Tsvetan Gantchev, Ph.D.

Interests: Structure of damaged DNA and nucleotide excision repair recognition of DNA bearing bulky lesions. Takes an account of radiation-induced DNA damage, PNA-DNA heteroduplexes/triplexes, and interactions of hydrated electrons with cisplatin modified DNA.

Ongoing Project: **Structural dynamics of damaged DNA**. Comprises covalent (fluorescein-thymidine) and non-covalent DNA adducts (peptide nucleic acids), intra- and inter-strand cisplatin crosslinked DNA, *etc*. and their recognition by the bacterial nucleotide excision repair (NER) system. The research includes experimental and theoretical approaches: i) estimation of binding affinities of modified-DNAs towards purified NER proteins by standard molecular biology techniques (EMSA, radio and fluorophore labeling) and ii) conformational dynamics of free and UvrA/UvrB-bound DNA to evaluate structural determinants involved in specific binding of NER protein components with DNAs bearing bulky lesions. The main methodology is based on molecular modeling and molecular dynamics (MD). Examples of structural distortions (large global bending and unwinding) evoked by an interstrand cisplatin-crosslink situated in the middle of a 72 b.p. DNA and PNA-invaded double stranded DNA (PNA-DNA_2 triplex) are illustrated in Fig. 1 (upper and bottom panels, respectively). Figure 2 presents snapshots from MD simulation trajectory of *bis*FT-DNA in the presence of $UvrA_2$ dimer (green): starting configuration when *bis*FT-DNA is away from the protein (upper panel) and a frame near the trajectory end, when *bis*FT-DNA is strongly $UvrA_2$ bound (bottom panel). *bis*FT-DNA binding is characterized by significant conformational rearrangements of both, the DNA and the protein. The protein conformational dynamics involves large-scale motion of entire DNA-binding domains (ID and SGN2) and the *bis*FT-modified site is in tight contact with the Zn3-finger motive. $UvrA_2$ also binds undamaged DNA, but the interaction pattern is different.

Fig. 1

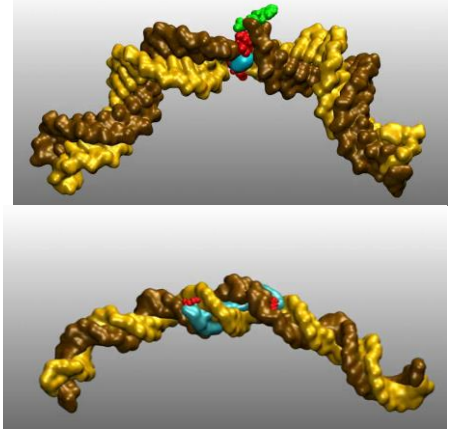
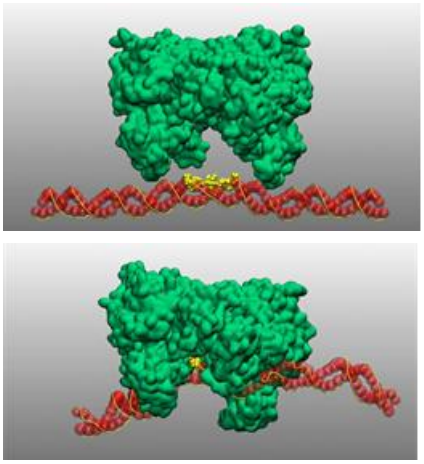


Fig. 2



Publications:

T. Gantchev, G. Encheva, V. Posheva, J. Todorova and, M. Skorvaga. Peptide nucleic acid (PNA) decoys are capable to recruit UvrA/UvrB damage-sensing proteins on DNA. *Comptes Rendu de l' Academie Bulgare des Sciences* (2016, in press).

T. G. Gantchev, P.S. Petkov and D. J. Hunting. Conformational rearrangements of 1,2-d(GG) intrastrand cis-diammineplatinum crosslinked DNA is driven by counter-ion penetration within the minor groove of the modified site. *J. Mol. Modeling* (2016, in press).

Meetings:

T. Gantchev. Structural insights in DNA lesions recognition by the bacterial UvrABC excinuclease. *COST Action CM1201: Biomimetic Radical Chemistry, Bucharest, Romania* (2016).