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on
Structural Systems Biology

19-21 June 2016
Centre of New Technologies, University of Warsaw
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Book of Abstracts

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Invited Lectures

Methylation/hydroxymethylation control of endonuclease activity

Honorata Czapinska [1,2], Karolina Mierzejewska [1], Asgar Abbas Kazrani [1], Wojciech Siwek [3], Monika Sokolowska [1], Krzysztof Skowronek [1], Janusz Bujnicki [1,4] and Matthias Bochtler [1,2]

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DNA modifications can control the susceptibility of DNA to endonucleases. We have focused on understanding the structural basis of this phenomenon. Typically, DNA modifications interfere with DNA cleavage, and restriction-modification systems exploit this effect to protect host DNA from endonuclease-inflicted damage. Protection is widely assumed to result from steric exclusion. Modified DNA does not “fit” into the binding site of the endonuclease in a productive manner, and thus molecular clashes should account for most of the protection. We have tested this concept statistically by grafting methyl groups “in silico” onto non-methylated DNA in restriction endonuclease co-crystal structures. Clash scores are significantly higher for protective than non-protective methylation ($p < 0.05\%$ by the Wilcoxon rank sum test). Protective adenine N6- and cytosine N4-methyl groups tend to clash more severely than protective C5-methyl groups. Structural data alone are sufficient to distinguish between protective and non-protective DNA methylation with 90% confidence (manuscript in preparation).
In certain other cases, DNA modifications are required for DNA cleavage. Weak van der Waals interactions do not easily explain the observed degree of discrimination. We have used crystallography and hydrogen-deuterium exchange to study the Type IIM REase R.DpnI, which cleaves G6mATC DNA efficiently only when both DNA strands are methylated. We show that the methyl groups in the 6mApT context are spatially close and bind as one combined hydrophobic unit in clefts of the two R.DpnI DNA-binding domains. Full methylation in the ApT context is incompatible with the B-form DNA conformation. We predict that R.DpnI and other 6mApT-binding proteins “read out” DNA methylation not only by direct interactions with the methyl groups and desolvation effects, but also indirectly through methylation-induced changes in DNA structure.
We have also studied the 5hmC-dependent REase, PvuRts1I. The structure of the enzyme without bound DNA shows that it consists of an Nterminal, atypical PD-(D/E)XK catalytic domain, and a C-terminal SRA domain that might accommodate a flipped 5hmC or 5ghmC. Changes to predicted catalytic residues of the PD(D/E)XK domain or to the putative pocket for a flipped base abolish catalytic activity. Surprisingly, fluorescence changes indicative of base flipping are not observed when PvuRts1I is added to DNA containing pyrrolocytosine in place of 5(g)hmC. Other enzymes of the PvuRts1I family also behave aberrantly in this respect. Notwithstanding, the structure suggests a model for PvuRts1I activity and presents opportunities for protein engineering to alter the enzyme properties for biotechnological applications.

Perturbing D76N β2-microglobulin dimerization by couplings to nanostructured surfaces

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Protein aggregation underlies an array of human diseases such as systemic amyloidosis which is a fatal disease caused by misfolding of native globular proteins damaging the structure and function of affected organs. Aggregation includes the formation of dimers and multimers in solution mediated by “apparently benign” interactors: the interactor could be a small ligand or even a large protein or protein complex. A very special class of interactors are nanoparticles because of the extremely efficient extension of their interaction surface. In particular citrate-coated gold nanoparticles (AuNPs) were recently addressed with amyloidogenic protein models and, contrary to expectations, no clear aggregation promotion was detected in the presence of citrate-coated AuNPs for the native β2-microglobulin (β2m) [1]. A different behaviour could be observed in the presence of amyloidogenic mutants of b2-m such as D76N and ΔN6. Contrary to native β2m, D76N variant has been shown to readily form amyloid fibrils in vitro under physiological extracellular conditions [2] since the thermodynamic destabilization caused by the mutation of the aspartate at position 76 into asparagine, plays an essential role in enhancing its amyloidogenic propensity [3]. However, the microscopic mechanism leading to protein destabilization is still unknown.
To advance the understanding of the role of mutations in favoring the dimeric association (seeding effect) of fibrils formed from D76N or ΔN6 at the beginning of the fibrillation process and to clarify the subsequent adsorption/deposition to nanostructured surfaces, we present a first comprehensive study based on the protein structural characterization by NMR and molecular simulations at multiple levels (enhanced sampling molecular dynamics, Brownian dynamics, and Poisson-Boltzmann electrostatics) explaining the origin of the observed protein perturbations.

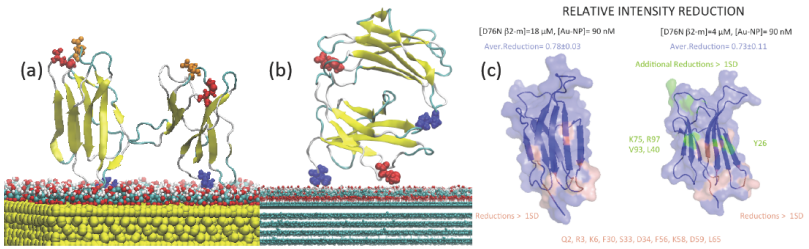

Fig. 1 Dimeric protein interacting with citrate-capped gold nanoparticle: (a) before dimeric seed formation (b) after seed formation (20 ns of T-REMD simulations) (c) NMR protein signal intensities

[1] (i) Brancolini, G. et al. ACS NANO, 2015, 9, 2600; (ii) Brancolini, G. et al. ACS Nano, 2012, 6, 9863
[2] (i) Mangione, P. P. et al., J. Biol. Chem. 2013, 288, 30917; (ii) G. Esposito et al. Subcell Biochem. 2012, 65, 165
[3] Natalello A. et al., J. Biol. Chem, 2016, 291, 9678

Computational modeling and design of RNA 3D structure and protein-RNA complexes

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Protein-RNA interactions play fundamental roles in many biological processes, such as regulation of gene expression, RNA splicing, and protein synthesis. The understanding of these processes improves as new structures of protein-RNA complexes are solved and the molecular details of interactions analyzed. However, experimental determination of protein-RNA complex structures by high-resolution methods is tedious and difficult. Therefore, studies on protein-RNA recognition and complex formation present major technical challenges for macromolecular structural biology. Alternatively, protein-RNA interactions can be predicted by computational methods. Although less accurate than experimental measurements, theoretical models of macromolecular structures can be sufficiently accurate to prompt functional hypotheses and guide e.g. identification of important amino acid or nucleotide residues. I will present an overview of strategies and methods for computational modeling of proteins, RNAs and their complexes with emphasis on software developed in our laboratory (available at http://genesilico.pl), and I will illustrate it with practical examples of structural predictions.

Self assembly of the protein α-synuclein at multiple lengthscales

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Alpha-synuclein (aS) is a disordered protein that can self-assemble into filamentous structures called amyloid fibrils. aS fibrils are chemically and mechanically very stable, once formed they tend to cluster and form intracellular inclusions. The formation of such inclusions is a hallmark of Parkinson's disease but their role in the disease process and the forces driving clustering remain elusive. Currently the discussion on the toxicity of aS aggregation focusses on soluble oligomeric aS aggregates instead of fibrils. Although aS oligomers are hypothesized to be toxic, the molecular architecture of these aggregates and the mechanisms by which they cause cell damage remain a mystery.
In this presentation, I will summarize our recent work on the self-assembly of aS at multiple length scales and discuss how we used a broad repertoire of quantitative single molecule and ensemble biophysical techniques, to characterize aS amyloid micro- and nano-structures and their interactions with lipid membranes to obtain insight into possible disease mechanisms.

Cation translocation in human ORAI channels: modeling and simulations.

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Ca^{2+}-release-activated Ca^{2+} channels, encoded by Orai channels, form an ubiquitous cellular Ca^{2+} entry pathway, and control diverse signalling processes including gene expression, cell proliferation and T-cell activation. The human genome contains three Orai isoforms; however it remains unknown if their sequence variations are required for specific Ca^{2+} signals. Orai1 senses the amount of cholesterol in the plasma membrane and apparently the interaction of Orai1 with cholesterol inhibits its activity, thereby limiting store-operated calcium entry [1]. High affinity Ca^{2+} binding to the pore entrance of Orai channels creates a local extracellular calcium accumulating region CAR and provides fundamental insight into the unique mechanism of Ca^{2+} permeation of Orai channels [2]. The combination of computational modeling of Orai channels and molecular dynamics simulations provided by the team in Nove Hrady, and functional patch clamp, site-directed mutagenesis and experimental biophysical experiments performed by the Linz Team allows to propose that the Orai1 channel architecture with a close proximity of CAR to the selectivity filter, which enables Ca^{2+}-selective ion permeation, enhances the local extracellular Ca^{2+} concentration to maintain Ca^{2+}-dependent gene regulation even in environments with relatively low Ca^{2+} concentrations [2].

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Folding and misfolding of large proteins using realistic all-atom force fields.

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In this contribution I will present some recent results which demonstrate that using a recent improvement of the so-called Dominant Reaction Pathway (DRP) path sampling technique [3] it is possible to simulate folding and misfolding of proteins of basically any size and folding times using state-of-the art all-atom force fields in both implicit and explicit solvent.
This new and improved version of the DRP approach was first directly validated against the results of plain MD simulations performed on the Anton supercomputer [1, 2]. Then, it has been applied to investigate a number of protein transitions which occur at time scales of the order of minutes or even hours, thus many orders of magnitude longer than those which can be covered by any existing or foreseen supercomputer.
In particular, in this workshop I would like to announce our recents results on the folding and misfolding of serpins, a family of fairly large proteins (about 400 amino acids) which are associated to a family of severe misfolding pathologies (serpinopaties).
Not only the DRP simulations of the folding of the wild-type human anti-trypsin serpin (ATA1) are in very good agreement with all existing experiments, but also they successfully predict the effect of point mutations on the misfolding propensity of these chains. Furthermore, our atomistic results allowed us to identify the physical interactions which are responsible for driving mutated proteins away from the correct folding rute, initiating the serpin polymerisation process at the base of serpinopaties.
Finally, DRP simulations have been used to characterise the serpin inhibitory mechanism and explain why the binding to specific drugs can promote their transition to a biologically latent state [3].

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[3] Cazzolli, G.; Wang, F.; a Beccara, S.; Gershenson, A.; Faccioli, P.; Wintrode, P. L. Proc. Natl. Acad. Sci. USA 2014, 111, 15414

G-protein-coupled receptor signaling

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G-protein-coupled receptors (GPCRs) constitute the largest family of cell-surface receptors and are involved in almost all physiological responses. They transduce signals mainly, but not exclusively, via hetero-trimeric G proteins, leading to a diversity of intracellular signaling cascades. Ligands binding at the orthosteric and allosteric sites of receptors have been classified as agonists, antagonists, and inverse agonists. GPCRs activate more than one G protein and signal through at least one G-protein independent pathway, arrestin. It is estimated that GPCRs are targets for about 30-50 % of currently used medicines, mainly due to their involvement in signaling pathways related to many diseases i.e. mental, metabolic including endocrinological disorders, immunological including viral infections, cardiovascular, inflammatory, senses disorders and cancer. As a result of their broad influence over human physiology and behavior, GPCRs are promising candidates for the development of new and more effective small molecule therapeutics. However, development of selective GPCR drugs is challenging for several reasons. First, there is a high degree of homology among many closely related receptor subtypes that can regulate diverse physiological functions. Also, a single GPCR may couple to more than one G protein, signal through G protein-independent pathways, undergo complex regulatory processes, and be allosterically regulated by small molecules and other proteins, including other GPCRs. Moreover, the predominant signaling behavior of a GPCR may differ for different cells or organs. Finally, drugs may preferentially activate or inhibit specific signaling pathways.
Several new lines of evidence now support a multi-state model of action of GPCRs, where the receptor can adopt multiple conformations, including active, inactive, and other intermediate ones. In such multi-state model, it is also inferred that ligands have the propensity of stabilizing a unique conformation leading to a specific signaling response, which may or may not always totally mimic the one induced by a natural ligand leading to severe side effects. Therefore, the so-called fine-tuning of GPCR responses, including GPCR-biased signaling, can be targeted by orthosteric/allosteric drugs. Biased ligands can stabilize a particular receptor conformation that mimics the ON conformation with respect to engaging one signaling pathway, while at the same time mimicking the OFF conformation for another signaling pathway that is normally activated by an agonist.

Supercomputing in the cellular jungle. Twisted DNA topologies, marching motor proteins and soft supermacromolecular citadels

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Now that techniques such as cryo electron tomography are revealing highly organised supermacromolecular architectures at the length-scale directly above that of single molecules, which was previously invisibile, there is a need for new computational tools to intepret these experiments. I will use our computer simulations of tiny DNA minicircles and of the molecular motor dynein in the axoneme to demonstrate that mesoscale super-macromolecular organisation cannot be ignored in mechanistic biology.

Direct observation of sub-microsecond motions in a transcription activator domain complex

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Dynamic flexibility is key to protein structure and function. A novel combination of single-molecule fluorescence with molecular simulations now allows us to probe this flexibility in a folded protein complex, with a surprising result. We directly observe nanometer distance fluctuations on a sub-microsecond timescale in the high-affinity complex of the intrinsically disordered interaction domains of CBP/p300 and ACTR, a p160 coactivator. The motions are only weakly coupled to solvent dynamics, but are dominated by interactions within the complex. An extension of our method to three- colors reveals that the breathing of the complex is well described as diffusion on a free energy surface with a low degree of collectivity between the coordinates. High affinity and high flexibility in folded protein complexes are therefore not mutually exclusive, particularly not for hub proteins that are evolutionary optimized to bind multiple ligands.

Car-Parrinello ab initio molecular dynamics explains the photophysical properties of 3-hydroxyflavone in organic solvents

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Car-Parrinello Ab initio molecular dynamics simulations have been employed to study how 3-hydroxyflavone (3HF, a widely used fluorescent dye and a model molecule for Excited-State Proton Transfer) modifies its photophysical properties by interacting with its molecular environment. To this aim, we have investigated 3HF in four different organic solvents which can be considered as prototypes of environments with different properties: CCl4 (apolar), acetonitrile (polar aprotic), methanol and 2,2,2-trifluoroethanol (protic solvents with different hydrogen bond donor acidity). This approach highlights the key role of the competition between intra- and inter-molecular hydrogen bonds involving the 3-hydroxy-4-keto moiety of 3HF. In particular, the obtained results show that the acidic hydrogen of 2,2,2-trifluoroethanol mainly interacts with the C=O and 3-OH groups of 3HF acting as an hydrogen bond donor, whereas for methanol the main feature is the interaction between the 3-OH group of 3HF and the solvent, the latter acting as an hydrogen bond acceptor. Similarly, in MeCN a weak hydrogen bond between the 3-OH group of 3HF (donor) and the nitrogen atom (acceptor) of the solvent is observed. Finally, interactions between CCl4 and 3HF resulted negligible, and the intra-molecular hydrogen bond between the 3-OH and the C=O moieties of 3HF prevails. Perturbation of this intra-molecular interaction in methanol, 2,2,2-trifluoroethanol and acetonitrile nicely explains the solvent dependence of several photophysical properties of 3HF: 1) modification of the UV-Vis absorbance profile; 2) spectral shape and quantum yield of fluorescence from the normal form and tautomeric form; 3) ground-state deprotonation of 3HF to yield a 3HF anion with different absorption and fluorescence spectra. Hints on how the solvent can influence the rate of Excited-State Intramolecular Proton Transfer reaction can also be drawn.

Coarse-grained modeling insights into the compaction of bacterial DNA

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The unconstrained genomic DNA of bacteria forms a coil, which volume exceeds 1000 times the volume of the cell. Since the DNA of prokaryotes is not bound by a membrane, in sharp contrast with the nucleus of eukaryotes, it may consequently be expected to occupy the whole available volume when constrained to fit in the cell. Still, it has been known for more than half a century that the DNA is localized in a well defined region of the cell, called the nucleoid, which occupies only about 25% of the total volume. Although this problem has focused the attention of many scientists for the past decades, there is still no certainty concerning the mechanism that enables such a dramatic compaction. In this talk, I will take stock of our knowledge on this question by listing possible compaction mechanisms with the desire to clarify the physical principles they are based upon and discuss them in the light of recent experimental results and the results of simulations based on coarse-grained models. I will argue that the importance of certain mechanisms, like supercoiling and the architectural properties of nucleoid associated proteins, may have been overestimated, whereas other mechanisms, like segregative phase separation and the self-association of nucleoid proteins, as well as the possible role of the synergy of two or more mechanisms, may conversely deserve more attention.

Coarse-grained modeling of protein structure, dynamics and interactions

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The traditional computational modeling of protein structure, dynamics and interactions remains difficult for many protein systems. It is mostly due to the size of protein conformational spaces and required simulation timescales that are still too large to be studied in atomistic detail. Lowering the level of protein representation from all-atom to coarse-grained opens up new possibilities for studying protein systems [1]. Possible strategies for efficient coarse-grained modeling and recent applications of CABS modeling tools are briefly discuses. CABS (C-Alpha, Beta and Side-chain) is a medium resolution model. In comparison with other realistic coarse-grained models, CABS provides similar resolution but it is based on qualitatively different interaction and sampling concepts. The choice of united atoms for modeling single amino acids is similar to that of UNRES except for the side chains which are represented by two spherical pseudo-atoms, one centered on Cβ and the other placed in the center of mass of the remaining portion of the side chain, where applicable. The main chain Cα positions are restricted to knots of a cubic lattice of small spacing, equal to 0.61 Å. This lattice Cα trace is used as the only independent variable that defines positions of other united atoms. Recently, we provided several easy to use web servers based on the CABS based modeling techniques (available at: http://biocomp.chem.uw.edu.pl/tools). The servers are dedicated to de novo and comparative modeling of structure prediction [2], studies of protein dynamics [3], and unrestrained, fully flexible, docking of peptides to protein receptors [4]-[5]. Multiscale modeling strategies combining CABS with all-atom Molecular Dynamics are briefly discussed.

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How do the local and long-range interactions encode the three-dimensional structures of biological macromolecules: a coarse-grained perspective

Adam Liwo [1], Adam K. Sieradzan [1], Agnieszka G. Lipska [1], Robert Ganzynkowicz [1], Bartosz Gryta [1], Michał Głuski [1]

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Coarse-grained models of proteins, nucleic acids, polysaccharides, lipid membranes, and other biological macromolecules and assemblies are nowadays widely used in large-scale modeling of these systems because they offer a tremendous increase of time- and size-scale of simulations compared to all-atom models. The effective coarse-grained energy function originates from the potential of mean force (PMF) of the system under study [1]. The coarse-grained energy terms can be identified with the Kubo's cluster cumulant functions [2] (PMF factors) in the expansion of the PMF. Further, by defining the rotation angles about the virtual site-site bonds as the major degrees of freedom to be averaged out, and expanding the PMF factors into Kubo's generalized cumulants [2], with all-atom energy expressed in terms of the squares of the interatomic distances, which are expanded into the power series about the distances between the site centers, analytical expressions for the effective energy terms can be derived, whose functional forms are consistent with the parent all-atom energy. Such expressions are very useful in the construction coarse-grained force fields. However their analysis can also be used to understand the formation of certain types of regular structures in biological macromolecules. In this talk this analysis is illustrated with the examples of coarse-grained local and correlation terms in the UNRES coarse-grained model for proteins and the NARES-2P model for nucleic acids, developed in our laboratory [3]. It will be demonstrated that the α-helical and β-sheet geometry of proteins and double-helix structure of DNA can be predicted by analyzing the angular dependence of the coarse-grained local and correlation terms. Results of simulations of real proteins and nucleic acids with the UNRES and NARES-2P force field containing the rigorously-derived terms will also be presented and discussed.

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Ion specificity at Graphene Oxide/Aqueous Solution interface

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The influence of different anions such as Cl^-, Br^-, SCN^-, $NO3^-$, $SO42^-$ and $CH3COO^-$ and cations such as Ca^{2+}, Mg^{2+}, Na^+ and NH^{4+} on the surface potential of graphene oxide (GO) suspension has been investigated both experimentally by zeta potential measurements and computationally by classical molecular dynamics (MD) simulations . The surface of GO has negative surface potential which can be varied by changing the pH of the solution as well as added inorganic ions. The surface of GO becomes hydrophobic in acidic medium due to the protonation thus the presence of inorganic ions affects the electrophoretic mobility of the dispersed phase within the GO suspension and influences its zeta potential. MD simulations were used to understand the interactions of ions within the slipping plane of GO which influences its zeta potential in salts solutions. The results suggested that the influence of the various inorganic ions on the electrokinetic potential of GO is ion specific and depends on nature of the ions. In this presentation the influence of ions on the surface of GO will be explained in molecular level and ion specificity at GO/solution interface will be compared with ion specificity at air/water and protein/solution interfaces.

Free-energy calculations for ligand binding: pathways and promiscuity

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Enhanced sampling methods are applied to quantify the interactions between small molecules and protein complexes. Hamiltonian replica exchange molecular dynamics simulations may be used to simulate reversible ligand binding along a judiciously chosen reaction coordinate. From these calculations, the potential of mean force (PMF) is readily computed from which the binding affinity can be estimated. Here, we suggest a grid-based reaction coordinate in which the shortest distance between the binding site and a ligand is determined avoiding routes that pass through the protein [1]. I will demonstrate this technique at the hand of various examples.
On the other hand, small modifications of the Hamiltonian of the ligand itself allows us to simulate the free energy differences between stereoisomers in a highly efficient way [2]. The sampling can be further enhanced by a combination with local elevation simulations [3]. Here, we describe all 32 aldohexopyranoses in the course of just a few molecular dynamics simulations, from which we predict free energies of solvation, anomeric preferences and free energies of binding to the promiscuous enzyme pyranose dehydrogenase for all 32 stereoisomers [4]. By reweighting intermolecular distances, observed reactivities may even be rationalized and predictions can be made.

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Water meets ionic liquids: from homogeneous mixtures to micellar systems in MD simulations

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Water and ionic liquids have not always been the best friends. However, in recent years the scope of ionic liquids as functional fluids has been expanded to include their mixtures with water for multiple appli-cations. The microstructure and heterogeneity in the liquid state, funda-mental aspects of pure ionic liquids, continue to exist in aqueous solution. For short chain imidazolium ionic liquids, the interaction with water is me-diated by the anions as they are capable to form hydrogen bonds with water in contrast to the imidazolium cations [1,2]. However, these aqueous ionic liquid mixtures do not seem to behave like normal electrolytes but resemble polar mixtures, in particular in dielectric spectroscopy [3,4]. Increasing the length of the alkyl chain attached to the imidazoliums leads to the formation of micelles. These can be analyzed experimentally by surface tension, conductivity and UV-Vis spectroscopy to determine the critical micelle concentration [5] or used as reaction media for catalysis [6]. In addition to these experiments we present first coarse-grained MD simulations to monitor the ``birth'' of a micelle and its further evolution.

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Prediction of protein-ligand binding poses via a combination of induced fit docking and metadynamics simulations

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Ligand docking is a widely used tool for lead discovery and binding mode prediction based drug discovery. The greatest challenges in docking occur when the receptor significantly reorganizes upon small molecule binding, thereby requiring an induced fit docking (IFD) approach in which the receptor is allowed to move in order to bind to the ligand optimally. IFD methods have had some success, but suffer from a lack of reliability. Complementing IFD with all-atom molecular dynamics (MD) is a straightforward solution in principle, but not in practice due to the severe timescale limitations of MD. Here we introduce a metadynamics plus IFD strategy for accurate and reliable prediction of the structures of protein-ligand complexes at a practically useful computational cost. Our strategy allows treating this problem in full atomistic detail and in a computationally efficient manner, and enhances the predictive power of IFD methods. We significantly increase the accuracy of the underlying IFD protocol across a large dataset comprising 42 different ligand-receptor systems. We expect this approach to be of significant value in computationally driven drug design.

Spectral Properties of the Spinach Aptamer, QM/MM Calculations

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Spinach aptamer was developed as an RNA analog of the Green Fluorescent Protein. The aptamer interacts with 3,5-difluoro-4-hydroxybenzylidene imidazolinone (DFHBI) molecule and modifies its electronic spectrum so that the chromophore emits bright light with wavelength of 501 nm. Song et al. have investigated modifications of the chromophore in their experimental study [1] and found that substitution of methyl group at position 2 by trifluoromethyl leads to emission wavelength of 523 nm in complex with the Spinach aptamer.
The crystal structure of the Spinach aptamer in complex with its original ligand has been published in 2014 [2] and it enabled us to study the system computationally. In this contribution, we will report several new modifications of the chromophore that cause further red-shift absorption electronic spectrum of the complex. Our results are based on combined quantum mechanical / molecular mechanical calculations in ONIOM with the choice of DFT as the quantum mechanics method. These were used for geometry optimization. The quantum mechanical (QM) region contained the chromophore and nearby nucleotides. Excitation energies were calculated by TDDFT method on the QM region, optimized in ONIOM, embedded in PCM continuum with solvent of medium dielectric constant.

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Knots in proteins and DNA - a tangled challenge

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Ever since Lord Kelvin has conjectured that atoms are composed of knots in the ether, these peculiar objects have stimulated the imagination of mathematicians and natural scientists alike. In recent years the field went through a renaissance and progressed considerably, spurred by the discovery of knotted DNA and proteins. From an evolutionary point of view protein knots [1] occur in all kingdoms of life and topology is typically preserved amongst homologs. Nowadays, knotted protein structures can even be created artificially, and knotted designs could be used in the future in the context of protein engineering. I will also demonstrate why the folding of knotted proteins may not be so difficult after all by explaining coarse-grained folding simulations of a rather complicated protein, which features six elementary crossings in a projection onto a plane [2]. While knots in globular homopolymers are abundant, protein knots are rare and occur in less than one percent of all known structures. To address this conundrum I will present simulations of a coarse-grained heteropolymer model and argue that the addition of sequence may facilitate evolution towards unknotted proteins even though on average globular heteropolymers are just as knotted as homopolymers [3]. In the second part I will discuss the occurrence and implications of knots in DNA. Viral DNA is known to be highly knotted in the capsid and shows a preference towards torus-type knots. These phenomena will be explained in the context of coarse-grained simulations of single semiflexible polymers in spherical confinement [4]. I will also present a mechanism, which allows two knots on a polymer chain to pass through each other and swap positions along the strand. Associated "topological" free energy barriers only amount to a few kT, which may enable the interchange of knots on a single DNA molecule [5]. This peculiar mechanism and the occurrence of knots in DNA is not only interesting from an aesthetic point of view, but may also play a role in future technological applications such as nanopore sequencing once strand sizes exceed 100000 base pairs.

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Molecular ageing

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The biological activity of proteins can be impaired when they are exposed to free radicals like reactive oxygen species (ROS). Radicals, particularly OH, can cause stereochemical changes by α-hydrogen abstraction in α-amino acids, which in turn can lead to the loss of biological activity of proteins. It has been shown that radicals are involved in the mechanisms that cause various diseases such as Alzheimer's disease, Parkinson's disease and schizophrenia. It has been demonstrated that oxidative stress can cause the racemization of L-amino acids and the accumulation of D-amino acids in living organisms.
We provide a systematic and comparative analysis on thermochemistry of oxidative stress, using first principle computation. Molecular dynamic computations will demonstrate the structural modification caused by oxidative stress.

Ligand-gated ion channels: from 3D structure to transmembrane signaling

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Neurotransmitter-gated ion channels of the Cys-loop receptor family mediate fast neurotransmission throughout the nervous system. The molecular processes of neurotransmitter binding, subsequent opening of the ion channel and ion permeation remain poorly understood. Here we present recent results of high-resolution X-ray crystallography, single particle imaging, and molecular modeling studies of a mammalian Cys-loop receptor, the mouse serotonin 5-HT3 receptor. We revealed at atomic detail how neurotransmitter binding on the extracellular domain of the 5-HT3 receptor induces sequential conformational transitions in the receptor opening a transmembrane ion channel: Agonist binding first induced distinct conformational fluctuations of particular side chains in the highly conserved ligand binding cage, followed by tilting-twisting movements of the extracellular domain which coupled to the transmembrane TM2 helices to open the hydrophobic gate and forming a continuous transmembrane water pathway. The structural transitions in the receptor's transmembrane part finally coupled to the intracellular region opening passages for ion release. The details of structural transitions of the 5-HT3 receptor deliver important insights for understanding the operating mechanism of mammalian Cys-loop receptors.

Regular Lectures

SimRNA: a coarse-grained method for RNA folding simulations and 3D structure prediction

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The molecules of the ribonucleic acid (RNA) perform a variety of vital roles in all living cells. Their biological function depends on their structure and dynamics, both of which are difficult to experimentally determine, but can be theoretically inferred based on the RNA sequence. We have developed a computational method for molecular simulations of RNA, named SimRNA [1].
SimRNA is based on a coarse-grained representation of a nucleotide chain, a statistically derived energy function, and Monte Carlo methods for sampling of the conformational space. The backbone of RNA chain is represented by P and C4' atoms, whereas nucleotide bases are represented by three atoms: N1-C2-C4 for pyrimidines and N9-C2-C6 for purines. Despite the bases being represented by only three atoms, other atoms can be implicitly taken into account in terms of the excluded volume. All base-base interactions were modeled using discrete three-dimensional grids built on local systems of coordinates.
All terms of the energy function used were derived from a manually curated database of crystal RNA structures, as a statistical potential. Sampling of the conformational space was accomplished by the use of the asymmetric Metropolis algorithm coupled with a dedicated set of moves. The algorithm was embedded in either a simulated annealing or replica exchange Monte Carlo method.
Recent tests demonstrated that SimRNA is able to predict basic topologies of RNA molecules with sizes up to about 50 nucleotides, based on their sequences only, and larger molecules if supplied with appropriate distance restraints. The user can specify various types of restraints, including restraints on secondary structure, distance and position.
SimRNA can be used for systems composed of several chains of RNA. It is also able to fold/refine structures with irregular (non-helical) geometry of the backbone (RNA pseudo knots, coaxial stacking, bulges, etc.). As SimRNA is based on folding simulations, it also allows for examining folding pathways, getting an approximate view of the energy landscapes, and investigating of the thermodynamics of RNA systems.
SimRNA is also available as a server: SimRNAweb [2].

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Accessing large-scale conformational changes in molecular docking of peptides to proteins: the interaction of p53 with MDM2

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The protein-peptide interactions are often associated with large-scale conformational changes of both the peptide and protein receptor structures. However, studying those changes is difficult, either by modeling or by experiment. In our work, we focused on the highly investigated protein-peptide complex that is an element of cell regulation system crucial for anti-cancer drug design – p53 binding motif with the MDM2 protein. The MDM2 receptor has two large intrinsically unstructured regions localized in the proximity of the binding site. Efficient modeling of intrinsically disordered MDM2 regions during docking is not possible using classical modeling techniques.
Using our newly developed multiscale method for flexible docking – the CABS-dock [1-3] - we were able to model the full flexibility of the appropriate MDM2 fragments together with the full flexibility of the peptide structure during the explicit docking simulations. In our simulations, we obtained protein-peptide models and the picture of the binding dynamics, which match well the experimental data. The results of our study suggest that the applied methodology can be helpful in the characterization of protein-peptide interactions that involve large conformational changes.

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Complex lasso proteins – how to form a topological link in protein

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Topologically complex protein, including knotted and slipknotted structures are nowadays well settled in biology [1]. However, in last year we discovered new entangled motif which we call complex lasso proteins [2,3].
Complex lasso motif occurs in structures with a covalent loop (closed e.g. by disulfide bond), which is then pierced by one of the tails. In total, 18% of non-redundant set of proteins with disulfide bridges are complex lasso proteins [2,3]. In this work we analyze the geometry of such structures correlating it with the protein properties and show, that the topological motif can have a biological meaning. Next, we identify the existence of topological links in proteins, realized by appropriate arrangement of disulfide loops and study folding of such structures [4]. We show, that in oxidative conditions the folding probability depends on the order of the covalent loop formation. We also identify topological traps in protein folding and relate them with the experimental data. This altogether shows, that topological analysis can be crucial factor in explaining experimental data and protein properties.

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Pair correlation preferences of amino acids in beta-sheets: a strategy to establish the best concept and dataset for proteins

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Beta pleated sheets are one of the most abundant and important secondary structure elements of natural proteins. The beta pleated sheets are subject to aggregation and it makes their structure investigation important as these sheets are hypothesized to be the seeds of aggregates (or plaques), associated with conformational illnesses (e.g. Alzheimer and Creutzfeldt–Jakob disease). In order to understand the forces behind the aggregation, the “building block” of beta pleated sheets was studied: amino acids “pairs” facing each other in the adjacent polypeptide chains. This “pair” contains the majority of the interactions that stabilize beta pleated sheets. Structure and stability of beta pleated sheet building units are strongly dependent on their H-bonding pattern (polar interactions) and on their side chain contacts, typically apolar for beta-sheets. In order to build a representative database for statistical analysis, a good quality data of non-homologous proteins should be prepared. Several selection algorithms and datasets (e.g. PDBSelect[1], WHATIF culled dataset[2], PISCES[3] etc.) were used for database building and the results from the different sets were systematically compared to each other. To make this statistical analysis user friendly and the regular database update straightforward, a portable framework has been developed in Java. Hereby we are presenting a strategy for getting the largest and the best quality database of amino acid pair correlations in beta sheets.

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The relationship of tRNA accommodation, EF-Tu dissociation, and kinetic proofreading in the ribosome

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To rationalize the apparent inconsistency between the fidelity of protein synthesis and the thermodynamics of tRNA-mRNA base pairing, Hopfield proposed that the ribosome may increase accuracy by utilizing an energetically-driven multi-step kinetic proofreading mechanism. While this established a theoretical framework, there has yet to be a structural description of selection that provides quantitative physical-chemical evidence that such a mechanism can be utilised by the ribosome. Here, we use energy landscape principles and molecular dynamics simulations to investigate the role of EF-Tu during aa-tRNA accommodation (i.e. the putative proofreading step). First we quantitatively identify distance-based reaction coordinates for investigating the accommodation motion through structure-based molecular dynamics simulations. Using these coordinates for analysis, we find that EF-Tu may effectively "push" the aa-tRNA into a metastable, partially-accommodated intermediate, as required by the kinetic proofreading framework. To interpret these results in a biological context, we integrate the findings within a multi-state kinetic model. From this, we find that the fidelity imparted by proofreading is dependent on the relative rates aa-tRNA accommodation and EF-Tu dissociation from the ribosome. Together, these results provide a structural and energetic description for how GTP-dependent driving of aa-tRNA accommodation by EF-Tu can enable a kinetic proofreading mechanism to be employed by the ribosome.

Formaldehyde and its tautomers as the basic building blocks of carbohydrate synthesis in outer-space

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Glycolaldehyhde or 2-hydroxyacetaldehyde has been detected in molecular clouds in interstellar mediums in outer space [1]. Molecular clouds are characterized by temperatures on the order of 10-20 K. At these temperatures there is insufficient energy for collisions to overcome any activation barriers in reactions, and the only gas phase chemical reactions that can proceed at such low temperatures are radical-radical reactions and ion molecule reactions, both of which are barrierless [2]. Several mechanisms have been proposed and all of them included radical formation. The present proposed mechanism starts from formaldehyde, which is the smallest of the [C(H2O)]n general carbohydrate formula. It can be formed from carbon monoxide and hydrogen (CO+H2) not only on earth but also in outer-space, as detected in 1969 [3].
Molecular Evolution, a substantial portion of organic chemistry, was used to demonstrate that glycolaldehyhde forms from singlet hydroxy carbene (H-C:-OH), instead of the previously expected closed-shell reagents. The Born-Oppenheimer approximation provides the theoretical evidence that suggests structures of CxHyOz comprise all of its isomers and their conformers.
The glycolaldehyde may be converted all the way to aldo- and ketohexoxes via a stepwise polymerization addition of hydroxycarbene (H-C:-OH), leading to trioses, tetroses, pentoses and hexoses.

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An integrated approach to the assessment of stimulant properties of novel psychoactive substances (NPS) – the case of the benzofuran 5-MAPB (1-(benzofuran-5-yl)-N-methylpropan-2-amine)

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Novel psychoactive substances (NPS) are increasingly prevalent world-wide although their pharmacological characteristics are largely unknown; those with stimulant properties, due to interactions with the dopamine transporter (DAT), have addictive potential which their users may not realise.
We evaluated the binding of 1-(benzofuran-5-yl)-N-methylpropan-2-amine (5-MAPB), one of the benzofuran class of NPS, chosen here for its suspected stimulant properties, to rat striatal DAT by means of quantitative autoradiography with the selective DAT-radioligand [^{125}I]RTI-121, and the effects of 5-MAPB on electrically-evoked dopamine efflux by fast cyclic voltammetry in rat brain slices. 5-MAPB displaced [^{125}I]RTI-121 in a concentration-dependent manner, with significant effects at 10 and 30 μM. The functional neurochemical data suggest that 5-MAPB reduces the rate of dopamine reuptake; while not increasing peak dopamine efflux the area under the curve was increased. 5-MAPB can also cause reverse transport. Taken together we suggest that 5-MAPB has stimulant properties, more similar to amphetamine than cocaine. Moreover, molecular modelling and docking studies were performed to compare the binding site of DAT in complex with 5-MAPB to dopamine, cocaine, amphetamine and RTI-121. This structural comparison reveals a binding mode for 5-MAPB found in the already established primary binding site, central to transmembrane domains 1, 3, 6 and 8, and which overlaps extensively with the binding modes of dopamine, cocaine and its analogues in DAT. Thus our data suggest the molecular basis for the reuptake inhibition and effluxion of dopamine by 5-MAPB at DAT.
The integrated approach demonstrated in this study underscores the benefits of combining computational methods of biophysics with neurobiological procedures relate novel insights into the structural determinants for binding of NPS to DAT, with their functional properties. In the present study DAT emerges as the main molecular target of stimulant drugs of addiction.

Ab initio-based combinatorial chemistry for better understanding of the chemical evolution

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Life on Earth is based on the most important feature of carbon: its ability to form long chains, several bond types and with a huge variety of atoms, thereby establishing the organic functional groups. This virtue provides the huge diversity of chemical reactions and biochemical processes [1]. At first glance, it may seem that recording and organizing all of these molecules is desperate. However, the enumeration of organic molecules corresponding to a given stoichiometry can be very simple in principle: a finite number of atoms with limited amount of different valences results a definable amount of molecules. If one considers nuclei as the nodes, and chemical bonds as the edges of a graph, molecules can be described using graph theory making them easier to be generated [2].
It is important to mention that existence of such molecular graph does not provide proper evidence for the existence of the represented molecule. The existence of chemical entity can be confirmed by adequate quantum chemical calculations. Based on the graph theoretical approach, all possible variation of chemical species – including all stoichiometric combinations and topological locations of atomic nuclei and electrons - define ensembles of molecules, which all together can be called chemical space.
Prebiotic formation of biomolecular building blocks such as amino acids has always been a question of considerable scientific interest and their non-enzymatic policondensation is still in debate. In this presentation, the most extended chemical space of the simplest amino acid, glycine, will be discussed from thermodynamic points of view [3]. The hydration effect will be also considered in the extended G3MP2B3 quantum chemical calculations.
Sidechain functional groups of the proteinogen amino acids can provide alternative chemical linkages of amino acids. By comparing the thermochemical properties of these condensation reactions, the alternatives are able to compete with the conventional peptide bond formation by the increased amount of intramolecular (H-bond) interactions.

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Mathematical representation of 20 amino acid diamide relaxed conformational potential energy surfaces

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The potential energy surface (PES) of a molecule provides insights on the relative stability of the possible conformations. However, the time and space complexity of electronic structure calculations, commonly used to generate PES, increases exponentially with increasing number of atoms.
The use of mathematical functions to model the topology of conformational PES is an alternative to more computer-intensive electronic structure calculations, but the choice and complexity of functions is crucial in achieving a desirable analytical fit.
This study presents a procedure to illustrate the topology of 20 amino acid diamide PESs, through a linear combination of a Fourier series and a mixture of Gaussian functions. Results yield a significantly small error, with respect to root mean square error and R^2 for all fits, which suggest that the functions may precisely represent the input PESs.
The procedure provides an alternative to study amino acid PES topology, with less computational time required and with decent accuracy, as compared to producing a fine-meshed PES from electronic structure calculations. The results of the study also provides a foundation for a framework on building polypeptide PES from individual amino acid PES.

The role of conserved C-terminal residues of influenza fusion peptide in membrane fusion

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Influenza is an enveloped virus which enters the host cell through endocytosis-mediated mechanism. To enable the release genetic material, a process of fusion between viral and host cell membranes occurs, which is mediated by influenza hemagglutinin (HA) protein. The N-terminal fragment of hemagglutinin HA2 subunit, directly interacting with the membrane, is named a fusion peptide (HAfp), since it is able to promote fusion also as a synthetic fragment. Its C-terminal part contains three residues (W21-Y22-G23), which are highly conserved among various serotypes of Influenza A. It has been shown that the peptide length has an influence on its structure: HAfp1-20 forms a boomerang in contrast to a tight helical hairpin formed by HAfp1-23.
To gain more insight into the role of the conserved residues, we studied the effect of peptide length on fusion properties, its structural dynamics, and partitioning to the phospholipid bilayer. By means of molecular dynamics simulations and spectroscopic measurements, we showed that the presence of three C-terminal residues in HAfp1-23 promotes the formation of hairpin structure. In contrast to less structured HAfp1-20, it orients perpendicularly to the membrane plane and induces more disorder in the surrounding lipids. Using a novel fusion visualization assay based on FLIM microscopy on giant unilamellar vesicles (GUV), we observed that HAfp1-23 promotes fusion to a higher extent than HAfp1-20. Moreover, we report cholesterol-enriched domain formation exclusively by the longer fusion peptide. This redistribution of membrane components in fluid phases is likely to play a role during membrane fusion.

Posters

Computational study on isocyanate-peptide adducts as potential biocompatible polymers

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Polyurethanes are the most well-known polymers which are synthetised from the reaction of di- or polyisocyanates and polyols. Several products are made from them. Producing biodegradable and renewable polyurethanes are one of the future aim of our collaboration.
Because of the reactive ability of the isocyanates they can easily interact with biochemical macromolecules causing allergic respiratory diseases. The specific mechanism by which these diseases occur is largely unknown. These type of reactions can be apply artificially. In this study we are going to utilise the spontenous reations occurred in the organism between the isocyanates and peptides organism to produce biopolymers.
According to previous studies diverse functional groups present in proteins including amines, amides, thiols, alcohols, and carboxylic acids present a large number of potential reaction sites for the isocyanate. Our main product are the toluene-diisocyanate (TDI) and methylene-diphenyl-diisocyanate (MDI). This research work is focused on the interactions between these diisocyanates and dipeptides. Computational chemistry is used for studying this new field of industrial chemistry.

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A mathematical representation of side-chain orientation in isoleucine diamide

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Protein folding is a crucial process to form functional three-dimensional structures [1]. Determining the optimized orientation of side-chain/backbone interaction can help produce a stable protein structure, which can later be used in pharmaceutics to minimized side effects when complexed with a drug molecule [2]. The relative energies (ΔE) associated with internal rotation were calculated using the B3LYP/6-31G(d) implementation of the density functional theory in gas phase using the Gaussian 09 software package. A conformational study of N-Acetyl-isoleucine N-methylamide was performed using four relative dihedral angles for (ϕ, ψ, $\chi 1$, $\chi 2$) within the interval [-π, π] at a grid point of 15^{o} increments. A PEHS of the four variable $\Delta E = f(\phi, \psi, \chi 1, \chi 2)$ was generated in order to investigate and locate the minima associated with side-chain backbone interactions [3].
The surface was represented by accurate mathematical functions. From these functions, the first and second derivatives were obtained to find the critical points and the minimum energy structures. Subsequently, the minimum structure of the backbone, side chain and the intramolecular interactions were located and conclusions were drawn related to the protein folding processes [4].

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Calculations of Magneto-Chiral Axial Dichroism and Birefringence Dispersion

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Magneto-chiral dichroism (MChD) is related to the difference in the absorption coefficients of a chiral molecule in a magnetic field parallel and antiparallel to the unpolarized incident light [1]. This phenomenon is considered to be a among the possible causes of the homochirality of life [2] but its detection in life-relevant substances has not yet succeeded. The only experimental reports of MChD spectra of organic molecules concern a porphyrin complex [3] and an artificial light-harvesting antenna [4]. Since the experiment is expensive, difficult to perform and long lasting, computer simulations could be of great help.
We propose a computational protocol for magneto-chiral dichroism and magneto-chiral birefringence (MChB) and present preliminary results of calculations for R-methyloxirane (propylene oxide) and L-alanine molecules.
The code was developed within the DALTON program [5]. We are planning an LSDALTON (Linear Scaling DALTON) implementation to study large systems.

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The novel coarse-grained model of protein structure, in which a Single United Residue replaces the Pre-Averaged Secondary Structure fragment

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Molecular modeling plays very important role in studies of protein structure, dynamics and interactions. Time scale of larger proteins and biological processes is a significant restriction for molecular dynamics (MD) simulations. This is a reason for coarse-grained (CG) modeling approaches.
Recently we develop a completely new and unique coarse-grained model of low resolution - SURPASS, in which a Single United Residue replaces the Pre-Averaged Secondary Structure fragment. These fragments partially overlapped each other along the protein sequence, so the number of SURPASS pseudo residues is proportional to the number of amino acid residues in the modelled protein. Knowledge-based statistical potentials encode complex interactions of these fragments and efficient Monte Carlo dynamics sampling protocol allows very fast simulation.
This model will allow to overcome the limitations of coarse-grained models, enabling efficient modeling of long time dynamics and structures of large proteins and multi-domain proteins and protein complexes. SURPASS can be successfully used as an initial stage of multi-scale molecular modeling. In the future the SURPASS approach can be potentially extended onto different types of biomacromolecules opening possibilities of efficient multi-scale molecular modeling of large systems.
This poster present a generic version of the SURPASS model, designed for simulation of single domain proteins, with the secondary structure is the only sequence-dependent input data for the interaction model used in the MC dynamics simulations.

PyRy3D: a software tool for modelling of large macromolecular complexes and its application in prediction of splicing factor 3b's structure

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One of the major challenges in structural biology is to determine the structures of macromolecular complexes and to understand their function and mechanism of action. However, compared to structure determination of the individual components, structural characterization of macromolecular assemblies is very difficult. To maximize completeness, accuracy and efficiency of structure determination for large macromolecular complexes, a hybrid computational approach is required that will be able to incorporate spatial information from a variety of experimental methods (like X-ray, NMR, cryo-EM, cross-linking and mass spectrometry, etc.) into modeling procedure. For many biological complexes such an approach might become the only possibility to retrieve structural details essential for planning further experiments.
We developed PyRy3D, a method for building and visualizing low-resolution models of large macromolecular complexes. The components can be represented as rigid bodies (e.g. macromolecular structures determined by X-ray crystallography or NMR, theoretical models, or abstract shapes) or as flexible shapes (e.g. disordered regions or parts of protein or nucleic acid sequence with unknown structure). Spatial restraints are used to identify components interacting with each other, and to pack them tightly into contours of the entire complex (e.g. cryo-EM density maps or ab initio reconstructions from SAXS or SANS methods). Such an approach enables creation of low-resolution models even for very large macromolecular complexes with components of unknown 3D structure. Our model building procedure applies Monte Carlo approach to sample the space of solutions fulfilling experimental restraints.
Splicing Factor 3b (SF3b) is a protein complex responsible for the recognition of the intron's branch site in U2- and U12-dependent introns. We applied the hybrid modeling approach implemented in PyRy3D software in order to build ensembles of structural models of the human SF3b complex that agree with currently available experimental and theoretical data.

Interdomain communication in type I restriction-modification enzymes

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Background: Type I restriction-modification enzymes are multifunctional heteromeric complexes with DNA cleavage and ATP-dependent DNA translocation activities located on motor subunit HsdR. Functional coupling of DNA cleavage and translocation is a hallmark of the Type I restriction systems that is consistent with their proposed role in horizontal gene transfer.
Method: In vivo and in vitro activity assays of WT and mutant protein are combined with computational modeling to probe interdomain contacts potentially involved in triggering DNA cleavage that occurs at nonspecific sites distant from the cognate recognition sequence.
Results: Analysis of the computational modeling allows to assign specific roles for the individual domains in either translocation or restriction and predicts interdomain engagement responsible for signal transmission between the endonuclease and helicase domains and interdomain contacts involved in global conformational changes connected to the enzymatic function.
Conclusion: The combined experimental and modeling results suggest that the ATP ligation state of the enzyme might be communicated through the endonuclease/motor subunit by a cascade of linked local and global conformational changes. Such large-scale domain motions are expected to be readily detected by the other enzyme subunits, and may represent a signal reporting the ATP ligation state of the endonuclease/motor subunit.

Qualitative analysis of triacylglycerols in millet seeds using normal phase liquid chromatography-positive electrospray mass spectrometry – LC-ESI Q-TOF

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Introduction
Triacylglycerols (TAG) are the source of 25% of calories consumed in developed countries [1]. For this reason studies on the TAG's composition are an important factor in determining the impact of their consumption on the human health. Due to the wide variety of fatty acids attached to a glycerol backbone, determination of the correct composition of TAGs is the challenging analytical problem. Therefore, the identification of triacylglycerols was carried out using many methods: ESI Fourier transform (FT), ion cyclotron resonance (ICR) MS, atmospheric pressure chemical ionization (APCI) LC-MS and matrix assisted laser desorption ionization (MALDI) [2]. In this study we established the TAG profiling method based on ESI-MS with a hybrid quadrupol-time of flight mass spectrometer (Q-TOF).
Materials and methods
Research material was an extract from the millet seeds. Chromatographic separation of TAG's was achieved using a nanoAcquity UPLC system. The triacylglycerols were measured as ammonium adducts ([M+NH4]+). Analysis in UPLC MS^E mode was carried out using a Xevo G2 Q-TOF mass spectrometer. For the qualitative analysis MassLynx software from Waters and LIPID MAPS® Lipidomics Gateway database were used.
Results and Discussion
The aim of the current study was to determine the composition of TAGs found in millet seeds and their semi-quantitative analysis. The use of mass spectrometer Q-TOF provides detailed and comprehensive qualitative information necessary for the proper determination of the composition and development of accurate quantitative profile.

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A mathematical model and analysis of backbone-sidechain interactions in N-acetyl-tyrosine N-methylamide with implications in protein folding

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The protein folding problem has long been an area of interest for researchers [1]. A typical protein can contain hundreds of amino acid residues, each with several dozens of atoms, yet take only a fraction of a second to fold [2]. As a result, there have been exhaustive studies built around the depedent protein primary structure and the final folded protein [3]. The relative energy, ΔE, associated with internal rotation were calculated by quantum mechanics using the Gaussian 09 software package and the B3LYP/6-31G(d) basis set in the gas phase. Calculations were carried out for a range of dihedral angles for (ϕ, ψ) and ($\chi1$,$\chi2$) of N-Acetyl-tyrosine N-methylamide on the interval [$-\pi$, π] with grid points at 15° increments to generate the potential energy surface and hypersurface.
The amino acid residue backbone was first analyzed, then the obtained minima structures were further inspected. The results allowed backbone-side chain interactions to be studied. In addition, a mathematical function using a combination of Fourier and Gaussian series was modelled for the hypersurface of tyrosine diamide. By studying the mathematical model of tyrosine diamide, it is possible to fit a dipeptide or polypeptide chain of Tyrosine residues via a composite function. Future directions for this study is the attempt to create functions that accurately model polypeptide chains containing different amino acid residues.

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Beta-binomial and empirical quantile models to detect rare mutations in pooled next-generation sequencing experiments

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With high-throughput technologies, namely next-generation sequencing (NGS), one can diagnose complex genetic disorders analysing exome or genome as a whole. Bioinformatics developed many pipelines for variant calling in NGS data, however performance' accuracy depends on the variant caller itself and on the calling strategy employed[3]. Available standard software is even less accurate when pooled NGS experiments are considered[1]. Flaherty et al.[2] used Beta-Binomial model for the detection of rare single nucleotide mutations for synthetic DNA samples, which was very accurate (98.8%) for detection of mutations at 0.1% level. We propose two novel variant calling approaches. We propose modification of Beta-Binomial model using posterior beta distribution instead of prior. Such approach should lead to more accurate results compared to initial model[2]. In addition, we relax assumption about constant variance across sequenced positions. Additionally, we propose empirical quantile method. It consists of two phases: computation of significance value α using binomial approximation of the data and computation of empirical quantile of the data. We employ proposed models for the detection of rare mutations in pooled experiments on 98 genes of 128 patients with a clinical diagnosis of muscular disease[1]. The results showed that Beta-binomial model and modification of it were highly specific (100 %) but had low sensitivity (less than 32 %) as empirical quantile model was quite sensitive (95.7 %) and specific (82.3 %).

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GapRepairer: a server for automatic reconstruction of missing parts in protein models - possible aplications

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X-ray crystallography, since it was used to discover the double helix of DNA, remains the leading way of "seeing" the structure of molecules. Number of known structures rises exponentially each year, yet due to technical difficulties of the method (eg. highly mobile regions of a protein leading to poor resolution of this part of the structure) as much as 25% of those contains unresolved fragments. This percentage grows even higher (up to 50%) for proteins with nontrivial topologies.
GapRepairer is a web server (gaprepairer.cent.uw.edu.pl, under development), which uses a homology modeling approach to fill-in missing parts of protein structures. By repairing a model in a topologically-conscious way it is possible to obtain better suited homologues - and broaden the possible applications of this approach by the reconstruction of deliberately removed fragments to force specific fold.

Production and examination of noble metal containing carbon nanotube supported nanocomposit catalysts

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Carbon nanotubes seem to be very promising catalyst support materials owing to their extraordinary properties. The absence of porous structure lead to the enchanched catalityc activity, because the efficient acces of the reactant molecules to the catalytically active sites are provided. The reaction rate is enchanced in case of carbon nanotube supported catalyst than traditional activated carbons, therefore several researches are still in progress concerning nano tubes in catalytic processions.
Bamboo shaped carbon nano tubes (BCNTs) are special types of multi walled carbon nano tubes (MWCNTs), as they are made from nitrogen containing carbon compounds. Additionally, BCNTs have defect sites, owing to the incorporated nitrogen atoms, which makes high energy absorption place for catalytically active metal particles. BCNTs were prepared from butylamine on MgO supported Ni (5 wt%) catalyst by catalytic chemical vapour deposition (CCVD). The carbon content of the samples was tested by thermogravimetry. HRTEM was made to check the diameters of nanoparticles in BCNT supported catalysts. The metal particle diameters in samples were followed: Pd/BCNT: 14.9 nm, Rh/BCNT: 7.0 nm and Ir/BCNT:7.1 nm.
The chemical forms of incorporated nitogen atoms to the wall of carbon nanotubes were examined by XPS (X-ray photoelectron spectroscopy) The deconvulated N1s spectrum assignment of different types of nitrogen deffects, at 398,4 eV binding energy indicated the pyridinic N atoms, the peak at 401,2 eV assigned type of quaternary nitrogen. The binding energy at 402-405 eV demonstrated adsorbed nitrogen or nitrogen oxides in the CNT lattice. The process of hydrogenation was examined by Fourier transform infrared spectroscopy (FTIR). The catalytic performance of the synthesized BCNT supported (Ir, Pd, Rh) catalysts were tested in the hydrogenation of 1-octadecene. The best results were achieved when the bamboo shaped nanotubes support were decorated with 5wt% palladium and 5wt% rhodium.
The catalytic activity of BCNT supported Ir catalyst was not effective enough.

Photosystem II: derive incomplete parameters for MD

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Photosystem II is a pigment-protein complex, which absorbs energy of the light and converts it to the energy, leading to reduction of plastoquinone to plastoquinol and water splitting. Electron separation occur in the reaction center, placed in the thylakoid membrane, consisting mainly of glycolipids (MGDG, DGDG, SQDG) [1].
Cofactors of reaction center are directly involved in the charge separation and electron transfer, however lipids found in the photosystem stabilize orientation of cofactors and play important role in protein function [1]. Thats why the first step in MD simulation of photosystem requires correct system definition and parameterization of force field. The crystal structure of reaction center of PS II from cyanobacteria T.vulcanus [2] was selected for calculation. Parameters of cofactors and lipids for classical MD simulation with Amber force field in Gromacs were obtained from [3] and [4]. The missing parameters for lipids were derived by Gaussian 09, Acpype and Antechamber.
The complex of PSII embedded in the membrane was parametrized. The system is now suitable for MD simulation with Amber in Gromacs and detailed study of interatomic interaction and QM/MM calculations of atom polarization can be performed.

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Charge distribution and transfer in photosystem II reaction center

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Photosystem II (PSII) is a pigment-protein complex containing around 25 subunits (depending on the organism) and approximately 100 cofactors. PSII is located in the thylakoid membrane of cyanobacteria, algae and higher plants. The heart of PSII is the reaction center (PSII RC) core, where light energy is converted to electrochemical potential in the form of a charge transfer state and where the water-splitting to oxygen and protons reaction occurs.

In our previous studies [1] of the PSII RC we focused on the role of the reduced pheophytin a (PHO) inducing conformational changes of the PSII RC protein environment and affecting interaction of the PSII RC chlorophylls. QM/MM approach with polarized embedding allows to study charge separation in the PSII RC pigments. The quantum-classical approach is used for kinetic study of charge transfer in the PSII RC pigments. The method is using the stochastic time evolution of charge on PSII RC pigments based on the combination of classical MD simulation with QM calculation of charge transfer rates. In a parallel direction we are developing model of thylakoid membrane (glycolipid membrane instead of our previous octane layer) to build complex model of PSII RC.

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Focusing on knowledge-based potentials in GPCR drug discovery

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To date, a small number of experimental structures of membrane proteins deposited in the Protein Data Bank imposed limitations on the statistical analysis of that distinct protein class. Only few studies referred to usage of membrane-fitted statistical potentials in structure prediction protocols, e.g., Rosetta membrane ab initio, BCL [1] and FILM3. On the contrary, quite a few knowledge-based methods for the membrane protein model quality assessment (e.g., ProQM) and prediction of one-dimensional features such as transmembrane topology (e.g., TOPCONS) were recently published. Here, we report details of our hybrid modeling protocol [2] used in the recent GPCR Dock 2013 competition which involves our web-service GPCRM (http://gpcrm.biomodellab.eu) [3] and knowledge-based potentials. The test cases of 5-HT1B and 5-HT2B serotonin receptors demonstrated that both the receptor structure and the ligand binding mode can be predicted with the atomic-detail accuracy as long as the target-template sequence similarity is relatively high. On the other hand, a low target-template sequence similarity observed, e.g., between SMO from the frizzled GPCR family and members of the rhodopsin family, seriously hampers the GPCR structure prediction and ligand docking. We showed that usage of knowledge-based potentials implemented in BCL together with ligand-based assessment of the GPCR binding site is an efficient way to cope with major bottlenecks in the GPCR structure prediction. We also demonstrated that the knowledge-based potentials for membrane proteins were significantly improved due to the recent surge in available experimental structures.

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A mathematical representation of side chain orientation in cysteine diamide

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ϕ, ψ, and χ1, χ2 are defined as the torsion angles located at the N-Cα, Cα-C backbone, and sidechain, respectively and they are essential in determining the relatively energy of amino acid conformers. Here, we applied the B3LYP/6-31G(d) implentaition of the density functional theory in the gas phase using the Gaussian09 software package to calcuate the relative energy (ΔE) of cysteine diamide conformers with different torsion angles. A potential energy hypersurface (PEHS) of the cysteine diamide was constructed using the torsion angles (ϕ, ψ) and (χ1, χ2) has been analyzed to investigate the effect of cysteine sidechain on the peptide backbone. Specifically,the interval [-π, π] was selected to be the range for the torsion angles with grid points at 15° increments. Usually, the mathematical functions can be used to fit in these surfaces, allowing us to locate the energy minmia and transtion states of the cysteine diamide from the critical points.
The cysteine diamide confromers corresponding to these critical points were studied in terms of the interactions between the side chain and the peptide backbone The result should give us an insight into the process of protein folding.

Characterization of selective inhibition of t-RNA-(N1G37) methyltransferase with different topology

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tRNA methyltransferases are a group of enzymes that participate in a process of great biological significance. The methylation of tRNA is needed because a nucleic acid without attached methyl group would block the translation. Both knotted and unknotted topologies can be found in this group of enzymes. Presence of a knot in the binding site forces a bent conformation of the ligand. The enzymes with trivial topology bind cofactor in an open conformation. This trait was used to form the knotted tRNA guanine methyltransferases-selective inhibitor [1] and methyltransferases inhibitor [2]. Knotted structures - TrmD, occur mostly in bacteria, while unknotted - Trm5, mostly in eucaryota. Such designed chemical compound could be used as a new antimicrobial drug for proteins with non-trivial topology. Using numerical simulation, the efficacy of the ligand can be studied theoretically. We performed inhibitor and natural substrate docking to proteins from various methyltransferases' families and organisms with distinct topologies, and on this basis we predicted their selectivity and effectiveness with respect to the knot and Rossmann fold. Moreover, we prepare the synthesis of three selective inhibitors to confirm the results of our calculation using in vitro methods.

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An overview of non-trivial topologies predicted in CASP experiment

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The Critical Assessment of protein Structure Prediction (CASP) is a global experiment for groups involved in developing efficient methods for predicting tertiary structure of proteins. It was created to evaluate current methods and select the most promising approaches in protein structure prediction. Data base of submitted models supply valuable information about the most common mistakes in protein modelling, eg. incorrect topology. Unusual topology makes knotted proteins and structures with lassos especially interesting in analysis of protein structure. Natively knotted chains encounter more difficulties during protein folding. Therefore, proteins with knots or slipknots are less favored during evolution. Here we search CASP database for theoretical methods that allow proteins with complex topologies.
The analysis of over 600 000 structures, submitted to CASP for presence of knots, slipknots and lassos have shown that nearly 4% of structures are knotted and 13% of disulfide loops contain lasso. We discovered that most of submitted structures that contained knot, slipknot or lasso was a result of a false prediction. The vast majority of complexity patterns detected among knotted predictions were non existing in PDB, thus, unreal and un-protein-like. Incorrect topology of a protein model can be easily avoided by introducing simple and efficient topological filters.

A mathematical representation of the side chain conformation of asparagine diamide

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Conformational analysis is a very powerful tool to investigate various geometric implications and energy changes associated with internal bond rotation. In this study, a multidimensional potential energy surface (PES) was generated for the asparagine diamide following internal rotations of dihedral angles in the backbone (ϕ,ψ) and the side-chain (χ1, χ2). Two dimensional cross sections $\Delta E = f(\phi,\psi)$ and $\Delta E = f(\chi1, \chi2)$ of the 4D-Ramachandran PES was used to locate minima associated with the side-chain to backbone hydrogen bonding interactions [1,2]. To find the possible optimized structures, mathematical functions were built using the four independent variables $\Delta E = f(\phi,\psi, \chi1, \chi2)$ to represent the PES.
Subsequently, the first and second derivatives were obtained from the functions in order to locate critical points and most importantly, the minimum energy structures. Using these results, it was possible to draw conclusions regarding the stabilizing interactions between the backbone and side-chain of asparagine as well as the implication of this individual amino acid in protein the folding processes [3].

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Molecular docking study of binding of green tea catechins to human serum albumin

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Catechins are the most abundant polyphenols in green tea. Their biological activities beneficial to human health [1] depend on their metabolism and free plasma concentration. In plasma, polyphenols bind to serum albumin, responsible for their transport and storage [2].
In our work, molecular docking has been performed in order to determine the binding specificity and affinity of catechins EGCG, EGC and EC, as well as their metabolites, for binding to site 1 of HSA. Higher affinity has been determined for larger ligands, with more polar or negatively charged groups, such as EGCG and sulfated or glucuronidated metabolites of catechins. The study shows comparable docking results to those of some drugs known to be good ligands of HSA, also indicating their potential competition.

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The influence of site Mutations on Activity of XPB Protein

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The ERCC3/XPB ATP-dependent DNA helicase is one of the ten subunits of the general transcription factor TFIIH. As the TFIIH is involved in transcription, nucleotide excision repair (NER) and cell cycle control the mutations in its subunits may have pleiotropic effects. There are known only several mutations not fatal for the cells, yet causing serious illnesses. Based on previous experimental work, we simulated wild type enzymes from archaebacteria and eukaryotes and 2 of its mutants.
All but one ERCC3 mutants were extremely sensitive to UV-irradiation. However, none of them was able to repair CPD or 6-4PP or to recover RNA synthesis after UV-irradiation. We have compared the most sensitive (UV24 cell line; S382P mutation) and most resistant (UV68 cell line; V471F mutation) mutants and found that the sensitive cells have more apoptotic cells, form more DSBs, have higher frequency of chromosomal aberrations and stronger G1/S block. Molecular dynamics analysis of the S382P ERCC3 protein has revealed significant fluctuation in protein loop next to DNA binding domain.

Conformational analysis of N-acetyl-threonine-N-methylamide to explore possible targets for cancer therapy in MAPK pathway

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MAPK (mitogen-activated protein kinase) signaling pathway is one of the fundamental pathways inside eukaryote cells [1]. Recent studies discovered that the overactive MAPK pathway acted as a significant factor in uncontrolled cell growth, as well as in cancer formation [2-5]. In this study, we worked on the conformational analysis of a threonine diamide, N-Acetyl-threonine N-methylamide, representing a characteristic TxY (threonine-x-tyrosine) motif in MAPK as a starting point to manipulate MAPK molecule.
The goal for this research is to locatize the global minima structure of the threonine diamide by comparing the relative energies (ΔE), calculated by quantum mechanics using B3LYP/6-31G(d) implementation of the density functional theory in gas phase in the Gaussian09 software package.
The calculations were carried out for dihedral angels ϕ, ψ of the threonine diamide in the interval [-π,π] with grid points at 15° increments. The most stable backbone structure for threonine was determined and with fixed ϕ, ψ values, sidechain backbone hydrogen bonding interaction was studied in detail by generating strcutures with differnet χ1,χ2 values. We then used extended Fourier expansions and other mathemathical functions to give a reasonable representation of the hypersurfaces.
The critical points of the functions can be calculated, which can determine the minium energy structure, if the functions are of sufficient accuracy. In general, geometry optimizations for a potential energy hypersurface of four independent variables: E=f(ϕ,ψ,χ1,χ2) was generated to represent the entire conformation of the molecule, and we also compared the results with those of other amino acid diamides.
By conformational analysis of the threonine diamide, we will obtain a clear insight into the threonine residue in TxY and try to target MAPK in later research on cancer therapy.

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Theoretical study of influence of mutations on superoxide dismutase SOD1 dimer and oligomer of alpha B crystallin by molecular dynamics simulations

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The human superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or SOD1 plays a very important role in the regulation of apoptosis cells. It is an enzyme that in humans is encoded by the SOD1 gene, located on chromosome 21. Mutations in this gene have been implicated as causes of familial amyotrophic lateral sclerosis (fALS). The mechanism by which mutant SOD1 exerts toxicity remains unknown. SOD1 is an important antioxidant defense in nearly all living cells exposed to oxygen.
The structures of human SOD1, involving dimer, which contains four binding sites for metal ions: two for Zn^{2+} and two for Cu^{2+}, were taken from the X-Ray structure from the Protein Data Bank (PDB id:2C9V) [1]. The Zn and Cu ion-binding site is built by the following amino acids: His44, His46, His61, His118, His69, His78, Asp81. The force field parameter and charges for the Zn-Cu binding site was created by the analogy to data obtained from previous quantum chemical calculations [2,3]. All energy minimizations (10 000) and molecular dynamics (MD) simulations were performed in the NAMD program v. 2.10 using an all-atom (37 000 atoms) force field CHARMM27 [4] in a periodic box (62x95x62 $Å^3$) and Langevin (stochastic) dynamics [5].
The following mutations: K3E, A4V, G41S, G72S, N86S, D90A, G93C, S105L, C11Y, N139D, L144S, L126X and the native protein were investigated by molecular dynamics simulations. The study of changing the mutated SOD1 structure during 20 ns all-atom MD simulations in explicit water environment were performed.
Another investigated protein, human alpha B crystallin belongs to the small heat shock protein family and functions as molecular chaperone that primarily binds misfolded proteins to prevent protein aggregation, as well as inhibit apoptosis and contribute to intracellular architecture. This protein (PDB id:2YGD) can form huge oligomers which are important for its function, so MD simulations were performed in implicit solvent. As before, energy minimizations and MD simulations were done in NAMD program v. 2.10 using all-atom force field CHARMM27 [4]. We investigated 6-mer oligomer in native state and the following crucial mutations: D109A and D109H. For both studied proteins we analyzed influence of mutations on the structure of protein and also how the potential interactions with other proteins could be altered.

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Dissociation of amyloid aggregates with photoswitchable molecular levers

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As a consequence of the society aging in Europe, the occurrence of cognitive impairment and dementia is rapidly becoming a significant challenge.[1] Up to 70% of dementia cases in EU is due to the Alzheimer's disease (AD) – a neurodegenerative disease with no cure. With the increasing proportion of the elderly among Europeans, this problem is dramatically growing, especially in Western Europe, where the population suffering from dementia is reaching now ~7.5 million people. Moreover, AD is becoming a severe economic issue. The cost of dementia for the 2015 in Europe has been estimated for 200 billion Euros, and increased by 25% in the last five years. Despite huge and long term research efforts there is still no cure for AD. Considering that, a question rises – where else shall we look for new and effective treatments? We believe that the answer for this big question may lie in a small but very portentous molecule called azobenzene. Azobenzene (azo) is an organic molecule which can achieve reversible changes in geometrical structure (cis/trans isomerism), electronic properties and nanoscale mechanics triggered by light. For that reason, azos have been widely used in Materials Science to build photo-mechanical responsive systems.[2] Azo-derivatives are extensively incorporated in electronic switchable devices, used for a large variety of applications, such as optical switching and data storage. Moreover, the recently proved ability of azos to modulate structure and physicochemical properties in response to energy input in vivo with no evidence of cytotoxicity, makes them very important functional materials for applications in biological systems.[3] In fact, they have been already used for modulating protein folding, enzyme activity or membrane transport.[4] The proposed project aims at exploring further the photoresponsive nature of newly designed azo- derivatives and exploiting the potential of these smart materials for the generation of novel low- cost diagnostics and therapeutic method for AD, which is associated with deposition of β- amyloid (Aβ) fibril plaques in brain. Aβ is built of tightly packed peptide β-sheets and reveals stability that inspires Materials Science in search for new biology-inspired solutions. Our idea is to design in silico, using the state-of-the-art simulation techniques, an azo- molecule which in its ground-state planar form will intercalate between Aβ layers and disrupt some of the main-chain hydrogen bonds between the two Aβ strands, as other small molecules usually do.[5] The novelty of our idea is based on the ability of an azo molecule to change conformation around the N=N double bond from the planar trans to the nonplanar cis upon photo-excitation. We believe that after the light stimuli, the cis isomer of azo-molecule shall put a mechanical stress on the protein strands, eventually leading to the mechanical dissociation of the assembly.[6] The designed azo-molecules will be functionalized in such a way that they will stabilize the dissociated proteins prevent their reaggregation. Additionally, the azo molecule can be labeled with a short-lived radioisotope to become also a safe and well-tolerated Aβ-tracer for Positron Emission Tomography (PET) diagnostics.[7] Based on the theoretical findings, new azo -derivatives with desired affinity and selectivity to the Aβ proteins will be synthesized and their ability to act as a photo-controlled molecular levers further investigated in in vitro and in vivo studies. A successfully designed photoswitchable azo-lever may become a core of a new, safe and low-cost treatment for people suffering from AD at all its stages. Besides the search for the new diagnostic and therapeutic approach, the project aims at a further development of the state-of-the-art experimental techniques for bioelectronics (electrolyte-gated organic transistors - EGOFET) bringing them to the industrial level of application.[8]

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Knots and slipknots in proteins – KnotProt

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Topologically complex proteins, including knotted and slipknotted structures, are nowadays well settled in biology [2]. Over 90% of knotted proteins are enzymes and all of them have active sides inside their knots, which strongly suggests important function of that topology. The problem which still needs to be solved is to understand that function.
KnotProt is the database and server, created by our group, which includes all knotted proteins from PDB, all statistics and all classifications - from topological and biological point of view, as well. I believe that this can be very important and helpful tool while trying to answer open questions connected with complex structures in proteins.

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Molecular dynamics study of decapping scavenger enzyme

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Molecular dynamics is a tool to study behaviour of biological macromolecules in full atomic detail. Such atomic-level of examined system gives an extensive characterization about protein - ligand binding. Especially, protein conformational responses of a enzyme by ligand binding event studies can be crucial for future drug design. We have used MD tool to study apo and holo Decapping Scavenger (DcpS) enzyme. DcpS enzyme takes part in mRNA degradation by hydrolyzing cap structure (m7GpppNn) occurring at 5' mRNA end. The results reveal diverse conformational changes of protein depending on the presence of ligand in the active site. To explore the main motions of protein, we applied PCA analysis. Molecular dynamics simulations are consistent with the experimentally observed DcpS enzyme motion features.

Mechanism And Energetics Of L-arginine Binding To Arginine Repressor Protein In E. Coli

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Arginine repressor protein provides feedback regulation of arginine metabolism upon activation by the negatively cooperative binding of L-arginine. Understanding this phenomenon requires the detailed analysis of each binding event and its effect on global motion of the complex.
Umbrella sampling technique was used to calculate binding energy (potential of mean force) of L-arginines to the ArgRC. Unbinding of L-Arg from ArgR was performed using steered dynamics. Potential of mean force (PMF) was calculated using weighted histogram analysis method in GROMACS. Differently ligated states were prepared either by deleting (from holo-ArgR crystal structure) or adding (to apo-ArgR crystal structure), using YASARA tool.
PMF for holo-5 state was ~12 kcal/mol, while in corresponding apo+1 state it was ~7 kcal/mol. PMF for holo-4 state and apo+2 state were ~4 kcal/mol and ~15 kcal/mol respectively.
The PMF of +1 and -5 states have similar values while that of -4 and +2 states are very different. The huge difference in the PMF between -4 and +2 states could be due to the differently occupied binding pockets in these two systems. Few more repetitions of +2 and -4 states are undergoing, once completed these will hopefully allow us to compare the binding affinity of differently liganded states of ArgRC and their effect on global motion of protein.

Asymmetrical behavior of knotted protein

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Correct post-translational modifications of both proteins and nucleic acids are crucial for the survival of any organism. An important group of enzymes involved in such reaction are the methyltransferases. An important characteristic of this group of proteins is that, while all analogous in function, they can be further divided into two distinct categories - by whether their backbone is knotted or unknotted. More importantly, the methylation-cofactor binding site is located within the knot in all of the non-trivial structures (more than 60 methyltransferases from various organisms [1]). Additionally, only the knotted structures functions as (homo)dimers - although this symmetry is deceptive. In theory capable of binding two ligand-substrate pairs, it has been shown for TrmD methyltransferase [2], that only one substrate is bound at a time. Using molecular dynamics to determine the possible mechanism of action of this protein we have found motions that can distort one of the binding sites, thus causing the apparent inequality. As the ligand binding pocket is formed by the knot, the asymmetry may be related to the topology, although the direct impact of the chain nontriviality on the protein function remains unclear.

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The simultaneous measurement of nicotinamide adenine dinucleotide, nicotinamide and nicotinic acid in biological samples using LC-ESI-MS

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Introduction
Nicotinamide adenine dinucleotide (NAD) is a significant coenzyme, which is involved in various redox reactions during glycolysis, β-oxidation and the tricarboxylic acid (TCA) cycle [1]. NAD is also a substrate for fundamental processes such as regulation of cell survival, gene transcription, DNA repair, cell cycle controlling and apoptosis [2]. Many diseases including the cancer progression is related to these processes. The NAD precursors, nicotinamide (NAM) and nicotinic acid (NA) have very similar biochemical pathways and it is believed that they protect cells against apoptosis induced by a multiple stress factors [3]. Better comprehension how the cellular level of NAD is regulated may be a key for explanation of NAD metabolism and pathomechanism of numerous diseases. To resolve this issue, a sensitive and highly specific procedures of determining of cellular NAD and related compounds levels should be developed [2].
Materials and methods
The experimental material was erythrocyte from patient's blood. The cellular NAD and related compounds were separated by liquid chromatography using a nanoAcquity UPLC system with a column HSS T3 1x50 mm. The level of these substances have been measured using a Xevo G2 Q-TOF. The acquisition and processing of all of the data were accomplished by using MassLynx software from Waters (Milford, USA).
Results and Discussion
The goal of our current studies was to set up a quantitative method for simultaneous and precision analysis of NAD and other compounds levels. Our outcomes are comparable with the other research results. The method has appropriate linearity and sensitivity and seems to be promising. However, further studies must be conducted to demonstrate more details.

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200 ns molecular dynamics of blood coagulation factor XI apple domain dimers

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Blood coagulation factor XI is significant protein of haemostasis and thrombosis forming dimers through N-terminal apple 4 domains. Known crystal and NMR structures of apple 4 dimers are slightly different. Therefore, dynamics of dimeric blood coagulation factor XI seems to be interesting phenomenon as crystal and NMR structures show differences, and the protein is responsible for thrombosis and hemophilia C. The current studies' objective was to perform series of 200 ns molecular dynamics of blood coagulation factor XI apple 4 domain dimers of mammals including the human molecule and the models of rabbit, opossum, platypus and echidna, with comparison to a paralogue – the model of human plasma prekallikrein. The homology models were based on 2F83 crystal structure of the human protein and the simulations were calculated by GROMACS 5 using PL-Grid Infrastructure with Zeus supercomputer CPU/GPU support. The studies revealed dimer-monomer equilibrium with differences in the dimer stability between mammals and with evident vulnerability of the human dimer, heterogeneity of extended interface loops with Cys-321 contributing in interchain disulfide formation and flexibility of C-termini. By comparing the modeled structures of different mammals the features of the coagulation factor XI apple 4 dimers, in even such distinct mammals like monotremes, were revealed, what obviously distinguished factors XI from plasma prekallikrein and could shape their biological function.

Structural studies of the type I restriction-modification system EcoR124I and its methyltransferase subunit: crystalloraphy and cryo-EM hybrid approach

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Type I restriction-modification enzymes are multisubunit, multifunctional molecular machines that recognize specific DNA sequences (~13 to 17 bp) and cleave randomly [1]. The low resolution structural information from a combinatorial methods such as negative staining using cryo-EM, small-angle scattering (both X-ray and neutron) or computational modeling reveal very little detail of the inter-domain and the subunit interactions [2]. The aim is to elucidate high resolution structure of the pentameric complex and the trimeric Mtase (2x HsdM and 1x Hsd S subunits) using a combination of X-ray crystallography, cryo-EM and computational modeling methods. The interdisciplinary approach of cryo-EM and X-ray crystallography caters perfectly to the objectives of the project. The crystal structure and cryo-EM maps would enable us to understand the structural transition between the open and closed (in complex with dsDNA) forms.
The cryo-EM experimental data has been obtained for both the forms using FEI's Titan Krios. A preliminary model of what appears to be the closed MTase complex has been obtained allowing us to build more volume for the entire complex using single-particle reconstruction. On the otherhand, X-ray crystallographic studies are on-going for the HsdM subunit and 3D reconstruction of preliminary model for the open form. Furthermore, the efforts are to obtain the whole cryo-EM models and crystal structure of the HsdM, HsdS subunits and the MTase complex. These models allow us to comprehend the interactions between HsdS and HsdM subunits and MTase intercation with HsdR subunit. It is crucial to decipher the way by which DNA-induced conformational changes occur.

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Theoretical study of crystal structure of WrbA from E. coli in complex with benzoquinone using QM calculations of charge transfer rates

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The computational methods are applied to compare the electron-transfer probability for two distinct crystal structures of the Escherichia coli protein WrbA, an FMN-dependent NAD(P)H:quinone oxidoreductase, with the bound substrate benzoquinone. The computational methods were based on the combination of quantum mechanics/molecular mechanics approach, semi-empirical methods and quantum mechanical (QM) calculations of charge transfer rates using Marcus equation. The calculations indicate that the position of benzoquinone in a new structure reported here and solved at 1.33 Å resolution is more likely to be relevant for the physiological reaction of WrbA than a previously reported crystal structure [1] in which benzoquinone is shifted by ~5 Å. Because the true electron-acceptor substrate for WrbA is not yet known, the present results can serve to constrain computational docking attempts with potential substrates that may aid in identifying the natural substrate(s) and physiological role(s) of this enzyme. The approach used here highlights a role for QM calculations in crystal structure interpretation.

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The endocytosis and intercellular transport of rare-earth doped nanoparticles in Caco-2 cell line

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Nanoparticles are structures, which we often meet in our lives. But generally, we do not even know about it. We are surrounded by silicates, carbonates, viruses or proteins, which are natural nanoparticles or by a lot of kinds of ashes, which are anthropological ones. In addition, we also have engineered nanoparticles. This kind of nanoparticles have a lot of applications in different industries and, which is very important, in medicine. Every kind of nanoparticles must be tested independently. Their size, shape, chemical composition and structure determines their properties.
The rare-earth doped nanoparticles belong to new generation of nanoparticles. They are stable and exhibit red autofluorescence. Earlier paper shows that nanoparticles can pass through the blood-tissue barriers and localize in different tissues. This properties allow to use them as intelligent drugs or for diagnosis of diseases, such as tumor. This nanoparticles seem to be promising materials of the future, so the investigation mechanism of endocytosis and intracellular transport of zirconium dioxide doped terbium nanoparticles is very important. This research was conducted on Caco-2 cell line and evaluated by confocal microscopy. MTT assay shows that used concentration of nanoparticles (0.001 mg/mL) has not got negative effect for cells. Colocalization of the nanoparticles with clathrins and caveolins indicates that clathrin-mediated endocitosis and caveolin-mediated endocytosis participates in absorption of nanoparticles. Our data show that both, cubilin and megalin receptors are involved in CME pathway. In cells, nanoparticles are associated with microtubules, so probably they are responsible for their transport through the cell. The transport of nanoparticles is fast, after 60 minutes most of them were outside the cell.
Previous data shows low toxicity of this nanoparticles, but this studies are the beginning research of absorption, distribution, metabolism, and excretion this nanoparticles.

Computational modeling of human 3'-phosphoadenosine 5'-phosphosulfate synthase

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The sulfur nucleotide PAPS (3'-phosphoadenosine 5'-phosphosulfate) is the universal sulfuryl donor of the cell. In mammals 3'-phosphoadenosine 5'-phosphosulfate Synthase (PAPSS), using ATP, converts biochemically inert inorganic sulfate to the metabolically active PAPS. It is a bi-functional enzyme and catalyzes the formation of PAPS in two sequential steps. In the first step, inorganic sulfate reacts with ATP to form APS and pyrophosphate. The resulting phosphoric-sulfuric anhydride bond has high energy that is the chemical basis of sulfate activation. The second step is catalyzed by the kinase domain of PAPSS and involves the reaction of APS with ATP to form PAPS and ADP. The proper function of PAPSS is essential for normal physiology in the human being. PAPSS deficiency in human results in osteochondrodysplasias or defective cartilage and bone metabolism as evidenced in the clinical condition of the recessively inherited, spondyloepimetaphyseal dysplasia (SEMD). In this project we try to understand how the three dimensional structure of PAPSS determines the enzyme function, focusing on the roles of specific amino acid residues/overall structures on the dynamics of the enzyme in aqueous solution and the related quaternary arrangements of the enzyme. Finally, we aim to predict/describe enzymatic reactions in three-dimensional space and to explore the reaction coordinate through the lens of molecular dynamics simulations. The poster gives a general introduction and first results of this Czech-US collaborative work are presented.

Synthesis of noble metal-content carbon nanotubes-based catalysts and examination of catalytic hydrogenation reaction

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The Multiwall Carbon nanotubes (CNT) are promising catalyst support materials because of their high specific surface area, good mechanical and thermal stability. Functional groups can be produced on their surface with oxidation processes which help to connect catalytically active metal ions. CNTs doesn't have micro pores therefore the catalysis can be faster and they more resistant to oxidation than the previously popular activated carbon. MWCNTs were prepared from acetylene on MgO-supported 2.5 wt% Fe and 2.5 wt% Co catalyst by catalytic chemical vapor deposition method (CCVD). The removal of the remained catalyst was carried out with concentrated hydrochloric acid. The purity, namely the carbon content was checked by thermogravimetry (TG), the MWCNT sample's purity was 95.37 wt%. The synthesized MWCNTs were used to prepare three type of catalysts: Pd/MWCNT. Pt/MWCNT, Ru/MWCNT. Each type contained 5 wt% of noble metals. The prepared catalyst's morphology and size of the metal particles were characterized by HRTEM, the diameters of particles were followed: palladium: 8.4 nm, platinum: 6.2 nm and ruthenium: 2.8 nm. The metal nanoparticles were also checked by XRD which determined that the particles were in elementary reduced state. The catalytic activity of the Pd/MWCNT. Pt/MWCNT, Ru/MWCNT samples were examined in the hydrogenation of octedec-1-ene. The process was monitored by using FTIR. The best results were obtained by Pd/MWCNTs. As it is shown in the figure, catalytic activity was not observed in case of Ru/MWCNT. The Pt/MWCNT catalyst's activity is lower to Pd/MWCNT.

Search for optimal contact map in knotted protein folding

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From more than two decades [1,2] knotted proteins are extensively studied by researchers with both experimental and theoretical methods. One of the most often studied knotted protein is YibK methyltransferase form haemophilus influenzae with the simplest $+3_1$ knot. But yet, even for this structure precise mechanism of folding remains elusive, as there is no model enabling for reversible folding of such protein. However, it was shown, that construction of a minimal contact map can facilitate the knotted protein folding with simultaneous retaining of the folding pathway [3]. In this work we try to tackle the problem of YibK folding by construction of a minimal contact map enabling to observe folding process with reasonable frequency. The map was built by subsequent selection of native contacts from the original contact map obtained with SMOG algorithm [4]. This methodology led us to selection of the most important contacts in YibK folding. In particular, we show, that the contacts in the vicinity of the knot and of the threading helix are indispensable for the protein knotting. On the other hand stiffening the helices by addition of interhelix contacts results in evident diminishing of the knot formation frequency. Finally, we were able to construct a contact map enabling to fold the protein in about 45% of trajectories.

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Toxicity and biodegradation of nitrophenol compounds by aerobic system

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Nitroaromatic compounds are relatively rare in nature and have been introduced into the environment mainly by human activities. These important class of industrial chemicals are widely used in the synthesis of many diverse products, including dyes, polymers, pesticides, and explosives. Unfortunately, their extensive use has led to environmental contamination of the soil and groundwater. The nitro group, which provides chemical and functional diversity in these molecules, also contributes to the recalcitrance of these compounds to biodegradation.
Wanhua-BorsodChem Zrt. gives a great deal of attention to the treatment of all wastewater generated by the factory, which are treated by the Waste-water Treatment Plant. Here, physical, chemical and biological purification are carried out. Our task was to examine the biodegradation of the possible isomer nitrophenols occurred in the waste-water and to analyse them ecotoxicologically. In the biodegradation experiment different waters were examined containing orto-, meta-,and para-nitrophenols.
In our experiments, a self-developed laboratory aerobic waste-water activated sludge treatment unit was used. In order to determine the precise biodegradation ability, the total organic carbon (TOC) and nitrophenol content were measured, as well. Beside of the biodegradation property ecotoxicology tests of the waste-waters were also executed. Seedling plant tests were used for studying the effect of the waste-waters on the other superior organism.
Orto-, meta-, para-nitrophenol solutions and different dilutions of them were examined. The treated waters which were oxidized by three different agents: Hypo, Fenton, ozone. Another type of experiment was the activated sludge examination. From the results it could be concluded that in the case of the water toxicology tests when seedling plant tests were carried out the 10 ppm meta,-orto nitrophenol is faintly toxic while the para-nitrophenol is not toxic. Another type of test was the activated sludge examination. The para and orto-nitro-phenol was added in an increasing amount. The phenol content of the output solution was generally less than 5 ppm.

In the wake of potentially new reaction pathways of the atmospherically relevant HCN + ·OH reaction system

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Alternative removal mechanism of HCN in the presence of OH radical has been investigated to find previously undiscovered minima on the reaction PES. Highly accurate calculations were performed by means of CHEAT1 protocol and the results were tested against previous published theoretical results [1-6]. The deviation in heats of reaction compared to other works has never achieved the value of 5 kJ/mol. Formation of an unreactive van der Waals complex (OH·HCN) with roughly 15 kJ/mol stabilization energy has been identified. The CHEAT1 barrier heights of the H- abstraction by OH and the OH addition channel found to be lower than in previous publications.

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Development of silver nanoparticle content additives to formation of antimicrobial surfaces

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Nowadays the urinary tract infection were cause a serious problem in health care, these infections were created by germs. Used of urinary catheter was lead to infection in bladder or kidney, owing to germs can travel along the catheter into a urinary system. Most important to provide the antibacterial properties for catheters, the solution may be nanotechnology. The pathogen microorganism were kill by silver nanoparticles, because the structural changes in bacterial membranes were caused the interaction between silver nanoparticle and the constituents of the bacterial membrane, and the death of the cell was caused the damage of membranes and intracellular metabolic activity. The 10 wt% metal contained silver colloid was synthesized in oleic acid from silver-acetate. In first step of the reaction the silver-oleate was formed, after the bonds of silver-oleate were ruptured at higher reaction temperature, and oleic acid stabilized silver nanoparticles were formed. The colloid was stable, and the nanoparticles were high dispersibility in nonpolar solvent. The diameter distribution of silver nanoparticles were performed with scanning electron microscopy, the average particle size was 4.7 ± 2.2 nm. Silicon based Foley catheter was treated with solution of the silver nanoparticle in either as a dispersion medium. The silver nanoparticles impregnated catheter was examined using scanning electron microscopy and energy dispersive X-ray spectrometry, the extension of silver particles on the catheter was confirmed by the elemental analysis. The antibacterial effect of catheter was examined on two pathogenic microorganism, namely escherichia coli and staphylococcus aureus, and the tests were efficient. The oleic acid stabilized silver dispersion was effectively usable at produced of antimicrobial, polymer based medical devices.

Water affinity to conserved hydration sites in protein kinases

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Water plays important role in most biological aspects of life. Aside from existing as embedding medium, it is often found deep inside protein structures in the form of solitary molecules, isolated from bulk solvent. Typically involved in specific hydrogen-bond networks, they contribute to the stability, dynamics and function of proteins.
The analysis of diverse protein kinases, which in spite of little sequence homology share high level of structure similarity, reveals several such buried water molecules at well conserved locations. Interestingly, most of them turns out to be localised within functionally important motifs. A question arises whether they play any functional role?
Using computational approaches, we investigate the role of selected, universally preserved water molecules for kinase function. We focus on answering the following questions:
1. Where are conserved hydration sites in kinases structure depending on different states (active/inactive)?
2. How tightly are localised water molecules bound?
3. What is the influence of the considered hydration sites on conformational mobility of kinase catalytic subunits?

Molecular dynamics studies of polymerase γ linker region variants

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Polymerase γ is one of the most important proteins in the mtDNA replication complex. It is a nuclear protein formed by two subunits - Pol γA (encoded by the POLG gene) which has an activity of polymerase, exonuclease, dRP-lyase [1] and reverse transcriptase [2] and Pol γ B homodimer (encoded by the POLG2 gene) which determines Pol γA catalytic functions. The main function of this enzyme is mtDNA replication.
It has been shown that some variants in POLG gene sequence can decrease enzyme processivity or damage it function, which can be a cause of mitochondrial diseases [3]. Most of those variants are located in the catalytically active regions of Pol γ A [4]. There are also many other variants with an unknown background, which are located in the Pol γ A linker region. The main function of this part of the catalytic subunit are interactions with the accessory subunit, which are required for proper enzyme functioning [5].
Here we show molecular dynamics studies of amino acid substitutions in the Polymerase γ linker region - they influence to the structure and interactions between Polymerase γ subunits. Based on the available structure of the enzyme, a structural modeling of missing structural elements was performed. The obtained model was the subject of molecular dynamics simulations, which were made to clarify the impact of substitution of one variant G517V into the enzyme an its structure and properties.

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A mathematical representation of side-chain orientation in leucine diamide

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The conformational change associated with the internal rotation of the backbone and side chain of a molecule can lead to energy changes [1]. The relative energies were calculated by quantum mechanics using B3LYP/6-31G(d) implementation of the density functional theory in gas phase using the Gaussian09 software package. N-Acetyl-leucine N-methylamide was studied in terms of its four relevant dihedral angles for (ϕ, ψ) and (χ1 , χ2) over the interval [-π, π], and grid points at 15° increments, which can be depicted as a 4D-Ramachandran PEHS of four independent variables ΔE=f (ϕ, ψ, χ1, χ2) in order to investigate the minima with intramolecular interactions [2]. The PEHS can be represented by accurate mathematical functions [3]. By using these functions, we can obtain the first and second derivatives to find critical points and the minimum energy structures. Using these results, we can locate the minimum structure of backbone, side chain and the intramolecular interactions, which can lead to a conclusion about protein folding processes.

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A mathematical representation of side chain orientation in the serine diamide

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Proteins have a variety of forms and structures, and for this is the reason why they are able to do multiple tasks in different systems in all organisms. The large conformational flexibility of proteins is mainly caused by the dihedral angle rotation of ϕ and ψ on the backbone and χ angles on the side chain of every amino acid that together makes the protein. Serine, one of the simplest amino acid capable of making hydrogen bond, is studied in its residual form as N-Acetyl-serine N-methylamide (Fig.1) in order to mimic polypeptide environment.
For our investigation, a mathematical approach of using Fourier and Gaussian expansion to generate a function of energy was taken to a model the energy change when the dihedral angles rotate. From the mathematical model, stable backbone conformations were found, and for each stable conformer side chain conformations are determined.
By observing the PES, important data can be collected, such as the ϕ,ψ,χ1,χ2 angles of the most stable conformers, the period of conformational change, and in between, the transition state location and its corresponding energy level. This fundamental study can suggest the serine behavior when it localized on a polypeptide, which can later affect peptide folding prediction.

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New 4D NMR techniques for backbone resonance assignment of intrinsically disordered proteins. Design and application to Tau3x protein

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The resonance assignment of signals in the NMR spectra, a necessary prerequisite for any further structural NMR studies, in the case of intrinsically disordered proteins (IDPs) often appears to be a challenging task due to severe signal overlap, especially in the case of big proteins.
Novel 4 dimensional techniques, exploiting tocsy type carbonyl-carbonyl coherence transfer using MOCCA-XY16 mixing block [1,2], providing valuable CON connectivities as well as easy proline residues resonance assignment are proposed. Application of two 4D experiments allowed full backbone resonance assignment of Tau3x protein (354 a.a.) which was not possible using standard set of 5D measurements.
All acquired spectra were nonuniformly sampled to provide high resolution in all indirectly sampled dimensions. 4D spectra were processed using cleaner4d [3] exploiting Signal Separation Algorithm to remove sampling artefacts from resulting spectra. All processing software used is free to use for academic users and is available on http://nmr.cent3.uw.edu.pl/software.

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