Universidad Nacional de Quilmes

Prof. H. Bernhard Schlegel
Associate Editor
Journal of Chemical Theory and Computation

Quilmes, 1st February, 2021

Dear Prof. H. Bernhard Schlegel,

We would like to submit the application note entitled “ANA, accurate analysis of changes of protein cavity volumes in predefined directions and flexibility” by German P. Barletta, Matias Barletta, Tadeo E. Saldaño and Sebastian Fernandez-Alberti for publication in Journal of Chemical Theory and Computation.

Dynamics of protein cavities associated with protein fluctuations and conformational plasticity are essential for their biological function. NMR ensembles, Molecular Dynamics (MD) simulations combined with Principal Component Analysis (PCA), and Normal Mode Analysis (NMA) provide appropriate frameworks to explore functionally relevant protein dynamics and cavity changes relationships.

Herein, we present ANA (Analysis of Null Areas), and accurate and efficient software suitable for the analysis of changes of cavity volumes We have presented ANA, an accurate and efficient software suitable for the analysis of changes of cavity volumes within ensembles of protein conformations obtained either experimentally (NMR, X-ray crystallography) or theoretically (MD simulations, and NMA among others). It has been developed to be robust enough for the quantification of cavity changes due to small structural distortions or numerical differentiations on specific collective coordinate displacements. Therefore, it can be used to calculate numerically stable partial derivatives of the cavity volumes with respect to predefined directions of motion (e.g. PCA and NMA modes or any other direction of motion associated to a specific conformational change).

We think that ANA can represent a significant contribution for researches that are interested in exploring protein fluctuations−cavity changes relationships. We show that changes in the cavity volume and flexibility can contribute to differentiate functional conformers within the protein native state. Besides, ANA can be used to monitor dynamical features of cavities during protein conformational transitions. Finally, we show how the extent of variability between protein backbone structural distortions, and changes in cavity volumes and flexibilities within an ensemble of NMR structures can be explored and compared.

We therefore believe that our work is suitable for publication in Journal of Chemical Theory and Computation. This paper is not being considered for publication elsewhere.

Thank you for your consideration.

Sincerely,

Sebastian Fernandez Alberti,
University of Quilmes, Argentine.