DNA Polymerase Fidelity and Human Telomeric Quadruplex Conformations

Thomas E. Exner

Universität Konstanz, Fachbereich Chemie, 78457 Konstanz, Germany, thomas.exner@uni-konstanz.de

Molecular dynamics simulations on two different systems will be presented. The first is a mutant of DNA polymerase I from Thermus Aquaticus (Taq) with higher fidelity compared to the wild type. The accurate replication of DNA is of the utmost importance for the maintenance of genomic integrity. Polymerases have evolved a very high fidelity with error frequencies of approximately one in $10^{3}-10^{6}$ bases synthesized. The even better mutant was identified by an efficient automated high-throughput setup for the rapid parallel screening of mutant libraries [1] developed to respond to the demands of numerous biotechnical applications like polymerase chain reactions (PCR) with their unnatural conditions. Simulations of Watson-Crick and mismatched incoming deoxyribonucleoside-triphosphates show that the high fidelity of the mutant can be partly explained by different specific interactions between amino acids of the enzyme and the DNA primer end as well as, in some mismatches, a displacement of the primer relative to the incoming nucleotide and the catalytic magnesium ion [2].

Guanosine-rich nucleic acids are known to fold into four-stranded structures called quadruplexes. Particular sequences, namely the telomeric repeats at the end of the chromosomes, have generated much interest. Due to the potential to switch between folded and unfolded state, the formation of quadruplex structures is suspected to play important roles in telomere maintenance and cell cycle control. The human telomeric repeat is known to adopt drastically different conformations depending on parameters such as the type of monovalent ions coordinated by the guanine tetrads and the nature of the examined sequence. Long-range distance measurements by spin-label EPR for investigating quadruplex structures suggest the presence of a 1:1 mixture of a parallel propeller and an anti-parallel basket structure in K⁺ solution [3]. Molecular dynamics calculations show that it is really possible to discriminate between these structures by the EPR-based distance measurements, so that they can be used to identify and quantify structural mixtures of DNA or RNA quadruplex with respect to experimental conditions.