USING MOLECULAR DYNAMICS SIMULATION AND CHEMICAL SHIFT PREDICTION TO UNRAVEL DYNAMICS IN DIFFERENT CRYSTAL FORMS OF UBIQUITIN

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Relaxation dispersion NMR spectroscopy is powerful tool to study functionally important protein dynamics on μs-ms time scale. These measurements allow one to localize the dynamics sites, determine the characteristic time constants and (under favorable circumstances) estimate the chemical shift difference between the two exchanging states. It remains very difficult, however, to translate this information into structural models of the dynamic states and to elucidate specific molecular events underlying the dispersion effects.

The emerging approach to interpretation of relaxation dispersion data takes advantage of the newly available ultra-long MD simulations. In brief, individual MD frames are used as an input for chemical shift prediction programs. The chemical shift modulation pattern calculated in this manner can be related to the observable dispersion profiles [1]. Thus one can obtain a direct insight into molecular origin of the dispersion effects.

We have implemented this approach in the context of the combined solid-state NMR and x-ray study of ubiquitin crystals [2]. Simulations of three different crystal forms of ubiquitin (PDB ID 3ONS, 3N30 and 3EHV), as well as ubiquitin in solution, have been carried out using the AMBER14 program with 99SB-ildn* force field. The simulated crystal fragments contained 24, 48, and 24 ubiquitin molecules, respectively, plus interstitial water; the length of each trajectory recorded on the GPU-equipped computers was 2 μs. The MD snapshots have been used to predict ^{15}N chemical shifts by means of the program SHIFTX2, including intermolecular contributions to chemical shifts [3]. The computational results proved to be broadly consistent with the experimental data. In particular, we have identified the mechanism of relaxation dispersion arising from interconversion between β turn type I and II in the region between residues 51 and 54. We have also found examples where dispersion effects are associated with the overall motion of ubiquitin molecules within the constraints of the crystal lattice (rocking dynamics). This work was supported by the RSF grant 15-14-20038.

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