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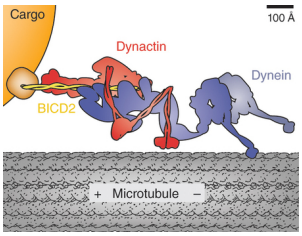

Dynein-dynactin complex and its cargo. From [RP15].

PhD thesis proposal

Modeling molecular machines

Context. A ribosome synthesizing a polypeptide chain from a messenger RNA or a dynein-dynactin complex cargoing molecules along a microtubule are example dynamic molecular machines. The study of such machines is extremely challenging for three main reasons. First, they involve a large number of subunits (proteins, nucleic acids), in the range 30..100 for the two examples above. Second, their dynamic nature makes it difficult to capture atomic resolution snapshots using biophysical experiments such as crystallography or cryo electron microscopy (EM). Third, fixed snapshots, when obtained, do not unveil the dynamic mechanisms at play. For these reasons, modeling such machines usually calls for the integrative modeling, a strategy mixing various experimental data and simulation techniques [WLVM$^+$14].

Goals. The goal of this thesis will be foster our understanding of molecular machines, with two related contributions respectively targeting static and dynamic aspects.

The first goal will be to develop high resolution static models by combining coarse grain information from EM, and atomic models of subunits coming from crystallography. Fitting crystal structures within EM maps was recently undertaken by solving an integer linear program [ACW15]. The goal will be to improve this strategy, based on a finer understanding of EM maps using Morse theory and persistent homology, and on more efficient algorithms to solve the fitting problem. Importantly, the improved method will enumerate solutions of equivalent quality and group them into equivalence classes.

The second goal will be to exploit these equivalence classes, so as to understand the dynamics in terms of Markov state models. Practically, models for the dynein-dynactin complex will be developed, a case for which experimental observations were recently obtained [SZUC15, UZD$^+$15]. This work will be conducted in collaboration with A. Carter (Cambridge University, author of [UZD$^+$15, SZUC15]), with whom preliminary discussions already took place.

Both modeling steps will benefit from the panel of tools available within the Structural Bioinformatics Library [CD16], developed within the project team.

Background. Master in applied mathematics, or theoretical computer science, or structural bioinformatics/biophysics.

References

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