Parameterizing Fluorescent Protein Chromophores for Molecular Dynamics Simulations

Cornell et al., OH N cc CA H1 Wang cd cd CD1 H1 W
OH O oh H4 CE2 mp2/cc B3LYP B3LYP B3LYP
Crystal Structure
Bond
2 H
N
N
is differences chromophore were atoms. All
Van Der Waals radius and well depth.
with a barrier height. Each atom is modeled with a point charge and
simulate the movement of the molecule.
protecting it from water. Since no cofactors or
Cyclization - H2O - H+ H+ O2 OH R 2 O NH C R NH NH O OH O OH R 2 NH RN N O OH O OH R 2 NH RN N O O - O

Fluorescent proteins (FPs) are important to many studies of protein function, and we plan to examine them in the future using molecular dynamics (MD) simulations. Before running MD, fluorescent protein chromophore parameters must be determined that are consistent with the latest version of theCornell et al. force field (1995), J. Am. Chem. Soc., 117, 458 (Maier et al., 2015, J. Comp. Theor. Chem.) along with the generalized AMBER force field (Wang et al., 2004, J. Comput Chem.). Parameterization was carried out using quantum mechanical calculations to determine the optimized geometry and electrostatic potential of each chromophore. The restrained electrostatic potential (RESP) charge fitting procedure was used to derive atomic charges. All other parameters (Lennard-Jones, Bond length, Bond Angle, Dihedral Angles) were assigned by analogy to pre-existing force field parameters. Complete MD parameters are presented for the chromophores of six common FPs: EGFP, mCherry, DsRed, EBFP, EFVP, and ECFP.

Abstract

Fluorescent protein chromophores were constructed from crystal structures. Geometry optimizations were carried out on each chromophore at the B3LYP/6-31G(d)/SMD(water) level. Electrostatic potentials (ESP) of the chromophores were derived at the HF/6-31G(d) level (specifically chosen to approximate aqueous conditions). The ESP was used to determine atomic charges via the restrained electrostatic potential (RESP) method.

Chromophore Atom Types

EGFP
Amino Acid Sequence: THR TYR GLY
Excitation Max: 496 nm
Emission Max: 509 nm

ECFP
Amino Acid Sequence: THR TRP GLY
Excitation Max: 432 nm
Emission Max: 475/505 nm

DsRed
Amino Acid Sequence: GLN TYR GLY
Emission Max: 555 nm

mCherry
Amino Acid Sequence: MET TYR GLY
Emission Max: 577 nm

EFVP
Amino Acid Sequence: SER HIS GLY
Excitation Max: 380 nm
Emission Max: 441 nm

mCherry
Amino Acid Sequence: SER HIS TYR GLY
Excitation Max: 587 nm
Emission Max: 610 nm

Charge Table for EGFP

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Figure 1. A visual representation of the electrostatic potential of the EGFP chromophore

Figure 2. 2D and 10 (inset) protein RMSD of all residues in the EGFP protein. Modest confirmation change confirms protein stability.

Figure 3. A. 2DRMS of the chromophore in the EGFP protein.
B. Integrates of dihedral angle between heavy chains show agreement between our parameters and QM/MM simulations.
C. EGFP alpha carbon distance for residue 138 and 285 to alpha beta barrel.
D. Representation of EGFP with medium 138 and 285 highlighted in red to show their relative location.

Figure 4. A. Plot of the charges of each atom in the EGFP chromophore for each of the different RESP files: free, rotational equivalence, constrained end-group charges, and fixed CONH charge values.

Figure 5. Representation of EGFP chromophore with atom names.

References

Simulation Results

A. 2DRMS of the chromophore in the EGFP protein.
B. Integrates of dihedral angle between heavy chains show agreement between our parameters and QM/MM simulations.
C. EGFP alpha carbon distance for residue 138 and 285 to alpha beta barrel.
D. Representation of EGFP with medium 138 and 285 highlighted in red to show their relative location.

Atom Charge Determination

Fluorescent protein chromophores were constructed from crystal structures. Geometry optimizations were carried out on each chromophore at the B3LYP/6-31G(d)/SMD(water) level. Electrostatic potentials (ESP) of the chromophores were derived at the HF/6-31G(d) level (specifically chosen to approximate aqueous conditions). The ESP was used to determine atomic charges via the restrained electrostatic potential (RESP) method.