Biophysical Journal
Volume 116, Issue 3, Supplement 1, 15 February 2019, Page 433a

Examining the Refolding of Perturbed Protein Structure Intermediates using Various Molecular Mechanics Force Fields

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https://doi.org/10.1016/j.bpj.2018.11.2330

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Molecular dynamics simulations allow for the prediction of protein folding trajectories in all-atom resolution, thereby providing information about the folding process that is difficult to obtain experimentally. If the molecular mechanics force field is incorrectly parameterized however, molecular dynamics simulations may fail to accurately predict folding intermediates and the overall folding trajectory. Therefore, experimentally known protein refolding intermediates based on force spectroscopy data may prove to be a helpful tool in validating the ability of molecular dynamics simulations to refold proteins. We created models of the perturbed intermediates of titin I91 (I27) domain and consensus ankyrin repeat structure, NI3C, using atomic force spectroscopy data. We then conducted refolding simulations of the intermediates using six different force field/water model combinations. In doing so, we observed that the Charmm22 *, Amber fb15, and Amber ff14SB without dihedral correction force fields had the easiest time refolding both protein intermediates. Additionally, it was observed that the dihedral correction to the Amber ff14SB force field prevents the timely refolding of both intermediates. These results suggest that the parameterization of side chain torsion angles can significantly help the refolding of protein structures. Additionally, the results imply that the ad hoc adjustment of dihedral angles may impede folding trajectory predictions.