Phenix *Python-based Hierarchical ENvironment for Integrated Xtallography*

Fitting to a Cryo-EM Map using MD Simulation

Contents

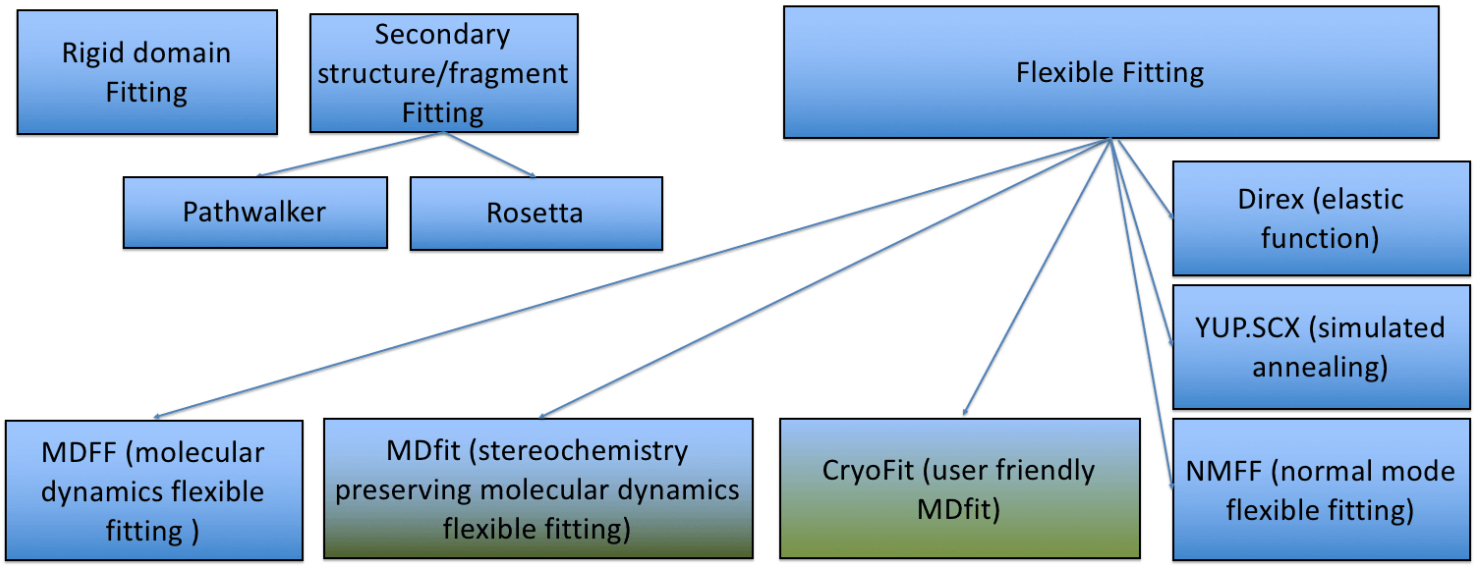
Overview

Cryo_fit fits biomolecule (protein and nucleic acids) to cryo-EM map that is reconstructed by single particle analysis using molecular dynamics simulation

Abstract

With many crystallography groups shifting to cryogenic electron microscopy (cryo-EM), there is a high demand for software that can produce atomistic models for high resolution cryo-EM datasets. Therefore, we are incorporating our automated cryo-EM density fitting method (cryo_fit) into a widely used software suite for macromolecular structure determination (PHENIX). Cryo_fit produces all-atom models highly consistent with the EM density and is being used to construct models for many functional complexes (including one of the first all-atom models of the human ribosome, revealing a new conformational change specific to eukaryotic ribosomes: subunit rolling). Two key advantages of the cryo_fit are its speed and the preservation of stereochemistry information. Its fast speed allows cryo-EM scientists to run on a single laptop (several hours for a ribosome modeling without the need for GPU) instead of thousands of cores. It uses a reduced model molecular dynamics potential that allows us to preserve stereochemistry information. As an additional advantage, secondary and tertiary contact potentials can be specified to place additional restraints on contacts within a cutoff keeping them intact during the fitting process.

How to Fit Cryo EM Maps



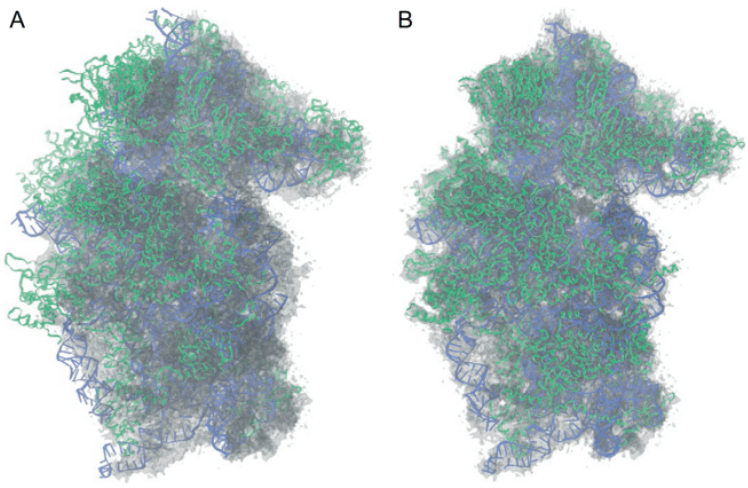
Advantages

Fast speed

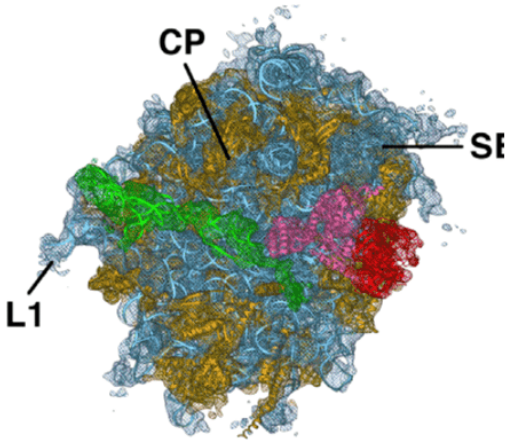
- Uses a reduced model (reduced energy units)
- Runs on a single laptop (several hours for a ribosome modeling without the need for GPU) instead of thousands of cores.

Preserving stereochemistry

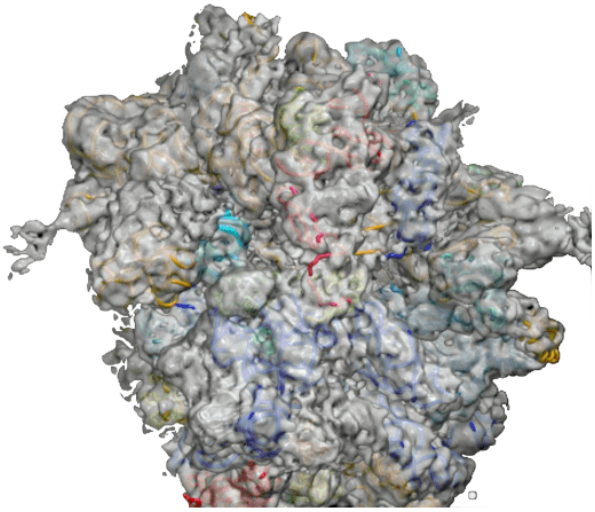
- Uses secondary and tertiary contact potentials
- Uses native contact potentials



before (A) and after (B) *Cryo_fit (Kirmizialtin et al, Methods Enz. 2015).*

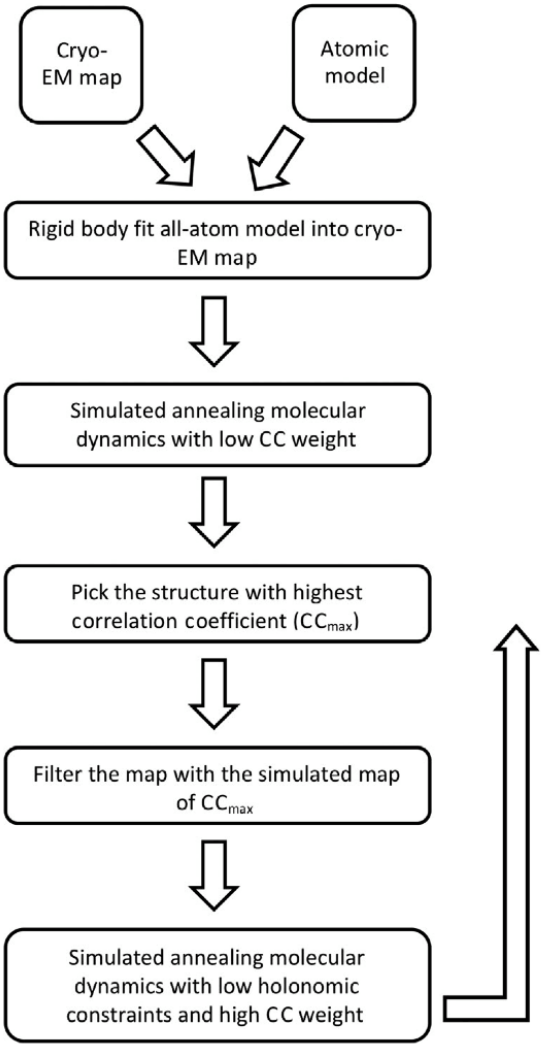


Example of MDfit: Human ribosome (Budkevich, et al., Cell 2014).



Example of MDfit: Head swivel intermediate of bacterial ribosome translocation (Ratje et al., Nature 2010).

How Cryo_fit Works



$$E = E(R) + E^{NC}(R) + w(1\text{-}CC)$$

- R: coordinate vector
  - classical MM: bond, angle, torsion, improper torsion and volume exclusion
- NC: native contact
  - compute all pairwise contacts for pairs such that i - j > 4 and with a distance cutoff condition of $d_{ij0} = |r_{i0}\text{-}r_{j0}| <= 4$ Å
- CC: The correlation coefficient between the cryo-EM map & the simulated map. (w = weight)

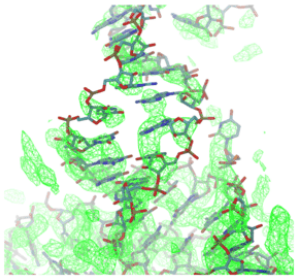
$$CC = \frac{\sum_k \rho^{EM}(k)\rho(k)}{\sum_k \rho^{EM}(k)^2 \sum_k \rho(k)^2}$$,

where $$\rho(k, \mathbf{r}_j) = \exp\left[-\frac{1}{2}\left(\frac{\mathbf{r}_k - \mathbf{r}_j}{\sigma}\right)^2\right]$$

masking the unresolved cryo-EM map

$$q(k) = \begin{cases} 0 & \rho(k) = 0 \\ 1 & \text{otherwise} \end{cases}$$

(Kirmizialtin et al, Methods Enz. 2015).



How to Run Cryo_fit

See the tutorial notes for cryo_fit

Reference

S. Kirmizialtin, J. Loerke, E. Behrmann, C. MT. Spahn, K. Y Sanbonmatsu, Using Molecular Simulation to Model High-Resolution Cryo-EM Reconstructions, Methods Enzymol., 558, 2015, 497-514