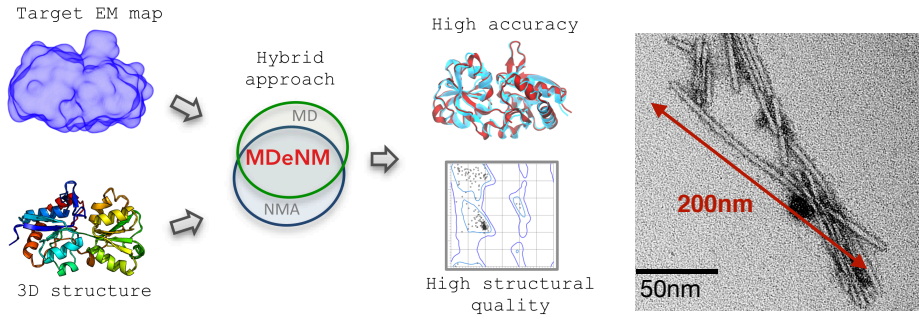
Proposition de stage Master2

Flexible fitting of an artificial virus made of self-assembling cyclodextrin and dsDNA by hybrid computational methods.

IMPMC UMR7590 Sorbonne Université, CNRS, Museum nationale d'Histoire naturelle
Campus Jussieu
4 Place Jussieu
75005 Paris
catherine.venien-bryan@sorbonne-universite.fr
david.perahia@gmail.com

Possibilité de poursuivre en thèse

Fitting of atomic structures into Cryo-EM 3D maps is a crucial step on the obtaining of high-resolution structures. In this task, simulation methods are applied to refine the structure molecular assemblies so that it closely fits in the electron density map obtained by Cryo-microscopy analysis. The fitting refinement process usually requires the introduction of structural flexibility to obtain a reliable solution. In this context, our group has recently developed a new tool called MDeNM-EMfit, which combines MD simulations and the excitation of intrinsic motions given by Normal Mode Analysis. (see Figure (left)). According to this method, sampling is guided towards conformations that exhibit maximum correlations with the experimental map.



The first part of this master project is to identify the optimal parameters for MDeNM-EMfit in order to obtain the maximum accuracy and performance on the flexible fitting process. This step will be required for the achieving the primary objective, which is obtaining of a high-resolution structure of a DNA/Cyclodextrin complex previously visualized by our group using electron microscopy (see Figure (right)). Long and rigid fibers were observed with a constant diameter ca. 6 nm and lengths of hundreds of nanometers, which is much bigger than the individual bricks of this assembly (20mer DNA=7nm, Cyclodextrin D=1nm).

This will help us to describe in great details the architecture of the assemblies and the precise interactions between the various molecules inside the assemblies at the highest possible resolution. The master-2 student will also use the methodology on the prediction of the shape of a hierarchical homogeneous self-assembly in solution, which is currently totally out of reach. This knowledge will be instrumental for further developments in gene therapy.

References

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