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Conformational study of a mutated protein complex in xeroderma pigmentosum disease using molecular dynamics and residue interaction networks

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Xeroderma Pigmentosum (XP) is a rare autosomal recessive disorder caused by mutations in seven genes that codify Nucleotide Excision Repair (NER) pathway proteins, named XPA to XPG. As a result of this, XP patients produce mutant proteins that compromise DNA lesion removal, resulting in a broad range of pathological symptoms. However, little is known about XP proteins structure or how these mutations affect NER complex assembly. Thus, to understand how these mutations impact on XP proteins, we obtained DDB2(XPE)-DDB1 protein complex (DDB-complex) PDB data, since this complex is necessary for damage recognition in NER and performed multiple molecular dynamics simulations. Simulations were performed in triplicates for wild-type DDB2, DDB1 and DDB-complex, as well as for the naturally-occurring mutations found in XP, namely DDB2R273H, which impair DDB2 DNA binding and DDB2L350P, which affect the DDB-complex (all simulated alone and assembled with DDB1). We also applied dynamic Residue Interaction Networks (RINs) analyses to observe how these mutations impact on structurally important residues and communities formation over simulated periods and combined these results with systems biology analysis of RINs. Hence, it was possible to observe conformational differences between wild-type and mutated proteins/complex, such as reduced local flexibility, residues imperative for communication between communities, complex instability, structurally critical residues and loss or gain of communities. The combination of in silico analyses employed arises as a promising method for studying protein structure and could be assigned to other relevant investigations, such as small molecules impact on proteins and recombinant proteins design.

Biography

Bruno Cesar Feltes is currently a PhD candidate in Cellular and Molecular Biology at the Federal University of Rio Grande do Sul, Brazil. His studies have been focused in bioinformatics with emphasis on systems biology, systems toxicology and systems pharmacology to answer biological questions related to developmental biology and aging mechanisms; he has published most of his works in these fields. Presently, he works with molecular dynamics simulations and network analysis applied to structural biology and diseases. His collaborations also extend to microarray and RNA-seq data analysis.

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