Investigating the opening mechanism of topoisomerase I B in complex with DNA by means of metadynamics

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Motivations:
Topoisomerases play a central role in DNA homeostasis and act on them through a catalytic cycle that comprises the opening of the protein clamp to embrace the DNA (at the beginning of the cycle) and opening to allow the release of the topologically relaxed substrate. Protein opening is hard to follow experimentally thus computational techniques are very handy in dealing with this transitions, although classical molecular dynamics is limited in following big conformational changes and slowly occurring transitions. Therefore we present a well-tempered Metadynamics study of hToP1 clamp opening in presence of a 22-bp long ds-DNA substrate.

Methods:

The protein structure of wild type hTopIB in complex with DNA has been obtained as previously reported. The hTopIB clamp around the DNA molecule has been destabilized by means of metadynamics using Gromacs-4.5.5 with the PLUMEDv1.3 patch. In the simulation, two Collective Variables have been used to describe the clamp opening: the distance between the center of mass of Cα atoms of the lip1 and of the lip2; and the number of hydrogen bonds between the protein and DNA.
Free-energy surface (FES) and the minimum energy path (MEP) connecting different minima were reconstructed using in-house written codes in Python.
Salt bridge analysis was conducted via Salt bridges extension of the VMD

program and other analyses were performed with the tools of the GROMACS package.

Results:

Results indicate that the lobes of the protein retain their domain structure during the opening that is characterized by an energy barrier of about 50 Kjoul/mole. Furthermore the DNA remains in contact with the Cap lobe, a fact that would enable the protein to perform 1D-diffusion in the DNA strand to enhance the specific activity by reducing the dimensional space it has to search between relaxation events.