Lipid bilayers as model plasma membrane systems: experimental/theoretical synergy to tackle increasing complexity

Biological membranes represent one of the most important structures in cell biology. Cell membranes act as a physical barrier separating the intracellular from the extracellular environment and maintaining cellular homeostasis; are involved in organelles compartmentalization, signal transduction, cell-cell interactions and ion conductivity. The structural part of the membranes is provided by a complex and highly dynamic bilayer with thousands of different phospholipids with a variety of saturation and length of acyl chains, and by membrane proteins linked to and/or embedded in it. The functional part of the membrane is related to in-plane segregated domains called *lipid rafts*, enriched in cholesterol, sphingolipids and GPI-anchor proteins. Dysfunctional maintenance of lipid rafts has been shown to be involved in several diseases, as neurodegenerative diseases and cardiovascular disorders. Also, their role in the formation of extracellular vesicles, new, powerful biological theranostics tools, has recently been discovered. However, due to their nanoscale size and transient nature, characterization of lipid rafts is still representing a challenging task. Given their importance in biology, we propose here to build up lipid bilayer systems, both as vesicles and as surface-supported films, with increased molecular complexity, and to characterize their structure and dynamics by means of atomic force microscopy, scattering (X-rays, neutron) and Foster resonance energy transfer (FRET) techniques. Moreover, we will adopt a bottom-up computational approach with the help of atomistic models, to build up molecular assemblies with a variability of neutral and ionic lipids. Classical molecular dynamics simulations of these systems will yield microscopic insights into the mobility of the lipids, the morphology of the interfaces in contact with water and ions and finally, dielectric properties of these systems. This will provide complementary information on the characterization of bilayers with a focus on the molecular scale fluctuations that underlie the rich physical and chemical properties of vesicles in biophysics.