the algorithm each protein molecule is represented as a 3D rigid body, its individual geometric surface is designed using the structure from the Protein Data Bank (PDB, www.pdb.org). There were no available structures of all of the proteins from one and the same species so in our simulation we used structures of spinach Pc (PDB entry 2PCF), structure of Cyt

bf complex from *Chlamydomonas reinhardtii* (1Q90), and of PSI with light harvesting complex I (2O01) from higher plants. The structure of Cyt f in the *Chlamydomonas reinhardtii* Cyt bf complex was substituted by the structure of turnip Cyt f (2PCF).

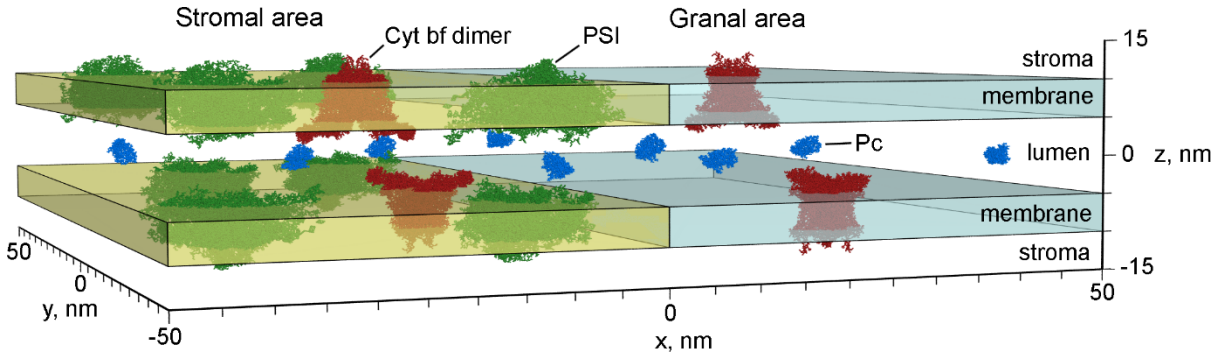

Fig. 2. Visualization of the part of the simulation area 100x100 nm. Two thylakoid membranes with protein complexes and luminal space between them are shown.

The information on the membrane area and distribution of the transmembrane complexes PSI and Cyt bf in the membrane was taken from (Albertsson, 2001). The membrane dimensions were 1500x400 nm, the number of PSI complexes in the stromal area is accepted to be 400, the number of Cyt bf dimers is 225 in the entire area of the membrane. The multisubunit protein-pigment complexes of PSI with LHCI and Cyt bf are fixed in the membrane whereas Pc molecules undergo translational and rotational diffusion in the lumen of thylakoid. To compute the displacement of Pc molecules at each time step in the model, the Langevin equation is solved numerically. The model uses a continuum electrostatic approach that describes molecules at the atomic level using a macroscopic description. The Poisson-Boltzmann formalism was used to determine the electrostatic potentials of the proteins. We used the model parameters of protein-protein association estimated in our previous papers for transient complex formation of Pc and Cyt f [1], Pc and PSI [2] in solution.

The model simulates protein-protein complex formation, electron transfer and complex dissociation reactions proceeding after a short light flash. The results of the simulation were compared with the experimental kinetic curves obtained on isolated spinach chloroplast samples [3]. Calculations correctly reproduce the experimentally registered kinetic curves of redox changes of the reaction center P700 of PSI and Cyt f. We studied the influence of Pc concentration and the geometrical shape of the thylakoid membrane on the shape of the kinetic curves. The spatial organization and dimensions of the thylakoid membrane were shown to have a strong effect on the actual kinetics of P700 reduction and especially on Cyt f oxidation. Computer simulation demonstrates that Brownian diffusion and electrostatic interactions in the complex interior of the photosynthetic membrane provide physical conditions for the directed electron flow along the electron transport chain. The simulation method presented in this work can be applied for the description of diffusion and functioning of many macromolecules that interact in the heterogeneous interior of subcellular systems.

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References:

[1] Kovalenko I.B. et al., *Phys. Biol*., **3**, 121–129 (2006).
[2] Kovalenko I.B. et al., *BioSystems,* **103**, 180–187 (2011).
[3] Haehnel, W. et al., *Biochim. Biophys. Acta,* **593**, 384–399 (1980).

1/f NOISE IN HYDRATION DYNAMICS ON LIPID MEMBRANE SURFACES

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Water molecules on lipid membrane surfaces are known to contribute to membrane stability by connecting lipid molecules as a water bridge. The residence times of water molecules on the lipid membrane surfaces follow power-law distributions [1]. These water molecules exhibit anomalous diffusion which comes from a combination of continuous time random walk (CTRW) and fractional Brownian motion (FBM) [2]. However, hydration dynamics near the membrane surfaces has been unclear.

Here we investigate hydration dynamics of water molecules on the surface of lipid membranes using all-atom molecular dynamics simulations. We show that hydration dynamics on the lipid membranes exhibits *1/f* noise [3]. The *1/f* noise is universally observed in nature, and it is known to generate a non-Poisson feature of water permeation in Aquaporin water channel [4]. Moreover, constructing a dichotomous process for the hydration dynamics, we find that the origin of the *1/f* noise is a combination of a power-law distribution with cutoff of interoccurrence times of switching events and a long-term correlation between the interoccurrence times. These results suggest that the *1/f* noise attributed to the correlated renewal process can contribute to the stability of the hydration layers and membranes.

References:

[1] E. Yamamoto et al., *Phys. Rev. E.*, **87,** 052715 (2013).
[2] E. Yamamoto et al., *Sci. Rep.*, **4,** 4720 (2014).
[3] E. Yamamoto et al., *arXiv:1404.4137 [physics.bio-ph]* (2014).
[4] E. Yamamoto et al., *Phys. Rev. E.*, **89,** 022718 (2014).

NEW CONTROL MECHANISMS OF WATER TRANSPORT IDENTIFIED IN AQP1 BY COMBINING MOLECULAR DYNAMICS SIMULATIONS AND EXPERIMENTS

Catherine Etchebest

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Collaborators: I. Mouro-Canteloup, P. Ripoche, S. Azouzi, S. Genetet, Y. Colin & C.Le Van Kim

The vast aquaporin superfamily gathers membrane proteins that are identified as selective water channels. The transport of water is bidirectional, extremely rapid and is driven by the osmotic pressure. High-resolution 3D structures have brought valuable information to characterize the translocation channel. However, a better understanding of the protein function requires a dynamic view of the transport process. Interestingly, the transport rate is compatible with current molecular dynamic (MD) simulations time-scale. Accordingly, MD simulations were extensively used to catch the details of the water transport mechanisms. Simulations helped in identifying two filter regions, one located in the central part of the channel and the other facing the extracellular medium, which both contribute to the selectivity of the channel. Recently, new control mechanisms have been proposed for different members of the family, e.g. AQP5, AQP0. Janosi & Ceccarelli [1] performed long simulations on AQP5 that highlighted the existence of a gate located on the cytoplasmic side. This gate would contribute to regulate water transport in different organisms, e.g. in plants in response to various environmental stresses.

In the present work, we revisited the transport of water in AQP1 by conducting a large set of molecular dynamics simulations with the AQP1 tetramer embedded in a solvated membrane environment. The length of the simulations enabled us to observe that the flux of water is disturbed by conformational changes of residues also located on the cytoplasmic side. In particular, we identified two titrable and highly conserved residues, H74 and E17 that contributed to the gating. We evaluated the pKa of all the residues for different conformations and observed how the protonation states influenced the permeation events. These results suggest that the intracellular pH (pHi) would play a role in the transport mechanisms.

In order to confirm this hypothesis, experimental measurements of the osmotic permeability (Pf) were conducted by following the fluorescence quenching of a pH-sensitive fluorescent probe, the 5(6) carboxyfluorescein. Different values of pH (pHi=pHe=6.5 or 7.2 or 8.0) were examined. The low Pf measured at pH=6.5 increased at pH=7.2 and pH=8.0. When pHi was fixed to 7.2 but the extracellular pH (pHe) varied, Pf was unchanged. These results clearly demonstrate the impact of the intracellular pH, pHi, on transport as suggested by MD simulations. It shows how by combining theoretical studies and experiments helps to enrich the spectrum of mechanisms that control AQP1 water transport.

References:

[1] Janosi L, Ceccarelli M. *PLoS ONE,* **8**(4): e59897 (2013).

PHASE DIAGRAM OF METHANE AND HYDROGEN HYDRATES FROM ATOMISTIC MODELLING

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Gas hydrates are crystalline water-based inclusion compounds in which guest molecules are trapped inside cavities of the hydrogen-bonded water network. Several clathrates and filled-ice structures are known. Structure type primarily depends on guest size, temperature and pressure. Gas hydrates allow compact storage of hydrocarbons since one volume of hydrate may contain 180 volumes of gas. Recently, they have attracted interest due to the possibility of being used for hydrogen storage. The pure hydrogen hydrates form at very high pressure, however, the addition of a promoter molecule, for example, tetrahydrofuran or methane, significantly reduce the formation pressure. Practical usage of hydrogen hydrates requires knowledge of their thermodynamic and kinetic properties, mechanisms of formation and decay in a wide range of pressures and temperatures.

In this work, we perform coexistence simulations of methane hydrates for pressures up to 5000 bar for different water models. We calculate the kinetic stability boundary of the superheated metastable sI structure and analyze the effects of the heating rate, system size and cage occupancy [1]. We also report molecular dynamics simulation of several possible structures for the new hydrogen hydrate clathrate. We show the strength of molecular simulation as a supplement tool for the analysis of experimental data [2].

References:

[1] Smirnov G.S., Stegailov V.V. *J. Chem. Phys.*, **136**, 044523 (2012).
[2] Smirnov G.S., Stegailov V.V. *J. Phys. Chem. Lett*., **4**, 3560 (2013).

DIMERIZATION OF GLYCOPHORIN A TRANSMEMBRANE DOMAIN: THE ROLE OF THE ENVIRONMENT

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Membrane receptors represent a wide class of proteins that have transmembrane (TM) alpha-helical segments. Association of TM helices plays an important functional role for these proteins. Dimerization or oligomerization of single-span receptors (like receptor tyrosine kinases) has been proved indispensable for signal transduction and TM segments have been shown to play a crucial role in this process. Based on the early pioneer works on Glycophorin A (GpA) the "dimerization motif" concept has been proposed [1], although the role of the membrane environment is still underestimated. It has been shown that lipids itself can form structured clusters, and in case of multiple-span membrane proteins there are specific lipid binding sites on their surface [2]. So, the same effects of lipid involvement on dimerization process can be suggested for other TM dimers as well. The present work is focused on GpA TM domain and its mutants T87V and G83A, and the role of membrane is considered in terms of energy and structure. To assess these parameters, computer simulations of molecular dynamics combined with weighted histogram analysis method were used [3]. Analysis of the calculated energy profiles reveals that these mutations are disruptive, but they act in a different way. While T87V mutation results in the loss of protein-protein interactions, G83A mutant shows almost the same protein-protein interaction profile as a wild-type dimer. So, its interaction with lipids is weakened by the mutation. It was also shown that all the dimers and even monomers can induce formation of neighboring specific lipid clusters. Lipids immobilize near the protein surface in the specific sites, and these clusters permit initial "communication" between the helices at the distance up to 30 A and evolve during the dimerization process. We therefore propose that the amino acid sequence determines not only protein-protein interactions, but also creates the lipid binding sites that are important for the dimerization process.

References:

[1] M.A. Lemmon, J.M. Flanagan, H.R. Treutlein, J. Zhang, D,M. Engelman, *Biochemistry,* **31**(51), 12719-25 (1992).
[2] D.V. Pyrkova, N.K. Tarasova, N.A. Krylov, D.E. Nolde, V.M. Pentkovsky, R.G. Efremov, *J. Biomol. Struct. Dyn.,* **31**(1), 87-95 (2013).
[3] A.A. Polyansky, P.E. Volynsky, R.G. Efremov, *JACS,* **134**(35), 14390-400 (2012).

ELECTRONIC STRUCTURE OF MAGNETIC ELEMENTS IN DILUTE MAGNETIC MATERIALS

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After the discovery of the ferromagnetism in dilute Mn-doped InP [1] and InAs [2], such materials doped with dilute magnetic elements in the non-magnetic semiconductors, which was called as Dilute Magnetic Semiconductor (DMS), have been extensively studied. At the earlier stage, III-V semiconducting materials were systematically explored and found some ferromagnetic ones. After these studies, other materials with larger band gaps were used as matrix, and several ferromagnetic ones by doping with magnetic elements into oxide matrix were found, which are called as Dilute Magnetic Oxide (DMO). Now these materials were combined into one called as Dilute Magnetic Material (DMM). Most of these materials have quite low Curie temperature, though this factor is quite important for the industrial applications of future development of spintronics. Then, most of the studies were devoted into elevating the Curie temperatures of these materials, and several room-temperature ferromagnetic DMMs were found. In order to understand the mechanism of appearance of ferromagnetism in DMMs, it is essential to know the local geometrical and electronic structures of doped magnetic ions. However, such studies have not been carried out much because of the difficulty of the analysis for such dilute dopants. We have successfully performed local environment analysis of doped magnetic ions in these dilute magnetic materials using the synchrotron radiation analysis with the aid of the first-principles calculations. One of the examples of such studies in our group is for the analysis of room-temperature ferromagnetic Mn and Fe co-doped In_2O_3 [3].

In the current study, our recent progress in the analysis of electronic structures of doped ions in DMMs using both experimental and computational methods is present. For the experimental analysis, the powder X-ray diffraction (XRD) and X-ray absorption near-edge structure (XANES) measurements by using the synchrotron radiation were employed. First-principles calculations based on the density functional theory were employed for the theoretical analysis. As an example, Co-L_3 X-ray absorption spectra of room-temperature ferromagnetic Co-doped CeO_2 are displayed in Fig. 1, which indicates that the doped Co ions in CeO_2 exist as metallic nano-sized particles.

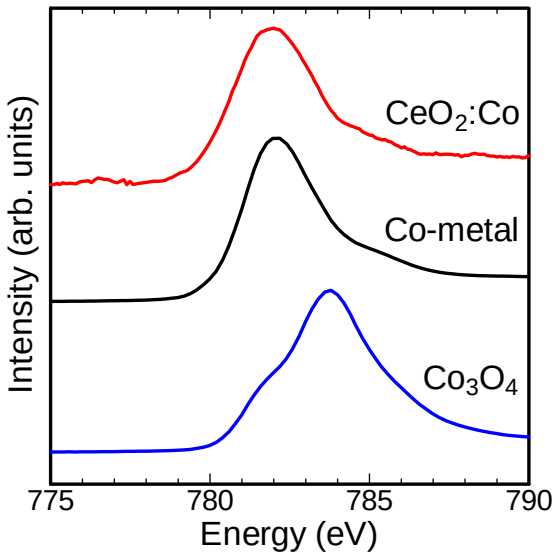

Fig. 1 Comparison of Co-L_3 XAS spectra of Co-doped CeO_2 ($Ce_{0.95}Co_{0.05}O_{2-\delta}$), Co-metal and Co_3O_4.

References:

[1] H. Ohno et al., *Phys. Rev. Lett.*, **68**, 2664 (1992).
[2] H. Ohno et al., *Appl. Phys. Lett.*, **69**, 363 (1996).
[3] T. Okazaki et al., *Solid State Comm.*, **151**, 1749 (2011).

ATOMISTIC BASIS FOR UNIQUE PHYSICAL PROPERTIES OF ARCHAEAL-LIKE MEMBRANES (DISCOVERED BY COMPUTER SIMULATIONS)

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Archaeal plasma membranes appear to be extremely durable and almost impermeable for water and ions, as compared to membranes of Bacteria and Eucaryota. Additionally, they remain liquid in 0–100° C temperature range. These properties most probably have determined evolutionary fate of Archaea, and may be adopted from the nature by bionanotechnology. This requires thorough understanding of how chemical structure of archaeal tetraether lipids determines the membrane properties. In this work, we use molecular dynamics (MD) simulations to assess on atomic level structure and dynamics of a series of model archaeal membranes — monolayers of phosphatidylcholine (PC) based tetraether lipids, whose hydrophobic tails contain in different proportion side methyl groups and cyclopentane moieties. Besides analysis of the effects of such "branching" on the membrane physical properties, the latter ones were compared with those for standard PC-based lipid bilayers. We conclude that the branched structure defines dense packing and low water permeability of archaeal-like membranes, but at the same time it ensures a liquid-crystalline state, which is vital for living cells. The most striking result is that archaeal membranes exhibit a peculiar dualism of their properties. Thus, they possess very rigid nonpolar core, without large-scale fluctuations inherent in common bilayer membranes. On the other hand, structural and dynamic organization of their water-membrane interface shares both common and rather specific properties with lipid bilayers. It is of note that some of the parameters of archaeal membrane mimics cannot be principally achieved in bilayer membranes. This makes tetraether lipid systems very promising in bionanotechnology and material science — for goal-oriented design of new unique membrane nanoobjects.

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STRUCTURAL AND HYDRATION EFFECTS OF PATHOGENIC POINT MUTATION T188R IN PRION PROTEIN: A MOLECULAR DYNAMICS SIMULATION STUDY

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Prion disease is one of the Transmissible Spongiform Encephalopathies (TSEs) which is the neurodegenerative diseases caused by the aggregation of prion protein misfolding [1,2]. The secondary structure conversion is key process of the prion disease, and is caused by pH [3], high temperature [4], or pathogenic mutation [5]; however, the process of this structural conversion remains poorly understood. In this study, we performed MD simulations of both human prion protein (WT-PrPc) and a pathogenic mutant prion protein (T188R) to clarify the effect of point mutation on second structure and hydration around the protein.

The secondary structure of WT-PrPc is not dramatically different from that of T188R; however, the magnitude of fluctuations of amino acids increases not only around the mutation point but also over a wide range of the protein. The secondary structure analysis reveals that there are more than two types of intermediate states in initial conversion process. We also find that the buried water molecule sites in WT-PrPc are disrupted by the pathogenic point mutation T188R. Furthermore, the disruption of buried water molecules causes the increase of amino acid fluctuations and secondary structure conversion. These results support that the disruption of buried water molecules may represent a first step in the conformational conversion and is a key event for destabilization of prion protein.

References:

[1] C. Soto, *Cell,* **149,** 968-977 (2012).
[2] S. B. Prusiner, *Science,* **216,** 136-144 (1982).
[3] S. Hornemann and R. Glockshuber, *Proc. Nat. Acad. Sci.,* **95**, 6010-6014 (1998).
[4] E. El-Bastawissy et al., *J. Mol. Graph. Model.,* **20**, 145-154 (2001).
[5] R. Riek et al., *Proc Nat. Acad. Sci.,* **95**, 11667 (1998).

DIFFERENCE OF BEHAVIOR OF DNA AND CPD IN THE REPAIRING MOLECULAR SYSTEM

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In the paper [1] was discussed the mechanism of charge transfer from active cofactor to the cyclobutane pyrimidine dimmers (CPD) before repairing and gets back it after finishing the process. As known [2,3], after splitting of thymine dimmers the DNA returns to its original at some steps (Fig. 1A).

In present work the behavior of DNA with flipped-in CPD was examined, and its properties were compared with those of normal (repaired) DNA.

Flavin (flavin adenine dinucleotide – FAD) has being essentially mobile molecule oscillates periodically around its equilibrium position; such flavin's motion is observed for both molecular system. The RMSD of damaged DNA is gradually increases from 2 Å up to 5 Å (Fig. 1B). Because, such characteristics of the repaired DNA is increases slowly, from 1.5 Å up to 3 Å. The RMSD of CPD is not increases, it fluctuate about 0.5 Å. The RMSD of repaired thymine is close to healthy DNA characteristics on the average.

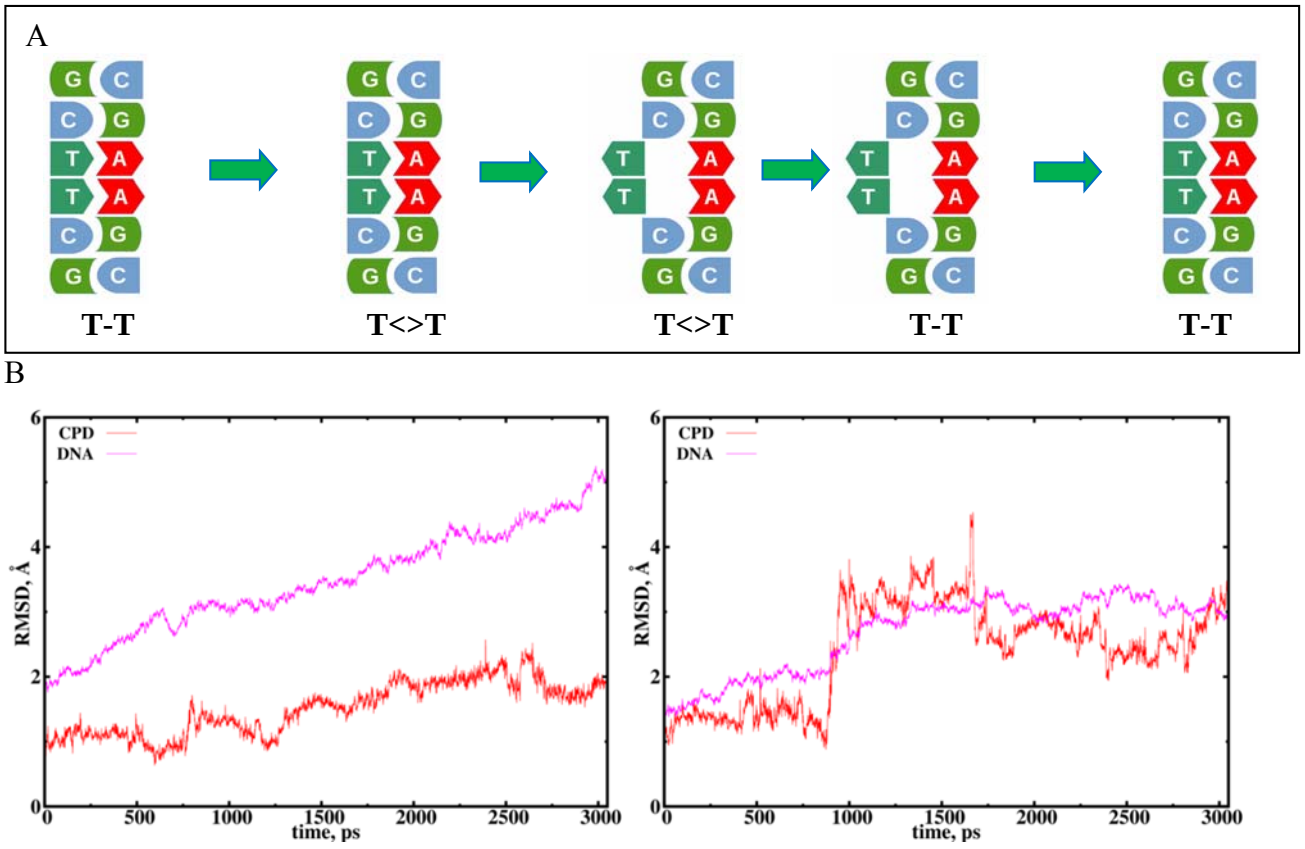

Fig. 1. The DNA molecule in the repairing medium. (A) A reaction mechanism of blue light-mediated repair of CPD lesion by DNA photolyases. (B) The RMSD for flipped-in T<>T (red) and corresponding DNA molecule (magenta) in the left and the RMSD for healthy DNA and T-T in the right.

Thus, we have observed distinct behaviors between two types of DNA and matching of the average characteristics of healthy DNA with its thymine. This gives us assume that under the influence of active cofactor damaged DNA begins to rotate around its symmetry axis, in order to flip out the CPD.

References:

[1] Dushanov E., Kholmurodov Kh., *The Open Biochemistry Journal*, **8**, 35-43 (2014).
[2] Mees A., Klar T., Gnau P., Hennecke U., Eker APM, Carell T., Essen L-O., *Science,* **306**(5702), 1789-1793 (2004).
[3] Sancar A. *Chem. Rev***, 103**(6), 2203-2238 (2003).

QSAR AND MOLECULAR MODELING IN THE DESIGN OF BIOACTIVE COMPOUNDS AND MATERIALS

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QSAR/QSPR (Quantitative structure-activity/property relationships) approaches can be considered as universal techniques for the modeling and prediction of nearly any properties of chemical compounds and many properties of materials. These approaches are based on the automatic analysis of structures and property values for a series of known chemical compounds with known properties, the chemical structures being described numerically with a series of parameters (descriptors). The structure-property relationships are usually evaluated using artificial neural networks. After creation of structure-property model it can be used for the prediction of properties for new chemical compounds for which these properties were never studied or compounds themselves were never synthesized. Good results of modeling had been obtained for the diffusion coefficients of small molecules in some polymers.

A large number of properties were modeled for various organic compounds basing on their structural formulas, e.g. density, boiling points, viscosity, surface tension, magnetic susceptibility, lipophilicity (octanol-water distribution coefficient), critical temperature, flash points, polarizability, enthalpy of evaporation, blood-brain barrier permeability, etc.

For the prediction of biological activity we have used both QSAR approaches and molecular modeling of ligand-receptor interactions, as well as molecular dynamics simulation; the structures of receptors themselves had been also modeled on the basis of homology. More than 20 receptors had been modeled and virtual screening system had been developed. Molecular Field Topology Analysis had been suggested and successfully used in quantitative structure-activity relationships studies for more than 100 different datasets.

The applicability of the developed techniques in conjunction with available professional molecular modeling software had been confirmed, e.g., by the development of the picomolar neuroprotective compounds which passed a preclinical stage, development of antiviral compounds, design of organic compounds with the required set of properties, etc.

SIMULATIONS OF VAPOR-TO-LIQUID NUCLEATION ON VARIOUS SOLID PRECURSOR PARTICLE CONFIGURATIONS BY MOLECULAR DYNAMICS

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Cloud formation and the steam created in industrial turbines are from vapor-to-liquid nucleation [1-4]. The phenomena in many cases incorporates heterogeneous nucleation from seed particles. This study is on how the seed characteristics affects heterogeneous nucleation and condensation, seed particles with different shapes and sizes were studied by molecular dynamics to examine the growth characteristics on the seed. One solid seed is placed inside a cubic system with supersaturated vapor of argon molecules. The seed is a sphere, cube, rod, or tube and is made aluminum or silicon atoms depending on the shape. Three different size classes were tested for the sphere, cube, and rod, whereas 4 different sizes were investigated for the tube. A broad spectrum of supersaturation ratios were simulated based on a canonical ensemble. The Yasuoka-Matsumoto method was used to calculate the growth rate around the seed [5, 6]. Though the number of molecules in the seed does not vary, just by changing the seed shape, the growth around the seed increases orderly for the cube compared to the sphere. Furthermore, the aspect ratio effect for different rod lengths with same number of molecules within each seed was observed, and the pore effect was verified for the tube.

The results of this study suggest that different rates of growth can be achieved by simply varying the initial shape of the precursor particle.

References:

[1] G. Winkler et al., *Zeitschrift Fur Angewandte Mathematik Und Mechanik,* **81**, 575 (2001).
[2] G. Winkler and G. H. Schnerr, *Zeitschrift Fur Angewandte Mathematik Und Mechanik,* **80**, 735 (2000).
[3] K. A. Koehler et al., *Physical Chemistry Chemical Physics,* **11**, 7906 (2000).
[4] H. Vehkamaki et al., *Journal of Chemical Physics,* **126**, 174707 (2007).
[5] K. Yasuoka and M. Matsumoto, *Journal of Chemical Physics,* **109**, 8451 (1998).
[6] K. Yasuoka and M. Matsumoto, *Journal of Chemical Physics,* **109**, 8463 (1998).

SOLUTE-SOLVENT INTERFACE PECULIARITIES FOR MONO-CARBOXYLIC ACIDS ORGANIC SOLUTIONS: POSSIBLE EFFECT ON SMALL-ANGLE NEUTRON SCATTERING DATA

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The methods of small-angle X-ray (SAXS) and neutron (SANS) scattering is based on the detection of the coherent scattering difference between a homogenous matrix and non-homogeneities (nanoparticles) in it. In a solution the solvent plays the role of such matrix. The method of SANS is widely used in the field of solutions microstructure investigations [1]. Organic solutions can be easily studied by SANS (in contrast to X-ray scattering) due to the fact of irregular scattering properties dependence on the atom type. For instance, hydrogen and its heavier isotope (^{2}H or D deuterium) have different scattering lengths (magnitude as well as sign) and, consequently, hydrogenated (solute) particles become "visible" in the deuterated media (solvent).

Mono-carboxylic acids solutions are of interest because of several reasons. Firstly, it is due to their possible practical applications as surfactants in the processes of the stabilized colloidal systems preparing [2, 3]. Secondly, acids in non-polar solutions form stable dimers and this effect studying can shed the light on the hydrogen bonding properties for such systems [4]. The SANS method is used for acid-acid interaction investigations. Recently, it was shown that for mono-carboxylic acids solutions in d-benzene (deuterated analog of benzene) studying the homogeneous Guinier approximations can be applied within the SANS data interpretation.

Indeed, in most cases when the characteristic particle size is much above the resolution limit of the method (1 nm), homogeneous approximation remains correct. A problem in describing the scattering curves is expected for small solutes with the size comparable with that of solvent molecules. It is understandable that for such type of solutions the scattering may be rather sensitive to possible specific organizations of the solvent molecules around the studied particle caused by the interaction effects. One of the possible ways for spatial SLD distributions analysis by the molecular dynamics (MD) simulations technique was described in [5]. The mentioned effects were evaluated by together MD-SANS approach in [6, 7] for mono-carboxylic acids in d-benzene and d-decalin solutions. As it was demonstrated the solute-solvent interface is considerably influence SANS for more complex solvent. Current research was aimed to clarify the differences between the two mentioned solvent types (benzene and decalin) are both widely used on practice. In the scope of used in [6, 7] rigid and non-associated molecules approximation the MD simulations were performed for myristic (MA) and stearic (SA) in benzene and decalin. SLD spatial distributions were analyzed in cylindrical coordinate system. The obtained profiles are shown in Fig.1 together with the specific averaging layer. Due to the fact of the obtained for one solvent type dependences similarity hereafter the averages dependencies were evaluated. The insets of Fig.1 contains forward scattering dependencies for benzene and decalin based solutions on the accounted solvation shell size, *R*, and, as can be seen, converge to their limit value with *R* increase.

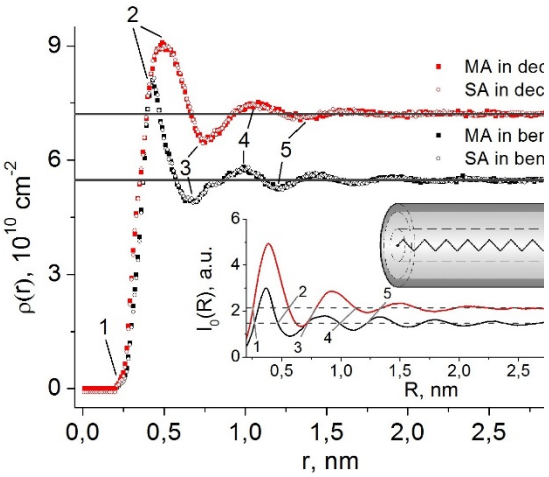

Fig. 1. The SLD profiles obtained from the MD simulations on the studied systems. Inset: Forward scattering dependence on the accounted solvation shell size, R. Cylindrical spatial averaging layer is schematically presented.

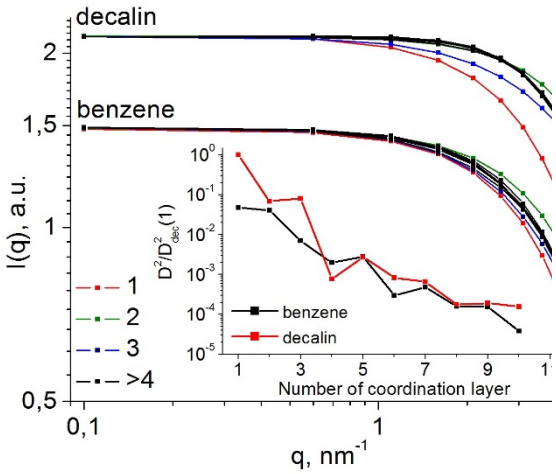

Fig. 2. The SANS curves calculated for SLD profiles local minima/maxima N=1,2,3,… Inset: The normalized difference functions D, calculated for obtained SANS curves as a point-by-point squared difference sum.

Next, for the single scattering particle the SANS curves were calculated for the *R* values corresponding to limit values coincide with SLD profiles local minima/maxima are marked by number, *N*, in Fig.1. The obtained curves are shown in Fig.2. In order to provide quantitate assessment the difference functions, *D*, were calculated for obtained SANS curves as point-by-point squared difference sum (see Fig.2 inset). As one can see, for both solvents types the curves are almost indistinguishable starting from the *N*=3. On the other hand, the differences between the curve corresponding to *N*=1 and the limiting one is greater for decalin based solutions. This observation allows us to conclude that, solvation shell is more inhomogeneous for decalin and significantly influence SANS. Despite the solvent type the region of at least 3 local minima/maxima of SLD profile should be analyzed for correct SANS data interpretation.

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References:

[1] Feigin, L. A.; Svergun, D. I. *Structure Analysis by Small-Angle X-ray and Neutron Scattering.* Plenum Press, New York (1987).
[2] Li Z., Zhu Y. *Appl. Surf. Sci.,* **211**, 315-320 (2003).
[3] Avdeev, M. V.; Bica, D.; Vekas, L.; Aksenov, V. L.; Feoktystov, A. V.; Marinica, O.; Rosta, L; Willumeit, R. *J. Colloid Interface Sci.*, **334**, 37-41 (2009).
[4] Pohl, H. A.; Hobbs, M. E.; Gross, P. M. *J. Chem. Phys.*, **9**(5), 408-414 (1941).
[5] R.Eremin, Kh.Kholmurodov, V.Petrenko, L.Rosta, M.Avdeev. *Chapter 10 "Molecular dynamics simulation for small-angle neutron scattering…"* pp. 139-154; Kh.Kholmurodov (Editor). *Models in bioscience and materials research….* Nova Sci. Pub., NY. (2013).
[6] Eremin, R. A.; Kholmurodov, K.; Petrenko, V. I.; Rosta, L.; Avdeev, M. V. *J. Appl. Cryst.*, **46**, 372-378 (2013).
[7] Eremin, R.A.; Kholmurodov, Kh.T.; Petrenko, V.I.; Rosta, L.; Avdeev, M.V. *Physics of the Solid State,* **56**, 81-85 (2014).

SYMBOLIC REGRESSION OF INTER-ATOMIC POTENTIALS VIA GENETIC PROGRAMMING

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One presents methodology and algorithm to find inter-atomic potentials for different kinds of material systems. We use ab initio potential energy calculations and symbolic regression using genetic programming, which is a generalization of genetic algorithms.

Many research in nuclear sciences and technologies are focused on aging of nuclear reactors and vessels, or on bio- logical molecules damages. In both cases, nuclear engineers and scientists are taking benefit from the fast evolution of powerful computing facilities to develop simulation tools in order to complete missing informations from experimentations. One of the main challenge is then multi-scale simulations with coupling of codes working at different scales, microscopic (ab initio), mesoscopic (molecular dynamics), macroscopic (structure calculations with finite elements).

Usually, material physicists are using molecular dynamic codes for calculations on alloys in order to determine thermo- mechanical constants, such as elastic constants, Young modulus... To achieve that, those codes need knowledge of well-suited inter-atomic potentials for each type of material system (molecule, alloy, ...), which yields to a long and very difficult development. Moreover, no mathematical shape can be speculated for binary and ternary alloys.

One presents first a systematic procedure using input/output data coming from experiments. It uses symbolic regression based on genetic programming. After that it is applied to material systems with experimental data and/or ab initio calculations for determining an analytical formula for inter-atomic potential. We exhibit some examples with numerical applications developed in *ruby* which is an elegant, powerful object oriented programming language.

References:

[1] A. Kenoufi, J.F. Osselin, B. Durand, ”System adjustments for targeted performances comining symbolic regression and set inversion, in ”*Inverse problems for science and engineering*”, 2012.
[2] J. R. Koza and R. Poli, ”Genetic Programming”, in “*Search methodologies: Introductory tutorials in optimization and decision support techniques*”, p. 127, Springer, 2005.
[3] W. B. Langdon and R. Poli, ”Foundations of Genetic Programming”, Springer-Verlag, 2002.
[4] J. Brownlee, ”Clever Algorithms: Nature-Inspired Programming Recipes”, ISBN: 978-1-4467-8506-5.

MOLECULAR DYNAMICS MODEL OF LIPOPOLYSACCHARIDE MOLECULE

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Sepsis is one of the important problems of modern medicine. Endotoxins which are the main component of the outer membrane of gram-negative bacteria play a key role in the development of system inflammatory response, sepsis and septic shock entering the bloodstream from the destroyed bacteria cells. By its chemical structure endotoxins are lipopolysaccharides (LPS). Recently methods of blood purification (removing LPS molecules from blood) by filtration became widely used in intensive care. Development of new sorbents requires understanding of the details of its interaction with LPS. High diversity of LPS molecule chemical structures hinders experimental study of the molecular details of its interaction with sorbents. We used molecular dynamic simulation method (MD) to find the possible spatial structures of LPS molecule.

We developed an all-atom model of LPS molecule (*Salmonella sp*.) on the base of the OPLS-AA [1] force field. Because of the high diversity of carbohydrate chemical structures, not all atom combinations in the LPS molecule are described in the OPLS-AA force field. For all undocumented fragments we have calculated missing force field parameters using quantum chemistry methods (QC, [2]).

First, we have computed partial charges on the atoms located at the junctions of standard atomic groups, described in OPLS-AA. Each missing in the force field fragment was extracted as a small molecule (fig. 1) for which we have performed QC calculations: system geometry optimization and electrostatic potential computation. Partial charges were calculated using the RESP procedure [3] which fits the obtained QC potential with point atomic charge potential. Final charge values were chosen to be close to the charges of atoms with similar types present in the force field and were corrected according to the RESP charge values.

Second, for all non-standard atom combinations we have calculated missing in the force field parameters of the energy of rotation around the corresponding bonds. For all the small molecules we have computed QC potential energy as a function of the corresponding torsion angle. Calculated energy profiles were fitted with the values of the full molecular mechanical (MM) energy so that only torsion angle energy parameters were variable during the fitting procedure while the parameters of other interactions (e.g. non-valent interactions) were fixed. Resulting MM torsion angle energy parameters and partial charge values were used for the further MD simulations.

The fragments extracted from the LPS molecule to calculate missing in the force field parameters are presented in fig. 1: α,α-dimetoxypropionic acid, 1-metoxyethylphosphate and dimethylpyrophosphate. Numbers correspond to the corrected partial charge values, bold lines mark torsion angles for which the parameter calculations were performed.

The next step of our work was to reveal the spatial O-antigen structure. There is no experimental data precisely describing the spatial conformation of this part of the molecule. O-antigen chain has a high amount of degree of freedom, so it was necessary to develop some method of classification of its possible conformations. We used the values of pairs of torsion angles formed

by O-glycoside bond between carbohydrate rings as the quantity characteristic defining the type of conformation.

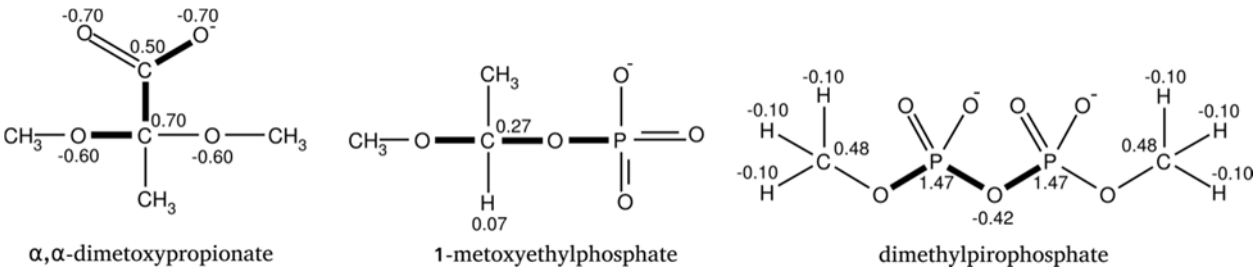

Fig. 1. Partial charges of the undescribed in OPLS-AA atoms from the LPS structure.

To analyze the conformational diversity of the non-core carbohydrate part of the LPS molecule we have extracted all the pairs of carbohydrate residues forming the main O-antigenic chain, as soon as they define its spatial structure. For these extracted disaccharides we have calculated MM potential energy as a function of the torsion angles using the PMF method ([4], fig. 2, left). Then, for these molecules we have performed a 300 ns MD simulation to check out if the obtained potential energy minima corresponds to the conformations presented in simulation. Analyzing the results of calculations we have obtained two-dimensional distributions of corresponding torsion angles values (fig. 2, right). From comparison of this graph with the potential energy map it is clear that the most probable torsion angle values correspond to the potential energy minima.

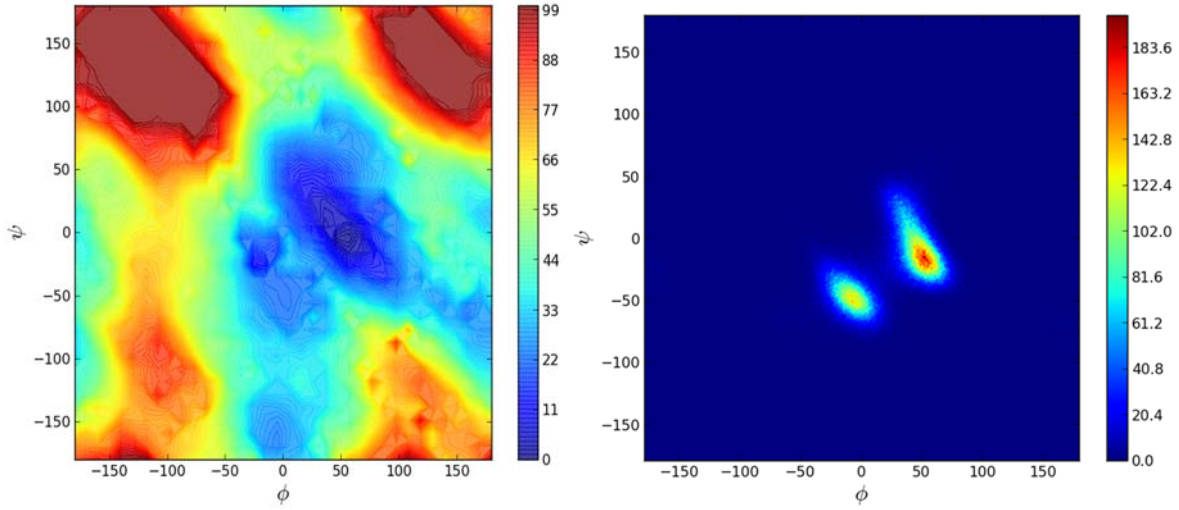

Fig. 2. Two-dimensioal distributions of the potential energy (left, kJ/mol) and probability density map for torsion angle values, for angles formed by the O-glycoside bond between rhamnose and mannose (right).

From the obtained data (fig. 2) it is clear that the energy minima are located in the 1-st and 3-rd quarters so that the corresponding molecule conformation could be both right or left helix. Indeed, in the pyranose chain for the units with the same sign torsion angles between them, the direction of rotation of the next chain unit remains the same along all the chain. In this case the chain with all the torsion angles being positive will form right-handed helix and conversely. Presence of both right- and left-handed helices in the O-antigenic structure distinguish it significantly from other biopolymers such as nucleic acids and proteins. Interchange of right- and left-handed helices along the O-antigenic chain results in the complex and extremely irregular spatial structure of the LPS molecules that hinders its experimental investigation.

Acknowledgements: The calculations were performed using supercomputer complex of Moscow State University.

References:

[1] W.L. Jorgensen, D.S. Maxwell, J. Tirado-Rives. *J. Am. Chem. Soc.,* **118**, 11225-11236 (1996).
[2] A.A. Granovsky, Firefly version 8.00, http://classic.chem.msu.su/gran/firefly/index.html.
[3] C.I. Bayly, P. Cieplak, W.D. Cornell, P.A. Kollman. *J. Phys. Chem.,* **97**, 10269-10280 (1993).
[4] R.K. Schmidt, B. Teo, J.W. Brady. *J. Phys. Chem.,* **99**. 11339-11343 (1995).

ON MOLECULAR DYNAMICS MODELING OF THE DNA–CNT INTERACTION PROCESSES: THE DIAGNOSTIC APPLICATION AND SIMULATION ASPECTS

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With regard to the different aspects of the DNA interaction and carbon nanotubes (CNTs) there has been a great discussion for today nano- and biotechnological innovation and application. The use of the DNA-CNT system (Figure 1) in DNA nanotechnology have intensively been discussed in molecular recognition processes, as a candidate material in cell drug delivery, as nucleic acid selection method (DNA aptamer) in SELEX (Systematic Evolution of Ligands by Exponential enrichment), so on. The conformational transition of aptamers (single chain DNA or RNA molecules that possess specific spatial structure) around CNT may cause some modification of the charge distribution on the CNT surface. It is worth noting that CNT surface has extremely sensitive to even a small change of the electrical charge of its environment. The replacement of even a single nucleotide for the DNA or RNA structure can modify, on the other hand, the charge environment around CNT. As a result, the CNT charge conductivity will be changed as well. So far, the DNA or RNA interactions with CNT could result to an essential modification for the charge distribution and consequent charge transfer through by the CNT surface. In the physics measurement the DNA-CNT charge distribution can be estimated trivially. This simple scheme from the point of view of application and diagnostic purposes has considered being one of the promising technologies in the DNA-CNT interaction processes with target proteins (say, of blood cells in human body).

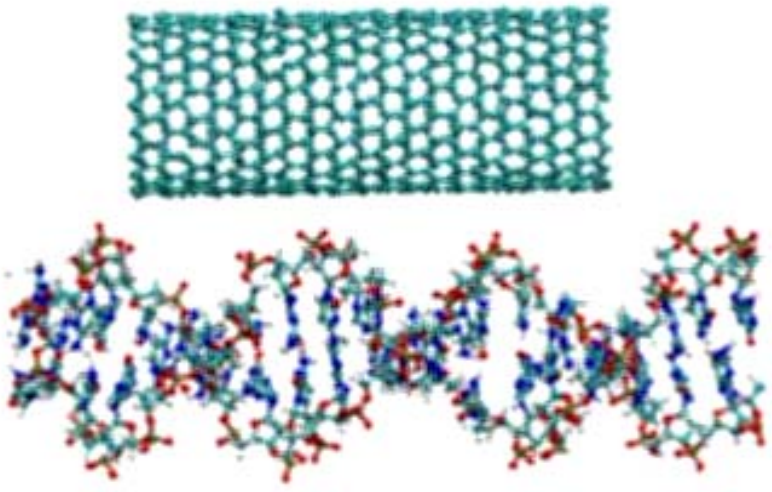

Fig. 1. A configuration snapshot of the CNT (top) and DNA (bottom).

Along with the DNA-CNT system the DNA–NP (nanoparticle) objects represent a great interest in today biomedicine applications due to diagnostic and treatment of oncology diseases.

Cancer, in which cells grow and divide abnormally, is one of the primary diseases with regards to how it responds to CNT drug delivery. Representing a revolutionarily potential for the biochemistry and medicine the use of CNTs in drug delivery has based on the enhancing of sufficient solubility and allowing of efficient tumor targeting. These aspects prevent CNTs from being cytotoxic and altering the function of immune cells. For today, cancer therapy involves surgery, radiation therapy, and chemotherapy. For example, recent experimental and simulation studies involve the interaction of DNA with highly localized high power beams and various nanoparticles (Ag, Au, etc.). These studies are aimed on targeted cancer therapy through the injection of metal micro- or nanoparticles into the tumor tissue with consequent local microwave or laser heating. Due to their good heat conductivities of NPs (Ag, Au, and so on) the experiments reveal that the only tumor cells to destroy, remaining normal cells undamaged. Nevertheless, such kind treatment methods are usually painful and kill normal cells in addition to producing adverse side effects. CNTs as drug delivery vehicles have shown a potential interest due to a targeting of specific cancer cells with a lower dosage rather than conventional drugs have [1-5].

So far, the studying molecular mechanism of the DNA-CNT reaction has seen strongly been motivated which MD (molecular dynamics) simulations were under the intense research in recent years. In this work we have employed the quantum chemistry Tersoff potential in combination with classical trajectory calculations to investigate the interaction of the DNA molecule with CNT. Tersoff potential is efficiently used for MD simulation of systems that contain carbon, silica, germanium, etc. alloys. In CNTs we have chemical bonding is hybridization sp2 (as graphite), which is stronger than sp3 bond (of diamond). The nature of chemical bonding in CNTs is described by quantum chemistry, through the process of orbital hybridization. The Tersoff potential in hybrid MD simulations correctly describes the nature of covalent bonding. It's good for simulating systems that contain carbon, silica, germanium and alloys of these elements. The peculiarity of Tersoff potential is that it allows the breaking and formation of chemical bonds. That is associated with hybridization process. Tersoff potential is pair wise potential, but coefficient in attractive term depends on local environment. Thus, Tersoff potential possesses a many body nature. It is also worth noting that CNTs exhibit a unique electrical and chemical properties for organic materials, they possess a great interest for the material research and electronic applications. Depending on their chemical structure, CNTs can be used as an alternative to organic or inorganic semiconductors as well as conductors. The chemical bonding of nanotubes is composed entirely of sp2 bonds, similar to those of graphite. This bonding structure, which is stronger than the sp3 bonds found in diamonds, provides the molecules with their unique strength. Nanotubes naturally align themselves into "ropes" held together by Van der Waals forces. The nature of the bonding of a nanotube is described by quantum chemistry, specifically, orbital hybridization.

The aim of this study is to perform the MD simulations to investigate the dynamical and structural behavior of the DNA–CNT model at ambient temperature conditions. The structural radial distribution functions and the dynamical configurations have built up for the DNA molecule interacting with the CNT. For the DNA–CNT system we have to observe an encapsulation-like behavior of the DNA chain inside the carbon nanotube to penetrate deep into. The discussions have made for possible use of the DNA–CNT formation as a candidate in drug delivery and related systems [6].

References:

[1] J. SantaLucia (Jr.) and D. Hicks, *Annu. Rev. Biophys. Biomol. Struct*., **33**, 415-440 (2004).
[2] K.J. Breslauert et. al., *Proc. Natl. Acad. Sci. USA*, **83**(11), 3746-3750 (1986).
[3] R. Dunford et. al., *FEBS Letters*, **418**(1), 87-90 (1997).
[4] T.A. Hilder, J.M. Hill, *Curr. Appl. Phys.,* **8**(3-4), 258–261 (2008).
[5] Kh. Kholmurodov (Ed.), "*Molecular Dynamics of Nanobistructures*", Nova Science Publishers Ltd., **2011**, 210p., ISBN: 978-1-61324-320-6.
[6] M. Khusenov et. al., *Journal of Modern Physics*, **5**, 137-144 (2014).

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IBCh, Moscow

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9^{30}–10^{00} Opening ceremony

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Drug design by generalized-ensemble simulations

10^{30}–11^{00} **Roman Efremov** (IBCh, Russia)
Topography of molecular surfaces — a new computational tool to study structure-activity relationships for proteins and biomembranes

11^{00}–11^{30} **Mitsuhiro Matsumoto** (Kyoto University, Japan)
Lubrication mechanism in joints – Role of Biopolymers

11^{30}–11^{45} **Ilya Kovalenko** (Moscow State University)
Protein-protein interaction in photosynthetic electron transfer chain: computer simulation

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Electronic structure of magnetic elements in dilute magnetic materials

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15^{45}–16^{00} **Katsufumi Tomobe** (Keio University, Japan)
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17^{45}–18^{00} **Abdelouahab Kenoufi** (Scientific Consulting for Research and Engineering, Strasbourg, France)
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18^{00}–18^{15} **Tatiana Galochkina** (Moscow State University)
Molecular dynamics model of lipopolysaccharide molecule

18^{15}–21^{00} Welcome Party

Co-organizers:

Dubna University, Russia
Waseda University, Japan
Nagoya University, Japan
Keio University, Japan