Session 29: Modeling of Radiation Damage to DNA

Lectures

L29.1

Free radical mechanisms of radiation damage to DNA

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Radiation damage to DNA results from roughly equal contributions of direct ionization of DNA including its first hydration layer (direct-type effects) and indirect effects from attack of mainly hydroxyl radicals (•OH) and aqueous electrons (e_{aq}^-). For DNA damage by direct-type effects the ionization and excitation events take place randomly over the DNA structure and its hydration layer in proportion to the electron density at each site. These initial ionizations are followed by charge migration to sites of low ionization energy and high electron affinity in competition with fast deprotonation of cation radicals and protonation of anion radicals. In addition, low energy electrons (LEE) produced during these ionization have been shown to lead to frank DNA strand breaks via dissociative electron attachment. A substantial understanding of both the mechanisms of radiation damage to DNA from the indirect effect (e_{aq}^- and •OH) and the direct effect has resulted from radiation chemical and experimental techniques including product analyses, pulse radiolysis, ESR, and theory. For the direct-type effect much has been learned about (a) hole and electron transfer, (b) reactions of LEE, (c) prototropic equilibria in DNA base pair ion-radicals, (d) the formation of sugar radicals by cation radical deprotonation and (e) the contribution of radiation-induced combined ionization-excitation events to DNA damage important in ion-beam (high LET) radiation. In this talk, an overview of the current status of our understanding of the effect of radiation on DNA will be presented with some attention to the role and reactivities of e_{aq}^- and LEE.

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L29.2

Can low-energy electrons produce DNA strand breaks in the physiological environment?

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The initial stage of the irradiation process involves the ionization of the material and the consequent generation of secondary electrons, holes and radicals. These species diffuse through the sample experiencing inelastic collisions with the medium until they find an opportunity to react, and produce chemical modifications that lead to various types of damage. For a long time it was deemed that the dominant damage mechanism was radical attack, e.g. OH radicals produced by ionization of the surrounding medium (water) would diffuse and react with DNA. This view, however, was challenged by the seminal paper from Leon Sanche's group in 2000 [1], which showed that electrons generated by ionization could also produce damage to supercoiled DNA via dissociative electron attachment (DEA). In this mechanism, secondary electrons are captured resonantly by DNA (generally at the bases) and stabilized by transferring energy to a vibrational degree of freedom, typically a bond stretch. If the energy transferred to the vibration is sufficiently large, then it can lead to bond dissociation. The theoretical description of this phenomenon requires a coupled treatment of electronic and vibrational dynamics, at a quantum mechanical level, which is quite complicated and computationally onerous [2].
We have explored an approximate scheme to overcome this problem that consists of decoupling the description of electron attachment from that of bond dissociation. We model post-DEA by adding an electron to the lowest unoccupied state of the neutral system and simultaneously injecting kinetic energy in the vibrational motion of a specific bond through a specified additional velocity. In this model we are assuming that electronic attachment and decay into a bound state (the LUMO in our case) occur in an extremely short time scale, in which the atoms in the bond have not yet began to move. We have studied the dissociation of a nucleobase and a nucleotide in three different environments: gas-phase, micro-solvated, and fully-solvated in the condensed phase, observing important caging effects that hinder the dissociation process. In this talk I will present these results and discuss the various factors that influence the dynamical processes ensuing the DEA process [3]. I will also discuss other protection mechanisms that are at play in the physiological environment.

References:
1. Boudaiffa B, Cloutier P, Hunting D, Huels MA, Sanche L (2000) *Science* **287**: 1658.
2. Rizzi V, Todorov TN, Kohanoff J, Correa AA (2016) *Phys Rev B* **93**: 024306.
3. Kohanoff J, McAllister M, Tribello G, Bin Gu (2017) *J Phys Condens Matter* **29**: 383001, and references therein.

L29.3

Probing the mechanistic pathways and structural aftermaths of complex DNA lesions

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The structural elucidation of complex lesions is extremely challenging and many questions unanswered and modelling insights are sought to corroborate multistep mechanisms that are currently only postulated, even for the prototypical 8-oxoguanine.
Static calculations, most often based on a DFT framework, have proved their relevance yet beyond single-nucleotide lesions we will show that they can be associated to a spurious description due to the formation of hydrogen bonds between dinucleosides and a deviation from an acceptable and representative pi-stacked structure. We lift these limitations resorting to hybrid QM/MM-MD simulations [1]: the B-DNA environment is realistically taken into account and we prove in passing that the B-helix embedding can reverse the intrinsic electronic reactivity of hydrogen-abstracted pyrimidines [2].
We also rely on classical MD simulations to generate representatives structures of oligonucleotides featuring one or several lesions. This enables to monitor the B-helix distortion and the outcome of the initial Watson-Crick pairing: this way, we shed light on the lack of repair of tandem lesions [3].

References:
1. Bignon E *et al.* (2016) *Nucleic Acids Research* **44**: 56-62.
2. Garrec J *et al.* (2012) *J Am Chem Soc* **134**: 2111-2119.
3. Dehez F *et al.* (2017) *Nucleic Acids Research* **45**: 3654-3662.