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
• Application of information-theoretic methods in protein-docking analysis
• Simulation of pH-effects on protein structure

Structure of the Professorship
Professors: 1
Personnel: 8
• Scientists: 3 (thereof funded externally: 2)
• Graduate students: 5

Special structural features
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiology as well as the Professorships for Bioinformatics and Molecular Imaging, respectively.

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). 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.

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 hallmarks of many neurodegenerative diseases.

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 that bind 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 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. In order to further increase the reliability of the predictions, modeling of sequence motifs in complex with the respective adapter domains is performed, thus allowing judging the likelihood of an interaction based on a three-dimensional structure.

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

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 are capable of preventing 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.

**Application of information-theoretic methods in protein-docking analysis**

Molecular docking represents a versatile computational method for determining the structure of protein-protein complexes. Despite considerable efforts to enhance the accuracy of docking predictions during the past years, a general solution to this problem is not yet within reach. One major challenge is the definition of suitable criteria for a scoring function that allows the identification of a good docking solution among many false arrangements. In our group, we have adapted the concepts from information theory to treat the biological problem of protein-protein docking. We have developed a formalism based on the concept of mutual information (MI) to investigate different features with respect to their information content in protein docking. We have also shown that the MI-values of these features can successfully be converted into a scoring function. Current work includes the analysis of larger data sets and more sophisticated structural features to obtain a robust and widely applicable approach.

**Simulation of pH-effects on proteins**

Changes in pH regulate many biological processes in bacteria, viruses, vertebrates, and plants. For example, some bacteria are able to survive the acidic conditions in the stomach of their host by using acid-activated chaperones which protect substrate proteins from aggregation. In viruses, some of the fusion proteins that mediate cell entry were described to act pH-dependently. Other proteins in vertebrates undergo pH changes on their way through the endolysosomal reticulum and the Golgi apparatus. In order to mimic pH-titration experiments, we investigate pH-dependent proteins by conducting molecular dynamics (MD) simulations, in which pH is changed gradually. This method allows the calculation of titration curves and pK_a values of ionizable groups. By using this strategy, we investigate on an atomic level the effects of pH changes which affect protein local conformations, macromolecular assemblies as well as structural stability.

**International Cooperations**

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

Dr. F. Halary, Université de Nantes, Nantes: France

Prof. Dr. M. Blaser, New York University School of Medicine, New York: USA

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

Dr. C. Brodski, Ben-Gurion University of the Negev, Beer Sheva: Israel

**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 programs Life Science Engineering and Integrated Life Sciences in collaboration with the Faculties of Engineering and Sciences. The Professorship also supervises Bachelor’s and Master’s theses as well as PhD theses.

**Selected Publications**


Socher E, Sticht H. Probing the Structure of the Escherichia coli Periplasmic Proteins HdeA and YmgD by Molecular Dynamics Simulations. | Phys Chem B. 2016, 120:11843-11855

**Structure of the complex between the chaperone HSP47 (grey) and collagen (purple, green, yellow).** The interaction is pH-dependent and is regulated by changes of the protonation state of HSP47 histidines (stick presentation). Mutations in HSP47 are observed in context of Osteogenesis imperfecta.