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### Three types of biomembrane effects of surfactants and how to distinguish them by ITC

Lipid-detergent-systems have important applications, for example in pharmaceuticals and membrane protein studies. Furthermore, principal phenomena observed in such systems (e.g., membrane curvature stresses, nonlamellar phases, etc.) play key roles also for drugs and biomolecules interacting with cell membranes.

Detergents that can “flip” across the membrane spontaneously follow the scenario described by the **three-stage-model**, typically. It has been shown long ago that ITC is the superior method to characterize such systems (Heerklotz et al., Chem. Phys. Lett., 199%). Detergents that do not cross the membrane built up asymmetry stress by inserting into the outer leaflet only. This stress can lead to transient membrane failure or, “**cracking in**” of the detergent, which again is detected by ITC (Heerklotz, Biophys. J. 2001) and followed by the well-known 3-stage behaviour. Alternatively, the stress can oppose further insertion of surfactant. For example, dodecyl-lysophosphatidylcholine (Fan et al., Langmuir 2016) and digitonin (Fan and Heerklotz, J. Coll. Interf. Sci., 2017) are **staying out** of the membrane beyond a certain stress and form micelles that do not equilibrate with the liposomes for hours.

