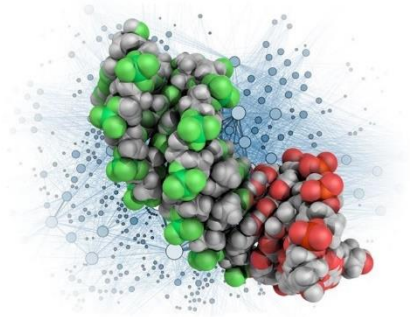


EJIBCE 2017

Encontro de Jovens Investigadores de Biologia Computacional Estrutural
Departamento de Física, Universidade de Coimbra, 22 de Dezembro

MDPI sciforum

MOL2NET, International Conference Series on Multidisciplinary Sciences
http://sciforum.net/conference/mol2net-03

Predicting HIV-1 resistance to protease inhibitors: A new structure-based algorithm exploring binding-site Molecular Interaction Fields dissimilarities

Nuno Guerreiro Alves (nunoagalves@gmail.com),[a] João P. Luís,[a] Carlos J. V. Simões,[a,b], João Pereira-Vaz,[c] Daniela C. Vaz,[a,d] Vítor Duque,[e] Rui M. M. Brito.[a,b]

[a] CQC, Chemistry Department, Faculty of Science and Technology, University of Coimbra, 3004-535 Coimbra, Portugal

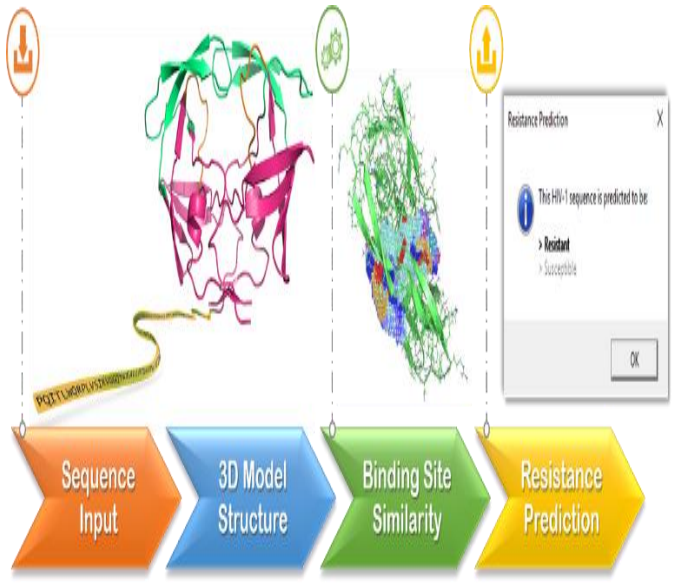
[b] BSIM², Instituto Pedro Nunes, 3030-199 Coimbra, Portugal

[c] Laboratory of Molecular Biology, Clinical Pathology Unit, Centro Hospitalar e Universitário de Coimbra, 3000 Coimbra, Portugal

[d] Health Research Unit, School of Health Sciences, 2411-901 Leiria, Portugal

[e] Infectious Diseases Unit, Centro Hospitalar e Universitário de Coimbra, 3000 Coimbra, Portugal

Graphical Abstract



Abstract.

Over the last 30 years, HIV has grown to a pandemic status with more than 36 million people infected worldwide. Current therapies provide a significant improvement in the quality of patients' lives, specifically the Highly Active Anti-Retroviral Therapy (HAART). Yet, viral resistance development towards anti-HIV medication stands as the main obstacle to an effective therapy, having also a substantial economic impact on healthcare systems worldwide. Such viral resistance is primarily related to mutations occurring mainly on the active site of viral key enzymes, capable of decreasing the pocket's capability to establish the necessary non-covalent interactions with the drugs. Even so, mutations outside the enzyme's active site can also lead to resistances, by causing changes on its structure and/or chemical environment. Among the two HIV virus types, HIV-1 stands as the most studied and prominent, with HIV-1 protease being one of the main viral targets for therapy.[1]

Given the ease of quickly and affordably sequence HIV from infected individuals, considerable progress

	– in the sense of predicting resistance towards drugs – could be made by developing tools to link specific genetic mutations with the resulting structural and chemical alterations in the active site of the target enzymes.[2] In recognition of a serious medical need identified by a team of virologists working at the University of Coimbra teaching Hospital and with the intent of helping rationalize and personalize the choice of anti-HIV therapies, we set out to develop a new computational algorithm to predict resistance to protease inhibitors in HIV-1 via detection of binding-site Molecular Interaction Fields (MIF) dissimilarities. Briefly, the algorithm works by 1) automatically generating high-quality 3D protein model structures from HIV-1 protease sequences; 2) capturing subtle, mutation-induced, chemical perturbations within the binding sites of resistant and non-resistant HIV-1 protease structures using a MIF-based approach; and 3) quantifying binding site dissimilarities based on MIF analysis, and translating these into a *resistance score*. In terms of its predictive power, preliminary testing of the algorithm using several different HIV protease sequences showed promising levels of sensitivity and specificity. Despite both sequence- and structure-based computational approaches to the prediction of HIV drug resistance have been proposed in the past, our present work stands out from other known algorithms as a first implementation of a fast structure-based algorithm capable of discriminating between HIV sequences that may be susceptible or resistant to commercially available protease inhibitors. Since the problem of mutation-induced resistance cuts across virtually all pathogenic virus, we believe that our approach may be extended to a wide range of viral targets besides HIV-1.

References:

1. Baxter D. J.; Chasanov M. W.; Adams L. J. *J AIDS Clin Res.* **2016**, 7, 581.
2. Weber I.; Kneller D.; Wong-Sam A.; *Future Med Chem.*, **2015**, *7(8)*, 1023-1038.