Dynamic fragmentation with static fragments (DF/SF) algorithm designed for ab initio fragment molecular orbital-based molecular dynamics (FMO-MD) simulations of polypeptides

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Abstract

The ab initio fragment molecular orbital-based molecular dynamics (FMO-MD) method was extended for simulation of solvated polypeptides by the introduction of an algorithm named dynamic fragmentation with static fragments (DF/SF). In FMO-MD, the force acting on each nucleus is calculated by the FMO method, which requires fragmentation of the simulated molecule. The fragmentation data must be redefined, depending on the time-dependent change of the molecular configuration, and the DF/SF algorithm governs this redefinition. In the DF/SF algorithm, some fragments are manually classified as static and unchanged, while others are considered dynamic and subject to change. Various options of the algorithm were implemented in the ABINIT-MP program. The options were tested and discussed as they applied to FMO-MD simulations of the solvated (Gly)2 dipeptide, in which the two amino acid residues of the peptide were regarded as static (invariable) while surrounding water molecules were regarded as dynamic (variable). Future prospects for the FMO-MD simulation of biopolymers are discussed based upon the tests of the DF/SF algorithm.

Key Words: Glycine, Energy Conservation, ABINIT-MP

Area of Interest: Molecular Computing
1. Introduction

The fragment molecular orbital-based molecular dynamics method (FMO-MD) [1] is an $ab\ ini\initio$ MD simulation based on the fragment molecular orbital method (FMO) [2]. In FMO-MD, the behavior of the electrons and that of the nuclei are separated according to the Born Oppenheimer approximation, the former being solved quantum mechanically by FMO while the latter is solved by classical MD. More precisely, FMO calculates the force (minus the energy gradient) acting on each constituent nucleus using its instantaneous 3D coordinates [3] and the force is then used to update the coordinates via the ordinary MD algorithm. FMO-MD thus simulates the time evolution of molecules while considering both the electronic and geometrical structure changes, like any $ab\ ini\initio$ MD method. Furthermore, FMO-MD can handle larger molecular systems than general $ab\ ini\initio$ MD methods can, thanks to FMO’s high parallelizability and precision. FMO-MD was originally implemented by combining ABINIT-MP [4], an FMO program, and PEACH [5], an MD program. The resultant FMO-MD simulator is called the PEACH/ABINIT-MP system [6][7][8]. For further details, readers are referred to reference [9] for fragmentation methods in general, to reference [10] for FMO, and to reference [8] for FMO-MD.

A technical difficulty exists in the interface between FMO and MD, however. Prior to an FMO calculation, the molecule(s) must be divided into several fragments depending on their configuration, that is, the spatial and chemical arrangement of the constituent atoms. The FMO program is then fed the data about each fragment’s constituent atoms and formal charge. Nonetheless, the molecular configuration is subject to change during the time course of the simulation. Accordingly, the need for redefinition of the fragmentation data arises; otherwise, the FMO calculation fails to converge and results in an abrupt end of the simulation.

We solved the difficulty by devising an algorithm named dynamic fragmentation (DF) and introducing it to the PEACH/ABINIT-MP system. The DF algorithm was first introduced as an ad hoc algorithm that was to be revised for each specific molecule [7], but it was soon generalized to apply to arbitrary molecules [11]. In the generalized DF algorithm, fragments are redefined at each MD step, so that a cluster of covalently bonded or coordinate bonded atoms form a fragment; in short, a fragment corresponds to a molecule or a coordination compound. The DF algorithm has been implemented also in the GAMESS software [12].

There remained a serious problem concerning DF: how can it handle a molecule that should be fragmented at covalent bonds? FMO is advantageous for handling macromolecules such as polypeptides and polynucleotides. These molecules should be fragmented at covalent bonds, mostly at $sp^3$ carbons, by a technique called bond detached atom (BDA) [4]. The generalized DF algorithm cannot handle such fragmentation.

In this study, we therefore modify the DF algorithm to handle molecular systems with BDA. We name this algorithm dynamic fragmentation with static fragments (DF/SF). In the DF/SF algorithm, some fragments are specified as static, i.e., invariable, to avoid their merger due to DF, while other fragments are subject to rearrangement by DF. This preserves inter-fragment bonds via BDA between static fragments.

We illustrate the DF/SF algorithm by fragmentation of a hydrated zwitterionic glycine dimer, (Gly)$_2$ (Figure 1), a typical simulation target of $ab\ ini\initio$ MD simulations (for example, reference [13]). This simplest available dipeptide retains the typical complexity of biological molecules, because it has both amino (-NH$_3^+$) and carboxyl groups (-CO$_2^-$), which can donate and accept $H^+$ from the surrounding media, respectively. There is also the possibility of an $H^+$ transfer within the peptide. Thus this dipeptide suffices for demonstration of the DF/SF algorithm.

In the rest of this communication, we describe the DF/SF algorithm (section 2), present a few
test calculations of (Gly)$_2$ (section 3), and summarize features of the algorithm and discuss its future application to biological molecules (section 4).

**Figure 1.** Definition of static fragments in (Gly)$_2$.

### 2. Methods

#### 2.1 Software

This time we directly implemented the FMO-MD algorithm in the ABINIT-MP program and then introduced the DF/SF algorithm. These modifications resulted in an extensive reorganization of the program. Although ABINIT-MP can stand alone as an FMO-MD simulator without the PEACH program, PEACH nonetheless remains as preprocessor/postprocessor software for ABINIT-MP by generating the FMO input file and also by analyzing the FMO output files.

#### 2.2 DF algorithm without static fragments

The DF algorithm without static fragments [11], upon which the new DF/SF algorithm is based, requires, as input data, each atom’s van der Waals radius ($R_i$) and instantaneous 3D coordinates, atomic composition, and formal charges of possible fragment species, as well as the threshold parameters described below ($\rho^{lim}_1$ and $\rho^{lim}_2$). We originally supported four DF modes: mode 0, no DF, using the initial fragmentation data throughout the simulation; mode 1, elementary DF, merging covalently connected atoms into a fragment; mode 2, advanced DF, unifying fragments produced by mode 1 into a larger fragment if they are forming an H-bond; and mode 3, extraordinary DF, intended for the construction of coordinate compounds. Mode 3 is no longer supported, however, because we found that mode 1 suffices for both modes 1 and 3.

The details of DF modes 1 and 2 are as follows. The distance between atoms $i$ and $j$ is referred to as $r_{ij}$, and their reduced distance, $\rho_{ij}$, is defined as follows:

$$\rho_{ij} = r_{ij} / (R_i + R_j).$$

For both modes 1 and 2, a threshold parameter, $\rho^{lim}_1$, must be input prior to the start of the simulation. Another threshold parameter, $\rho^{lim}_2$, is needed for mode 2. In mode 1, heavy atoms $i$ and $j$ are regarded as forming a covalent bond if $\rho_{ij} \leq \rho^{lim}_1$ and thus are united into a fragment. Then, each H atom is assigned to a fragment containing its closest heavy atom, the closest distance being measured by $\rho_{ij}$ rather than $r_{ij}$. At this stage, each fragment is assigned its formal charge according to its atomic composition, as given in the fragment table prepared beforehand. In mode 2, a fragment containing a heavy atom ($i$) and another fragment containing an H atom ($j$) are regarded to form an H-bond if $\rho_{ij} \leq \rho^{lim}_2$ and are united into a larger fragment.
2.3 DF algorithm with static fragments (DF/SF)

For the new DF/SF algorithm, we consider a molecular system containing some static fragments whose definition, i.e., atomic composition, remains unchanged from the beginning until the end of the simulation. The DF/SF algorithm is specified by two modes; one is the DF mode described in the previous subsection, and the other is the SF mode described below. Thus, in addition to DF modes, one has to select one from three SF modes, 0, 1, and 2. In SF mode 0, no static fragment is present, and all the fragments are subject to redefinition by the DF algorithm described in Sec. 2.2. In SF mode 1, all the atoms belonging to specified static fragments are completely static. In SF mode 2, only heavy atoms (non-H atoms) are static, and H atoms are subject to change, depending on the criteria of the DF algorithm. Thus, modes of the DF/SF algorithm are denoted as DF\(i\)/SF\(j\), where \(i\) is the DF mode and \(j\) is the SF mode. For instance, DF2/SF1 stands for DF mode 2 combined with SF mode 1.

We test the DF/SF algorithm by fragmentation of a hydrated zwitterionic glycine dimer, (Gly)\(_2\) (Figure 1). Several fragment species can be generated by various options of the DF/SF algorithm (Figures 2A-G).

In DF0, the default fragmentation data generated by the preprocessor is used throughout the simulation and no SF mode is specified. DF0 is thus equivalent to SF1 without dynamic fragments. In DF0 the dipeptide is divided into two fragments, and each water molecule constitutes a fragment (Figure 2A).

![Diagram](image)

**Figure 2.** Option-dependent fragment sets of the hydrated (Gly)\(_2\) dipeptide. Those atoms subject to possible fragment-reassignment are shown in bold-face. Neighboring fragments are classified by color.
DF1/SF0 and DF2/SF0, allowing no static fragments, should give the same result as the previous DF algorithm does (Figures 2BC). Namely, the dipeptide will constitute a single fragment, sometimes capturing some water molecules, especially in DF2/SF0 (Figure 2C). Obviously, neither DF1/SF0 nor DF2/SF0 is applicable to a system containing large molecules, because they will produce unacceptably huge fragments.

DF1/SF1 and DF2/SF1, completely fixing static fragments, will give suitably sized fragments (Figures 2DE). Nonetheless, SF1 would be appropriate only for molecular systems where static fragments never show H⁺ transfers, but in reality H⁺ transfer is unavoidable. Therefore, DF1/SF2 or DF2/SF2 is needed, which fixes only heavy atoms of static fragments but allows for H⁺ transfer among both static and dynamic fragments (Figures 2FG). In these SF2 options, the fragment formal charge is reassigned by counting the number of added or subtracted H atoms. The SF2 options presumably give a variety of fragments, depending on the molecular configuration. In DF1/SF2, the most abundant configuration of the dipeptide must be a zwitterionic form (Figure 2F configuration 1). However, a different fragment set will be generated when H⁺ is transferred from the solvent water to −CO₂⁻ (Figure 2F configuration 2). It is also possible that an H⁺ transfer within the peptide will produce different fragments (Figure 2F configuration 3). The variety further increases in the DF2/SF2 option, which unifies two fragments mediated by H⁺ (Figure 2G). In DF2/SF2, even static fragments are subject to merger with dynamic fragments (Figure 2G configurations 1 and 2). Also, two static fragments can be united if any H-bond is formed between them (Figure 2G configuration 3).

Thus, the DF/SF algorithm can produce different fragmentation patterns depending on various options, even in the simple case of (Gly)₂. We will evaluate these options in the following section.

2.4 FMO-MD simulations

We tested the various options of the DF/SF algorithm by performing FMO-MD simulations of the hydrated dipeptide (Gly)₂. The following methods and conditions were used commonly in the classical and FMO-based energy minimization (EM) and MD calculations. The solvent was confined within a sphere (radius = 7.3 Å) with a harmonic restraint (force constant = 0.75 kcal/mol/Å²) centered at the centroid of the dipeptide. A Nosé-Hoover chain thermostat was employed to achieve the NVT ensemble [14], the time constant being set to 100 fs for classical MD and to 1 fs for FMO-MD. The time step was fixed to 1 fs. The translational and rotational motions were removed at every MD time step.

We prepared the initial structure via classical MD/EM calculations because we had previously found that use of classically annealed initial configurations results in faster stabilization of FMO-MD trajectories[7]. Specifically, the initial structure of the hydrated dipeptide was prepared as follows by PEACH ver. 8.4 with the AMBER99 force field for the peptide and TIP3P water for the solvent. Each bond length was fixed by the SHAKE/RATTLE method [15][16]. The dipeptide was generated in the extended conformation, optimized by the steepest descent EM, and then immersed in a spherical solvent. The solvent was relaxed by classical MD at 300 K for 100 ps, annealed to 5 K within 100 ps, and finally optimized by the conjugate gradient EM. The optimized structure thus generated (Figure 3) served as the initial configuration for the subsequent FMO-EM/MD calculations. Prior to the test simulations, the classically optimized structure was further optimized by steepest descent and conjugated gradient FMO-EM calculations and then heated to 300 K within 0.25 ps by FMO-MD under the DF1/SF2 option.
Figure 3. Initial configuration of the hydrated (Gly)$_2$ prepared by classical MD and EM.

Hartree-Fock (HF) FMO-MD simulations were conducted with seven options: DF0, DF1/SF0, DF2/SF0, DF1/SF1, DF2/SF1, DF1/SF2, and DF2/SF2. The 6-31G basis set was used throughout. Each test simulation started from the heated structure described in the previous paragraph, then continued for 1 ps under the NTV ensemble at 300 K and for an additional 1 ps under the NVE (microcanonical) ensemble. The threshold values were 0.8 for $\rho^{lim_1}$ and 0.6 for $\rho^{lim_2}$. The original energy gradient [3], not the latest analytic one [17], was employed in all the FMO-EM/MD calculations. FMO-MD with two-body expansion, FMO2-MD, was performed for all the HF simulations.

MP2 simulations were conducted for the DF1/SF2 option to evaluate the inclusion of the electron correlation. Specifically, MP2/FMO2-MD, MP2/FMO3-MD, and MP2/FMO(3)-MD were tested, where FMO(3) denotes FMO3 for HF and FMO2 for MP2 [18].

All the FMO-MD simulations were performed on a PC cluster with an Intel(R) Xeon(R) CPU E5490 (2.66 GHz) under an MPI environment. The wall clock time spent for an FMO-MD step was measured on 64 cores, while eight cores were allocated for each fragment.

2.5 Analyses of the trajectories

We analyzed the generated FMO-MD trajectories to investigate the frequency of fragment rearrangement (redefinition) by the DF/SF algorithm and its effect on the continuity of the trajectory. Instantaneous frequency of fragment rearrangement was calculated as the number of rearrangements per step (1 fs) averaged over 50 steps. The continuity of the trajectory was investigated based on the time-dependent change of three energies: the Nosé Hoover Chains conservative energy ($E_{NHC}$) for the NVT ensemble (0-1 ps), the total energy ($E_{TOT}$) for the NVE ensemble (1-2 ps), and the potential energy ($E_{POT}$) for both. Either $E_{TOT}$ or $E_{NHC}$ is strictly sensitive to the noise upon rearrangement of fragments [11]. $E_{POT}$ is less sensitive to the noise but reflects the overall stability of the molecular configuration.

3. Results and discussion

In this section, stability and cost of the various FMO-MD options are discussed. The stability was investigated based on the time-dependent changes of the rearrangement frequency and energies (Figures 4 and 5). The cost was measured based on the wall-clock time spent for an MD step (Tables 1 and 2). We present the results of HF (subsection 3.1) and MP2 (subsection 3.2) separately.
Table 1. Computation time for HF/FMO2-MD under various DF/SF options.
The wall clock time (s) per step for each HF/FMO2-MD simulation was measured on 64 cores of Intel(R) Xeon(R) CPU E5430 while assigning 8 cores for a fragment.

| SF options: | none | SF0 | SF1 | SF2 |
|-------------|------|-----|-----|-----|
| DF options: |      |     |     |     |
| DF0         | 31   | -   | -   | -   |
| DF1         |      | 46  | 31  | 31  |
| DF2         |      | 58  | 31  | 32  |

Table 2. Computation time for MP2/FMO-MD.
The wall clock time (s) per step for each MP2/FMO-MD simulation under the DF1/SF2 option was measured on 64 cores of Intel(R) Xeon(R) CPU E5430 while assigning 8 cores for a fragment.

| FMO2 | FMO3 | FMO(3) |
|------|------|--------|
| 136  | 1503 | 340    |

3.1 DF/SF options for HF/FMO-MD

All of the DF/SF options were first applied to HF-level FMO2-MD simulations. The computation cost was ca. 30 s/step for all the options except DF1/SF0 and DF2/SF0 (Table 1). The lack of variety among the options probably originated from the fact that the rate-limiting step of FMO without load balancing is the computation of the largest fragment, that is, the second Gly residue of the dipeptide in this case (Figure 1). Only in the SF0 options did the whole dipeptide constitute the largest fragment, which should have increased the computational demand. This situation can change if a load-balancing scheme is introduced to the ABINIT-MP program.

Regarding the stability of the DF/SF options, we present a brief description of the results of each option below.
Figure 4. DF/SF FMO2-MD simulations at the HF/6-31G level.
Note that labels A-E correspond to those in Fig. 2. Under each label, the upper chart contains ENHC, ETOT, and fragmentation rearrangement frequency per step and the lower chart contains EPOT. Energies are shown in kcal/mol. The x-axis of each chart corresponds to the simulation time (ps).
3.1.1 DF0 option

DF0 uses the initial fragmentation set throughout the simulation run and requires no SF modes. In the test run, DF0/FMO2-MD failed in monomer-SCF at 0.14 ps (Figure 4A). This failure was not unexpected, as H⁺-transfer reactions among water are unavoidable when the molecular system is not fully equilibrated [18]. In addition, the approximate energy gradient could have enhanced the artificial H⁺-transfer by introducing noise to the simulated system. In principle, the DF0 option cannot readjust the fragments once an H⁺ is transferred among fragments. Thus, DF0 should be avoided when simulating hydrated molecular systems.

3.1.2 SF0 options (DF1/SF0 and DF2/SF0)

SF0 turns off static fragments, and hence all the fragments are subject to rearrangement by the DF algorithm. Both the DF1/SF0 and DF2/SF0 options generated stable trajectories for 2 ps (Figures 4BC). This result is a reflection of the robustness of the pure DF algorithm (subsection 2.2) in handling solvated molecules. A serious concern about SF0 options is the size of the solute, however. The currently simulated solute is a small dipeptide that may constitute a reasonably sized fragment, but the DF/SF algorithm is generally intended for much larger polypeptides and polynucleotides. Even for this small peptide, a longer computation time was needed for the SF0 options than for the SF1 and SF2 options (Table 1). Hence, the SF0 options should be used only for small solute molecules.

3.1.3 SF1 options (DF1/SF1 and DF2/SF1)

In the SF1 options, all the atoms including H in the static fragments are assigned to the same fragments throughout the simulations. In the test runs, both DF1/SF1 and DF2/SF1 failed at the early stage of the simulation (Figures 4DE). The results are reasonable, because SF1 allows no H⁺-transfer between the peptide and solvent. Therefore, SF1 should be used only if no H⁺-transfer occurs between the static and dynamic fragments. Note that the charts of DF1/SF1 (Figure 4D) agreed closely with those of DF0 (Figure 4A). This agreement was only natural, because the most probable fragment set produced by the DF1/SF1 option (Figure 2D) conforms to the default fragmentation set used for the DF0 option (Figure 2A).

3.1.4 SF2 options (DF1/SF2 and DF2/SF2)

The SF2 options fix only heavy atoms of static fragments and allow for rearrangement of H atoms. The test runs generated fairly stable trajectories despite the frequent rearrangement of fragments (Figures 4 F G). We observed some discontinuous change of the conservative energy (ENHC) during the first half of the simulations, however, reflecting instability of the simulated system. E\text{TOT} nonetheless was stable during the latter half, indicating that the system became sound. In DF1/SF2, the frequent rearrangement brought about an extensive rise of the potential energy, showing structural perturbation of the molecular system. Note also that the DF1/SF2 algorithm did not fail even at this perturbation, indicating the robustness of the algorithm. The DF2/SF2 option was more stable than the DF1/SF2 option, a conclusion reached based on the stability of the potential energy, which was obviously due to the larger size of each fragment. We should also keep in mind that a larger average fragment size may increase the computation cost even under a load-balancing scheme, which is yet to be implemented in the ABINIT-MP program.
3.1.5 Summary of tests of DF/SF options against HF/FMO-MD

As presented thus far, DF0, DF1/SF1, and DF2/SF1 failed to produce stable trajectories, while DF1,2/SF0 and DF1,2/SF2 succeeded. DF1/SF0 and DF2/SF0 are intended for a small solute molecule, which needs no intra-molecular fragmentation. We therefore conclude that DF1/SF2 and DF2/SF2 are the most practical of the currently available DF/SF options for simulating a large solute molecule.

3.2 MP2 (DF1/SF2)

In this subsection, we turn to MP2, a post HF calculation. FMO2, FMO3, and FMO(3) combined with MP2 are tested with the DF1/SF2 option, whose robustness was demonstrated in the previous subsection.

The MP2/FMO2-MD trajectory showed a rather low level of precision; the fragment was rearranged frequently, and the time integration came to an abrupt rupture at 0.108 ps (Figure 5A). Since the perturbational nature of MP2 has vulnerability in the case of deformed geometry, the errors in FMO2-MP2 might be worse than those in FMO2-HF. Fortunately, the robustness of MP2/FMO-MD was largely recovered by the introduction of FMO3 and FMO(3) (Figures 5BC) due to the three-body corrections. Neither showed fragment rearrangement, suggesting the stability of the molecular conformation. FMO3-MD in particular conserved the conservative energies beautifully (Figure 5B), but at the cost of computation time; MP2/FMO3 consumed ten times more time than MP2/FMO2 did (Tables 1 and 2). FMO(3)-MD showed lower precision but was acceptable (Figure 5C), and its computation time was only 2 to 3 times that of FMO2-MD (Table 2). Hence, FMO(3)-MD can be a practical choice for MP2.

![Figure 5](image_url)

**Figure 5.** DF1/SF2 FMO-MD simulations at the MP2 level. See Fig. 4 for legend and labels.

4. General discussion and conclusion

Of all the various combinations of the DF/SF algorithms tested, DF1/SF2 and DF2/SF2 were found to be the most stable, robust, and practical. The better utility of SF2 over SF1 was not
unexpected, because the hydrated peptide constituted a network of H-bonds, where an H\(^+\)-transfer occurs, regardless of whether the transfer is spontaneous or accidental. SF1 may suffice for the simulation of a purely hydrophobic molecular system such as an organic solvent, but not for biological molecules.

In a comparison of DF1 and DF2, DF2 generally showed greater stability than DF1 did, because DF2 combines H-bonded molecules. DF2’s superiority over DF1 in energy conservation was also observed in an FMO2-MD simulation of hydrated H\(^+\) [11]. DF2’s disadvantage is, however, the possibility of the generation of unacceptably huge fragments that could hamper the performance. Note also that the difference between DF1 and DF2 disappears in FMO3-MD simulations [11]. Thus, the choice between DF1 and DF2 is reduced to a matter of computation time.

MP2/FMO2-MD was less stable than HF/FMO2-MD. Hence, either FMO3 or at least FMO(3) was necessary to achieve reliable MP2/FMO-MD simulation. Considering the computation cost, FMO(3) may be a practical compromise for MP2 simulations. Introduction of the four-body corrected MP2 gradient, FMO4-MP2 [20], should further improve the MP2/FMO-MD simulation, though its cost of use is larger than that of FMO3-MP2.

A notable disadvantage of the current version of ABINIT-MP is the lack of the fully analytic energy gradient implemented in the GAMESS software [21], which was proven to conserve energy better than the original gradient did [12][17]. Many of the FMO2-MD simulations presented in this paper showed rather poor conservation of the conservative energies and unrealistically frequent H\(^+\)-transfers, presumably due to the incomplete analytic energy gradient. We therefore plan to improve the force evaluations in ABINIT-MP with the fully analytic gradient formula at the HF/FMO2 level, with which we expect to attain better energy conservation for both HF and MP2 at a reasonable computation cost.

Though not faultless, the current implementation of FMO-MD with the DF/SF algorithm has finally enabled us to perform fully \textit{ab initio} FMO-MD simulations of solvated proteins and polynucleotides. The most important recent work in this regard is that performed for the solvated bovine pancreatic trypsin inhibitor [22]. This was a QM/MM-MD simulation, however, in which the protein and crystal water molecules were fully \textit{ab initio}, while the surrounding solvent was classical. We hope that fully \textit{ab initio} FMO-MD with DF/SF will describe more realistically the protein-water interface, give a detailed account of any time-dependent charge transfer and polarization, and eventually simulate the process of biochemical reaction.

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