Correcting Force Field Bias in Pin1WW Folding

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Every protein folds into specific secondary structures, which allows them to properly interact with their surroundings. Therefore the importance of accurate protein folding simulations cannot be overstated. Pin1WW is a small fast folding protein made up of β-sheets that has been a workhorse in folding calculations. However, in a recent state of the art simulation, Pin1WW failed to sample its native conformation.[1] This has been attributed to errors in the CHARMM27 force field, which is biased toward helical conformations. Our goal is to avoid force field bias by folding Pin1WW using density functional theory (DFT). Therefore we are screening different density functionals for intrinsic bias. This will be accomplished by using DFT to approximate free energies of native and non-native conformations of Pin1WW. Thus the free energies of the various misfolded conformations were compared to the free energy of the crystal structure.

[1] Freddolino PL, Liu F, Gruebele M, Schulten K (2008) Ten-microsecond molecular dynamics simulation of a fast-folding WW domain. Biophys J 94: L75–L77