Institute of Biochemistry – Emil-Fischer-Center

Professorship of Bioinformatics

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Research focus
- Computational analysis of host-pathogen interactions
- Investigation of the aggregation behavior of the Aβ-peptide of Alzheimer's disease
- Structure-based evaluation of protein variants
- Structure of receptor-ligand complexes

Structure of the Professorship

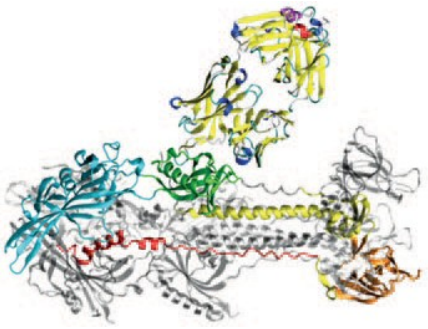
Professorship: 1
Personnel: 7
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 4

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

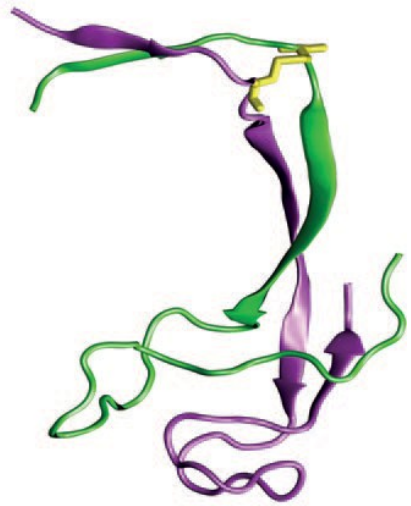
The research focus is on the computational characterization of protein-protein interactions. The identification of the underlying principles of molecular recognition is important for the understanding of regulatory mechanisms as well as for the prediction of novel, physiologically relevant protein interactions. The bioinformatics group investigates molecular interactions by a variety of computational tools (e.g. sequence data analysis, molecular modeling, and molecular dynamics).

Computational analysis of host-pathogen interactions
Specific interactions with host proteins are pivotal for a successful infection by a pathogen. This project focuses on the prediction and structural characterization of host-pathogen protein interactions using computational tools. The recognition processes either occur between short sequence motifs and complementary adapter modules or between pairs of globular protein domains. These types of interactions do not only differ from a structural point of view, but also with respect to the computational tools required for their prediction and analysis.
One particular challenge for the prediction of functional interaction motifs is the short length of the respective sequence patterns resulting in a large number of false-positive hits in conventional predictions, which prove to be non-functional in subsequent experiments. Therefore, we aim at improving the specificity of the predictions by assessing the importance of motif-specific flanking sequence regions.
For the analysis of host-pathogen interactions formed between globular protein domains, a combination of molecular modeling, docking, and molecular dynamics simulations is used. The latter technique provides information about the conformational stability and energetics of an interaction that can hardly be deduced from static structures alone. These methods are for example applied to study the structure of herpesviral glycoproteins that are pivotal for binding to the host cell and following fusion with the cell membrane. Furthermore, we investigate the molecular dynamics of viral regulator proteins and their interaction with cellular targets.



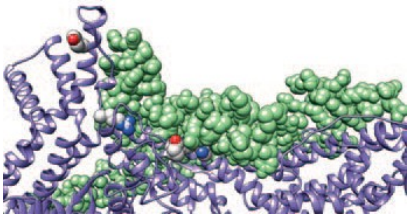
Model of the antigen-binding fragment of a neutralizing antibody bound to Domain-II (green) of the HCMV gB homotrimer
One protomer is colored according to its five domains.

Investigation of the aggregation behavior of the Aβ-peptide of Alzheimer's disease
Protein conformational diseases are unique since they result from a drastic change in protein three-dimensional structure. Most often, the change in conformation involves a structural conversion from primarily α-helical conformation with good solubility to an insoluble β-sheet conformation. Cells have evolved mechanisms to clear these insoluble deposits; however, once clearance pathways are overloaded, these proteins are deposited in the form of insoluble intracellular inclusions or extracellular plaques. Protein deposits or aggregates are also hallmark of many neurodegenerative diseases.
The most prevalent neurodegenerative disease is Alzheimer's disease, which is characterized by extracellular protein deposition of the peptide fragment Aβ from the amyloid precursor protein, and intracellular tau-containing filaments, called neurofibrillary tangles. The 3D structure of the Aβ deposits revealed the overall topology of the fibrils, but gives only limited information about the role of individual residues for fibril formation. The latter type of information, however, is important for the development of novel drugs that can prevent aggregation or of solubilizing aggregates by targeting those residues that represent the hot spots of binding affinity in the fibrillar structure. We address this point by molecular dynamics simulations of Aβ oligomers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such Aβ oligomers.



Model of the designed S8C variant of the Aß-peptide, which forms neurotoxic dimers
The two peptide chains are shown in magenta and green, respectively, and the disulfide bond is highlighted in yellow.

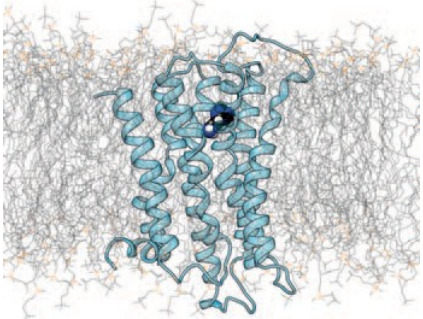
Structure-based evaluation of protein variants
High-throughput DNA sequencing studies revealed a large number of genetic variants between individuals. Many of these sequence variants lead to amino acid exchanges, some of which are linked to disease. Due to their large number (> 10,000 per genome), it is impossible to characterize all sequence variants by experiment, rendering computational prediction tools of utmost importance for the identification of pathogenic variants. Most of the current methods use evolutionary conservation and other sequence-based features to identify damaging variants, but they cannot predict the effects these variants have on protein function. Despite its innate linkage to function, structural information is yet only considered to a very limited extent in the predictions. In addition, the few existing structure-based prediction methods mainly focus on one distinct aspect of protein structure (e.g. protein stability or protein interactions) and do therefore not allow a comprehensive structural and functional annotation. The aim of the present project is to develop a robust computational framework for a comprehensive structure-based analysis and interpretation of high-throughput sequencing data.



Structure of the protein-protein complex between CYFIP (purple) and WAVE1 (green) Mutations of some CYFIP residues, which are located close to the interface, are related to intellectual disability These residues are shown in space-filled presentation and colored by atom-types.

Structure of receptor-ligand complexes

G-protein coupled receptors (GPCRs) are transmembrane proteins that recognize extracellular ligands and thereby trigger intracellular signaling processes. We use methods of molecular modelling and molecular dynamics to study the structure of GPCRs in complex with different small molecule ligands or intracellular interaction partners. Aspects investigated include the prediction of the binding modes of small molecule ligands, conformational changes in GPCRs as a result of ligand binding, and the influence of mutations on GPCR function and interaction. In addition to conventional MD simulation methods, computationally demanding metadynamics simulations are also used. In addition to GPCRs, we also investigate other classes of membrane receptors using similar methodological approaches. Systems studied include the glycine receptor, at which we characterize the binding site of saccharides as allosteric modulators. In the case of the macrophage surface receptor Mincle, we are investigating the binding of synthetic glycolipids, which should support the long-term development of better adjuvants for vaccines.



Structure of the Histamine-H1-Receptor (blue ribbon) with the modelled binding site of histamine (space-filled presentation). The lipids of the cellular membrane are depicted as grey/orange lines.

Teaching

The Professorship of Bioinformatics organizes lectures, seminars, and tutorials in the course program of Molecular Medicine. In addition, the Professorship is involved in interdisciplinary teaching in the master degree programs Life Science Engineering and Integrated Life Sciences in collaboration with the Faculties of Engineering and of Sciences, respectively.
The Professorship also supervises Bachelor's and Master's theses as well as PhD theses.

Selected publications

Söldner CA, Horn AHC, Sticht H. A Metadynamics-Based Protocol for the Determination of GPCR-Ligand Binding Modes. Int J Mol Sci. 2019, 20:1970

Boonsawat P et al. Elucidation of the phenotypic spectrum and genetic landscape in primary and secondary microcephaly. Genet Med. 2019, 21:2043-2058.

Marschall M et al. Nuclear Egress Complexes of HCMV and Other Herpesviruses: Solving the Puzzle of Sequence Coevolution, Conserved Structures and Subfamily-Spanning Binding Properties. Viruses. 2020, 12:683.

Pachathundikandi SK et al. T4SS-dependent TLR5 activation by Helicobacter pylori infection. Nat Commun. 2019, 10:5717.

Söldner, C et al. A survey of biological building blocks for synthetic molecular communication systems. IEEE Communications Surveys & Tutorials. 2020, 22:2765-2800.

Conrad M, Söldner CA, Miao Y, Sticht H. Agonist Binding and G Protein Coupling in Histamine H2 Receptor: A Molecular Dynamics Study. Int J Mol Sci. 2020, 21:6693.

International cooperations

Prof. Dr. H.-G. Breitinger, German University in Cairo, Cairo: Egypt

Prof. Dr. A. Rauch, Universität Zürich, Zurich: Switzerland

Prof. Dr. H. Durmus, Istanbul University, Istanbul: Turkey

Prof. Dr. Y. Miao, University of Kansas, Lawrence: USA

Prof. Dr. C. Zweier, Universität Bern, Bern: Switzerland