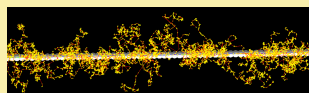


Purpose

Simulation of biological effects induced on DNA by ionizing radiation is an active and multidisciplinary field of research requiring, at least, the simulation of three stages: physical, physico-chemical and chemical. In the simulation of these stages, the description of the target is needed at different scales: cell nucleus, nucleosome, double helix, nucleotide pair etc. In this work we present the DnaFabric software [1] that is dedicated to the **generation, modification** and **real-time visualization** of such multi-scale models. Using DnaFabric, models of the DNA content of several cell nucleus were created in order to be used in simulations based on the Geant4-DNA MC code [2].

A geometrical DNA model is required to compute radio-induced damages after those three stages.

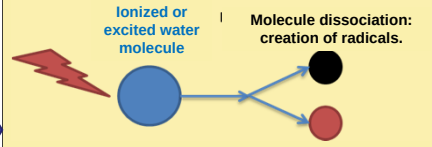
Physical stage



Simulation of the physical interactions at the nanometric scale.

Objective in this work: To design a DNA model in which the simulation of the physical interactions can be performed down to the nanometric scale.

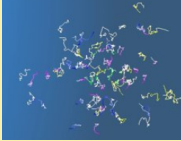
Physico-chemical stage



Simulation of the dissociation channels used for the ionized or excited water molecules [3].

Objective in this work: The geometrical DNA model is required to prevent DNA molecules to be converted into water radicals.

Chemical stage



Simulation of the radical diffusion as well as their chemical reactions in liquid water [3].
Objective in this work: The DNA model is required to allow the individual identification of each DNA molecules: 2-deoxyribose, phosphate, adenine, guanine, cytosine and thymine.

Final Objective

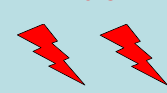
Comparison: simulation vs experimentation

Main DNA damages

- **Simple strand break (SSB)** occurring directly (physical step) or indirectly (chemical step) on sugar-phosphate moiety.
- **Double strand break (DSB)** caused by two SSB separated by less than 10 base pairs and localized on opposite strands.

DSB are DNA damages difficult to repair that can lead to cell death or cell inactivation.

Cell irradiations with light ions



DSB detection using different experimental technics:

- Foci (γH2AX)
- Pulsed field gel electrophoresis

The DnaFabric software

Software main characteristics

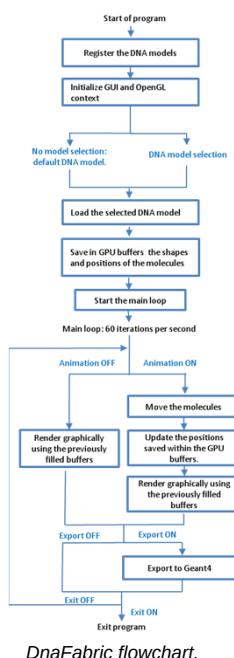
Architecture

The DnaFabric code is organized in modules that correspond to different fields of expertise. The different modules are:

- The **Run** module is in charge of the general DnaFabric processes such as the main loop or the start and stop functions.
- The **GUI** module is based on the Qt library and setups the user interface.
- The **3D** module manages all the visualization capabilities of DnaFabric. It encapsulates OpenGL functions in order to add an abstraction level between OpenGL and a DnaFabric user.
- The **Scene** module contains the files required to define and analyzed the hierarchical relationship between the different object placed in a geometry.
- The **Engines** module offers facilities for the user to code simulations meant to modify the geometry
- The **Utils** module is a placeholder locations for general scope functions such as time retrieval calls.

DnaFabric specificities

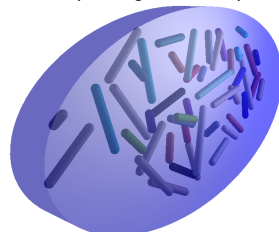
- ✓ Work with a lot of elements that can be individually accessed: several billions of objects can be used in a DnaFabric model.
- ✓ Such complex models can be visualized thanks to the custom 3D engine included within the 3D module.
- ✓ Engines module allows to run calculations that can interact with a model. Thus, the model can be modified in real-time depending on the evolution of the ongoing calculations → calculation monitoring.



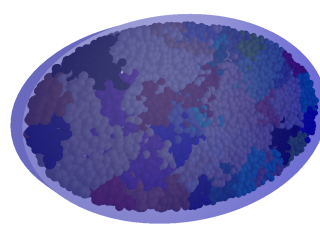
DnaFabric flowchart.

Cell nucleus modeling

1. Choose a cell nucleus type: fibroblast, endothelial or lymphocyte.
2. Choose a genome type: male or female. The genome will be randomly generated in a condensed state.
3. Simulate the relaxation of the genome [4] thanks to the Engine module. The resulting genome is in a state corresponding to the G0 phase of the cell cycle.



An endothelial cell nucleus with a condensed male genome. The 46 chromosomes are represented by 46 cylinders.



An endothelial cell nucleus with a relaxed male genome. The 46 chromosomes are represented by the colored areas, themselves made of concatenated spheres that stands for the chromosome domains. The domains are empty at this stage.

Cell	Shape	Dimensions
Fibroblast	Ellipsoid	semi-major : $9.85 \cdot 10^3$ nm semi-minor : $7.1 \cdot 10^3$ nm semi-minor2 : $2.5 \cdot 10^3$ nm
Lymphocyte	Sphere	radius : $5.0 \cdot 10^3$ nm
Endothelial	Elliptic cylinder	semi-major : $9.5 \cdot 10^3$ nm semi-minor : $5.1 \cdot 10^3$ nm height : $1.0 \cdot 10^3$ nm

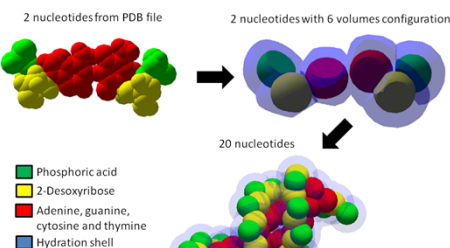
Different nucleus generated using DnaFabric.

The relaxed or condensed genome and its nucleus can be saved in a ".fab" file in order to be loaded in the future.

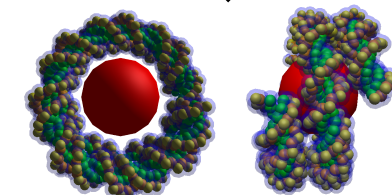
Modeling of a human genome in a endothelial cell nucleus

Construction of a DNA model

Using the features provided by DnaFabric, a model describing the DNA from the molecular level up to the chromatin fiber was created. This model is highly adaptable and can be customized to suit the need of different users. For example, the placement of the voxels described in 4) to build a DNA filament going from a point A to a point B is fully automated.

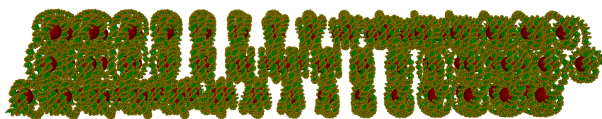


1) Starting from an atomistic description of a nucleotide pair, a 6 volumes nucleotide pair model is generated. Then, several nucleotide pairs are stacked on each others to create the DNA double helix.

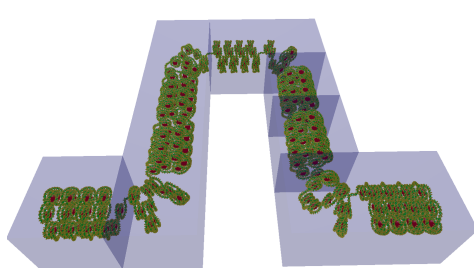


2) The DNA double helix is twisted around a red sphere that represents a complex of histone proteins. The resulting construction is called a nucleosome [5].

Characteristic	Compacted fibre
Number of nucleosomes	90
Pitch	10 nm
Helix radius	10.46 nm
Nucleosomes per turn	6
Delta angle	60 deg
Fibre radius	17 nm
Fibre length	160 nm



3) A heterochromatin DNA fiber made of 90 linked nucleosomes. The fiber contains about 18000 nucleotide pairs.

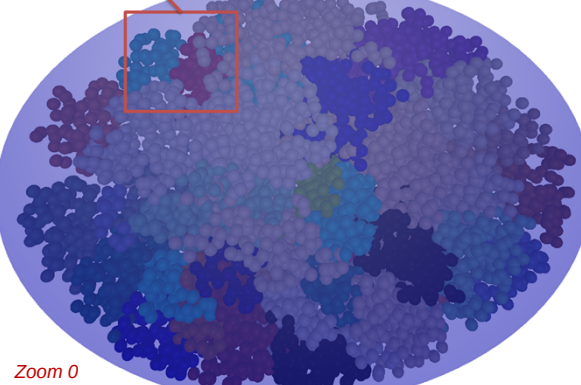
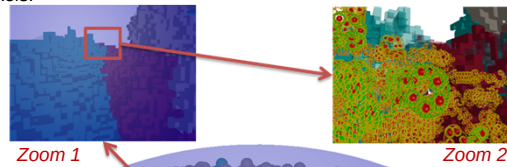


4) The fiber is cut and put in voxels to allow the creation of a continuous chromatin filament. This chromatin filament can follow almost any path providing start and end points.

The filling of a cell nucleus model with DNA

Any relaxed genome within a cell nucleus can be filled with voxels to add DNA molecules in the nucle us. This filling can be done by two algorithms included in the Engines module of DnaFabric:

1. A **loop algorithm** that will positioned the voxels to reproduce the loops performed by the chromatin filament in each domain (colored spheres) of a chromosome.
2. A **space filling algorithm** that do not reproduce the loops but focus on maximizing the space occupied by the voxels.



A fibroblast cell nucleus with a genome in a relaxed state. The genome was filled with voxels thanks to the loop algorithm. As a result and with DnaFabric, it is possible to zoom in toward the nucleus to see individual molecules (zoom 2) or, voxels (zoom 2) and to zoom out to watch the 46 chromosomes territories (zoom 0).

This model can be exported to a ".fab2g4dna" file readable by dedicated Geant4 user-applications. The use of those user-applications in a calculation chain with a slightly modified Geant4 version (Geant4.LDRI.01) allows to perform the simulation of the physical, physico-chemical and chemical stages taking into account the DNA content of a whole human genome (~36.10⁹ DNA molecules).

Conclusion and perspectives

- The DnaFabric software was used to generate several nucleus (fibroblast, endothelial and lymphocyte) with condensed and relaxed genomes (male and female).
- The genomes were filled with one continuous chromatin filament per chromosome through the use of voxels and one of the two filling algorithms included in DnaFabric.
- Nucleus with or without filled genomes can be explored in real-time thanks to the 3D engine of DnaFabric.
- Nucleus and genomes can be exported to ".fab2g4dna" files in order to be read by dedicated Geant4 user-applications.
- Using such user-applications, a calculation chain was developed to simulate the physical, physico-chemical and chemical stages following the irradiation of a cell nucleus filled with DNA (condensed and filled genome). The calculations are currently ongoing.

References

- [1] S. Meylan, U. Vimont, S. Incerti, I. Clairand, C. Villagrasa, *Geant4-DNA simulations using complex DNA geometries generated by the DnaFabric tool*, Computer Physics Communications 204 (2016) 159-168.
- [2] S. Incerti, G. Baldacchino, M. Bernal, R. Capra, C. Champion, Z. Francis, S. Guatelli, P. Guèye, A. Mantero, B. Mascialino, P. Moretto, P. Nieminen, A. Rosenfeld, C. Villagrasa and C. Zacharatou, *The Geant4-DNA project*. Model. Simul. Sci. Comput. (2010)
- [3] M. Karamitros et al, *Diffusion-controlled reactions modeling in Geant4-DNA*, Journal of Computational Physics 274 (2014): 841-882.
- [4] G. Kretz et al, *Radial arrangement of chromosome territories in human cell nuclei: a computer model approach based on gene density indicates a probabilistic global positioning code*, Biophysical journal 86 (5) (2004) 2803-2812.
- [5] M.A. Bernal, D. Sikansi, F. Cavalcante, S. Incerti, C. Champion, V. Ivanchenko, Z. Francis, *An atomistic geometrical model of the B-DNA configuration for DNA-radiation interaction simulations*, Computer Physics Communications. (2013)