Computational study of DNA three-way junctions

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DNA is a highly flexible biomolecule, which can adopt several types of structures besides the well-known double helix. When the DNA is under stress (for example during replication), and if the sequences allows it, DNA can form a three-way junction (TWJ) where three strands form a structure with a prismatic cavity (see Figure 1). This cavity can be filled with a ligand, which can block the replication if the ligand is well suited for the binding site. Thus, stabilizing TWJ can lead to cell deaths, and ligands for TWJ are putative anti-cancer drugs.

Several promizing ligands were identified by our experimentalist colleagues[1], but the optimization and rational design of new ligands is a long and tedious task, limitated by the complexity of the organic synthesis[2]. We have thus decided to rely on computational chemistry to (1) reproduce experimental data, and then (2) propose new ligands. The main physico-chemical data to characterize the DNA/ligand interactions are folding temperatures: spectroscropic measurements at differents temperatures were performed and fitted to a sigmoid curve, which provides the temperature at which 50% of the structure is folded. We have thus designed a simulation protocole to compute folding temperature. After initial failure with brute force calculations, we have adopted a protocole based on hamiltonian replica exchange (REST2) which is a technique that is used for enhanced sampling. Promizing results were obtained, and a satisfactory correlation between computational and experimental temperatures were obtained. Thus, we have developed a protocol that can be used prior to synthesis to screen ligands.

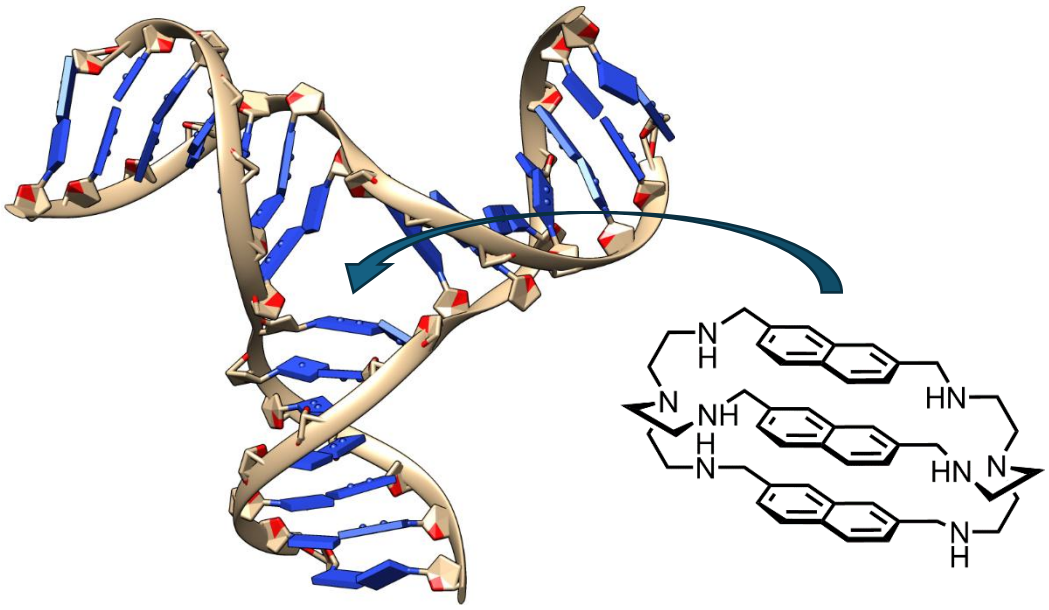

Figure 1. Model structure of DNA three-way junctions and example of a ligand.

[1] K. Duskova, P. Lejault, E. Benchimol, R. Guillot, S. Britton, A. Granzhan, D. Monchaud, *J. Am. Chem. Soc. Vol. 142* (2020) 424–435.
[2] J. Zell, K. Duskova, L. Chouh, M. Bossaert, N. Chéron, A. Granzhan, S. Britton, D. Monchaud, *Nuc. Ac. Res. Vol. 19* (2021) 10275–10288.

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