

participate in formation of protein fold. They are however often influenced by the sequence variability and ligand binding. For this reason, identification of similarities and differences between SSEs can help us in the analysis of individual proteins within a protein family.

To utilize the SSEs for research of individual protein families, we need to have the SSEs easily and automatically intercomparable within one protein family. Specifically, the corresponding SSEs should have the same name (annotation) and there should be a transparent schema of their localization in the protein structures.

Unfortunately, SSE annotations are still performed mainly manually and universal automatic approach to assign SSE names is not available yet. Moreover, current methods focused on 2D visualization of SSEs (e.g., PROMOTIF, Proorigami, HERA) do not consider information about real distances of SSEs. Therefore, even when two proteins from the same family differ only slightly, their SSE 2D diagrams can be totally different.

For this reason, we developed a tool set which can perform SSE annotation and 2D visualization in such a way that structural information is kept. Applicability of this approach is shown in a case study focused on cytochromes P450. This protein family of drug-metabolizing enzymes has currently available more than 750 structures from about 30 organisms and each cytochrome P450 contains more than 20 SSEs for which there is a stable annotation used through the community. Our approach can be further extended to other protein structural families, which will allow family-wide SSE annotations and comparisons in a simple visual manner.

243-Pos Board B13

Interactive 3D Macromolecular Structure Data Mining with MolQL and Litemol Suite

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¹Central European Institute of Technology, Brno, Czech Republic, ²National Centre for Biomolecular Research, Brno, Czech Republic, ³Protein Data Bank in Europe (PDBe), Hinxton, United Kingdom, ⁴RCSB Protein Data Bank, San Diego, CA, USA, ⁵Palacký University, Olomouc, Czech Republic. Macromolecular 3D structure is critical in understanding the function and mechanism of biomacromolecules. Recent advances in 3D structure determination techniques have facilitated the study of large macromolecular machines, leading to a rapid increase in the number, size, and complexity of biomacromolecular structures available in the Protein Data Bank (PDB). Facilitating data mining of this large data set will not only help in addressing the challenges in translational research but also allow improved understanding of biological systems. The LiteMol suite offers an innovative approach to data archiving (BinaryCIF), data delivery (CoordinateServer and DensityServer), and 3D molecular visualization (LiteMol Viewer). The newly developed Molecular Query Language (MolQL) enables describing substructures in macromolecules using a wide range of expressions, including the support for Jmol, PyMol, and VMD selections; and the ability to extract data based on structural relationship between individual parts of the molecule. Together, these technologies allow users to mine the 3D structural data in the PDB (e.g., ligand binding sites) by providing a user friendly web based interface to aid translational research and make it easier for non experts to assess and exploit 3D macromolecular structure information. Visit litemol.org and molql.org for more information.

244-Pos Board B14

The Protein Recycling Machine of the Cell - Insights through a Novel Hybrid Integrative Modeling Approach

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Protein recycling is a key process crucial to a wide spectrum of regulatory processes within living cells. The executive player in this process is an ATP hydrolysis driven molecular machine called 26S proteasome, that recruits, unfolds, and degrades poly-ubiquitin tagged proteins through a complex interaction clockwork of 33 different protein subunits. Given its critical role, the proteasome is involved in multiple human diseases, and it serves as a perfect target for a plethora of different drugs, most prominently, those commonly used in chemotherapy of cancer. Despite its substantial role in the cell's life cycle, the proteasome is one of the last key molecular machines, which detailed atomic mechanism still remains elusive.

Driven by the revolutionary advance of electron microscopy I developed an integrative modeling approach to derive structural models from 3 to 12 Å resolution cryo-EM densities. My approach combines molecular dynamics flex-

ible fitting (MDFF) with *de novo* structure prediction algorithms in an interactive way allowing for incorporation of user expertise into model building. This approach is in particular beneficial as presently it is highly challenging to employ crystallographic modeling software to obtain models for cryo-EM densities with a resolution of ~4 Å.

Employing this approach we obtained in collaboration with the Baumeister department (MPI for Biochemistry) the first atomic structure of the human 26S proteasome with bound nucleotides (Schweitzer et al. PNAS 2016) based on a 3.9 Å resolution cryo-EM density. In a follow up study, we derived four more structural models of the yeast proteasome in different conformational states (Wehmer et al. PNAS 2017). These models provide the first atomic insights as to how ATP hydrolysis in the engine of the proteasome unwinds proteins and steers them towards the degradation chamber.

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Structural Analysis of Human Glycoprotein Butyrylcholinesterase using Atomistic Molecular Dynamics: The Importance of Glycosylation Site ASN₂₄₁

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Human butyrylcholinesterase (BChE) is a glycoprotein capable of bio-scavenging toxic compounds such as organophosphorus (OP) nerve agents. For commercial production of BChE, it is practical to synthesize BChE in non-human expression systems, such as plants or animals. However, the glycosylation profile in these systems is significantly different from the human glycosylation profile, which could result in changes in BChE's structure and function. From our investigation, we found that the glycan attached to ASN₂₄₁ is both structurally and functionally important due to its close proximity to the BChE tetramerization domain and the active site gorge. To investigate the effects of populating glycosylation site ASN₂₄₁, monomeric human BChE glycoforms were simulated with and without site ASN₂₄₁ glycosylated. Our simulations indicate that the structure and function of human BChE are significantly affected by the absence of glycan 241.

246-Pos Board B16

Accurate Prediction of Forster Resonance Energy Transfer during Co-translational Folding with Coarse-Grained Molecular Dynamics Simulations

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Protein folding, the assembly of a protein molecule or domain into a tertiary structure, can occur as a protein is being synthesized by the ribosome in a process referred to as co-translational folding. Forster resonance energy transfer has recently emerged as a technique for monitoring co-translational folding in vitro and probing its pathways. Holtkamp et al. 2015 found using FRET assays that the N-terminal domain of the E. coli protein Hemk folds co-translationally via a compact state. Our computational study addresses key questions about the co-translational folding of the Hemk N-terminal domain. We will determine if coarse-grained molecular dynamics simulations with explicit representations of FRET dyes are able to accurately reproduce experimental FRET curves. We will also ascertain by what pathways the co-translational folding of HemkNTD occurs and to what extent FRET can serve as an order parameter for folding. This project will also experimentally verify our approach to modeling co-translational protein folding.

247-Pos Board B17

Flexibility of Free and AcrB-Bound AcrA in the AcrAB-TolC Multidrug Efflux Pump of *Escherichia coli* Determined using 3D PMFS

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Key components of the emerging global epidemic of antibiotic resistance are the multidrug efflux pumps of pathogenic, Gram-negative bacteria, which span the periplasmic region between the inner and outer membranes of the cell. These protein complexes are an innate resistance mechanism, removing harmful antibiotics from bacteria. Until 2014 many aspects of the mechanisms for pump activity remained elusive due to the lack of structural data. Since then several increasingly detailed electron microscopy maps of an entire efflux pump complex, AcrAB-TolC, have been resolved, resulting in atomic-level structural models. Using these new models, we performed molecular dynamics simulations to study one of the key components of the protein complex, AcrA, which connects the inner-membrane-bound AcrB to the outer-membrane-bound TolC. We determined the flexibility of free AcrA by calculating a three-dimensional potential of mean force (PMF) focused on three angles that govern AcrA's conformational dynamics. AcrA shows a wide range of accessible orientations, with two main energy basins separated by a low