Liquid-Liquid Phase Separation in Protein Solutions Induced by Multivalent Salts

Marcell WOLF,[1] Felix ROOSEN-RUNGE,[1] Roland ROTH,[2] Fajun ZHANG,*[,1] and Frank SCHREIBER[1]

[1]*Institut für Angewandte Physik, Universität Tübingen, Auf der Morgenstelle 10, 72076 Tübingen, Germany*
[2]*Institut für Theoretische Physik, Universität Tübingen, Germany*

Liquid-liquid phase separation (LLPS) in protein solutions plays an important role for protein crystallization as well as for protein association related diseases. Here, we summarize recent experimental studies of the phase behavior of model globular proteins in solution in the presence of multivalent salts. We demonstrate that a metastable LLPS in solutions of globular proteins can be induced by multivalent metal ions at room temperature for proteins, which otherwise show no LLPS in the accessible temperature range. The salt and protein partitioning in the two coexisting phases are determined using X-ray and UV-visible light absorption, respectively, which defines the boundary of LLPS. The effective interactions between proteins are characterized using small angle X-ray scattering (SAXS). The structure factor obtained by SAXS provides direct evidence for a short-ranged attraction, which leads to the metastability of the LLPS. We also discuss the underlying mechanism along the lines of charge inversion and reentrant condensation, and the application of this framework for protein crystallization.