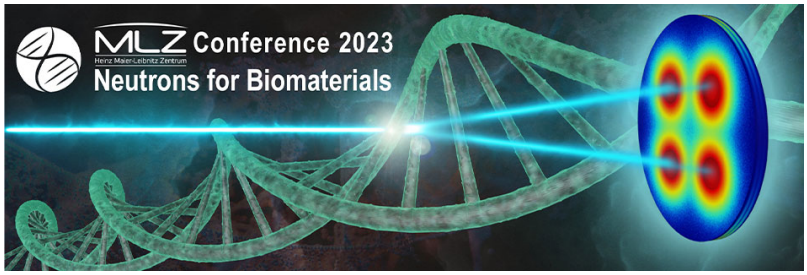

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Exploring the limits of passive macromolecular translocation through lipid membranes

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Translocation of macromolecules through the cellular membrane mostly occurs via pore formation involving a strong local disruption of the membrane, or via endocytosis, which requires the second translocation step – endosomal escape. Passive translocation of macromolecules is highly desirable for biomedical applications but rare due to their size, complexity, polarity, or other factors. We found that non-ionic alternating amphiphilic polymers (AAP) can generally cross lipid membranes passively without damaging the membrane.[1] The ability to tune AAP average polarity and polarity profile by changing the lengths of the building blocks and their mass ratio[2] allowed us to get many insights into the mechanism of AAP translocation mechanism and explore the limits of passive macromolecular translocation.
The translocation process was studied by time-evolution Pulse Field Gradient (PFG) NMR with the support of Neutron Reflectometry (NR) using Phosphatidylcholine (PC) lipid bilayers as model membranes. PFG NMR allows to access independently adsorption and desorption, as well as the concentration of the translocating species in/at the membrane, whereas NR is useful to describe the localization of AAP inside the membrane.
We show that the translocation process consists of a fast, molecular weight (MW) dependent AAP membrane saturation in conjunction with a slow MW-independent release process. With the help of NR we find that the AAPs with short blocks can fully solubilize in the membrane interior while translocation, whereas the AAPs having long hydrophilic blocks adsorb to the membrane only by the hydrophobic blocks leading to the translocation via flip-flop mechanism. Therefore, varying the AAP polarity profile from homogenous to block-like changes the translocation mechanism, but does not restrict the translocation. The translocation time of the AAP through lipid membranes can be varied from minutes to many hours depending on the AAP molecular weight, polarity, polarity profile, lipid composition of the membrane, temperature, and other parameters.
We believe that the detailed and systematic study of the AAP translocation phenomenon will be useful for the fundamental understanding of the macromolecular translocation processes and can lead to interesting biomedical applications.

[1] E. Kostyurina, J. Allgaier, M. Kruteva, H. Frielinghaus, A. Csiszár, S. Förster, R. Biehl, J. Am. Chem. Soc. 2022, 2022, 15348–15354.
[2] E. Kostyurina, J. U. De Mel, A. Vasilyeva, M. Kruteva, H. Frielinghaus, M. Dulle, L. Barnsley, S. Förster, G. J. Schneider, R. Biehl, J. Allgaier, Macromolecules 2022, 55, 1552–1565.

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