Review

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Fragment Molecular Orbital Method: Application to Protein-Ligand Binding

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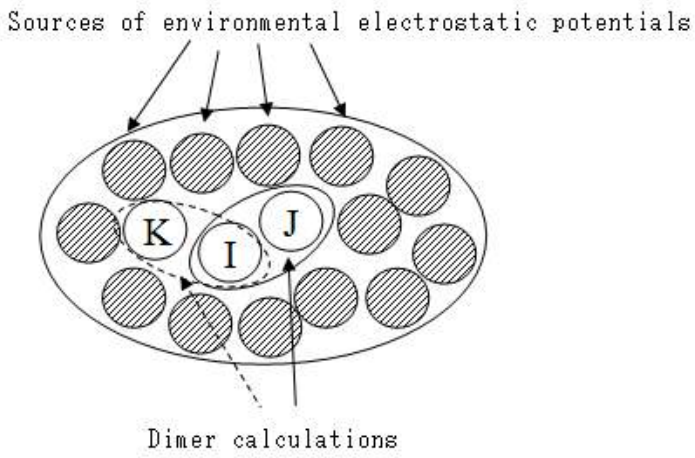
SYNOPSIS

Fragment molecular orbital (FMO) method provides a novel tool for ab initio calculations of large biomolecules. This method overcomes the size limitation difficulties in conventional molecular orbital methods and has several advantages compared to classical force field approaches. While there are many features in this method, we here focus on explaining the issues related to protein-ligand binding: FMO method provides useful interaction-analysis tools such as IFIE, CAFI and FILM. FMO calculations can provide not only binding energies, which are well correlated with experimental binding affinity, but also QSAR descriptors. In addition, FMO-derived charges improve the descriptions of electrostatic properties and the correlations between docking scores and experimental binding affinities. These calculations can be performed by the ABINIT-MPX program and the calculation results can be visualized by its proper BioStation Viewer. The acceleration of FMO calculations on various computer facilities is ongoing, and we are also developing methods to deal with cytochrome P450, which belongs to the family of drug metabolic enzymes.



Keywords: fragment molecular orbital method, protein-ligand binding affinity, QSAR

Introduction

The accuracy of force field is essential for reliable and predictable analysis of protein-ligand binding. There are mainly three elements in conventional force fields of which ab initio calculations (Szabo et al., 1982) can significantly improve the accuracy (Řezáč et al., 2008). The charge transfer and polarization effects associated with the electronic degree of freedom can be coped with when ab initio calculations are carried out. The dispersion forces, which are represented in terms of the van der Waals interactions, can be described when the electron correlation effects are taken into account appropriately. The bonding interactions associated with the dihedral angles formed by constituent atoms also provide a very important element in force field (Yoda et al., 2004), whose improvement by ab initio calculations has been found to play a vital role for accurate evaluation of ligand binding affinity (Fujitani et al., 2009). There are two kinds of approaches by which ab initio calculations can improve the accuracy of force field. The first one is to directly perform ab initio calculations for pertinent system, thus making a full treatment of the electronic degree of freedom. The second one is to parameterize a force field used for classical molecular dynamics / molecular mechanics (MD/MM) simulations on the basis of the results obtained by ab initio calculations. It is supposed that these two approaches would be developed in complementary ways in future.

In this article we will briefly review the current status of ab initio FMO approaches to protein-ligand binding issues. After a short introduction of FMO method, we will illustrate a variety of FMO applications in the following sections.

FMO method

Fragment molecular orbital (FMO) method (Kitaura et al., 1999) enables us to deal with whole large biomolecules in ab initio manner with remarkably reduced computational cost. In this approach, biomolecules are divided into a collection of small fragments and we then perform molecular orbital calculations for each fragment (called monomer) and fragment pair (called dimer) as seen in Figure 1. Total energy is represented by the following formula:

$$E_{\mathrm{FMO}} = \sum_{I} E_I + \sum_{I<J} \left(E_{IJ} - E_I - E_J \right)$$

This simple calculation scheme significantly reduces computational time with keeping good accuracy in molecular energy. One of great advantages of FMO method is that it can be combined with a number of current quantum chemical techniques. Thus, we can choose an appropriate method for each system. It is

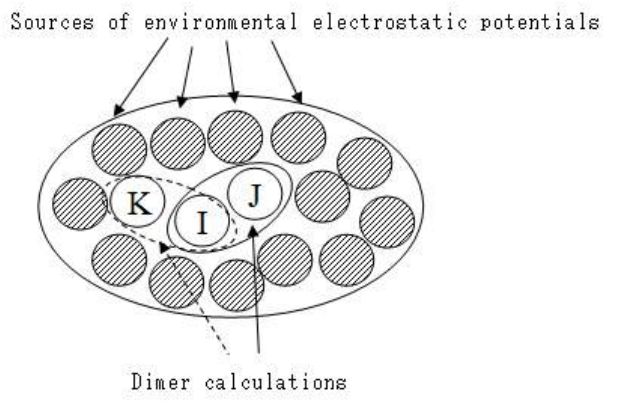


Figure 1. Schematic picture of FMO method.

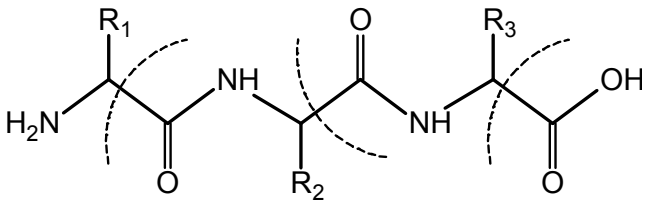


Figure 2. Fragmentation scheme for peptide.

emphasized here that incorporation of dispersion interactions is very important in biomolecular systems and the FMO method provides useful calculation scheme for dealing with these effects. To take into account the dispersion interaction, the Moeller-Plesset second-order perturbation (MP2) method (Szabo et al., 1982) is employed with relatively small computational cost and it describes this effect fairly well (Mochizuki et al., 2005a, 2005b). The fragmentation scheme for peptides is shown in Figure 2. In this scheme, neighboring two fragments are detached at carbon, C . It may be possible that this scheme impairs the computational accuracy because the covalent bonds are detached. However, in the FMO method, the accuracy is kept by employing projection operators made from the sp^3 hybrid orbital. In addition, some approximations related to the environmental electrostatic potentials from far regions and about the dimer calculations for distant dimers further reduce the computational time (Nakano et al., 2002).

FMO analysis tools for protein-ligand interactions

The FMO method provides a wealth of computational tools for quantitatively analyzing protein-ligand interactions, most of which are implemented in ABINIT-MPX program (Nakano et al., 2000, Mochizuki et al., 2008) and associated GUI called BioStation Viewer.

The inter-fragment interaction energy (IFIE) is one of the most useful quantities that FMO calculations can provide. This quantity is obtained as a natural output of the FMO calculation as

$$\Delta E_{ij} = \left(E'_{ij} - E'_i - E'_j \right) + Tr\left(\Delta P_{ij} V_{ij} \right)$$

where P_{IJ}, V_{IJ}, E_I' and E_{IJ}' are the difference density matrix, the environmental electrostatic potential for dimer IJ, the monomer energy without environmental electrostatic potential and the dimer energy without environmental electrostatic potential, respectively. The IFIE analysis has played a vital role for identifying important residues in receptor proteins in those ligand-binding systems such as estrogen receptor (ER) (Fukuzawa et al., 2006), retinoid X receptor (RXR) (Ito et al., 2007, 2008 a, 2008 b), vitamin D receptor (VDR) (Yamagishi et al., 2006), and HIV protease. For example, in the case of ER, important hydrophobic residues which show moderate attractive interactions with estradiol (EST) were appropriately identified through FMO-MP2 calculations. These attractive interactions are associated with the dispersion force and can be described by relevantly taking into account the electron correlation effects. These specific parts of effective inter-fragment interactions can also be described in terms of FILM (fragment interaction based on local MP2) picture, where only the electron correlation energies between the fragments are appropriately extracted (Ishikawa et al., 2007, 2008). The two-dimensional map for the IFIEs, referred to as IFIE map (Kurisaki et al., 2007), also provides a useful tool for specifying the “hot spot” of receptor-ligand interactions.

The visualized cluster analysis of protein-ligand interaction (VISCANA) was also proposed for the virtual ligand screening based on the FMO method (Amari et al., 2006). This methodology makes use of the dissimilarity of IFIE patterns among various

Table 1. Features of interaction analysis tools based on FMO method.

	IFIE (inter-fragment interaction energy	CAFI (configuration interaction)	FILM (fragment interaction based on local MP2)
Type of interactions	Full interaction (electrostatic, van der Waals, etc.)	Charge transfer and polarization	wdW attraction (dispersion interaction)
Description of interactions	Fragment level (symmetric)	Orbital level (unsymmetric)	Orbital level (symmetric)

ligand-receptor systems, which are sorted by a hierarchical clustering procedure. The VISCANA thus enables us to classify the structurally similar ligand molecules in terms of the interaction patterns of a ligand with amino acid residues of the receptor protein.

The CAFI (configuration analysis for fragment interaction) (Mochizuki et al., 2005) provides another useful tool for analyzing the fragment interactions. This methodology can efficiently identify essential factors which stabilize the electronic state of pertinent FMO system at molecular orbital level. The relevant charge-transfer (CT) and polarization components for the energy relaxation are obtained by performing the appropriate CIS calculations within each dimer with the concurrent electron relaxation functional (CERF). In the case of ER-EST complex, for example, the CAFI performed at the RHF/6-31G* level illustrated the strength and the direction of hydrogen-bond networks at the ligand-binding site (Fukuzawa et al., 2006). The strongest CT interaction was found from the lone-pair orbital of carbonyl oxygen of Glu353 to the σ^*_{OH} orbital of the hydroxyl group of EST, which could thus be regarded as the major controlling factor of ER-EST binding.

FMO derived charges

Since ab initio molecular dynamics (MD) or molecular mechanics (MM) calculations demand great computational cost even with the FMO method, we would still need to rely on classical force field calculations for structural optimization or dynamics of biomolecular systems. One reasonable strategy is to improve the quality of force field on the basis of ab initio FMO calculations. It has been observed that the FMO method provides a very good description of electrostatic fields around biomolecular systems, thus enabling the improvement of atomic charges in the force field. In fact, the Mulliken charges obtained by FMO calculation have been found to improve the docking score of current force-field model in comparison with experimental values when applied to the ER-ligand binding analysis (Fischer et al., 2006).

In this context, a computational scheme has been developed in which atomic charges in biomolecular systems are determined so that they reproduce the electrostatic fields obtained by the FMO method as well as possible. It has thus been found that the ESP (electrostatic potential) charges such as Merz-Kollman or RESP (restrained ESP) ones based on the FMO method can reproduce the electrostatic fields calculated quantum-mechanically much better than the charges employed in the original AMBER force field (Okiyama et al., 2008). One problem has still remained, however, concerning the stability of charge values, that is, some atomic charges sometimes take unphysically large amplitudes when the grid points for the electrostatic fields are sparse. This difficulty has then been overcome by a way that some restraints are imposed on the values of atomic charges so that they would not deviate from the reference values such as those employed in the original force field (Okiyama et al., 2009). Thus, it is expected that we can obtain the atomic charges which satisfy both the conditions that they would reproduce the FMO electrostatic fields accurately and do not take unphysical values. These atomic charges vary according to the changes of molecular structure and environment, and are expected to improve the quality of docking score, taking into account the charge transfer and polarization effects effectively.

Binding affinity evaluation by FMO method

It has been found that the binding energies between receptor proteins and ligand molecules evaluated by the FMO method show good correlations with experimental binding affinities in some examples such as estrogen receptor (Fukuzawa et al., 2005) and progesterone receptor systems (Harada et al., 2008). Some FMO studies concerning the mutation effects on the binding energies have been attempted as well. Here, it should be noted that the entropic contribution to the binding affinity has not been taken into account in the usual FMO calculations performed to date. In addition, most of FMO calculations have also been carried out in vacuo without considering the solvation effects due to water and counterions explicitly or implicitly.

In this context, a recent investigation in which theoretical binding affinities between FKBP and its ligand molecules are evaluated and assessed through FMO, QM/MM, MM-PBSA (Poisson-Boltzmann surface area), and classical MD-based free energy calculations in comparison with experimental results (Watanabe et al., 2010) is informative. In this study, it has been found that the calculations can provide fairly good correlations with experiments even when the entropic effects have been ignored. As for the FMO calculations, the importance of the inclusion of solvation effect has been remarked, suggesting the unbalance between the electrostatic and dispersion forces in the MP2 calculations in vacuo. Thus, it may be suggested that the accurate evaluations of the receptor-ligand interactions and of the solvation energies would be essential for the good correlations with experimental values over a wide range of ligand species even without the consideration of the entropic effects. The inclusion of implicit solvent effect in the FMO calculations has already been performed by means of the PCM method (Fedorov et al., 2006, Li et al., 2010). Development of a methodology in which the solvation effect is incorporated into the FMO calculations in terms of the Poisson-Boltzmann equation is also in progress.

FMO-QSAR

The QSAR has been employed as a useful tool for practical drug design. In the context of ab initio calculations for receptor-ligand systems, there would be an expectation that the FMO calculations can provide a number of novel descriptors to enhance the accuracy and availability of conventional QSAR approach. This direction of research has already been attempted for the case of HIV protease (Yoshida et al., 2008, 2009), in which new QSAR descriptors such as the transferred charges and the IFIEs between the ligand molecule and the amino acid residues were used. By developing further descriptors, we could expect that the applicability of these FMO-QSAR approaches would be extended, including the application to enzymatic reactions.

Future directions

Possibility of massively parallelized computations based on high-performance supercomputers would further extend the applicability of FMO-based calculations for protein-ligand binding. Thousands of protein-ligand complexes could be processed if we would perform the parallelized FMO calculations utilizing petaflops supercomputers. In this connection, a recent study concerning the acceleration of MP2 calculation in terms of the Cholesky decomposition is very promising, in which the MP2 part of the FMO calculations could be accelerated by approximately ten times (Okiyama et al., 2010).

Considering the application to drug design, on the other hand, the FMO approach may be utilized for so-called ADME/Tox issue as well. In this context, it is interesting to consider the possibility of FMO application to the analysis of cytochrome P450 (CYP). For this analysis, further computational tools such as MCP (Ishikawa et al., 2006) and CASSCF would be required, whose developments are under way in the framework of FMO.

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