Exploring exhaustively the conformations of a tandem domains protein using a discrete Distance Geometry approach

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Résumé

The optimization problem encountered in protein structure determination is undergoing a change of perspective due to the larger importance in biology taken by disordered regions of biomolecules. In such cases, the convergence criterion is more difficult to set up; moreover, the enormous size of the space makes it difficult to achieve a complete exploration. The interval Branch-and-Prune (iBP) approach, based on a reformulating of the Distance Geometry Problem (DGP) provides a theoretical frame for the exhaustive sampling of the conformations. An implementation of the iBP approach, oriented toward the sampling of protein structure, was recently proposed (Worley et al, 2018; Malliavin et al, 2019).
The development of structural biology conducted to the discovery of numerous tandem domains related by a flexible linker. Solution NMR, sensitive to the internal mobility, and SAXS, sensitive to the gyration radius, are quite often used in parallel to investigate such systems. Here, we propose a pipeline based on the iBP approach to determine the set of representative conformations of the tandem domains as well as the weights of these conformations. This pipeline has been applied on the tandem PDZ domains (Delhommel et al, 2017), playing an essential role in the function of whirlin, involved in the hearing and vision systems. The obtained conformations of the tandem PDZ domain along with their weights will be analyzed according to the biological context.
References
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