Session: Electrostatics & Polarization in Inhomogeneous Media: Physico-Chemical Effects at the Interface of Macromolecule-Water Phases: Protonation & pKa

Electrostatic forces are crucial for many key biochemical processes. For example all energy transduction processes, such as catalysis, proton transport, electron transfer, ion homeostasis, involves electrostatic interactions. However, modeling electrostatic forces and effects in inhomogeneous media in the cellular environment is not a trivial task. We propose to organize a symposium entitled “Electrostatics and polarization in inhomogeneous media: Physico-chemical effects at the interface of macromolecule-water phases” to bring together researchers working in the general area of electrostatics of biological macromolecules. The goal of this symposium is to bring together researchers with common interests in electrostatic and polarization effects in biological macromolecules to forge new collaborations or strengthen ongoing collaborations of common interesting questions. A symposium with researchers utilizing and developing different experimental and computational methods certainly helps reveal the strengths and weaknesses of these approaches and make further improvements. The symposium can also be used to identify important new questions for which experiment is necessary for physical insight, to guide extension of theoretical and computational models, and to provide quantitative data for benchmark of models.

Oral presentation – 4098643

Computational method to capture pH effects at the macromolecule-water interfaces

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Many biomolecules have their structure, stability, and reactivity properties significantly modulated by pH. The pKa values of common titratable sites in proteins, peptides, lipids, or other simple organic molecules are usually coupled with their conformation and the observed electrostatic environment. In inhomogeneous media, this coupling becomes harder to capture and sample correctly using our state-of-the-art computational methodologies, like constant-pH MD (CpHMD) [1]. This is particularly important to study protein-protein and protein-drug binding or membrane permeability values. We will show our most recent methodological developments where CpHMD and an Umbrella Sampling scheme [2] were coupled to calculate the donepezil binding affinity to acetylcholinesterase and the membrane permeability coefficients of several chemotherapeutic drugs (tyrosine kinase inhibitors), including sunitinib and nintedanib. The results will showcase the effectiveness of our methodologies in predicting key attributes related to drug design, trafficking, and affinity toward the target.