The effects of acidosis, Cu2+-binding, oxidation, and lipid membranes on the conformational dynamics and aggregation of Aβ

Dr. Birgit Strodel, Forschungszentrum Jülich

Alzheimer's disease (AD) is the most common form of dementia, which is characterized by the abnormal deposition of extracellular fibrillar plaques, of which the primary component is amyloid-β (Aβ) peptides ranging from 39 to 43 residues. There is strong evidence suggesting that small-size oligomers, which are transiently formed during the aggregation process, are the most neurotoxic species rather than mature fibrils. However, the structural properties of Aβ oligomers are still poorly understood.[1] Using atomistic MD simulations combined with a novel transition network analysis method we emphasize the role of the oligomer shape in the early aggregation process of the two alloforms Aβ40 and Aβ42 and propose that extended conformations are the main driving force behind the aggregation into larger oligomers, while compact oligomers are the metastable ones.[2] By comparing our simulation results to data from sedimentation velocity centrifugation and small angle neutron scattering (SANS), we were able to show that in solution Aβ42 pentamers and hexamers are the smallest oligomers which are metastable.[3] In light of the high affinity of Cu^{2+} for Aβ and its ability to subsequently catalyze the formation of radicals, we further examined the effects of Cu^{2+} binding, Aβ oxidation, and an acidic environment mimicking brain inflammation on the conformational dynamics of the Aβ42 monomer and the smallest oligomer, the Aβ42 dimer. Transition networks calculated from Hamiltonian replica exchange MD simulations revealed that the decreased pH considerably increased the β-sheet contents whereas Cu^{2+} binding increased the exposed hydrophobic surface area, both of which can contribute to an increased oligomerization propensity and toxicity.[4,5] In the final part of my talk I will discuss how lipid membranes of different compositions modulate the characteristics of Aβ as it is becoming increasingly evident that the plasma membrane of neurons plays a role in Aβ aggregation.[6]

[1] L. Nagel-Steger, M. C. Owen, and B. Strodel. An account of amyloid oligomers: facts and figures obtained from experiments and simulations. *ChemBioChem* 17: 657-676 **(2016)**

[2] B. Barz, Q. Liao, B. Strodel. Pathways of amyloid-β aggregation depend on oligomer shape. *J. Am. Chem. Soc*. 140: 319-327 **(2018)**

[3] M. Wolff, B. Zhang-Haagen, C. Decker, B. Barz, M. Schneider, R. Biehl, A. Radulescu, B. Strodel, D. Willbold, and L. Nagel-Steger. Aβ42 pentamers/hexamers are the smallest detectable oligomers in solution. *Sci. Rep*. 7: 2493 **(2017)**

[4] Q. Liao, M. Owen, O. O. Olubiyi, B. Barz, and B. Strodel. Conformational transitions of the amyloid-β peptide upon copper(II) binding and pH changes. *Israel J. Chem*. 57: 771-784 **(2017)**

[5] Q. Liao, M. Owen, S. Bali, B. Barz, and B. Strodel. Aβ under stress: the effects of acidosis, Cu^{2+}-binding, and oxidation on amyloid β -peptide dimers. Under revision **(2018)**

[6] M.C. Owen, W. Kulig, C. Poojari, T. Rog, B. Strodel. Physiologically-Relevant Levels of Sphingomyelin, but not GM1, Induce a β-Sheet-Rich Structure in the Amyloid-β(1-42) Monomer. BBA-Biomembranes, DOI: 10.1016/j.bbamem. 2018.03.026 **(2018)**

Probing polymer chain conformation and fibril formation of peptide conjugates

Bruno Voigt, Zhanna Evgrafova, Monika Baumann, Madlen Stephani, Wolf-gang H. Binder, Jochen Balbach

The parathyroid hormone (PTH) is an 84 residue peptide produced by the parathyroid glands controlling the calcium and phosphate level in human blood. The peptide adopts an α-helical conformation at the *N*-terminus and is intrinsically disordered at the *C*-terminus. Amyloidogenic properties of PTH have been reported [1]. To get further insights into the mechanism of amyloid fibrillation we investigated the effect of thermoresponsive polymers on PTH [2]. We covalently attached polyacrylate based polymers to ^{15}N isotope labelled PTH 1-84 and employed two dimensional NMR spectroscopy techniques for the characterization of the resulting chimaeras. This allows the visualization of amino acid specific changes of the peptide backbone according to the conformation of the conjugated polymer. The studies revealed strong dependencies of chemical shifts on the temperature, the peptide attachment site and the polymer molecular weight. However, conjugated PTH is still able to form amyloid fibrils though it shows altered aggregation kinetics.

[1]Gopalswamy, M.; Kumar, A.; Adler, J.; Baumann, M.; Henze, M.; Kumar, S.T.; Fändrich, M.; Scheidt, H.A.; Huster, D.; Balbach, J., Biochim Biophys Acta **2015**, 1854, 249-257.
[2] Funtan, S.; Evgrafova, Z.; Adler, J.; Huster, D.; Binder, W.H., Polymers **2016**, 8, 178.

Single Amyloid Fibrils studied in a thermophoretic trap

Martin Fränzl, Universität Leipzig

One of the difficulties in studying protein aggregation, i.e. into fibrillar structures, is the heterogeneity of the ensemble at all stages of the aggregation process. A mixture of monomers, oligomers and fibrils of various sizes determines the measurement outcome and commonly hides growth details such as secondary nucleation process. Here we try to remove this ensemble average by trapping a single fibril in a dynamic temperature field. Our studies show that fibrils can be observed over time periods of at least several 10 minutes and a whole variety of properties can be accessed. In particular, the strong length dependence of the rotational diffusion provides a promising indicator for the real-time observation of the growth of a single fibril.

Single Spins in Diamond - Precision Metrology at the Nanoscale

Dr. G. Balasubramanian, Max-Planck-Institut
für biophysikalische Chemie Göttingen

Understanding physical quantities at the nanoscale is a frontier research topic that has profound and broad impact covering fundamental physics to emerging technologies. The spins associated with Nitrogen-Vacancy (NV) centres in diamond has unique advantages as a nanoscale sensor for precision measurement of magnetic field, electric field, temperature and strain. Among several applications, I will introduce the need for sensing single biomolecules and the prospects of an NV spin magnetometer for developing such a microscope to probe molecular structure and dynamics. I will also present some developments and challenges in NV based precision sensing and imaging of magnetic and electric fields. The talk will cover aspects of NV defects in diamond, Nanoscale magnetic sensing, Spin noise spectroscopy, Quantum controls and Nanoscale NMR/MRI.

Ricardo Kurz

SFB/TRR 102: Polymers under Multiple Constraints

The SFB/TRR 102 is a Collaborate Research Center (CRC) at the Universities of Halle and Leipzig. Our focus is lying on open problems of polymer research which are characterized by the occurrence of strong correlations between local structure and global conformation of the chain. We investigate processes of structure formation and self-assembly of synthetic and biological chain molecules, for which the formation of molecular structures and the molecular dynamics are strongly affected by constraints like specific internal interactions, external forces, geometrical confinement, crowding or topological restrictions. Two prominent examples for such processes and central topics of the CRC are crystallization in the area of synthetic polymers and the formation of amyloids in the area of biopolymers.

Further information about our activities including the **Integrated Research Training Group 'Polymers: random coils and beyond'** can be found at: www.natfak2.uni-halle.de/sfbtrr102.

Local Organizer

Prof. Dr. Frank Cichos
Peter Debye Institute for Soft Matter Physics
Faculty of Physics and Earth Sciences
Universität Leipzig
Linnéstraße 5
04103 Leipzig, Germany
Phone: +49 341 97 32571

Office SFB/TRR 102

Beate Horn, Nicole Haak and Dr. Thomas Michael
Martin Luther University Halle-Wittenberg
Faculty of Natural Sciences II
Von-Danckelmann-Platz 4
06120 Halle (Saale), Germany
Phone.: +49-345-55-25342

web: http://www.natfak2.uni-halle.de/sfbtrr102

Email: SFB-TRR-102-office@physik.uni-halle.de

Mini Symposium

Universität Leipzig (8. 6.2018)

Carl-Ludwig-Institute for Physiology
Liebigstraße 27
Small Lecture Hall (Room 103)

www.natfak2.uni-halle.de/polymer-minisymp5

12.00 pm	Snack buffet (foyer)
1.00 pm	Talk by Dr. B. Strodel, Forschungszentrum Jülich
1.40 pm	Talk by Bruno Voigt, MLU Halle-Wittenberg
2.00 pm	Talk by Marin Fränzl, Universität Leipzig
2.20 pm	Coffee break (foyer)
2.50 pm	Talk by Dr. G. Balasubramanian, Max-Planck-Institut für biophysikalische Chemie Göttingen
3.30 pm	Talk by Ricardo Kurz, MLU Halle-Wittenberg