Exploring computational tools for protein modeling in cryo-electron microscopy density maps: I-tasser and Amber

P01-23

C.F. Rodríguez[I], F. Martino[I], H. Muñoz-Hernández[I], O. Llorca[I]

[I] Centro de Investigaciones Biológicas. CIB-CSIC., Madrid, Spain

The number of near-atomic resolution maps of proteins obtained using cryo-electron microscopy (cryo-EM) is increasing rapidly, due to availability of new microscopes and especially new direct electron detectors. Despite the advantage of cryo-EM to directly image proteins frozen in solution, modeling atomic structures *de novo* on those maps is still a difficult problem. In contrast to X-ray diffraction, in cryo-EM the resolution is typically not sufficient to identify all the side chains of the protein.

Here we explore how several computational tools can help modeling proteins on cryo-EM maps at near-atomic resolution, using homology modeling and molecular dynamics (MD). Structural motifs in proteins are widely conserved in all living organisms, and usually a sequence identity of 30% is enough for tools like I-tasser [1] to identify the secondary structure and provide a rough model of a given domain. After building a model with I-tasser, we used a cryo-EM map at ~4 Å to perform rigid fitting of this model into the density, from the beginning to the end of the map following the mainchain, and backwards to avoid biasing. Using Amber to run MD simulation of the model [2], it is possible to set a soft restrain force constant towards the map. Amber force field is keeping the right geometries for the protein while is fitting better into the density along the simulation. Once the model reaches a stable conformation inside the map, we can identify some well-placed side chains to validate our model.

[1] Y Zhang. I-TASSER server for protein 3D structure prediction. (2008) BMC Bioinformatics, 9: 40 .

[2] AMBER 2016, (2016), University of California, San Francisco.