University of Crete
Department of Physics

Physics Colloquium

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Multiscale Modeling of Biomolecules and Materials

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ABSTRACT

The talk will discuss method development and applications of multiscale computational techniques for the modeling of materials and biomolecules ranging from atomistic and coarse-grained Molecular Dynamics (MD) simulations, Monte Carlo, Markov state models, and Machine Learning with applications in drug design and drug delivery design. Biological membranes comprise fascinating examples of soft matter interfaces involved in a wide range of biological and industrial functions. Several aspects of the structure and dynamics of biomembranes as well as methodologies for targeting specific membrane interfaces for developing novel drug candidates and nanoparticle delivery systems will be presented.

Atomistic MD simulations and neutron scattering calculations of sterols in membranes shed light into the evolutionary advantage of cholesterol in higher vertebrates [1,2]. To study longer time and length scales, coarse-grained molecular representations may be employed for observing spontaneous bilayer self-assembly and constructing phase diagrams of ternary lipid mixtures [3,4]. These systems can be used to study the behavior of the partitioning and self-assembly of nanoparticles in lipid membranes [5,6]. To study in atomic-level detail metal nanoparticles, a major hurdle is the creation of the nanoparticle crystal habit, which is required for accurate modeling of crystal nanoparticles. We discuss a novel implementation of the Wulff morphology from the crystallographic unit cell [7]. We further employ this algorithm in the study of coated magnetic nanoparticles to investigate the model cell membrane-nanoparticle interactions and the effect of their surface coating [8].

The cell membrane hosts up to two thirds of known druggable targets. Therefore, in order to design more efficient drugs and drug delivery systems, a better understanding of the physicochemical interactions that govern biomembrane interfaces is needed. We present a novel ensemble machine learning algorithm designed to predict protein-membrane interfaces, where potential drug targets can bind [9]. We apply biased and unbiased MD simulations coupled with PCA, dynamical network analysis, binding site identification, virtual screening, lead optimization, and subsequent in vitro and in vivo assays, for understanding the oncogenic potential of PI3Kα and to identify the first allosteric PI3Kα inhibitors selective for PI3Kα mutants [10-14]. Finally, we use Markov State modeling to identify metastable states and kinetic networks for identifying biologically relevant molecular states.

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