Analysis of changes of cavity volumes in predefined directions of protein motions and cavity flexibility

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September 24, 2021

Abstract

Dynamics of protein cavities associated with protein fluctuations and conformational plasticity is 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. Within this context, we have developed ANA (Analysis of Null Areas), an efficient method to calculate cavity volumes. ANA is based on a combination of algorithms that guarantees its robustness against numerical differentiations. This is a unique feature with respect to other methods. Herein, we test ANA as a biophysical and bioinformatic method to analyze different structural and dynamics properties of cavities. In order to address this task, we have developed an updated and improved version of ANA that expands it use to quantify changes in cavity features, like volume and flexibility, due to protein structural distortions performed on predefined biologically relevant directions, e.g, directions of largest contribution to protein fluctuations (PCA modes) obtained by MD simulations or ensembles of NMR structures, collective NMA modes or any other direction of motion associated with specific conformational changes. A web page has been developed and its facilities are explained in detail, making the software available to all users. Firstly, we show that ANA can be useful to explore gradual changes of cavity volume and flexibility associated with protein ligand binding. Secondly, we perform a comparison study of the extent of variability between protein backbone structural distortions, and changes in cavity volumes and flexibilities evaluated for an ensemble of NMR active and inactive conformers of the epidermal growth factor receptor (EGFR) structures. Finally, we compare changes in size and flexibility between sets of NMR structures for different homologous chains of dynein.

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