Master Proposal

Multiscale Simulations of Radical Cation Guanine in the Nucleosomal DNA

NucleoMAP ANR Project

Contact : Natacha Gillet natacha.gillet@ens-lyon.fr, *Laboratoire de Chimie, Ecole Normale Supérieure de Lyon, UMR-CNRS 5182, 46 allée d'Italie, 69364 Lyon Cedex 7.*

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 its relatively small ionization potential, guanine is the most sensitive target for DNA oxidation. However, the formation, the propagation and the reactivity of the radical cation guanine involves a complex and combinatorial chemistry where the sequence, the structure and the environment of the DNA duplex play a 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 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.

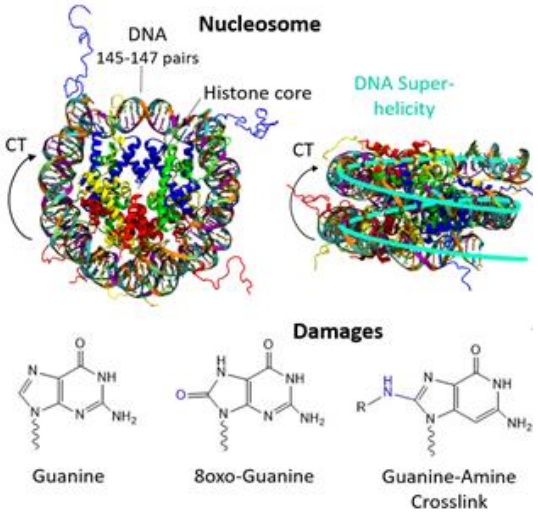

Figure 1 : Representation of a nucleosome unit and the different charge transfers (CT) along the DNA sequence or between two strands in the superhelical conformation. Guanine and two products of guanine oxidation are also represented: 8oxo-guanine and guanine-amine Crosslink (for example, guanine-lysine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

In this project, we propose to use a combination of state-of-the-art classical and QM/MM 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 to determine the ionization potential of the different

nucleosbases and draw a first map of the most likely oxidation sites.[3] The student will benefit from an access to the local mesocenter PSMN and a privileged access to the Jean-Zay GPU machines for the simulations. This master internship takes place in the context of the NucleoMAP ANR project and will be followed by a 3 years PhD contract.

The NuceoMAP project include the more complex simulation of charge transfer mechanism along DNA and the implementation of machine learning protocols 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.

The candidate should have a background in chemistry, physical chemistry or biochemistry. He/she should present a strong interest in computational approaches and biochemical issues.

References:

1. E. Dumont, A. Monari Front. Chem, **2015**, 3, 43 https://doi.org/10.3389/fchem.2015.00043
2. H. Sun, L. Zheng, K. Yang, M. M. Greenberg, JACS, **2019**, 141, 10154-10158 https://doi.org/10.1021/jacs.9b03686
3. T. Kubar, M. Elstner, PCCP, **2013**, 15, 5794-5813 https://doi.org/10.1039/C3CP44619K
4. O. Fleetwood, M. A. Kasimova, A. M. Westerlund, L. Delemotte, Biophysical J, **2020**, 118,765 https://doi.org/10.1016/j.bpj.2019.12.016