**Project C5: Thermodynamics of membranes with complex lipid compositions**

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**Current state of the research.** Research on phospholipid bilayers is an important branch of soft matter science. Fundamental questions involve the role and organization of the lipids in the membrane, the ionic permeation of the membrane, or its response to environmental changes (temperature, pH, stresses, etc.). When two or more lipid species are associated in a single bilayer, a complex phase behaviour emerges. The chemical diversity of the common lipid species explains the nonideal character of the mixtures: variable head-group sizes and charges, presence of unsaturations in the hydrophobic regions and mutual hydrophobic mismatches due to conflicting structural parameters. Lipids have variable melting transitions. As the fluid and the gel conformations of the lipids are mutually exclusive, the mixture of one low melting point and one high melting point lipid is characterized by a large miscibility gap in a given temperature interval. Finally, cholesterol molecules, often present in considerable amount in eucaryotic membranes, alter significantly the structure and the dynamics of the major phospholipid components, resulting in the emergence of new ordered fluid phases.
The phase behavior of complex lipid mixtures poses a number of challenges. Criticality is one of them. Critical regions have been detected, in particular in vesicles made of biomembrane extracts. The precise location and the extent of these critical regions remain to be predicted and understood. The consequence, in term of critical dynamics and thermodynamics, of the presence of a large number of lipid components, is a widely open issue. The evolution of lipid mixtures in response to oxidation, consecutive to light irradiation in the presence of photosensitive dyes, is another open issue. A third issue consists in understanding how the lipid diversity changes the interaction properties between membrane proteins and the lipid phase around it. Is the protein solvation improved? Do chemically mediated interactions between proteins emerge? Are the protein-lipid complexes favoured or hindered, with the addition of lipids with conflicting intrinsic properties (charge, size, intrinsic curvature, thermotropic behavior...)?

**Research project and collaborations.** To address these issues, we propose to elaborate a multiscale approach, combining realistic molecular dynamics (MD) and lattice models. Coarse grained MD is helpful for understanding the lipid conformations and interactions, and to obtain structural information on the bilayer systems. However, it remains very difficult to determine the thermodynamic phase diagrams, and also to consider systems with low amount of impurities. Critical fluctuations stand beyond reach. On the other hand, lattice models can lead to numerically well-defined phase diagrams, including the critical regions, and efficient sampling can be achieved. Unfortunately, their validity relies on a realistic choice for the coupling interactions between nearest neighbours. One of research project main directions will be to perform MD simulations in order to provide the lattice system with accurate nearest neighbour interactions inferred from a statistical analysis of MD trajectories. A conventional Monte-Carlo sampling of the lattice systems will provide the desired phase diagrams. A second main research direction consists in studying lattice systems of complex composition (say, a number of species equal to or larger than 3), with a particular focus on the evolution of the critical regions, or the domain interfacial profiles (determination of line tensions). If successful, this approach will make it possible for the lipid community to know the phase behaviour of an arbitrary lipid mixture, provided the microscopic lipid properties are satisfactorily described by the numerical molecular model.

**Work plan.** Most of the MD part of the project will be carried out in Freiburg. One third of the time will be spent in Strasbourg where aspects related to phase behaviour and phase diagram predictions will be addressed. Collaboration with the experimentalists in the Marques group at the ICS is planned.