Folding of the human Pin1 WW domain using molecular dynamics simulations

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In recent years, there has been significant progress in the field of Molecular Dynamics Simulations, providing us with the ability to understand the behavior and dynamics of molecular systems at the atomic level. The challenges and failures encountered by researchers in their efforts to create effective force fields have been insightful. Understanding the folding process of a *β*-sheet, which is a dominant secondary structure, is of great importance. In this communication, we explore these possibilities using the well-studied *β*-sheet fold of the Fip mutant, which constitutes the WW domain of the Pin1 protein. Our objective is to analyze and confirm whether the applied force fields and parameters are capable of successfully simulating the folding process of our protein. Two separate folding attempts of the Fip protein were conducted using MD simulations, with the peptide chain initially unfolded. The first attempt involved using the Amber ff99SB-ILDN force field for a 10 μs simulation and the second attempt used the Amber ff99SB*-ILDN force field for a 15 μs simulation. For our analyses, we extensively utilized the user-friendly (GUI) Grcarma, which is based on the Carma program. Remarkably, the ff99SB*-ILDN force field, in contrast to the ff99SB-ILDN force field, successfully folded our protein in approximately half the total simulation time (around 7.2 μs). The main findings from this folding event, with emphasis on the observed folding pathways are presented. In conclusion, our study highlights the importance of Molecular Dynamics Simulations in understanding the folding of the *β*-sheet structure in protein Fip.

[1] K. Lindorff-Larsen et al., "Improved side-chain torsion potentials for the Amber ff99SB protein force field," Proteins Struct. Funct. Bioinforma., vol. 78, no. 8, pp. 1950–1958, 2010, doi: 10.1002/prot.22711.
[2] R. B. Best and G. Hummer, "Optimized molecular dynamics force fields applied to the helix-coil transition of polypeptides," J. Phys. Chem. B, vol. 113, no. 26, pp. 9004–9015, 2009, doi: 10.1021/jp901540t.