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Theoretical study on the base-sequence dependency on ligand distribution along DNA groove

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Sequence specific DNA-ligand interaction plays an important role in a variety of biological processes. However, the base-sequence dependency of ligand distribution along DNA groove is not well understood yet.

Here we calculate the interaction free energy (ΔA) landscape([1]) of DNA-water and some DNA-amino acids side chains. ΔA values are calculated along DNA groove and obtained ΔA landscape represents the spatial distribution of ligand along DNA groove. ΔA landscape is comparable to the experimental ligand distribution extracted from structural database.

To sample conformational space efficiently, multicanonical Monte Carlo (MMC) sampling is used. A ligand molecule moves around the space around the fixed DNA during the MMC sampling. Energy of the system is calculated by force field (DNA: Amber or ab initio potential[2], water: TIP3P). The space around DNA is divided into small cubic cells and the frequency (the number of times ligand visited the cell) is counted during the simulation. ΔA landscape at desired temperature is obtained by reweighting the frequency at each cell.

DNA sequence is quite diverse, so we calculate ΔA landscape for the 32 kinds of 3bp DNA and combining them to get ΔA landscape for any longer DNA sequences. Resulting ΔA landscape is visualized as isosurface around DNA. We compare obtained ΔA isosurface and position of the ligand found in the structural data base. We found that resulting ΔA isosurface clearly depend on DNA sequence and site of lower ΔA value correspond to the recognition site of the ligand. By using ΔA landscape, it is possible to predict recognition sites of ligands along DNA groove.

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