Exploring the mechanisms of damage of biomolecules under ionising irradiation with numeric simulations

BOUKEKE-LESPLULIER Thomas[A,B]; **CAILLIEZ Fabien**[A]; **GILLET Natacha**[B]; **DE LA LANDE Aurélien**[A]

A) Insitut de Chimie Physique, Université Paris-Saclay, CNRS 15 avenue Jean Perrin F-91405 Orsay;
B) Laboratoire de Chimie, Ecole Normale Supérieure de Lyon, 44 allée d'Italie, Lyon 69007, France

thomas.boukeke@universite-paris-saclay.fr

The study of the irradiation of living matter is a field of major clinical interest, whether it be for its deleterious physiological effects or for its use in radiotherapy. We work on the damage caused by ionising irradiations on two biosystems, one extracellular and one intracellular. The first is a triple helix of the polypeptide (Proline-Proline-Glycine)$_{10}$ designated as collagen mimetic peptide (CMP) **Fig. 1**, as it mimics the collagen protein, the main component of the extracellular matrix of animals. The second is the nuceosome **Fig. 2**, composed of an octamer of histone proteins around which a 147 bp long fragment of DNA is wrapped.

For these two systems, our approach aims at describing the whole phenomenon of the ionising irradiation in which we distinguish three phases. First the energy deposition, which takes place at a timescale inferior to 1 fs, corresponds to the impact of the ionising particle or photon on the electron cloud. We chose a QM/MM approach that allows to consider the entire molecular structure. The QM part is simulated under the Born- Oppenheimer approximation with RT-TD-DFT[1]. Then, the energy is dissipated into the vibrational modes of the bonds, which can lead to breaks. At this point, the B-O approximation is off, and we use an Ehrenfest method for the classical dynamics part of the QM/MM modeling. The corresponding timescale expands from 1 fs to 1 ps. Finally, we look at more macroscopic architectural modifications (ns to µs) with pure MM.

We started our simulations with CMP, as mass spectrometry experiments have been carried out to study the effects of ionising irradiation of CMP in the gas phase[2]. It provides us with a precise landscape of the disssociation and fragmentation at stake, which will allow us to test our simulation methodology, especially for the QM/MM-Ehrenfest part. We will see how our simulated products of ionising irradiation compare with the experimental data. If both match in a convincing manner, we will be able to focus on the molecular detail of the damage mechanisms. Thereby, we intend to use the CMP as proof of methodology to apply it to the nucleosome which is ten times larger than a CMP. Moreover, there is no available data about irradiations products of nucleosome, and no molecular entity of this size has ever been simulated using QM/MM-Ehrenfest.

Figure 1. Collagen mimetic peptide[1]

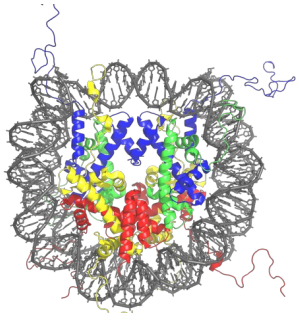

Figure 2. Nucleosome, © Richard Wheeler – Nuffield Department of Medicine, University of Oxford

Keywords: ionizing radiation, direct effects, biomolecules, QM/MM

[1] Karwan Ali Omar, Karim Hasnaoui, Aurélien de la Lande **First-Principles Simulations of Biological Molecules Subjected to Ionizing Radiation** Annual Review of Physical Chemistry 2021 72:1, 445-465

[2] M. Lalande, M. Abdelmouleh, M. Ryszka, V. Vizcaino, J. Rangama, A. Méry, F. Durantel, T. Schlathölter, and J.-C. Poully **Irradiation of isolated collagen mimetic peptides by x rays and carbon ions at the Bragg-peak energy** – Phys. Rev. A 98, 062701 – Published December 2018