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Application de la dynamique moléculaire à plusieurs échelles au complexe hélicase humaine: Pontine/Reptine

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Pontin/Reptin complexes offer new therapeutic opportunities despite the fact they are still not well known. Indeed, both homologous proteins belong to the AAA+ super-family, they were identified as over-expressed in various cell lines involved in many oncogenic protein systems. In addition to their ATPase activity, multimeric complexes of Pontin/Reptin were reported as hélicases able to unwind nucleic acids. During the last decade, several structural studies provided proofs for assemblies of six to twelve sub-units with a Pontin/Reptin alternation, thanks to X-ray crystallography and cryo-electron microscopy. However, the human complex details remain unclear, with bad resolutions or even incomplete due to their high conformational plasticity. In order to make a rational design of the ATPase activity or protein-protein interactions inhibitors, a better understanding of the multimeric states is required. Molecular modeling techniques are a powerful tool to study proteins, thus both a docking and molecular dynamics were applied. Considering the size of a twelve sub-units complex, simulations taking into account all atoms were too expensive in terms of computational costs. A mesoscopic approach, called coarse-grain, was used to reduce the number of particles by merging together up to four heavy atoms in only one interaction bead. The calculation time saved with this model allowed the study of Pontin/Reptin complexes in the presence of diverse partners like small ligands (ATP or ADP) and/or nucleic acids. Starting from one incomplete crystallographic structure, assembly reconstruction and dynamics revealed a set of specific conformations at the monomeric and multimeric level. Despite the necessary approximations with this level of abstraction, the coarse-grain approach was able to reproduce protein-ligand behaviours for the first time. Studies in the presence of different DNAs allowed the evaluation of the influence of nucleic acids on the complex conformational equilibrium. Reverse transformation from coarse-grain to the atomic level led to a DNA double helix opening along to the single strands rearrangement. Several mechanistic hypotheses for the complex helicase activity were formulated from these results.

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