

A new genome geometrical model with atomic resolution based on HiC-maps.

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Background: A DNA geometrical model is required for carrying out Monte Carlo simulations of the radiation-DNA interaction process. This approach has been successfully applied in the Computational Radiobiology field. Here, a new model with atomic resolution, going from the nucleotide pair up to the chromosome, is presented. The structure of the chromosome was extracted from high resolution HiC-maps [1].

Material and Methods: The 3D structure of a single chromosome, built from HiC-maps with 5 kbp resolution, was used in conjunction with a model of the 30-nm chromatin fiber to build a complete model of the chromosome in question with atomic resolution. A mathematical formalism was developed for finding the closest DNA atom to an arbitrary point in space, which may represent an energy deposition or a chemical species. Three different chromatin fiber pitches were tested and their impact on DNA damage yields was studied. Simulations were done with the Geant4-DNA package, where energy depositions were superimposed on the DNA geometrical model using a home-made post-processing code. Only direct DNA damage was accounted for in these preliminary results, but we are working on implementing the chemical mechanism as well.

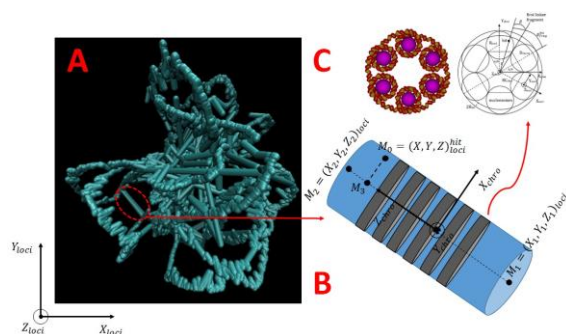


Figure 1: Atomistic geometrical model of a chromosome based on HiC-maps.

Preliminary results:

Table 1 shows preliminary results for direct total and double strand break yields determine with 2 MeV protons. Three chromatin fiber pitches were used to study the influence of this parameter on damage yields. It should be remarked that chromosome 3D structure built from HiC-maps does not carry information on absolute dimensions. Thus,

nuclear size was used as a reference to scale the genome dimensions. Total strand break (TSB) yields are comparable, within the uncertainty, for the three chromatin pitches used. However, double strand break (DSB) yields seem to be influenced by this parameter. The study will be completed using other particles and energies. In addition, the chemical damage will be studied as well.

Table 1. Preliminary results on damage yields for three different chromatin fiber pitches.

Chromatin pitch (nm)	7.11	10.77	14.44
Dose (Gy)	1.61±0.03	1.57±0.08	1.5±0.1
TSB yield (1/GyGbp)	63±7	69±8	77±7
DSB yield (1/GyGbp)	2.0±0.5	4±1	3.5±0.9

This full atomistic geometrical model of chromosomes may be used for better describing the DNA repair process after radiation-induced damages and the subsequent induction of complex DNA damages, such as chromosome aberrations. To accomplish this task, the whole cell genome must be incorporated into the model.

References

[1] S. Rao et al. A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping. Cell 159, 1665–1680, 2014.