Mapping Guanine Oxidation in Nucleosomal DNA using Multiscale Simulations

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Light, oxidative stress or exogenous molecules can modify the well-designed structure of DNA by inducing nucleobases lesions. The accumulation of these damages can hinder the DNA transcription or replication and lead to mutations, cell apoptosis or cancers. As a consequence, numerous studies focus on the elucidation of the mechanisms of damages formations or their repair by dedicated proteins. Because of the complexity of the DNA molecule in its biological context, the problem becomes rapidly combinatorial, involving sequence, structural and dynamical effects. Indeed, beyond the double strand structure, the DNA polymer is wrapped around a core of eight proteins call histones to form nucleosomes.[1] This specific and dynamical environment mechanically constrains the DNA conformation and creates an heterogeneous electrostatic field. Then, the physicochemical properties of the nucleobases and their reactivity can become strongly dependent on their position around the histone core (see for example [2]), especially the redox properties of the nucleobases.

The recent efforts to increase computational power of simulations have permitted the first all-atom classical simulations of a nucleosome at a microsecond timescale[3], and our group also perform long timescale classical simulations of damaged DNA [4–6] We present here our guanine oxidation map obtained using efficient FO-DFTB/MM approach [7] over 20 µs all-atom simulations. We focus on the importance of different parameters such as sequence, nucleobase position and tail proximity on the guanine redox properties. All our data will be used to feed machine learning algorithm to provide a better understanding of the environmental factors which can play a role on these properties and facilitate the analysis of our complex simulations.
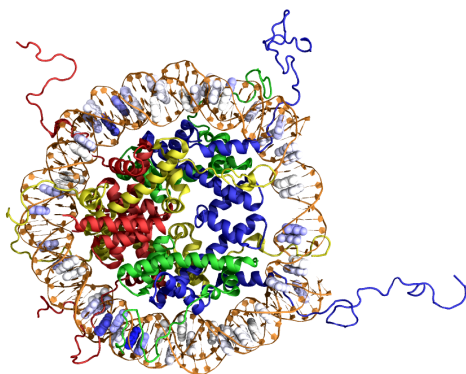

Figure 1: Nucleosome particle with guanine colored depending on their ionization potential from white (low ionization potential) to blue (high ionization potential)

References

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