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Abstract

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PhD

Multiscale modeling of new fluorescent cholesterol analogs in membranes

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This thesis has two focus areas: 1) the use of computational methods for development of new fluorescent cholesterol analogs, and 2) validation of polarizable embedding (PE) models in various contexts.

Despite the severity of diseases associated with cholesterol accumulation, such as atherosclerosis, the mechanisms underlying cholesterol uptake and transport into cells are poorly understood at the molecular level, and the development of new fluorescent analogs of cholesterol and ergosterol for use in fluorescence imaging is therefore highly important. We use a multiscale modeling approach to design and evaluate new analogs of cholesterol, ergosterol and related oxysterols. The analogs' ability to mimic the membrane-ordering properties of the natural sterols is investigated by performing classical molecular dynamics simulations of a membrane containing the analogs. The absorption and fluorescence properties are evaluated with electronic structure calculations employing time-dependent density functional theory (TD-DFT). The influence of the membrane on both one- and two-photon absorption properties is analyzed using the effective external field extension of the PE model (PE-EEF) in combination with TD-DFT. This embedding model allows for mutual polarization of the analog and the membrane surroundings in the ground state as well as during the excitation process. Our studies justify the use of the available intrinsically fluorescent analogs dehydroergosterol and cholestatrienol as sterol probes and suggest a number of new and improved probes with extended conjugated double-bond systems, where the methyl substituents in the steroid ring system are retained in order to maintain the ordering properties of the parent sterols. The trends in optical properties observed in gas phase are also observed when the probes are embedded in a membrane. Finally, it was found that the membrane has a large enhancing effect on the two-photon absorption strength of the analogs.

Furthermore, we examine the importance of polarization in the classical region when describing excitation processes in the green fluorescent protein by comparing the use of fixed-charge electrostatic embedding and the PE-EEF model. We find that the convergence of the absorption spectrum with respect to the size of the quantum region is significantly faster with the PE-EEF model compared to with fixed-charge electrostatic embedding, which gives opposite and erroneous environment effects. We also explore the influence of Pauli-repulsion, a purely non-classical effect. Pauli-repulsion is modeled in polarizable density embedding (PDE), which we use to evaluate the absorption spectrum of a cholesterol molecule surrounded by a non-polar solvent. It is shown that in this specific case, Pauli-repulsion must be included in the embedding model to obtain a qualitatively correct description of the absorption process.