## Single-molecule sensing of protein oligomerization and phosphorylation states in solution

Quan Wang, Lewis-Sigler Institute
for Integrative Genomics, Princeton University

Oligomerization and phosphorylation are critical processes that modulate protein function. I will describe our recent advances in sensing these processes at the single-molecule level. Our scheme to identify oligomerization states is based on precise measurements of the diffusion coefficient of individual molecules captured in an anti-Brownian trap.

In a case study, we found the oligomerization pathway of tobacco Rubisco activase to be nucleotide dependent and directly observed assembly and disassembly of single complexes. On the other hand, phosphorylation modifies the charge state of biomolecule, which results in a shift in the molecule's response to external electric fields (i.e. electrokinetic mobility) in the anti-Brownian trap. As a proof-of-principle demonstration, we monitored the phosphorylation of peptides by cAMP-dependent protein kinase A with single-molecule resolution. We envision these new capabilities to enable new in vitro single-molecule measurements of complex biological processes

## Structure formation of single polypeptide chains in computer simulation

Arne Böker, MLU

The main culprit in amyloid diseases like Chorea Huntington is nowadays suspected to be an oligomer state of certain peptides rather than the actual amyloid fibril. Knowing the morphology of such oligomers or of single disease-related peptides is therefore a crucial step towards understanding those diseases. For this reason, we set out to study the structure formation of isolated polyglutamine and polyalanine chains - associated with Chorea Huntington and other diseases - by means of computer simulation. We are using an intermediate-resolution model named PRIME20 to achieve reasonably accurate results over a wide range of temperatures. Because this model has been published in two slightly different variants, the first task is an assessment of their fitness for our simulation, which will be presented in the talk. Further on, the folding behaviour of polyglutamine and polyalanine and its dependence on chain length will be discussed.

## Excluded Volume Studies on a Single Semi-Flexible Polymer Chain

Tobias Thalheim, Klaus Kroy, Frank Cichos, Leipzig University

Long-range interactions of distant segments of the same polymer due to the finite spatial volume of these segments, which are known as excluded volume effect or self-avoidance, were first discussed by Kuhn [1] and in a very successful theoretical approach subsequently described by Flory [2] in a mean-field-type calculation. Flory's theory derives an exponent which describes among other things the scaling of the equilibrium size of a polymer on the number of its monomers within an accuracy of one percent compared to the best simulation results although profiting from an amazing cancellation of two errors [3]. A whole bunch of theoretical work was done on excluded volume effects subsequently spanning perturbation calculations, mean field theories and renormalization group theories pursuing better theoretical predictions also for charged chains where Flory's approach fails. Within the frame of renormalization group theory, Schäfer and Krüger derived a probability distribution of the total segment density about the center of mass (COM) for an isolated polymer involving these long-range interactions [4].

Using our previously introduced thermophoretic trap [5] we have the possibility to cancel the Brownian motion of single DNA molecules which are homogeneously labeled with an intercalating fluorescent dye giving direct access to the density distribution of the molecule. Mean images calculated from a whole measurement thus allow for testing the theory by Schäfer and Krüger for the first time to figure out the impact of volume exclusion of different types of single DNA molecules in free diffusion and in a compressed state.

References

[1] W. Kuhn *Über die Gestalt fadenförmiger Moleküle in Lösungen.* Kolloid-Zeitschrift 68, 2-15 (1934)
[2] P. J. Flory *The Configuration of Real Polymer Chains.* J. Chem. Phys. 17, 303-310 (1949)
[3] P. G. de Gennes *Scaling Concepts in Polymer Physics* (Ithaca, NY: Cornell University Press, 1979)
[4] L. Schäfer and B. Krüger *Segment distribution about the center-of-mass in an isolated polymer coil. A renormalization group study.* J. Phys. 49, 749-758 (1988)
[5] M. Fränzl, T. Thalheim, J. Adler, D. Huster, J. Posseckardt, M. Mertig, and F. Cichos *Thermophoretic trap for single amyloid fibril and protein aggregation studies.* Nat. Methods 16,611-614 (2019)

## The autocatalytic amplification of amyloid fibrils through secondary nucleation

Alexander K. Buell, Department of Biotechnology and Biomedicine, DTU

Amyloid fibrils are filamentous assemblies of proteins that are associated with biological function and disease. In our research, we try and dissect the complex overall mechanism of amyloid fibril formation into individual molecular steps and we try to determine the kinetics and thermodynamics of these steps. In recent years, it has emerged that some amyloid fibrils are able to efficiently self-replicate through secondary nucleation, i.e. the fibrils catalyse their own formation.

In this seminar I will present some progress on the mechanistic understanding of secondary nucleation of both the amyloid beta peptide and alpha-synuclein. Furthermore, I will present recent results on the efficient inhibition of secondary nucleation of alpha-synuclein amyloid fibrils.

Relevant publications:

Buell et al., PNAS 2014
Saric et al., Nature Physics 2016
Cohen et al., Nature Chemistry 2018
Agerschou et al., eLife 2019
Peduzzo et al., chemRxiv 2019, pre-print

## The impact of nanostructured interfaces on amyloid peptide aggregation

Torsten John[1,2] Herre Jelger Risselada,[1,3] Bernd Abel[1,2],
[1]Leibniz Institute of Surface Engineering (IOM)
[2]Wilhelm-Ostwald-Institute for Physical and Theoretical Chemistry, Leipzig University
[3]Institute for Theoretical Physics, Georg-August-Universität Göttingen

The aggregation of peptides into β-sheet rich oligomers and fibrils is a characteristic phenomenon observed for amyloidogenic peptides. These fibrillation processes have been linked to the onset of ageing-related diseases, such as Alzheimer's disease or type 2 diabetes. [1] The conditions that cause the aggregation of the soluble peptide monomers into insoluble amyloid plaques is still under investigation. Next to the physicochemical environment, surfaces have been identified to influence the aggregation kinetics. Particularly relevant are nanostructured interfaces due to their high surface-to-volume ratio, and thus large overall surface area. [2]
Nanostructures are abundant in nature in the form of liposomes or synthetic nanoparticles. Both accelerating and inhibiting effects on peptide aggregation into amyloid have been observed, depending on a number of parameters, such as surface coating, nanoparticle size or buffer conditions. [2-4] We have used experimental methods in combination with molecular dynamics (MD) simulations to study the mechanism of peptide aggregation into amyloid at gold nanoparticles. The results on the role of functionalized gold surfaces and citrate-coated gold nanoparticles of varying size are presented. A model that incorporates the competition between peptide-surface attraction and intrinsic aggregation propensity is discussed. [2, 3]

References:
[1] F. Chiti, C. M. Dobson, *Annu. Rev. Biochem.* **2017**, 86, 27-68.
[2] T. John, A. Gladytz, C. Kubeil, L. L. Martin, H. J. Risselada, B. Abel, *Nanoscale* **2018**, 10, 20894-20913.
[3] A. Gladytz, B. Abel, H. J. Risselada, *Angew. Chemie - Int. Ed.* **2016**, 55, 11242-11246.
[4] A. Gladytz, M. Wagner, T. Häupl, C. Elsner, B. Abel, *Part. Part. Syst. Charact.* **2015**, 32, 573-582.

## 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.
Since the third funding period, researchers are also investigating hybrid polymers that consist of biological and synthetic parts. We want to gain a better understanding of how these novel hybrid molecules influence each other and which properties result from their interaction.

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
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
# of the SFB TRR 102

## Universität Leipzig (13.12.2019)

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

| | |
|---|---|
| 12.00 pm | Snack buffet (foyer) |
| 1.00 pm | Talk by Dr. Quan Wang, Lewis-Sigler Institute for Integrative Genomics, Princeton University |
| 1.40 pm | Talk by Arne Böker, MLU Halle-Wittenberg |
| 2.00 pm | Talk by Tobias Thalheim, Universität Leipzig |
| 2.20 pm | Coffee break (foyer) |
| 2.50 pm | Talk by Prof. Dr. Alexander K. Buell, Department of Biotechnology and Biomedicine, Heinrich-Heine-Universität Düsseldorf |
| 3.30 pm | Talk by Torsten John, Leibniz-Institut für Oberflächenmodifizierung (IOM) |

www.natfak2.uni-halle.de/polymer-minisymp7

SFB TRR 102