

A new method for protein flexibility studies combining molecular dynamic simulations and normal mode analysis applied to the HIV-1 protease

Paulo R. Batista^{1&2}, Charles Robert², Jean-Didier Maréchal³, Pedro G. Pascutti¹, Paulo M. Bisch¹ & David Perahia²

¹*Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro – RJ - Brasil*

²*Laboratoire de Modélisation et d'Ingénierie des Protéines, Université Paris-Sud 11, 91405 Orsay,– France*

³*Department of Chemistry, University Autonomous of Barcelona, 08913 Bellaterra– Spain*

The idea of the structure/function relationship is very well accepted in the science community but recently another issue was included, forming the triplet structure/dynamics/function. Numerous experimental, computational and theoretical methods have been applied to explore the flexibility in order to better understand the dynamical behavior of several proteins involved in physiological and pathological processes. Here we present a new method to achieve protein flexibility that mixes molecular dynamics (MD) – solution of Newton equation of movements – and normal modes analysis (NMA) – calculation of the low-frequency/large amplitude movements – using the HIV-1 protease (PR) as a case study. PR is one of the most studied proteins with more than 200 structures solved (X-ray and NMR) and very extensive MD studies carried out. This method consists in considering a set of snapshots from MD trajectories and thereafter in performing NMA over each PR structure. Until this point there is nothing new. But the problem arises when one has to consider a large amount of normal modes (~100) over 20 structures that can result in nearly 2.000 different movements to be explored and some of them could be irrelevant. The question is how to join the information of each snapshot in a single set of modes, called here “consensus modes”, that reflect the mean behavior of all MD trajectories. We calculate the “consensus modes” from the first nanosecond (each 50 ps) of a 10ns MD simulation, after an accurate equilibration. The fluctuations derived from the “consensus modes” had a very good correspondence (correlation factor, R=0.69) with the ones derived from the crystallographic B-factor and with the quasi-modes calculated over the full 10ns MD (R=0.76). We found in the slowest “consensus modes” more information than the quasi-modes calculated directly from the 10 ns MD trajectory, including the open/close movement of the flaps and a very good correspondence with the NMR N-H S2 order parameters. These results show that “consensus modes” better reflect the potential energy topology than the quasi-modes. We were able to predict using few snapshots of a short MD (only 1ns) the principal movements occurred in 10 ns with a very good correspondence with both NMR and X-ray experimental results. As perspectives, this new method can be applied to PR mutants, and several other proteins with very flexible domains.

