Efficient frequency calculations in QM/MM using the Mobile Block Hessian method

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Normal mode analysis (NMA) is a well-known technique which estimates the intrinsic frequencies of chemical systems by assuming a harmonic shape for the potential energy surface. Despite its simplicity, it is still a popular approach to predict vibrational IR and Raman spectra, to identify chemical groups [1], or to study the large motions involved in conformational changes of biomolecules [2]. The method is based on the diagonalization of the Hessian matrix, which contains the second derivatives of the potential energy with respect to the *3N* nuclear coordinates. In extended QM/MM systems, however, its calculation, storage and diagonalization is an expensive computational task. Even in the case of a small QM region, the numerous derivatives of the QM/MM interaction terms still form a bottleneck in the frequency calculation: each MM atom displacement atom affects the charge distribution in the QM region, resulting in a large number of coupled perturbation self-consistent field (CPSCF) equations [3].

Recently, the Mobile Block Hessian (MBH) method was developed in order to reduce the dimensionality of the Hessian [4,5]. The main concept is the introduction of blocks that move as rigid bodies during the vibrational analysis. This block concept is now combined with the QM/MM scheme. Block motions replace the individual atom motions in the CPSCF equations, thus reducing the number of equations drastically.

We have derived and implemented a parallel version of both the full QM/MM Hessian calculation and the QM/MM Mobile Block Hessian calculation in the Q-Chem/CHARMM [6,7] interface. The reduced computational cost opens the path to a broad range of applications of normal mode analysis. As an example, the oxidative deboronation of the drug bortezomib is presented, which is suspected to induce cell death of cancer cells [8]. Application of MBH in the QM/MM scheme realizes a speed up of a factor 200 compared to the full QM calculation, while the estimated free energy difference are within less than 1 kJ/mol accuracy.

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