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The role of charge for interactions intrinsically disordered proteins with bio-membranes.

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Intrinsically disordered proteins (IDPs) are a class of proteins that do not have a defined three-dimensional structure but may fold if a binding partner is present. In our current research we focus on the interaction of two neuronal IDPs with bio-membranes where binding to the membrane induces configurational changes or folding:

α -Synuclein (α Syn) is associated with various neurogenerative disorders, including Parkinson's disease, which is characterized by fibril formations in the human brain. α Syn plays an important role in synaptic vesicle trafficking and is involved in membrane interactions[1,2]. NMR and MD simulation showed that α Syn interacts with the membrane by partially forming α -helices, starting at the N-terminus and including a kink in the alpha helix. The fraction of α Syn in the bound α -helical state at the N-terminal increases with the amount of charged lipids in the membrane [3]. While the disordered C-terminal region stays disordered. Interaction of α Syn with differently charged lipid bicelles was measured by Circular Dichroism (CD) Spectroscopy at SOLEIL and showed increasing of α -helical structure for charged membranes.

Synaptobrevin-2 (Syb2) is a vesicle-associated integral membrane protein. Syb2 plays an important role in vesicular membrane fusion at the neuronal synapse by participating in the dynamic formation of the SNARE complex. Syb-2 anchors with a short transmembrane region to the membrane and has a large intrinsically disordered soluble region (1-96) which shows a gradually increasing rigidity from the N to C terminus that correlates with an increase in lipid binding affinity.

One of the techniques is Neutron Reflectometry, which we plan to use to investigate the interaction of α Syn and Syb2 with membranes (DMPC/DMPG) of varying charge composition (fraction of negative DMPG in neutral DMPC) to examine the configuration in/at the membrane and in the adjacent solution.

[1] Gitler et al., Proc. Natl. Acad. Sci. U. S. A. 2008, 105, 145.

[2] Bellani et al., Common. Integr. Biol. 2010, 3, 106.

[3] Viennet et al., Commun. Biol. 2018, 1, 1.

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