Polymers under Multiple Constraints

Polymer- & Soft-Matter-Seminar

Tuesday, 24th November 2015

at: **5.15pm**

VDP4 1.27, Von-Danckelmann-Platz 4, 06120 Halle

Prof. Birgit Strodel

(Computational Biochemistry Group
ICS-6: Structural Biochemistry, Forschungzentrum Jülich)

"Thermodynamics and kinetics of amyloid aggregation from atomistic simulations"

A major cause for cellular toxicity involved in the onset of several neurodegenerative diseases is the aberrant aggregation of proteins into oligomers and eventually fibrils. In the case of Alzheimer's disease, the main aggregating protein is the amyloid β-protein with two main alloforms of 40 (Aβ40) and 42 (Aβ42) amino acids. Numerous experimental studies have shown that early oligomers on the pathway to fibril formation are toxic, with Aβ42 showing a higher toxicity than Aβ40.[1] Recently, a secondary nucleation mechanism in the presence of fibrils has been proposed to produce toxic Aβ42 oligomers that might have different conformation than oligomers formed in the absence of fibrils.[2] To explore the aggregation mechanisms and differences in the oligomeric conformations we follow the aggregation of Aβ40 and Aβ42 from isolated monomers in the absence of fibrils [3] as well as in the presence of Aβ42 fibrils. We use all-atom molecular dynamics simulations to explore the aggregation process (up to 20-mers) and describe the kinetics of aggregation and differences in the pathways due to differences in the sequence and environment using transition networks.[4]

References:

[1] Bernstein et al. *Amyloid-β protein oligomerization and the importance of tetramers and dodecamers in the aetiology of Alzheimer's disease*, Nat. Chem., 1, 326-331 (**2009**)

[2] Cohen et al. *Proliferation of amyloid-β42 aggregates occurs through a secondary nucleation mechanism*, Proc. Nat. Acad. Sci., 110, 9758–9763 (**2013**)

[3] *B. Barz, O. Olubiyi, and B. Strodel.* ***Early amyloid β-protein aggregation precedes conformational change*****, Chem. Commun., 50, 5373-5375 (**2014**)**

[4] *B. Barz, D. J. Wales, and B. Strodel.* ***A kinetic approach to the sequence–aggregation relationship in disease-related protein assembly,*** **J. Phys. Chem. B, 118, 1003-1011 (**2014**)**