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Visualization of the interfacial electrostatic complementarity: A method for analysis of protein-protein interaction based on fragment molecular orbital method

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Protein–protein interactions (PPIs) are extensively investigated due to their important roles in numerous biological processes, resulting in that PPIs are now spotlighted as a new target of drug discovery. Additionally, a detailed understanding of PPIs is essential for the design of antibodies used for various research purposes and/or therapeutic applications based on their high affinity and target specificity. Therefore, the importance of computational approaches to provide physicochemical insight into PPIs has increased. To accurately evaluate the charge transfer and polarization caused by the protein–protein bindings, quantum chemical approaches are desired.

Very recently, we developed a method for analyzing the PPI based on the *ab initio* fragment molecular orbital (FMO) method [1,2], which is called visualization of the interfacial electrostatic complementarity (VIINEC). In this method, electrostatic interaction at the protein–protein interface can be visually analyzed using the electron density (EDN) and electrostatic potential (ESP) obtained from the FMO calculation of the complex. VIINEC was implemented in PAICS (one of the FMO program packages) [3,4], and several calculations showed that VIINEC quantitatively evaluates the electronic induced fit due to the complex formation by comparison with the ESPs calculated in the isolate condition. The degree of the contribution of each amino acid to the electrostatic complementarity between the proteins was also quantitatively calculated. In addition, a part of the mechanism of the specificity of the target recognition of anti-bodies could be addressed.

Here we report the methodological aspects of VIINEC and illustrative calculations for the complexes of programmed cell death-1 (PD-1) with its ligand or anti-bodies targeting PD-1, which demonstrates the potential of VIINEC in life-science researches.

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