Hybrid DFT/DFT simulation method for biological systems

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We have developed a hybrid computational method combining *ab initio* Kohn-Sham (KS) DFT and orbital-free (OF) DFT. The KS DFT is used to describe the chemically active part of the system and its first solvation shells, while the OF DFT is used to treat the rest of the solvent. The OF solvent molecules are assumed to be rigid and have frozen electron densities, which allows for their efficient treatment. The hybrid method defines a single energy functional for the whole system, provides seamless description of the boundary between the subsystems and allows for the flow of molecules across the boundary, resulting in exchange of solvent molecules between the subsystems. Tests on a liquid water system show that the total energy is well conserved during molecular dynamics and that the effect of the solvent environment on the KS subsystem is adequately described.

As a first application, binding of copper ions to the prion protein, PrP, which is responsible for a group of neurodegenerative diseases, is studied. It is well known that the PrP can efficiently bind copper ions; four high-affinity binding sites located in the so-called octarepeat region of PrP are now well known. Recent experiments suggest that at low copper concentrations new binding modes, in which one copper ion is shared between two or more binding sites, are possible. Using this experimental evidence, the hybrid DFT/DFT method is used to obtain detailed binding geometries and to determine the most favorable one among several possibilities suggested in experiment. The molecular dynamics simulation on the full PrP shows that the copper ion has stabilizing effect on PrP, suggesting that it may play a protective role against neurodegenerative diseases.

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