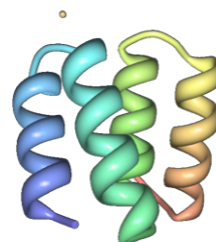


## Molecular Dynamics Investigation of a Tetratricopeptide Repeat Protein

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Repeat proteins are a class of proteins that contain a number of highly homologous secondary structure elements arranged in tandem. Unlike their globular counterparts, the folding pathway of repeat proteins is thought to be fairly simple: short-range and regularized interactions between the tandem secondary structure elements give rise to a repetitive and often elongated structure. In many repeat proteins, this elongated structure functions as a binding site. One such family of repeat proteins is comprised of tetratricopeptide repeat (TPR) proteins. A single TPR unit is made up of 34 amino acids in a helix-loop-helix motif. Three or more TPRs in tandem gives rise to super helical tertiary structure, with a groove suitable for binding the alpha helix of target proteins and other small molecules.



**Figure 1.** Two TPRs in tandem.



**Figure 2.** Superhelix formed by 13 TPRs.

It is believed that one such TPR protein is the Kinesin molecular motor protein. Kinesin's motor functionality allows it to actively transport intracellular cargos by walking along microtubules. The binding activity is facilitated by the tail domain, which is believed to contain six TPRs. The objective of this research is to determine if the tail domain contains TPRs and if these TPRs give rise to a superhelical structure.

We have constructed six homology models of the individual Kinesin TPRs using the TPR crystal structure of a synthetic consensus sequence. For each homology model, we performed fifteen 100 ns molecular dynamics simulations in explicit water with a variety of standard force fields and solvent models. Our findings suggest that the Kinesin sequence is capable of adopting six highly stable TPR units. Using representative structures from the individual TPR ensembles, our next step was to construct various models for the superhelical topology by connecting the six individual TPR units in tandem. We performed a total of ten 300 ns simulations on the various superhelical models according to our previous methods. Our findings suggest that the optimized secondary structural elements give rise to an overall superhelical tertiary structure. Based on these findings, it is our belief that Kinesin cargo-binding activity is indeed facilitated by the presence of TPRs.