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Force Field Parametrization of the Fe2+4S2–4 Clusters in Dihydropyrimidine Dehydrogenase, the 5-Fluorouracil Cancer Drug Metabolizer: Facilitating In Silico Pharmacogenomic Studies

Force Field Parametrization of the Fe2+4S2–4 Clusters in Dihydropyrimidine Dehydrogenase, the 5-Fluorouracil Cancer Drug Metabolizer: Facilitating In Silico Pharmacogenomic Studies
Maureen Bilinga Tendwa1,, Lorna Chebon-Bore1,, Kevin Lobb1,2, Thommas Mutemi Musyoka1, *and Özlem Tastan Bishop1*
1Research Unit in Bioinformatics (RUBi), Department of Biochemistry and Microbiology, Rhodes University, Makhanda 6140, South Africa ; bilingatendwa@gmail.com (M.B.T.); lornajemosop@gmail.com (L.C.-B.); k.lobb@ru.ac.za (K.L.)
2Department of Chemistry, Rhodes University, Makhanda, 6140, South Africa
*Correspondence: mutemibiochemistry@gmail.com (T.M.M.); o.tastanbishop@ru.ac.za (Ö.T.B.)
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Dihydropyrimidine dehydrogenase (DPD), a dimeric enzyme has attracted significant scientific attention for its role in metabolizing 5 fluorouracil (5-FU) anticancer drug in humans. These metalloprotein consist of highly specialized 4 × Fe2+4S2-4 clusters per monomer. A finely orchestrated inter- and intra-monomer electron transfer chain reaction through these clusters activates a redox metabolic reaction of the rate-limiting step in pyrimidine degradation. During this process, the majority of administered 5-FU drug is catabolically deactivated, while the remaining amount is activated to nucleic acid antimetabolites. DPD mutations in the general population, including people of African descent causes adverse toxicity effects in patients due to altered 5-FU metabolism. Therefore, understanding the impact of mutation on the catalytic mechanism of DPD protein is crucial, particularly in precision oncology medicine. Molecular dynamics simulations, principal component analysis, and dynamic residue network analysis can be used to decipher the effects of missense mutations in proteins. However, the Fe2+4S2-4 clusters in DPD protein require additional force field parameters to adequately describe the Fe2+ center coordination geometry. Consequently, new AMBER force field parameters for DPD enzyme Fe2+ center were derived using the original Seminario method and collation features visual force field derivation toolkit (VFFDT) as a supportive approach. The overall study took ~ 2400 CPU hours and was run on 240 cores at the Centre for High-Performance Computing (CHPC) in Cape Town, South Africa. Validation of the derived parameters with a 150 ns MD simulation revealed that both methods produced force field parameters that accurately described the Fe2+4S2-4 cluster architecture of the human DPD protein. These findings lay the groundwork not only for future research in the fields of in silico cancer pharmacogenomics studies, but also for novel drug discovery and repurposing studies involving the human DPD enzyme.

Student?

Yes

Supervisor name

Prof Ozlem Tastan Bishop

Supervisor email

o.tastanbishop@ru.ac.za

Primary author: Dr TENDWA, Maureen Bilinga (Rhodes University)

Co-authors: Mrs CHEBON-BORE1, Lorna (RhodesUniversity); Dr MUSYOKA, Thommas Mutemi (Rhodes University); Prof. LOBB, Kevin (Rhodes University); Prof. TASTAN-BISHOP, Ozlem (Rhodes University)

Presenter: Dr TENDWA, Maureen Bilinga (Rhodes University)

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