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Use of molecular interaction fields to understand drug resistance in HIV 1 protease caused by single point mutations

Daniela C Vaz[1,4], Rui M M Brito[1,2], Ana I Mata[1], Joao P Luis[1], Nuno G Alves[1], Carlos J V Simoes[1,2], Joao Pereira Vaz[3] and Vitor Duque[3]
[1]University of Coimbra, Portugal
[2]Instituto Pedro Nunes, Portugal
[3]Centro Hospitalar e Universitário de Coimbra, Portugal
[4]Polytechnic Institute of Leiria, Portugal

Molecular Interaction Fields (MIF) is an archetypal computational chemistry technique that can be applied to capture a singular fingerprint of an ensemble of atoms on a protein and encode its physicochemical environment. Thus, MIFs have particular relevance in the context of binding hot spots and binding site analysis. Taking HIV 1 Protease (HIVPR) as case study, the present work focuses on a MIF-based *in silico* approach to achieve a qualitative interpretation and quantitative determination of mutation effects on HIVPR's binding site, to help to understand translated changes in the enzyme's structure and physicochemical environment. Assuming that binding sites with similar chemical environments have similar affinity for inhibitors, our method calculates and compares MIF similarities, visually assessing structural differences and quantifying their overlap through a Tanimoto coefficient. To assess the method's ability to capture mutation induced chemical perturbations within HIVPR's binding site, we collected 48 X-ray structures from the Protein Data Bank (PDB), from HIV strains either resistant or susceptible to protease inhibitors and quantified their binding site MIF similarities against a high quality, susceptible, reference structure. We observed and defined a threshold that discriminated most susceptible and resistant structures, confirming the MIF's suitability for our approach. Subsequently, we built homology models containing different reported single point resistance-conferring mutations using a single high-quality PDB structure as template. Root-Mean-Square Deviation (RMSD) values between template and model structures were calculated on residue by residue basis, confirming that the mutation was the only structural change. Then, the MIF similarities were determined, showing that this technique effectively captured subtle changes on HIVPR's binding sites induced by the studied mutations. Along with the perspective of following an equivalent ligand based approach, we believe our results can be a promising starting point for developing an algorithm with drug resistance predictive power.

Biography

Daniela C Vaz has completed her PhD in Biological Chemistry from the University of Coimbra. Her research focuses mainly on protein structure, folding and stability, in relation to function and disease. She is currently working as a Professor at the School of Health Sciences of Leiria and is also a Member of the Coimbra Chemistry Centre at the University of Coimbra, Portugal.

dvaz@uc.pt

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