Ecole Doctorale des Sciences Fondamentales

Title of the thesis: Traffic on mitochondrial DNA: an experimental and numerical study of DNA polymerase roadblocks

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Summary :
Mitochondria are organelles that produce ATP (cellular 'fuel'), which powers most reactions in the cell. They contain their own DNA (mtDNA), and the genes on this genome are copied (replicated) by the DNA polymerase. The number of mitochondria and the amount of mtDNA produced by the replication machinery correlate directly to the cellular energy output. Thus mtDNA replication represents a fundamental process which tunes the cellular metabolism. The mtDNA replication machinery has been reconstituted *in vitro*, increasing the biochemical understanding of mitochondrial functioning. Yet, in the cell, mtDNA is hardly ever bare; instead, it is crowded with multiple proteins orchestrating the reading, the duplication and the maintenance of the genetic material. DNA-binding molecular motors, such as DNA polymerase, have to progress on such busy tracks, making collisions between proteins inevitable. Yet, the dynamic interactions between a moving DNA polymerase and roadblocks on mtDNA remain mostly unexplored.
The goal of this thesis is to obtain a quantitative understanding of the dynamics of mtDNA roadblocks and of their interactions with a moving DNA polymerase. To obtain a complete picture, a systematic approach will be used, combining quantitative experiments and mathematical modeling. For the experimental approach DNA roadblocks and DNA polymerases will be visualized while they are 'on the job' using single-molecule biophysics tools, such as acoustic pushing, DNA stretching and fluorescent microscopy. For the numerical simulations, we will use Langevin dynamics, which take into account the details of DNA and proteins, and Monte Carlo simulations to access time and length scales similar to the experimental ones.

Key words:
Experimental biophysics, single molecule techniques, numerical simulation

References:

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