Dynamics of Proliferating Cell Nuclear Antigen Loaded onto Double-stranded DNA
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**Abstract**

We have studied the interactions of human and Archaeoglobus fulgidus Proliferating Cell Nuclear Antigen (PCNA) with double-stranded DNA using multi-nanosecond classical molecular dynamics simulations. We examined in detail the interactions of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We observed pronounced tilting of the axis of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We attribute this to non-specific motion of the PCNA subunits and the tilt angle with respect to PCNA. First, the relatively rigid structure of the sliding clamp preserves the integrity of the sliding clamp helix. There are two reasons for this: the interactions between the positively charged protein residues and the negatively charged phosphodiester groups of the DNA backbone in the canonical B-form (~24 Å). The second factor has to do with the diameter of the central hole of PCNA (~35 Å), which is larger than the lateral extent of both strands of the DNA minor groove and are almost exactly perpendicular to the axis of the ε-helixes forming the inner surface of PCNA. The global motions of the sliding clamp with respect to the sliding clamp appear to be well correlated to the internal motions within the PCNA ring.

**Introduction**

We have studied the interactions of human and Archaeoglobus fulgidus Proliferating Cell Nuclear Antigen (PCNA) with double-stranded DNA using multi-nanosecond classical molecular dynamics simulations. We examined in detail the interactions of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We observed pronounced tilting of the axis of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We attribute this to non-specific motion with respect to the sliding clamp. We observe pronounced tilting of the axis of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We attribute this to non-specific motion with respect to the sliding clamp. We observe pronounced tilting of the axis of DNA passing through the PCNA ring, the contacts formed, overall orientation and motion with respect to the sliding clamp. We attribute this to non-specific motion with respect to the sliding clamp.

**Computational details**

Two systems set up for classical molecular dynamics simulation:

1. PCNA from Archaeoglobus fulgidus
2. Human PCNA (initial structures from PDB: 1RWZ and 1VYM)
3. Canonical d(dsDNA) [5'ACGTTGACTACCGTCTTGAGGCAGAGTC3'] was inserted vertices through the central hole of PCNA
4. Added hydrogen atoms, counterions and solvent (pre-equilibrated TIP3P water molecules).
5. Both Cl− and Na+ ions were used to mimic physiological conditions with salt concentration of ~120 mM.
6. Production runs of 25.5 ns for system (i) and 24.5 ns for system (ii) in the equilibration for 1.5 ns.

**Protein DNA Interactions**

- Time evolution of the interactions between the sidechain H atoms of basic (arginine, lysine) groups of hPCNA located within 7 Å of the nucleic acid backbone P atoms. Data for aPCNA and hPCNA is shown in blue and green, respectively. The red curve represents the weighting function that was used to select "close" interactions.

- Experimental vs. Computed B-factors:
  - Computed versus experimental B-factors: a) for hPCNA and b) for aPCNA

**Experimental vs. Computed B-factors**

- Histogram of the interactions between the sidechain H atoms of basic (arginine, lysine) groups of hPCNA located within 7 Å of the nucleic acid backbone P atoms. Data for aPCNA and hPCNA is shown in blue and green, respectively. The red curve represents the weighting function that was used to select "close" interactions.

**Conclusions**

- The most prominent structural feature of the PCNA/dsDNA complex is the pronounced tilt (approximately 20°) for hPCNA in the case of dsDNA with respect to the plane of the PCNA ring.
- There are two reasons for the observed changes in orientation of the DNA helix with respect to PCNA. First, the relatively rigid structure of the sliding clamp preserves the integrity of the sliding clamp helix. The second factor has to do with the need to maximize the interactions between the positively charged protein residues and the negatively charged phosphodiester groups of the DNA backbone.
- The ε-helices forming the inner surface of PCNA track along part of the DNA backbone on both strands of the DNA minor groove and are almost exactly perpendicular to the axis of the ε-helices forming the inner surface of PCNA.