## Comparison of the fine structure and dynamics of damaged and intact DNA

Mahmut Kara and Martin Zacharias , Physik-Department T38, TU München

## Introduction

O(6)-alkylguanine (6AG) is the major mutagenic and carcinogenic lesion in DNA induced by simple alkylating mutagens because of its preference for pairing with thymine during DNA replication. (Fig. 1). DNA containing a 6AG can be recognized and repaired by specific repair protein, such as O6alkylguanine DNA alkyltransferase [1](Fig. 2). DNA damage may alter the DNA fine structure and dynamics which in turn could be of importance for rapid recognition and repair of DNA damage. Classical molecular dynamics (cMD) simulations and a recently introduced enhanced sampling method (biasing potential replica exchange (BP-REMD) [4] have been applied to investigate differences in structure and dynamics of intact DNA and DNA containing O(6)-alkylguanine.


Fig 1: Chemical structure of 6 MG and guanin


Fig 2: Schematic illustration of the transfer of the methyl group to the AGT protein and restores the guanine to normal.

## Material \& Methods

MD and BP-REMD simulations were carried out starting from a crystal structure [2, (pdb-id: 153D)] containing O(6)-methylguanine (6MG). Intact DNA was created by in silico mutation of 6MG to guanin. Additionally Arnott-BDNA of both systems (intact \& damaged) were created. The force field parameters for 6MG were taken from SantaLucia [3]. The Amber Molecular Dynamics Package [5] was used for the simulations and were performed in explicit water (TIP3P) including sodium counter ions and using the parmbsc0 force field. Four unrestraint 100ns cMD (damaged \& intact crystal structure and damaged \& intact bdna model) were performed at constant temperature (300K) and pressure (1 bar). Additionally, four BP-REMD simulations, each with 5 replicas ( $4 \mathrm{~ns} /$ replica) were used to enhance sampling of relevant epsilon/zeta and alpha/gamma nucleic acid backbone dihedral angles [4, illustrated in Fig. 3].


Fig 3: (A) Course of the BP-REMD simulation with five replicas. (B) $2 D-\varepsilon / \zeta$ dihedral space. A digit (1) indicates that different levels of a biasing (bump) potential are added to the force field of the replicas.( C) Form of the dihedral angle $B P$ in 1D. (D) Form of the dihedral angle $B P$ in 2D.

## Results \& Conclusion

- The BI/BII population of guanine is in good agreement with the results of Lavery. et. al [6].
- Comparison of $\mathrm{Na}+$ distribution indicates different populations for 6MG and Guanin containing DNA which might be important for rapid indirect readout recognition (Fig 4).
- BP-REMD allows much more rapid identification of putative substates compared to cMD.
- In the case of 6MG new substates for the coupled $\varepsilon / \zeta$-backbone dihedral angles have been observed (Fig 5)
- BDNA-models simulations shows comparable results to crystal structure MD Simulations
- 6MG has a strong influence to the conformations of his nearest neighbors


Fig 4: Comparison of $\mathrm{Na}+$ distribution (A):6MG and


Fig 5: Sampling of $\varepsilon / \zeta$ backbone dihedral angles

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