PhD proposal 2020-2023

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Multiscale Simulations of Radical Cation Guanine in the Nucleosomal DNA

The oxidation of nucleobases, induced by light absorption or oxidative stress, creates a highly reactive radical moiety which can leads to the formation of deleterious DNA lesions. With the lowest ionization potential among nucleobases, guanine is the most sensitive target ("hotspot") for DNA oxidation. However, the formation, the propagation and the reactivity of the radical cation guanine underlies a complex and combinatorial chemistry where the sequence, the structure and the environment of the DNA duplex play a decisive role. Our group has developed efficient computational protocols to characterize DNA damages using both classical and quantum mechanical /molecular mechanical (QM/MM) simulations at large timescale (nano to microseconds).[1] This PhD project proposes to go beyond the double-helix DNA (B-DNA) and simulate the radical cation guanine propagation within a nucleosomal structure.

The nucleosome is the elementary unit of the chromatin and consists in a B-DNA segment of 146-147 base pairs of nucleobases wrapped around a protein core of eight histones. In this structure, the guanines undergo a specific environment depending on the sequence, but also on their position in the nucleosomal DNA and the interactions with the proteins, which modulates their ionization potential and the competition between radical transfer and radical reactivity.[2] The transient character of radical moieties makes their experimental detection difficult while very efficient computational protocols are required to describe the nucleosome behavior at relevant timescales.

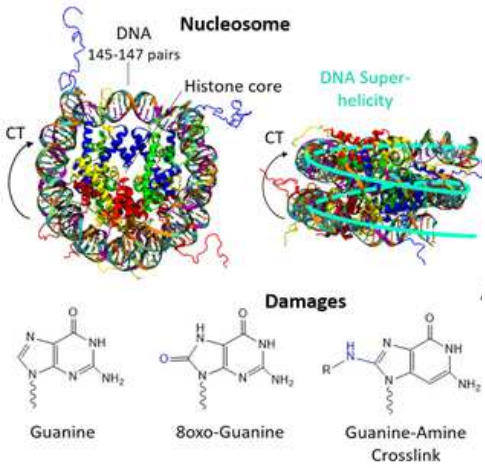

Figure 1 : Representation of a nucleosome unit and the different charge transfers (CT) along the DNA sequence or between two strands in the superhelical conformation. Guanine and two products of guanine oxidation are also represented: 8oxo-guanine and guanine-amine Crosslink (for example, guanine-lysine or guanine-arginine).

In this project, we propose to use a combination of state-of-the-art classical and QM/MM (DFT/MM and DFTB/MM) simulations to determine the behavior of radical cation guanine within a nucleosome unit. Multiples and microsecond timescale classical simulations will provide a large conformational sampling of the DNA and the guanines (about 60). They will be used as starting point to long-range charge transfer simulations allowing a large QM zone to follow the radical cation propagation and to determine the most likely oxidation sites.[3] Machine learning protocols will be implemented in order to analyze the large amount of data generated by the multiscales simulations.[4] This work will be support by a strong interaction with experimentalists: the group of M. Greenberg (Johns Hopkins University, USA), experts in the detection and localization of DNA damages in nucleosome and the Cibest team at the CEA Grenoble, with a strong expertise in DNA damages. The goal of the PhD project is to draw rules for the sequence and environment impacts on the preferential oxidation site in the nucleosome. It will take advantage of the framework of the PRIMES Labex consortium.

The candidate should have a strong background in chemistry and physical chemistry. A knowledge about computational chemistry and molecular dynamics is welcome, as well as a strong interest in biochemical issues.

References:

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