Deciphering the fuzzy interaction between the Tau-R2 repeat and tubulin C-terminal tails with classical MD simulations

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Fuzzy complexes are a relatively new type of protein interaction involving one or more intrinsically disordered elements, which proved more and more biologically important in the past two decades. Intrinsically disordered protein Tau is known to stabilize microtubules (MT), but little is known regarding its interaction with the intrinsically disordered C-terminal tails (CTTs) of tubulins. We used all-atom molecular dynamics simulations to decipher the behavior of the R2 repeat domain of the Tau protein in complex with 3 tubulin monomers β-α-β. We built the C-terminal tails corresponding to isotypes βI-αI-βI and βIII-αI-βIII by homology. Our analysis confirmed the existence of a highly stable interface area involving Ser289, a serine notably phosphorylated in Alzheimer’s disease, and revealed a modification of the dynamics of CTTs in presence of R2. The latter result gives more weight to Lessard and Berger’s idea that interactions between kinesins and MT could be indirectly mediated by the presence of Tau [5]. We also propose a “wrapping mechanism” of the CTTs around R2 which might provide more insight regarding the stabilizing impact of CTTs in Tau/MT complexes. Finally additional simulations with explicit phosphorylations of R2-Ser285, R2-Ser289 and R2-Ser293 reveal interesting interaction patterns between the Tau peptide and tubulins involving sodium counterions.

![Figure 1. Starting structure of the tauR2/tubulin assembly for the βI-αI-βI isotype](image)

**Keywords:** Molecular Dynamics, protein interactions, tubulin, tau, disordered proteins.

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1. Sacquin-Mora S, Prévost C (2021) Biomolecules 11, 1529