MS01 MX/Cryo-EM software development

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New Tools and Pipelines for Continuous Heterogeneity Analysis from Cryo-EM using Normal Modes and 3D Zernike Polynomials

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Abstract

Cryo-EM is now able to reveal continuous heterogeneity and dynamics with many groups developing methods to analysis this, including ours, which we are making available in Scipion [1], which integrates multiple software packages into pipelines.

Simple computational biophysics models and methods such as elastic network models (ENMs) and normal mode analysis (NMA) can efficiently identify key motions of biological relevance, even for large system studied by Cryo-EM [2]. These methods have been demonstrated to be beneficial for Cryo-EM continuous heterogeneity analysis some years ago with the hybrid electron microscopy normal mode analysis (HEMNMA) [3], which has recently been integrated into Scipion through the ContinuousFlex plugin [4], and its extension HEMNMA-3D for tomography [5].

We now extend the capabilities for using such approaches further by integrating the ProDy Python package for protein dynamics [6] into a Scipion plugin with new protocols for atom selection and alignment, analysis of deformation vectors associated with pairwise conformational changes, ENM NMA, construction of structural ensembles and principal component analysis (PCA) of them, and comparison of these different motions derived from theory and experiments.

Another approach that is proving successful in our lab, which is being implemented with Xmipp [7] and associated Scipion plugins, makes use of 3D Zernike polynomials to describe conformational changes [8]. This approach can combine information from images, volumes and atomic structures into a common framework, optimising the coefficients of the polynomials to describe transitions between them and create a rough conformational space. Applying these polynomials and coefficients creates new volumes and structures corresponding to particular regions of the space.

We can also convert Zernike bases and coefficients to corresponding ones for normal modes and vice versa, providing a more direct connection between Cryo-EM data and physically realistic motions. There is also the potential to integrate with other computational biophysics methods, such as molecular dynamics simulations, and other molecular modelling procedures, allowing refinement of the resulting structures and landscapes.

We demonstrate using the SARS-CoV-2 spike and AMPA-type ionotropic glutamate receptors how such new pipelines combining different approaches within Scipion will allow a richer ability to understand protein dynamics, landscapes and mechanisms.

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