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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 decades¹. 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 tubulins². 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 β I- α I- β I and β III- α I- β III by homology. Our analysis confirmed the existence of a highly stable interface area involving Ser289, a serine notably phosphorylated in Alzheimer's disease³, and revealed a modification of the dynamics of CTTs in presence of R2⁴. 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 Tau⁵ [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.

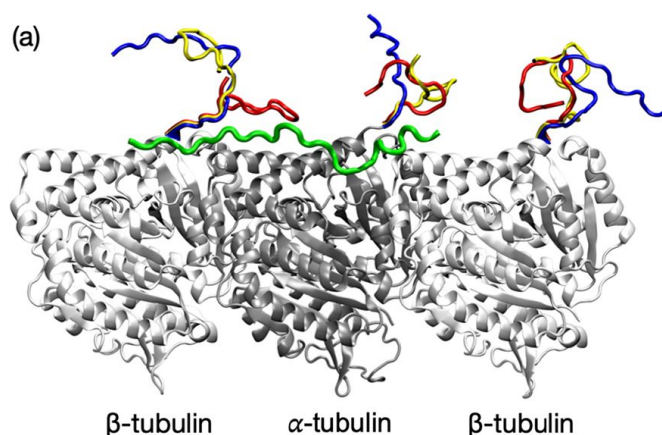


Figure 1. Starting structure of the tauR2/tubulin assembly for the β I- α I- β I isotype

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

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

² Hinrichs, M. H., Jalal, A., Brenner, B., Mandelkow, E., Kumar, S., and Scholz, T. (2012) *J. Biol. Chem.*, 287, 38559-38568

³ Drummond E, Pires G, MacMurray C, Askenazi M, Nayak S, Bourdon M, Safar J, Ueberheide B, and Wisniewski T. (2020) *Brain*, 143, 2803-2817

⁴ Marien J, Prévost C, and Sacquin-Mora S (2023) *Biochemistry*, 62, 2492–2502

⁵ Lessard, D., and Berger, C. (2021) *BioRxiv*, doi:2021.2008.2011.455914