C-1-19

FMO-based electron density analysis to protein structure refinement

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Keywords: Electron density, Refinement, Optimization, Fragment molecular orbital (FMO) method, ABINIT-MP, BioStation

Electron densities obtained by X-ray diffraction analyses for biomolecules determine the nuclear coordinates with some ambiguities in position of hydrogen atoms, protonation, conformation of amino acid residues, and orientation of ligand binding, and so on. Optimization using the classical molecular mechanics (MM) generally refines the coordinates to obtain the final structures, which are registered to PDB entry and used to understand functions of biomolecules. However, the MM optimization often fails to reproduce the distance of hydrogen bonding and such optimized structure has inadequate coordinates in the framework of quantum mechanics for example. For drug discovery using *ab initio* fragment molecular orbital (FMO) method [1], refinement of the structure determination is thus needed to evaluate protein-ligand interaction and reaction mechanism more properly. In this study, we examine an electron density analysis for the refinement by comparing between X-ray and FMO-based electron densities using Crambin protein.

The FMO-based electron densities are prepared as below: First, stating form the high-resolution (0.48Å) X-ray crystal structure of Crambin including hydrogen atoms (PDB-ID: 3NIR), multiple conformations are obtained by MM and QM optimizations: Next, FMO calculations of these conformations are carried out to generate FMO-based electron densities at MP2/6-31G* level by using a development version of BioStation [2] on K-computer. We here reveal position of hydrogen atoms, protonation, and conformation of amino acid by assessing the original X-ray electron density and the FMO-based ones each other. In addition, the same analysis is performed using the low-resolution (2.0Å) structure. Finally, we investigate how the optimized conformations based on low-resolution X-ray electron density, which are used in generally drug design, reproduce the original high-resolution X-ray electron density.

[1] “The Fragment Molecular Orbital Method: Practical Applications to Large Molecular Systems” ed D. G. Fedorov and K. Kitaura (Taylor & Francis/ CRC Press, Boca Raton, FL, 2009).
[2] The calculations and visualization of electron density are performed by a development version of BioStation (download site; http://www.ciss.iis.u-tokyo.ac.jp/dl/index.php.).

Acknowledgment
This research was supported by the grant for “Strategic Programs for Innovative Research” Field No. 4: Industrial Innovations from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT)’s “Development and Use of Advanced, High-Performance, General-Purpose Supercomputers Project.”