Knotted proteins exist in all kingdoms of life [1] and new such structures are being discovered regularly. Recent experiments confirm that knotted proteins are able to fold to their native knot spontaneously. Unfortunately, experimentally probing how these proteins fold is extremely difficult. Therefore currently only theoretical investigations can shed some light on this hidden process and characterize physical features that can be unambiguously measured in experiments. This work provides the first study of a protein folding into a knot in unbiased explicit-solvent simulations. In simulations totaling 40 ms, we find that five out of fifteen simulated trajectories reach a knotted native-like state when started from unknotted, intermediates with so-called slipknot geometry [3]. Comparison of explicit-solvent to structure-based (SBM) simulations [4] shows that similar native contacts are responsible for threading terminal with slipknot geometry through the loop, however competition between native and non-native salt bridges during threading results in increased energetic roughness. These results confirm the viability of the “slipknotting” folding route predicted by simplified models directly using a physical forcefield.

References