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PhD Project:

Understanding formation and repair of 8-oxoguanines damages in the nucleosomal DNA using multiscale simulations

Supervisor: Natacha Gillet (natacha.gillet@ens-lyon.fr)

Place : Laboratoire de Chimie (Lyon, France)

Duration: 3 years

Project

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, which impacts the physicochemical properties of the nucleobases, their reactivity and their accessibility to protein interacting with DNA.

In this project, we focus on the 8-oxoguanine damage which results from the oxidation of a guanine. This damage is known to modify the DNA conformation, and also to evolve to secondary damages and abasic sites because of its redox properties. On the other hand, it is recognized by several proteins such glycosylases for its repair. We thus plan in this project to use classical and QM/MM molecular dynamics simulations to explore the conformational behavior of the 8-oxoguanine in the context of nucleosomal DNA, its redox properties and its possible interaction with repair proteins. These methods have been successfully used in our group for simulations of damaged nucleosomal DNA [2-4] and glycosylase-damage DNA interaction [5]. We aim to go further in the analysis of the combinatorial mechanisms at play in the damage behavior in the nucleosomal DNA environment by inclusion of dedicated machine learning approaches.

The candidate must have a solid background and interest in physical chemistry, biochemistry or molecular biology. Competences in programming, computational chemistry or bioinformatics are also welcomed.

cnrs

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