HIV-1 protease double mutants analysis by NMA indicates convergence to flexibility of the wild type

Antônio S. K. Braz[1], Valderes De Conto[1], David Perahia[2], Luis P. B. Scott[1]

[1] Laboratório de Biologia Computational e Bioinformática, Universidade Federal do ABC , Santo André, Brasil

[2] Laboratoire de Biologie et Pharmacologie Appliquée (LBPA), Ecole Normale Supérieure de Cachan, Cachan, France

The emergence of drug resistant mutations to the selective pressure exerted by antiretrovirals, including protease inhibitors (PIs), remains a major problem in the treatment of AIDS. During PIs therapy, major mutations are selected reducing both affinity for the inhibitors and the viral replicative capacity compare to protease wild type (wt). Additional mutations cancompensate for this reduced viral fitness. For investigate this phenomenon from the structural changes viewpoint, we combined MD and NMA to analyze the variations of the C-alpha flexibility and h-bond formation of wild type, single and double mutants of HIV-1 PR. Flexibility behavior of the double mutants was significantly closer to the wt than of the related single mutants. All single mutants showed a significant alteration in h-bond formation in comparison to wt. Most of the significantly changes occur in the border of flap/cantilever region. All the double mutants considered have their h-bond formation significantly altered in comparison to their respective base mutant with a probable effect that their flexibility pattern becomes more similar to wt. This methodology can be applied for investigate the structural effects of a large number of mutations in studies involving pathogen drug resistance and fitness.