Laboratoire de Biochimie Théorique
Institut de **B**iologie **P**hysico-**C**himique
13, rue Pierre et Marie Curie
75005 PARIS

S E M I N A I R E

Taras Pogorelov

Department of Chemistry, University of Illinois at Urbana-Champaign, USA

« Capturing dynamic signaling biomolecular structures in complex environments:making a match between simulations and experiments «

The cell is a complex, tightly-regulated, heterogeneous environment shaped by various biomolecules. Structural functional dynamics of these molecules spans orders of magnitude. Experimental techniques provide a wealth of information on various spatial and temporal scales. To resolve cellular events on the atomistic scale a close collaboration with computational methods is needed. Likewise, computational observations need to be validated by experiments. Here we present two directions, united by the common theme of cell signaling, membrane-associated phenomena and protein folding, where computation (molecular dynamics and quantum chemistry) and experiments (fluorescence and NMR spectroscopies) are used in synergy. With our novel highly mobile membrane mimetic (HMMM) model we address functional interactions of ions and peptides with fluid membranes. Calcium ions are important cellular messengers, spatially separated from anionic lipids. Upon cell injury, disease, or apoptotic events, anionic lipids are externalized to the outer leaflet of the plasma membrane and encounter calcium, resulting in dramatic changes in the plasma membrane structure and initiation of signaling cascades. We find that major structural characteristics of these modeled nanoclusters, including inter-lipid pair distances and chemical shifts, agree with measured NMR parameters. Simulations reveal that lipid-ion nanoclusters are shaped by two characteristic, long-lived lipid structures induced by divalent Ca2+. Using ab initio quantum mechanical calculations of chemical shifts on MD-captured lipid-ion complexes, we show that computationally observed conformations are validated by experimental NMR data. Predicting the mechanism of protein folding is another of the key challenges in molecular biophysics of cell signaling. MD simulations have been used to visualize the process of protein folding at atomic resolution. We enhance the structural resolution of the five-helix bundle lambda repressor domain by engineering into it three fluorescent tryptophan–tyrosine contact probes designed to report on the formation of tertiary contacts between these α-helices. Temperature and pressure jump relaxation experiments on these three mutants in combination with all-atom molecular dynamics provide an atomistic description of the folding process that proves to be reaction coordinate dependent and includes compact desolvated but non-native structural ensembles. Our combined computational and experimental approaches presented here can be applied to other complex molecular systems.

Lundi 17 décembre 2018
14h00

BIBLIOTHEQUE