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# A Novel Method for Inference of Collective Motions in Bio-Macromolecules Based on Graph Theoretical Instances

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## 【Introduction】

One of the innate and most outstanding characteristics of a living organism, and life in general, is motion. Motion is observed, both, at the holistic level of analysis of the biological system as well as when a reductionistic approach to understand it is undertaken. The latter, in particular, brims with a diversity of molecular and sub-molecular movements that are directly related to particular biological functions, let alone atomic and sub-atomic vibrations. Bio-macromolecules in general, and proteins in particular are self-endowed of the ability to use their intra-molecular energy (bond and angle bending, torsional, electrostatic, hydrophobic, etc.) to produce nanometer-scale motions that trigger a large number of the intra and extra-cellular processes in living organisms, constituting what can be called "Protein Machines". However and in spite of the outstanding role of these sub-molecular motions in proteins, new suitable and cost-effective computational methodologies for their inference are, at best, at an embryonic phase, while conventional methods are based on expensive molecular dynamic simulations, clustering of the conformations generated along a certain simulation path being their main modus operandi. In the present study we present a new algorithm to infer collective motions in proteins, directed mainly to assist and improve protein-protein, as well as other bio-macromolecular interactions, in docking studies within the framework of the system for macromolecular interaction assessment system MIAX[1].

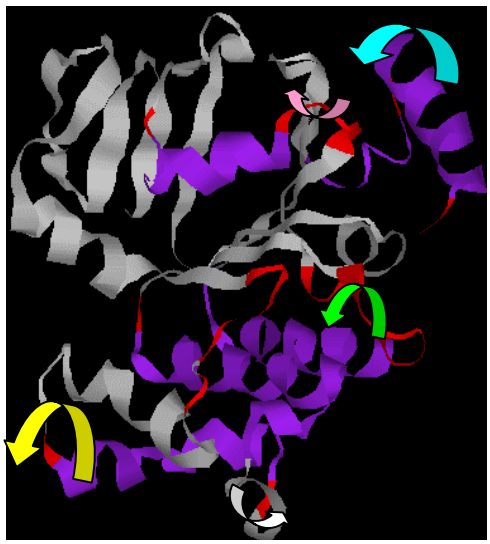

Fig. 1. Collective Motions depicted by MIAX in the ABC transporter.

## 【Methodology】

The hydrophobic collapse that drives proteins into their final folded state can be traced by inferring meta-stable intermediate states with well formed secondary structure characteristics. This assumption, supported by evolutionary, experimental, and phenomenological folding instances underlies the methodology proposed here, which consists in inferring clusters of rigid and flexible structural constituents for the molecule using a graph theoretical methodology. We define rigid, pseudo-rigid, and flexible structural clusters based on the number of independent hinges of the clusters. Flexible clusters are frequently constituted by atoms forming an internal loop or coil structure, while pseudo-rigid clusters are those partial structures constituted by a piece of structure of well defined secondary structure connected to the rest of it by no more than two bonds at their extremes. Rigid clusters are usually the partial structures of the core of the molecule where the atoms are confined to no more than local vibrations. The algorithm to infer flexible bonds is described elsewhere[2].

## 【Results and Conclusion】

Fig 1. illustrates the results of our collective motion prediction module for the ABC transporter molecule. Rigid, pseudo-rigid and flexible clusters are shown in different color tones. Inferred main direction movements for the cluster of atoms constituting a collective motion are depicted with arrows. The hydrophobic core of the protein (gray) being the most rigid part of the molecule, is surrounded by cluster of atoms (pseudo-rigid: regions purple) that can undergo collective movement by structural distortions in the flexible clusters of the molecules (flexible regions: red). Visual inspection of these clusters using structural visualization software, coincides with the results of the automatic inference performed by the algorithm.

*1)Del Carpio et al. PROTEINS: Structure, Function and Genetics, 48:696-732, 2002*
*2)Del Carpio et al. Genome Informatics 16-2:148-160,2005*