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Molecular Dynamics Simulations of a Protein Crystal

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Molecular dynamic simulation is becoming an indispensable tool complementary to experimental means to elucidate the structures, energies, dynamics and functions of biomolecules. Molecular dynamic simulation has provided insight into protein folding, refinement of homology models and predicted structures, complex conformational changes and their relation to function, and computer-aided drug-design [1-5]. The majority of molecular simulations were performed in water boxes to mimic the aqueous environment of biological systems. Recently, the application of Molecular Dynamics (MD) to simulate crystal unit cells or super cells began to emerge [6]. MD simulations on crystals not only open a new avenue to assess force field models, but also have potential application on protein crystal structure refinement.

An ideal protein system for crystal simulation is scorpion protein toxin which has 64 amino acids cross-linked by three disulfide-bonds. The crystal structure (PDB Code 1AHO) was solved at a very high atomic resolution of 0.96 Å [7]. Moreover, the relatively simple crystal condition at nearly neutral PH and room temperature (287 K) make it possible to construct a model system very close to the real situation. A cartoon model of the crystal structure was shown in Figure 1. In the pioneer work of crystal simulation by Cerutti, Freddolino, Duke and Case, this protein was studied extensively using different combinations of force fields and water models [8]. In this work, we further explored how well MD simulations reproduce the structural and dynamic properties of this protein in crystal.

A super cell was constructed by aligning 2, 2 and 3 copies of the unit cell along the X, Y and Z-axis, respectively. 78 acetate and 30 ammonium together with 8902 water molecules were added to the super cell using the AddToBox program in AMBER12 [9]. The FF99SB force field [10, 11] and TIP3P water model [12] which have achieved the best performance in the study by Cerutti et al [8] was applied to model the protein and water molecules; as to the solvents of acetate and ammonium, their molecular mechanical models were described by GAFF [13] and prepared by the Antechamber module in AMBER12; [14] A delicate step-by-step protocol was applied to relax the system in both minimizations and molecular dynamics simulations using PMEMD in AMBER12. First of all, 10000 steps of minimizations with a series of restraints (20, 10, 5, 2, 1 kcal/mol/Å^2) on the main chain atoms were carried out; then 10000 steps minimization with all degrees of freedom was performed; next 100 picosecond MD heating up simulations at a series of temperatures (103.15, 153.15, 203.15, 253.15, 273,15 K) were conducted; in the following equilibration phase, 1 nanosecond MD simulation at 287 K was ran with the time step of 1 femtosecond followed by 2 nanosecond MD simulation using the time step of 2 femtoseconds; finally in the sampling phase, 110 nanosecond MD simulations at 287 K was performed. 11000 MD snapshots were collected for post-analysis. Other major minimization and MD parameters are listed as follows: periodic boundary condition to produce isothermal-isobaric ensemble, the Particle Mesh Eward method for electrostatic energy [15], and temperature was regulated using the Langevin dynamics [16] with the collision frequency of 5ps^{-1} and pressure regulation was achieved with anisotropic position scaling.

In the post-analysis phase, the volumes of the super cell were calculated and the mean value is 675182±611Å^3, which is within 0.06% of the experimental value (674768 Å^3). Lattice RMSDs were than calculated using the following procedure for each MD snapshot: the imaging operation was first conducted with the current simulation box; then superposition was performed using the monomer located in the center of the simulation box; the simulation box was then scaled to exactly match the crystal super cell; next the best translational vectors were determined using a least-square fitting, and finally the MD simulation box was aligned to the crystal super cell by pure crystallographic translation using the determined translational vectors. Three types of RMSD were calculated in this work: (1) Lattice RMSD Type 1 – direct calculation using all the monomers as a whole, (2) Lattice RMSD Type 2- the mean of the RMSDs of 48 monomers, (3) LSF RMSD – the mean of LS fitting RMSD of 48 monomers. It is demonstrated in Figure 2 that both lattice RMSDs I and II are much larger than LSF RMSD as the former describes not only the conformations of monomers, but also the relative positions and orientations of monomers in crystal. Lattice RMSDs are better metrics to evaluate how well MD simulations maintain the crystal structure. In Figure 3, the last snapshot of the MD simulation which has a lattice RMSD Type I of 1.35 Å were compared to the crystal super cell.

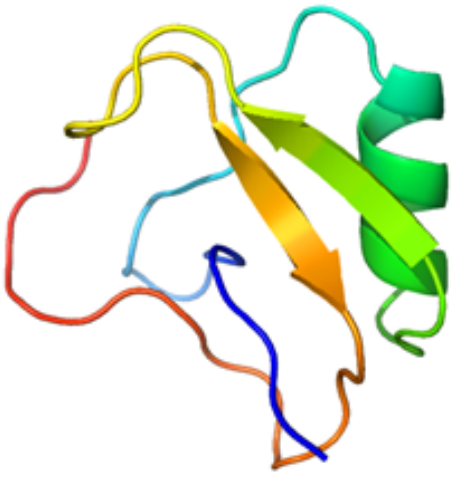

Figure 1: Crystal structure of scorpion protein toxin (1AHO)

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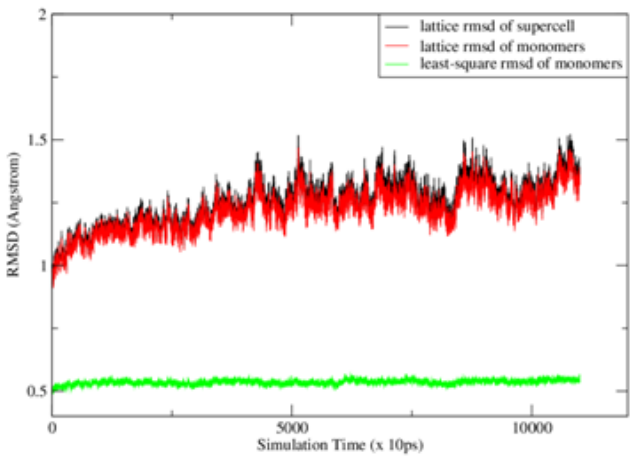

Figure 2: Plot of lattice RMSDs along the MD trajectory

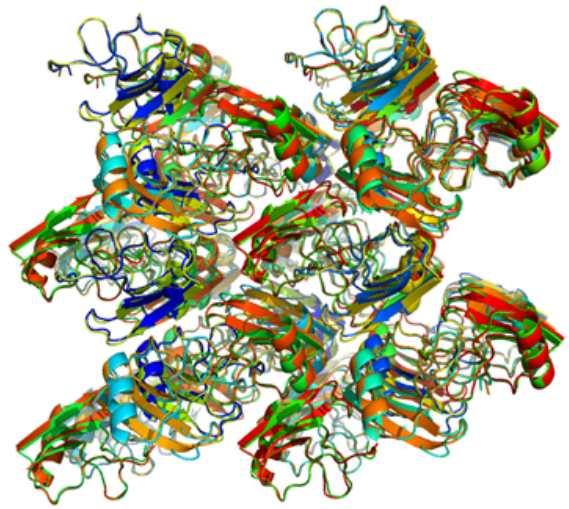

Figure 3: Superposition of the super cell of 1AHO by X-ray diffraction and molecular dynamics simulations

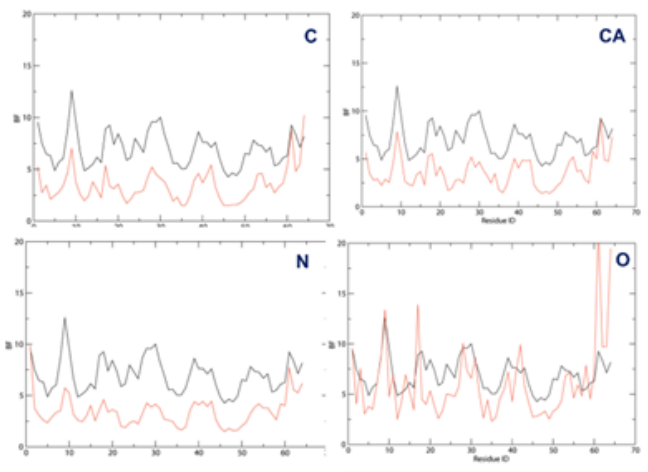

Figure 4: Comparison between experimental and predicted B-factors for carbonyl carbon (top left), α-carbon (top right), amine nitrogen (bottom left) and carbonyl oxygen (bottom right)

	C	CA	N	O
AUE	3.58	3.35	3.55	2.30
RMSE	3.75	3.51	3.74	3.11
R2	0.46	0.63	0.50	0.36

Table 1. Performance of MD simulations on B-factor prediction

The B-Factor (BF) was calculated using Equation 1, where F is the root-mean-square atomic displacement. To calculate BF, we first generated the average structure of the collected snapshots, then for each snapshot, the root-mean-square atomic displacements compared to the average structure were calculated. In the last step, the predicted BF, which are the averages of all snapshots were computed. In this work, four types of atom types, which are carbonyl Carbon (C), α-carbon (CA), amide Nitrogen (N) and carbonyl Oxygen (O) were selected for the B-factor calculations.

$$BF = 8\pi^2 F^2/3 \quad (1)$$

As illustrated by Figure 4, the trends of B-factor along the primary protein sequence are well predicted, even though the MD curves (in red) were shifted down in most scenarios. The Average Assigned Error (AUE), Root-Mean-Square Error (RMSE) and the correlation coefficient square (R^2) were listed in Table 1. As the systematic errors are very small for the carbonyl oxygen, it is not a surprise that their BFs have smallest prediction errors and R^2.

In summary, the state-of-art molecular dynamics is able to well reproduce the X-ray diffraction structure of the scorpion protein toxin under the crystal condition. Moreover, the picture of the dynamics of main chain atoms can be well captured by MD. Although this performance was achieved for a nearly ideal protein crystal, we expected that MD simulation could play an important role in refining low-resolution crystal structures as long as the model systems are appropriately constructed.

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