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Quantum Simulations of Solvated Biomolecules Using Hybrid Methods

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One of the most important challenges in quantum simulations on biomolecules is efficient and accurate inclusion of the solvent, because the solvent atoms usually outnumber those in the biomolecule of interest. We have developed a hybrid method that allows for explicit quantum-mechanical treatment of the solvent at low computational cost. In this method, Kohn-Sham (KS) density functional theory (DFT) is combined with an orbital-free (OF) DFT. Kohn-Sham (KS) DFT is used to describe the biomolecule and its first solvation shells, while the orbital-free (OF) DFT is employed for the rest of the solvent. The OF part is fully O(N) and capable of handling 10^5 solvent molecules on current parallel supercomputers, while taking only ~ 10 % of the total time. The compatibility between the KS and OF DFT methods enables seamless integration between the two. In particular, the flow of solvent molecules across the KS/OF interface is allowed and the total energy is conserved. As the first large-scale applications, the hybrid method has been used to investigate the binding of copper ions to proteins involved in prion (PrP) and Parkinson's diseases. Our results for the PrP, which causes mad cow disease when misfolded, resolve a contradiction found in experiments, in which a stronger binding mode is replaced by a weaker one when concentration of copper ions is increased, and show how it can act as a copper buffer. Furthermore, incorporation of copper stabilizes the structure of the full-length PrP, suggesting its protective role in prion diseases. For alpha-synuclein, a Parkinson's disease (PD) protein, we show that Cu binding modifies the protein structurally, making it more susceptible to misfolding – an initial step in the onset of PD. In collaboration with W. Lu, F. Rose and J. Bernholc.