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Motion at Biointerfaces: From Single-Liposome- to Single-Lipid-Assays

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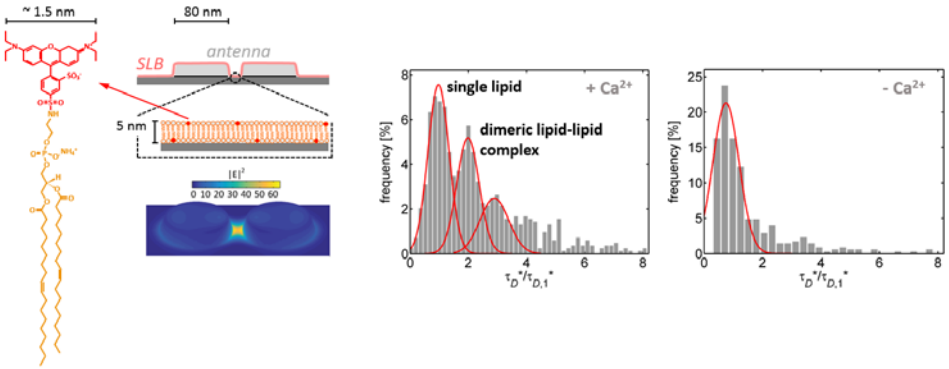
Life depends on complex networks of precisely fine-tuned interactions between different types of biological molecules. Many of these processes are orchestrated by a thin lipid bilayer, acting for example as compartmentalizing hydrophobic barrier, but also allowing for a selective molecular transport through the barrier based on specialized, bilayer-embedded membrane proteins. Membrane functions often depend on the local, nm-scaled bilayer assembly, which is, since being far below the diffraction limit of optical microscopy, challenging to characterize under physiological conditions. This talk presents two examples, in which a supported lipid bilayer (SLB) is locally modified by formation of lipid complexes (formed either by interaction with virus proteins or with divalent calcium ions), whose properties are probed based on measuring their mobility within the SLB.

The first example focusses on multivalent virus-lipid interactions, which are typically weak in the sense that a single virus has to bind to multiple lipid receptors in parallel to ensure firm bilayer attachment. Quantification of the interaction valency (*i.e.*, the number of receptors involved in the virus attachment) is demanding, strongly limiting our knowledge about virus entry and egress due to the strong dependence of valency on the virus off-rate. Motivated by our previous work on SLB-tethered liposomes,[1,2] we estimate here the valency of single influenza A viruses (interacting with the SLB-bound receptors) by measuring virus mobility using total internal reflection fluorescence microscopy (TIRF) and single particle tracking (SPT), allowing the complex off-rate distribution to be deconvoluted from valency effects. Application of this approach to quantify changes of multivalent virus-lipid interactions caused by addition of virus inhibitors will be discussed.

A second example focusses on salt-mediated formation of lipid complexes, a process that is well established from molecular simulations, but has not yet been experimentally studied with single-complex resolution. By combining fluorescence correlation spectroscopy (FCS) with nanoplasmonic antennas that shrink the FCS probe volume down to the ~20 nm length-scale, we probe the mobility of single dye-conjugated lipids on the nm-scale with high temporal and spatial resolution and show that these lipids diffuse either as single entities or as complexes in the presence of calcium ions.[3] Removal of Ca^{2+} almost completely removes this complex formation. Further application of antenna-enhanced FCS to stimuli-induced lipid clustering (*e.g.*, by salts, virus proteins) will be discussed.



[1] Block, S. *et al.* "Quantification of Multivalent Interactions by Tracking Single Biological Nanoparticle Mobility on a Lipid Membrane." (2016) **Nano Letters** DOI: 10.1021/acs.nanolett.6b01511.
[2] Block, S. *et al.* "Two-Dimensional Flow Nanometry of Biological Nanoparticles for Accurate Determination of Their Size and Emission Intensity" (2016) **Nature Communications**; DOI: 10.1038/ncomms12956
[3] Block, S. *et al.* "Antenna-enhanced fluorescence correlation spectroscopy resolves calcium-mediated lipid-lipid-interactions" (2018) **ACS Nano**; DOI: 10.1021/acsnano.7b07854