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

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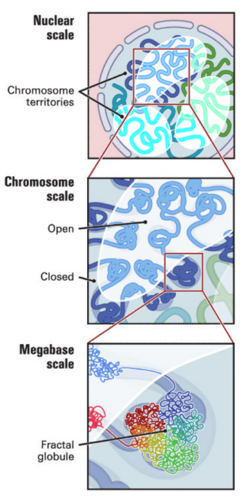
IV Geant4 International User Conference at the physics-medicine-biology frontier. Napoli.
October 24-26, 2022

Introduction

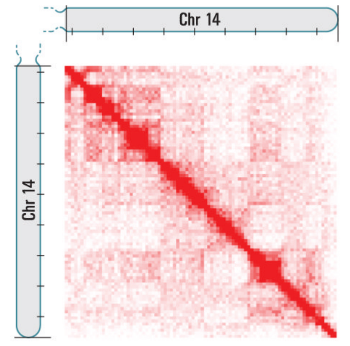
- Ionization radiation produces DNA damage by direct and indirect mechanisms.
- Radiation-DNA interaction can be simulated combining MC simulation+DNA geometrical model+biophysical model
- A polymer-type model for chromosomes can be built from HiC-maps

Introduction

Genome structure



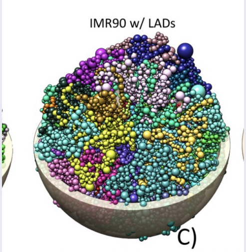
HiC-map



Lieberman-Aiden et al. Science 326(5950): 289–293 (2009)

Introduction

Genome HiC model available



Ingram et al. PLoS Comput Biol 16(12): e1008476 (2020)

HiC-maps

- Non molecular model.
- Track structure influence on damage pattern is not accounted for

Our goal

To develop a DNA geometrical model with atomic resolution, based on HiC-maps.

Our approach

- Chromosome 1 structure from HiC-maps at 25 kbp resolution for A549 cell line (Genome Structure Database (GSDB) @ http://sysbio.rnet.missouri.edu/3dgenome/GSDB/)
- A549 nucleus radius: $\sim\ 5\mu m$
- Use of the previously developed atomic model for chromatin fiber to fill chromosome structure
- Test the model by irradiating it with protons

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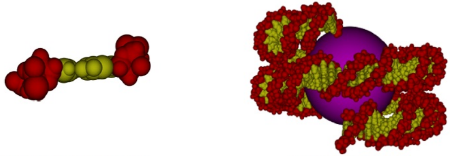
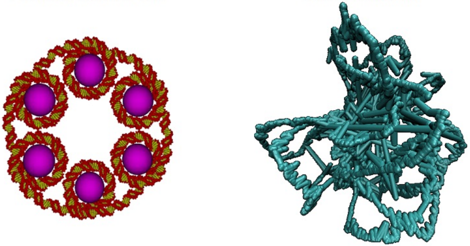
Our approach. Geometrical model

Chromosome 1



Level 1: Double helix DNA

Level 2: Nucleosome

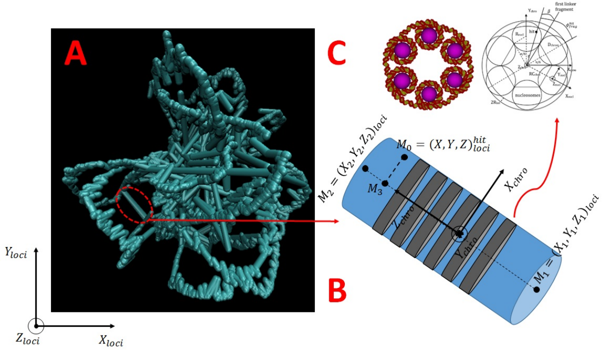


Level 3: 30 nm chromatin fiber

Level 4: Chromosome

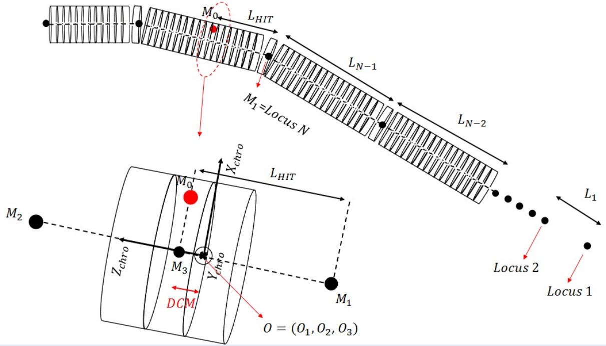
Our approach. Geometrical model

Filling the chromosome



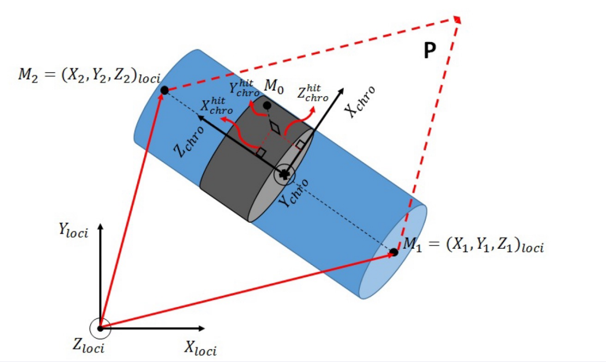
Our approach. Geometrical model.

Geometrical formalism



Our approach. Geometrical model

Reference plane



Tests

Testing the model

- Use of 3 chromatin pitch values: 7.11 nm, 10.77 nm, and 14.44 nm (HiC map reconstruction lacks of scale).
- G4.10.2, G4EmDNAPhysics physics constructor.
- 1.06 g/cm^3 water as transport medium
- SSB-induction threshold was 8 eV.
- Irradiates with 2 MeV protons

Preliminary results

Preliminary results for direct damage only

Proton - 2 MeV	7.11nm	10.77nm	14.44nm
Mean Total Dose (Gy)	0.46 ± 0.04	0.38 ± 0.05	0.40 ± 0.04
TSB yield(1/GyGbp)	46 ± 9	83 ± 15	105 ± 10
Vol. (μm^3)	13x13x12	20x20x16	28x26x22

Results different from abstract due to adjusments in the model.

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Analysis of preliminary results

- TSB yield should be independent of the chromatin pitch.

$$
\begin{aligned}
TSBY &= \frac{NTSB}{D \times NBP} \\
NTSB &= SHP \times NDep \\
D &= \frac{\bar{\epsilon} \times Ndep}{\rho \times V} \\
SHP &= \frac{2 \times NBP \times V_{target}}{V}
\end{aligned}
$$

Combining all these equations, we get

$$
\begin{aligned}
TSBY &= \frac{2 \times V_{target} \times \rho}{\bar{\epsilon}} \\
&= \frac{2 \times 0.13\ nm^3 \times 1.06 \times 10^3/m^3}{16\ eV} \qquad (1) \\
&= 108\ 1/GyGbp
\end{aligned}
$$

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Conclusions and perspectives

- Damage yields are consistent yet there is considerable superposition of genetic material for short chromatin pitches
- The junction between two consecutive chromatin segments must be improved.
- It is possible to build up a genome geometrical model with realistic chromosome structure (yet there is a lot of work to do).
- This model could be used in conjunction with coarse-grain molecular dynamics or Monte Carlo to simulate DNA repair process
- Having into account the whole genome should allow to simulate chromosome aberration induction

Acknowledgements

- Geant4-DNA collaboration.

FAPESP
FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

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