Molecular dynamics simulations of TBP complexed with diverse TATA variants

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Motivation

Promoters of many genes transcripted by RNA polII contain a consensus sequence TATAt/aAt/aX called TATA box, which is positioned 25-30 basepairs upstream of the transcriptional binding site. This sequence is recognized by the transcription factor TFIID, which binds to DNA via its subunit TBP. The crystallized complex TBP-DNA shows that TBP binds to the minor groove of the TATA element, which is strongly bent towards the major groove. Binding affinity and transcriptional efficiency critically depend on the DNA sequence. Recently, a set of diverse DNA patterns was analyzed by a neural network method, providing a ranking in terms of probability of being TATA sequences. This work aims at correlating the proposed classification of TATA sequences to structural features of the corresponding DNA-TBP complexes, as they emerge from molecular dynamics simulations.

Methods

The crystal structure of a human TATA-TBP complex (PDB code 1C9B) was used as starting model for four different low and high score DNA patterns. Mutations in the TATA sequence were modelled with CHARMM and the CHARMM27 force field starting from the wild type structure. After solvating the complex using the TIP3 water model, a system of orthorombic shape made of about 25000 atoms is considered for NPT MD simulations with CHARMM, timestep 2 fs and Verlet algorithm. Trajectories on the nanosecond scale are obtained for each DNA pattern. Structural analysis is carried out at two levels: first, the bending of DNA during dynamics is studied by means of MADBEND and CURVES. Second, the protein-DNA interface is analyzed in terms of hydrogen bonding pattern and van der Waals contacts.

Results

The analysis suggests that TATA sequences which obtain a high score in the neural network might be correlated to a high flexibility of the DNA segment when complexed with TBP, given by significant fluctuations of the conformation and larger bending. In order to interpret this result the interactions at the protein-DNA interface, as a way to identify sequence dependent differences, are under investigation.

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