Recent Developments in the Geant4-DNA Toolkit

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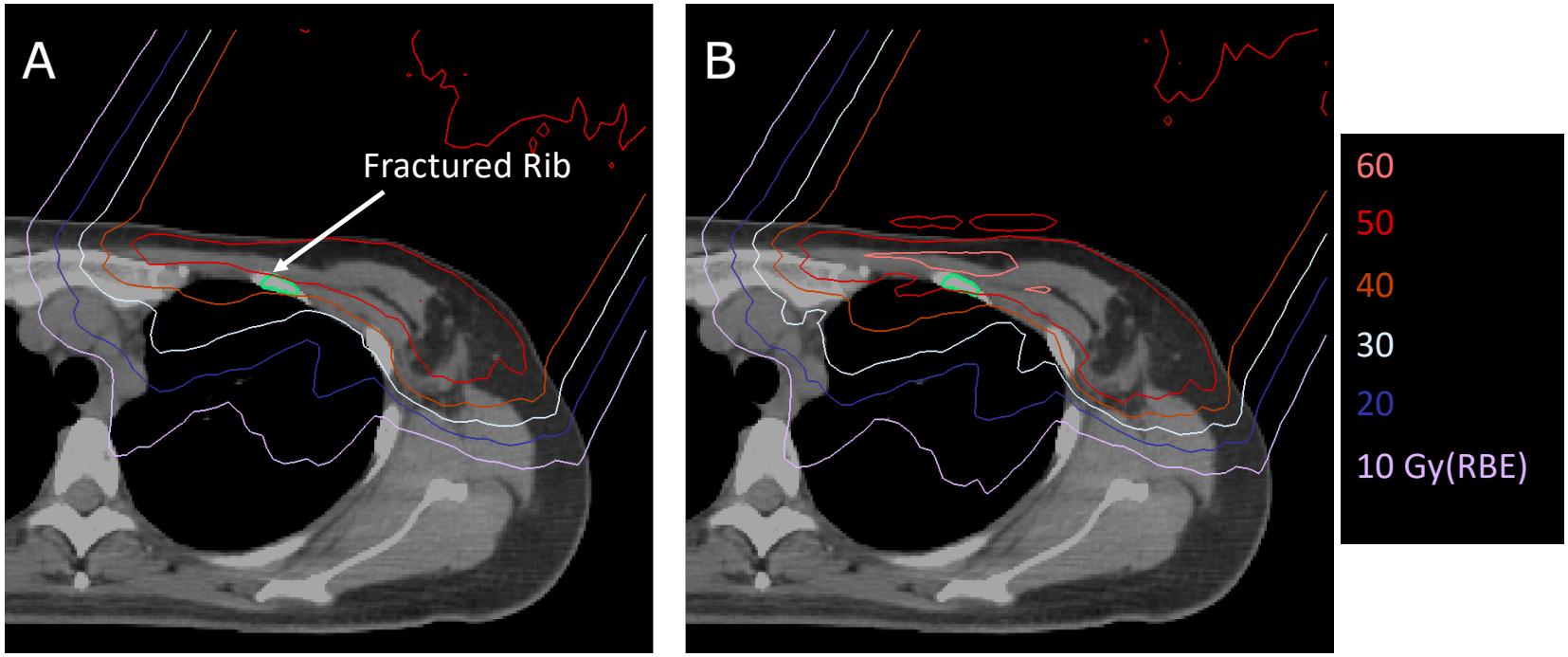
Harvard Medical School

MOTIVATION

- LET/RBE predictions in patient simulations
  - Rib fracture in breast patients locates at distal edge of proton beam. LET model predicts a higher dose than the 1.1 scaled dose.



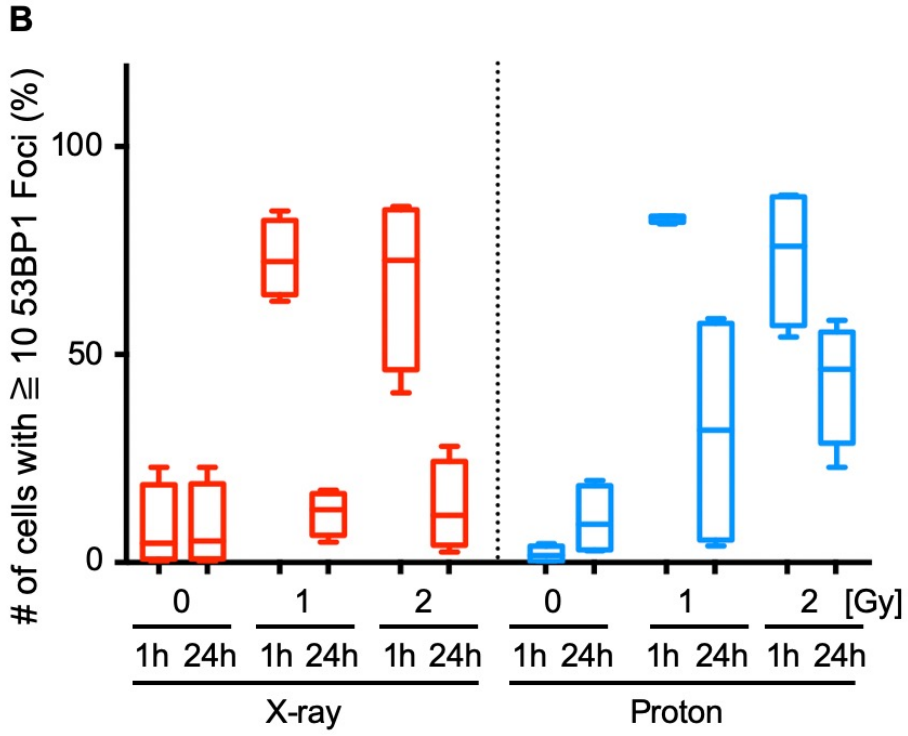
RBE = 1.1

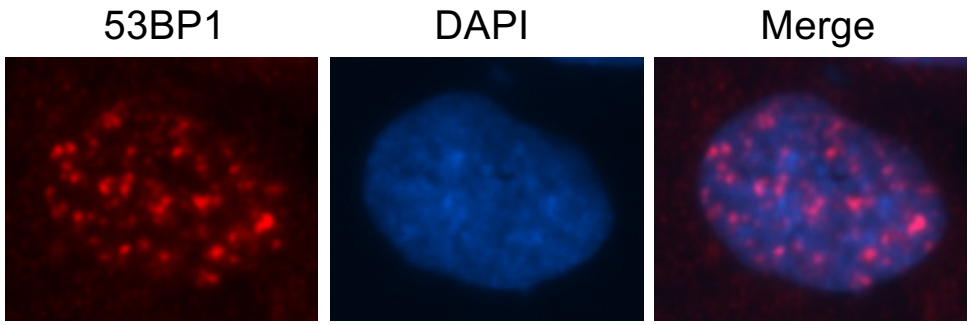
LETd-weighted dose

Wang et al. (2019) Int. J. Radiat. Oncol. Biol. Phys. 105(1) E61.

MOTIVATION

- Cell experiments show proton irradiated bone cells (osteocytes) have persistent DNA damage, while photon irradiated cells repair foci damage.



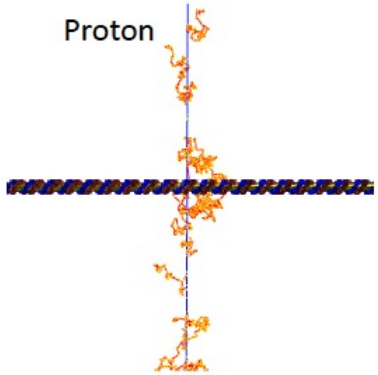


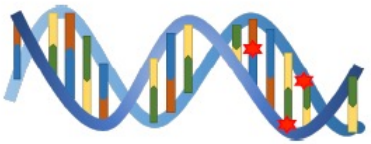
THE NEXT STEP

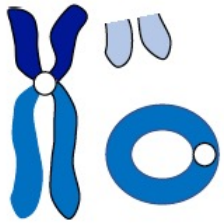
- Clinical endpoint of interest is a biological effect not the physical dose.
- Understand how radiation interacts with tissue on a cellular level.
- New advances are most likely to come from the interface of biology, chemistry and physics.

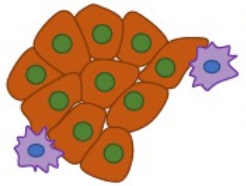
How do we model biological effects?

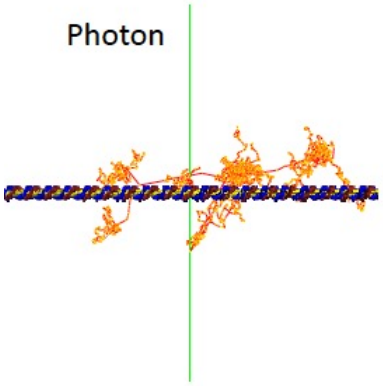
MECHANISTIC MODELING

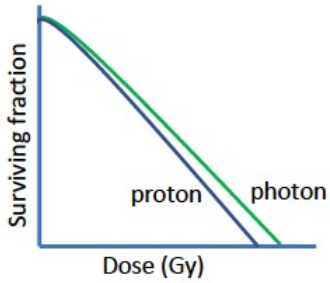


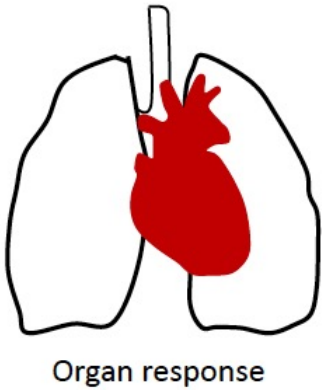


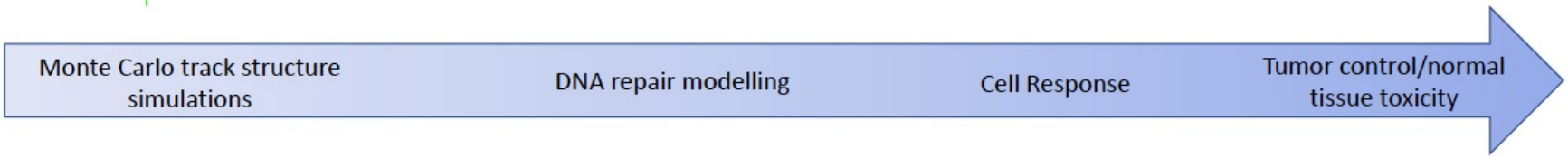






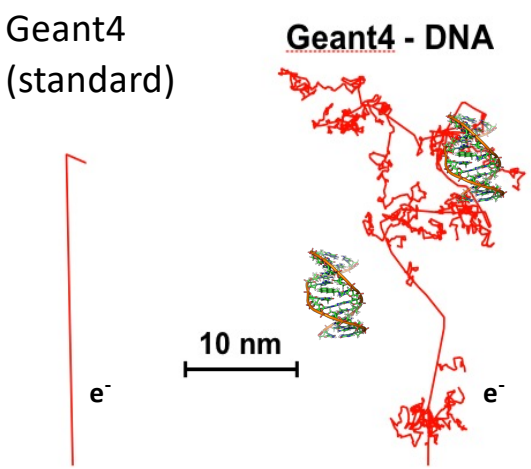


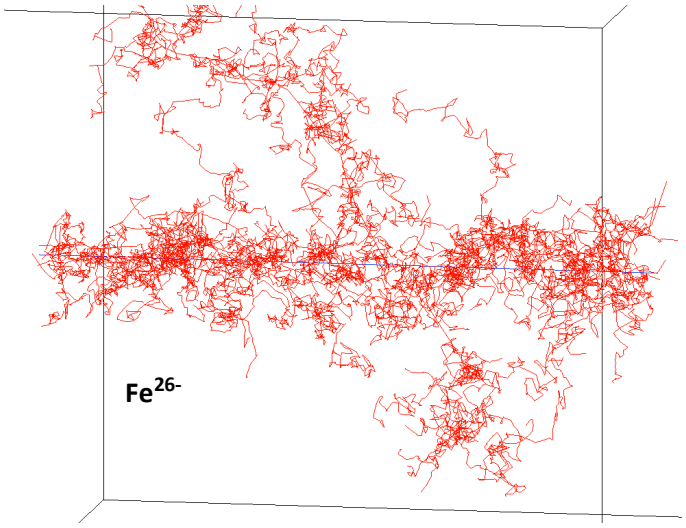




TRACK STRUCTURE MODELING

- Monto Carlo simulation on a nanometer scale.
- Physics processes and models simulate step-by-step interactions of particles in liquid water to the eV scale.
- Physico-chemistry and chemistry processes for water radiolysis.
- Geant4-DNA, PARTRAC, PITS, RITRACKS …





Bernal, et al. (2015), Phys. Med. 31, 861-874
Incerti et al. (2010), Med. Phys. 37,4692-4708

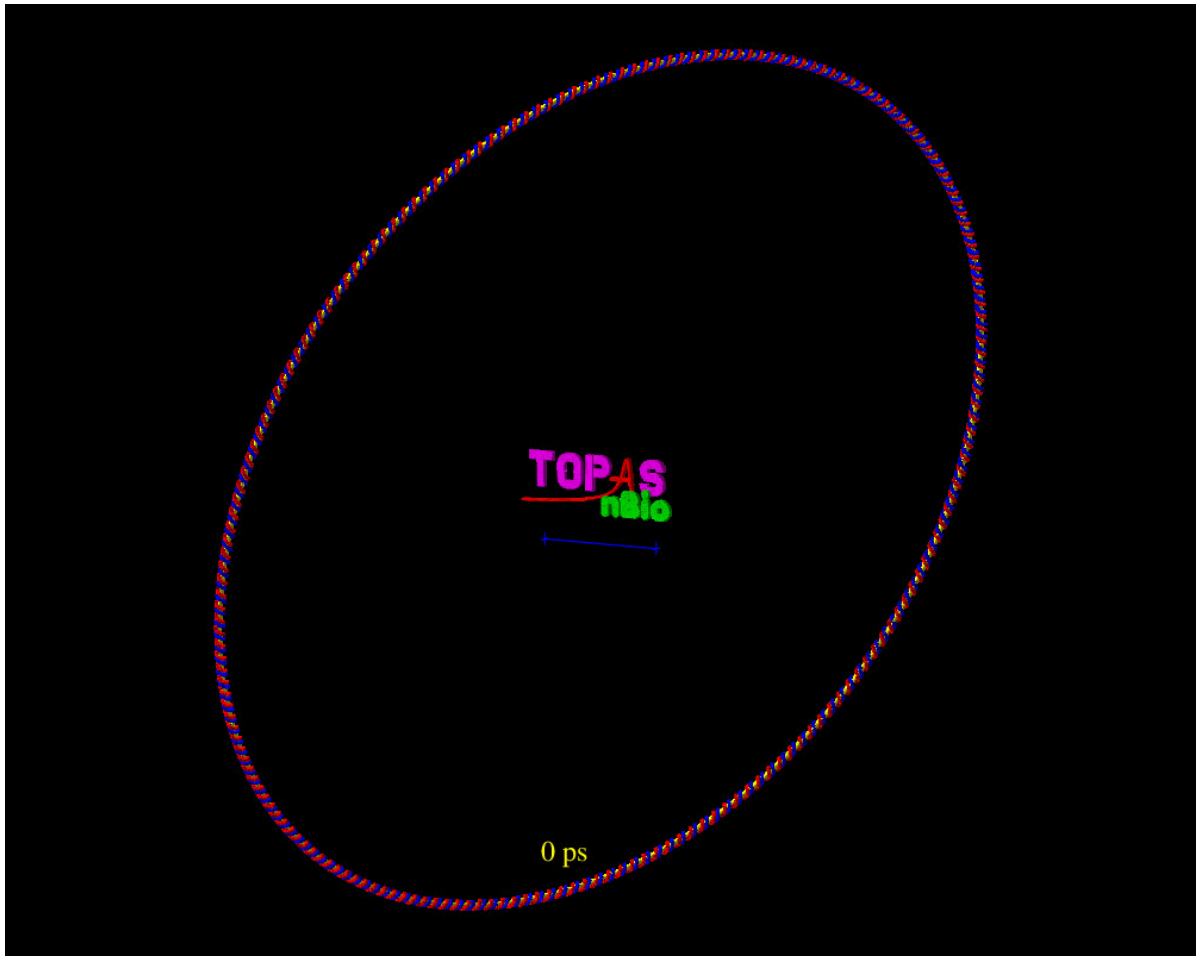
TOPAS-nBio

- Provide MC simulation on a nanometer scale. Wrapper for Geant4-DNA toolkit.
- Extension to TOPAS.
- Easy-to-use parameter files, users do not need advanced programming skills.
- Aimed at radiation biology researchers and physicists with interest in biology.

- TOPAS and TOPAS-nBio are freely available.
- TOPAS : www.topasmc.org
- TOPAS-nBio : https://github.com/topas-nbio/
- Documentation : https://topas-nbio.readthedocs.io

SIMULATIONS

- 1 MeV proton in water.
- Plasmid DNA ring consisting of 2000 base-pairs.



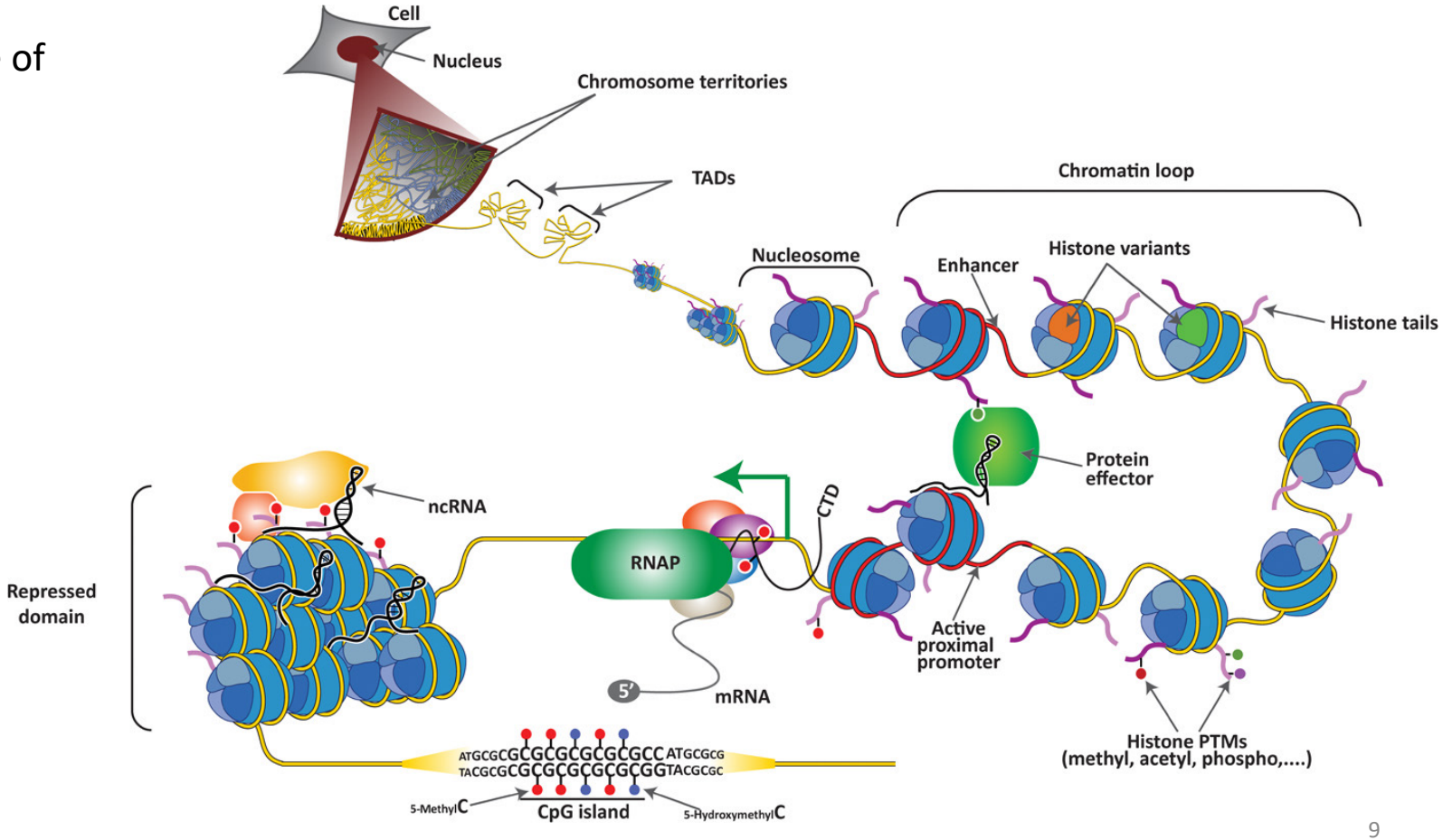
Physics:
proton
electron
Ionization event

Chemistry:
OH
e^-_{aq}
H_3O^+
H_2O_2

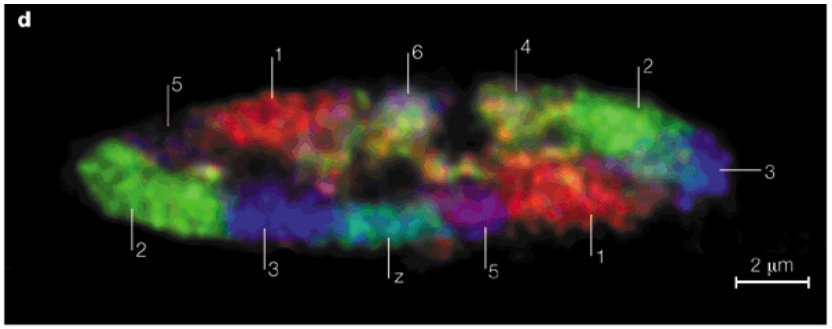
GEOMETRIC MODELS

TOPAS-nBio catalogue of geometries:

From macroscale (cell/organelle) to nanoscale (DNA molecule).

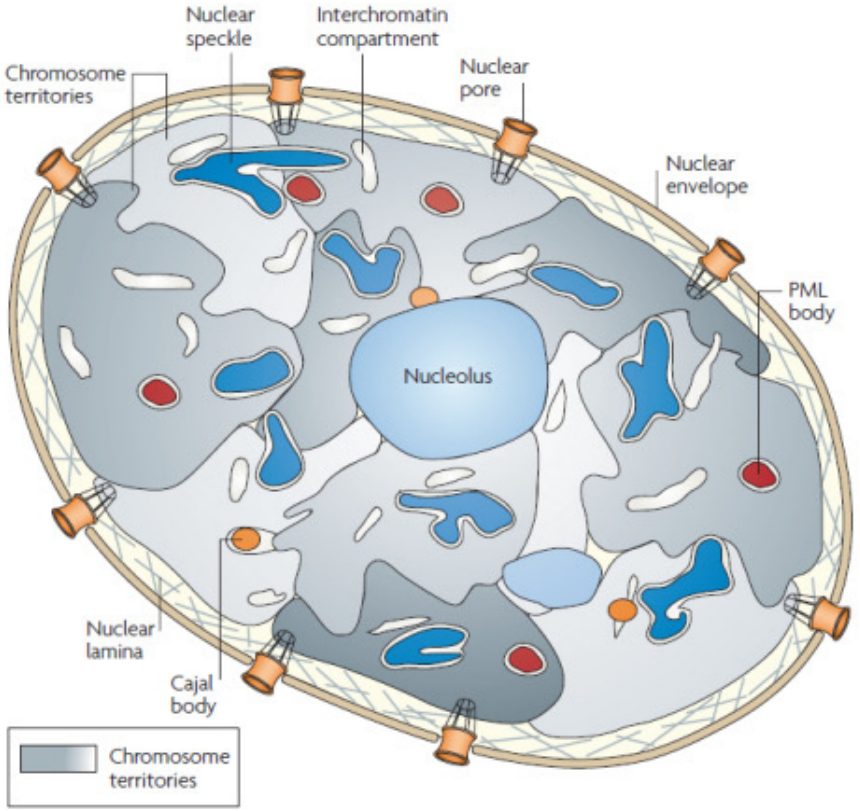


NUCLEUS MODELS



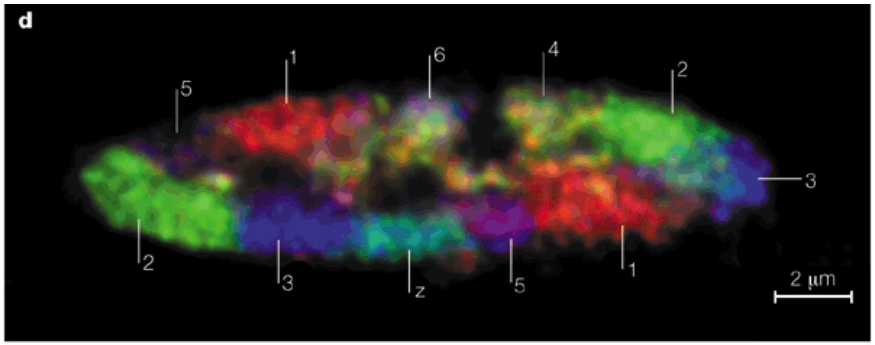
Nature Reviews | Genetics

Mid-plane light optical section through a chicken fibroblast nucleus shows mutually exclusive chromosome territories (CTs) with homologous chromosomes seen in separate locations.

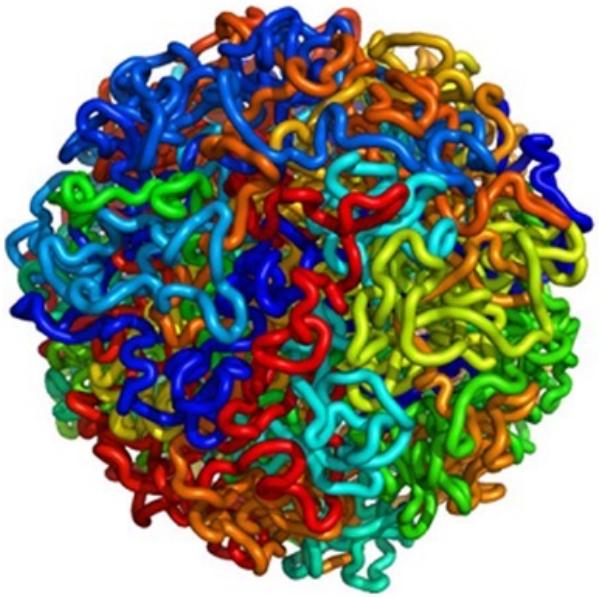


T. Cremer & C. Cremer, *Nature Reviews Genetics* **2**, 292-301 (2001)
Lanctôt, C., Cheutin, T., Cremer, M., Cavalli, G., & Cremer, T., *Nature Reviews. Genetics*, *8*(2), 104–115 (2007).

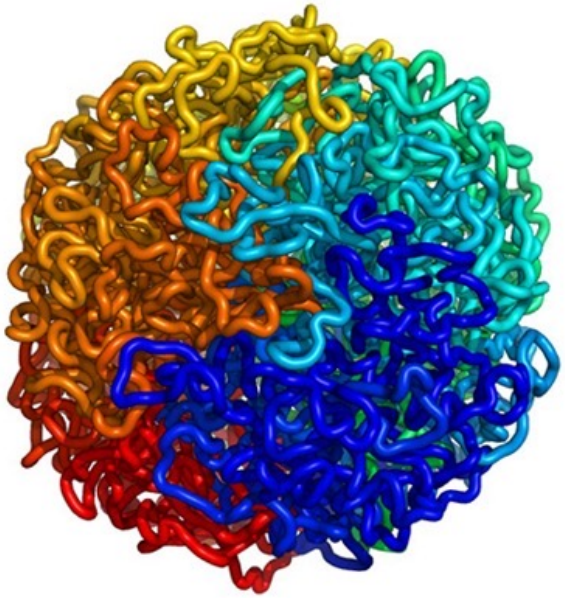
NUCLEUS MODELS



Random walk

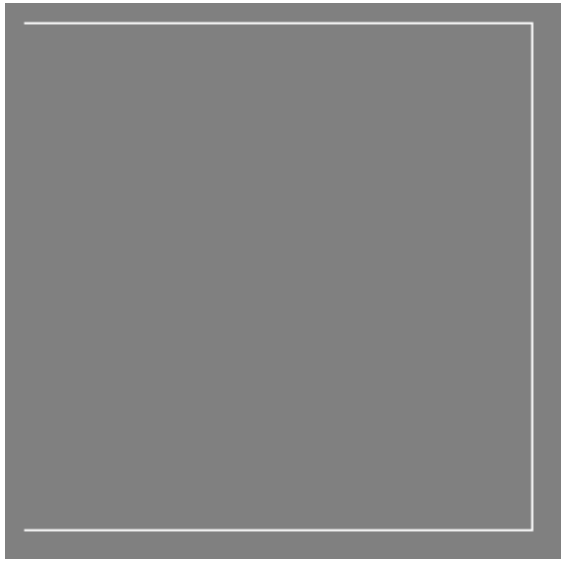


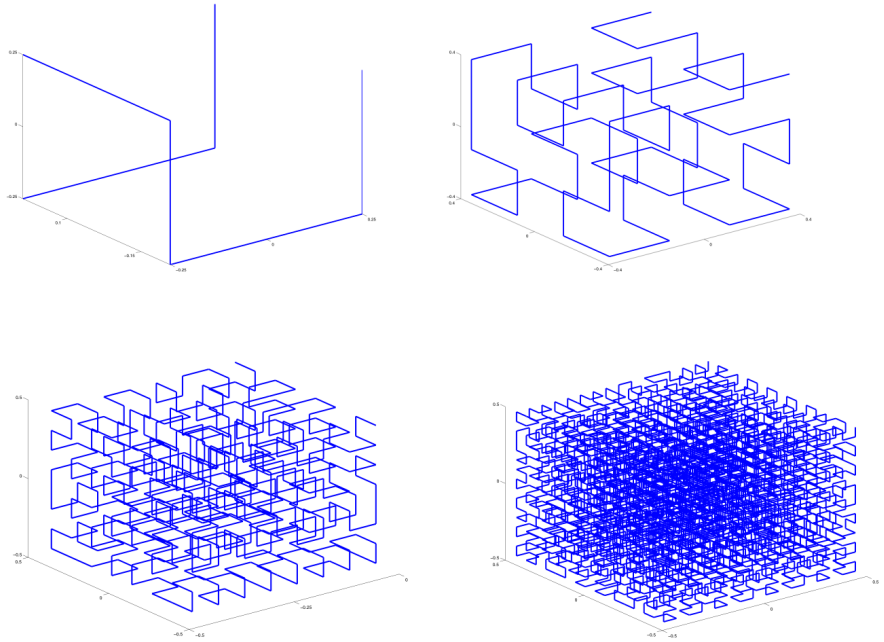
Factual globule



Lieberman-Aiden et al. (2009) Science, 326, 289

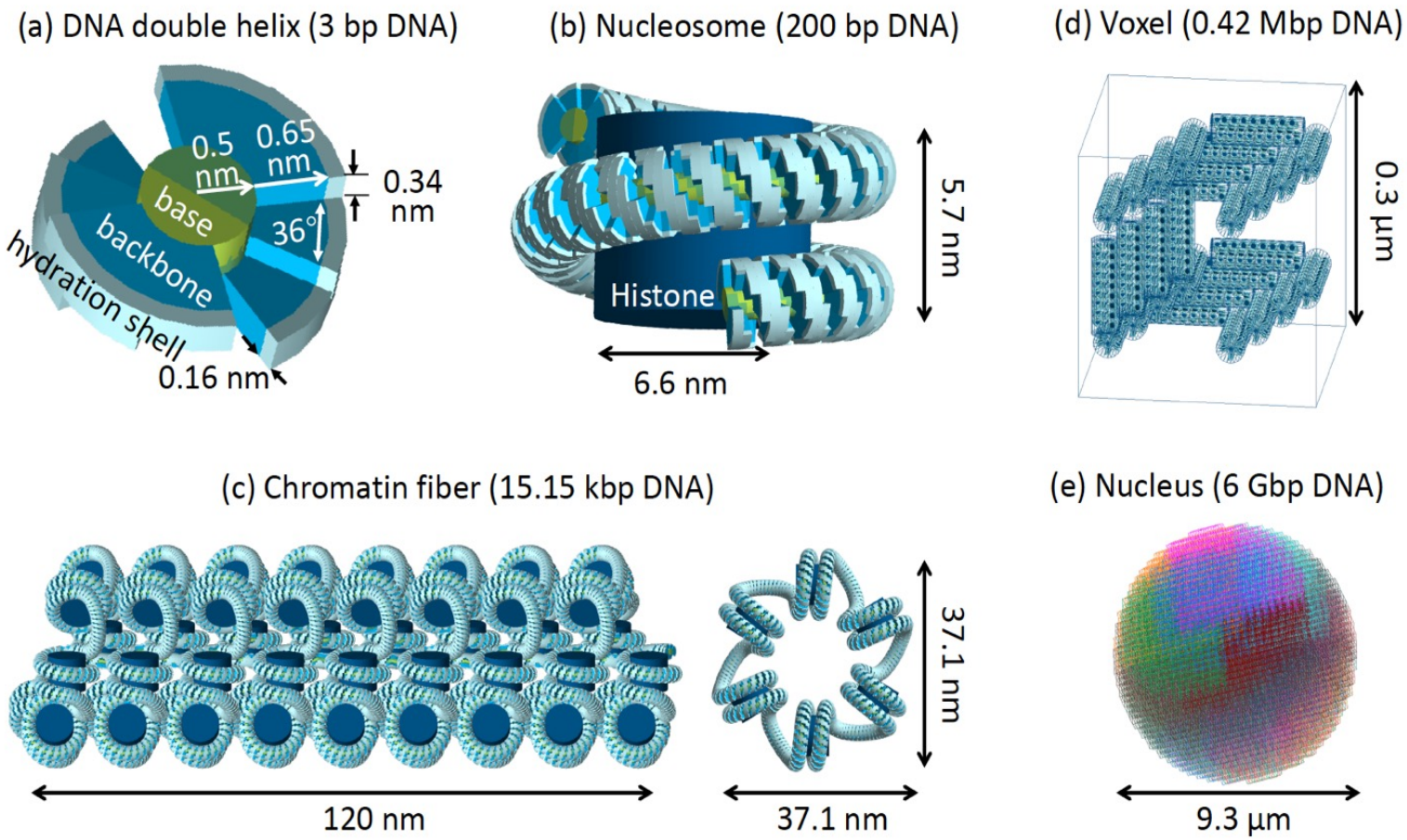
NUCLEUS MODELS





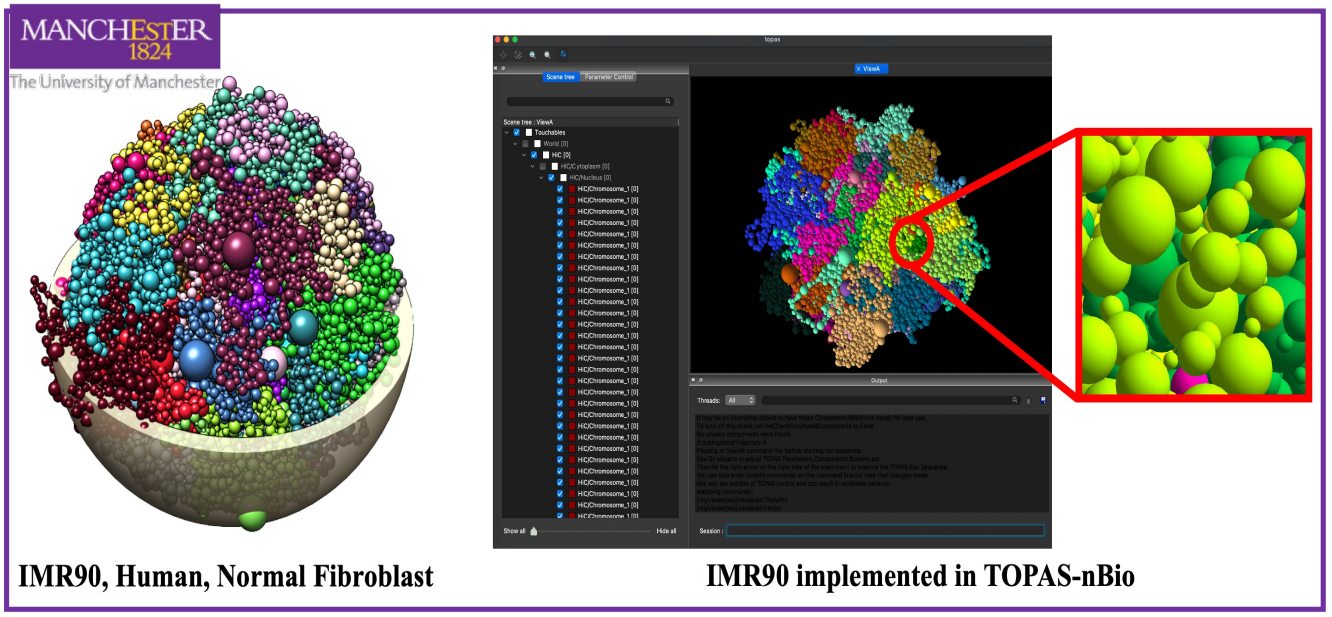
3D Hilbert Space filling curve

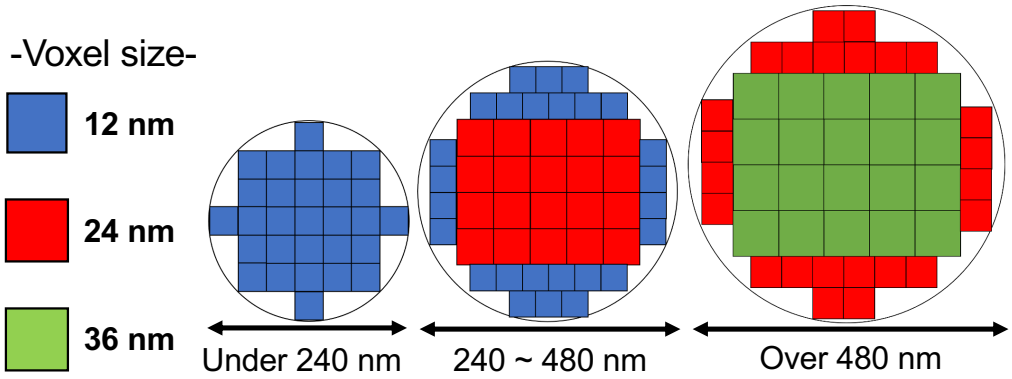
TOPAS-nBio NUCLEUS MODEL



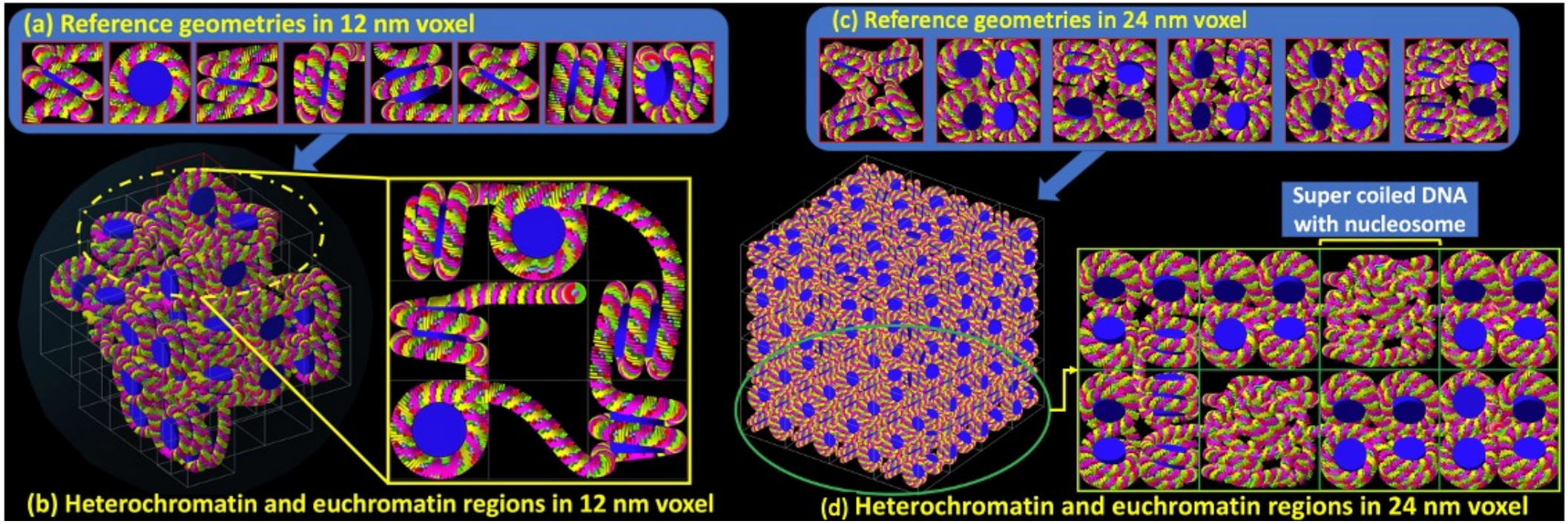
Zhu et al. (2020) Radiat. Res 194, 9.

TOPAS-nBio NUCLEUS MODEL

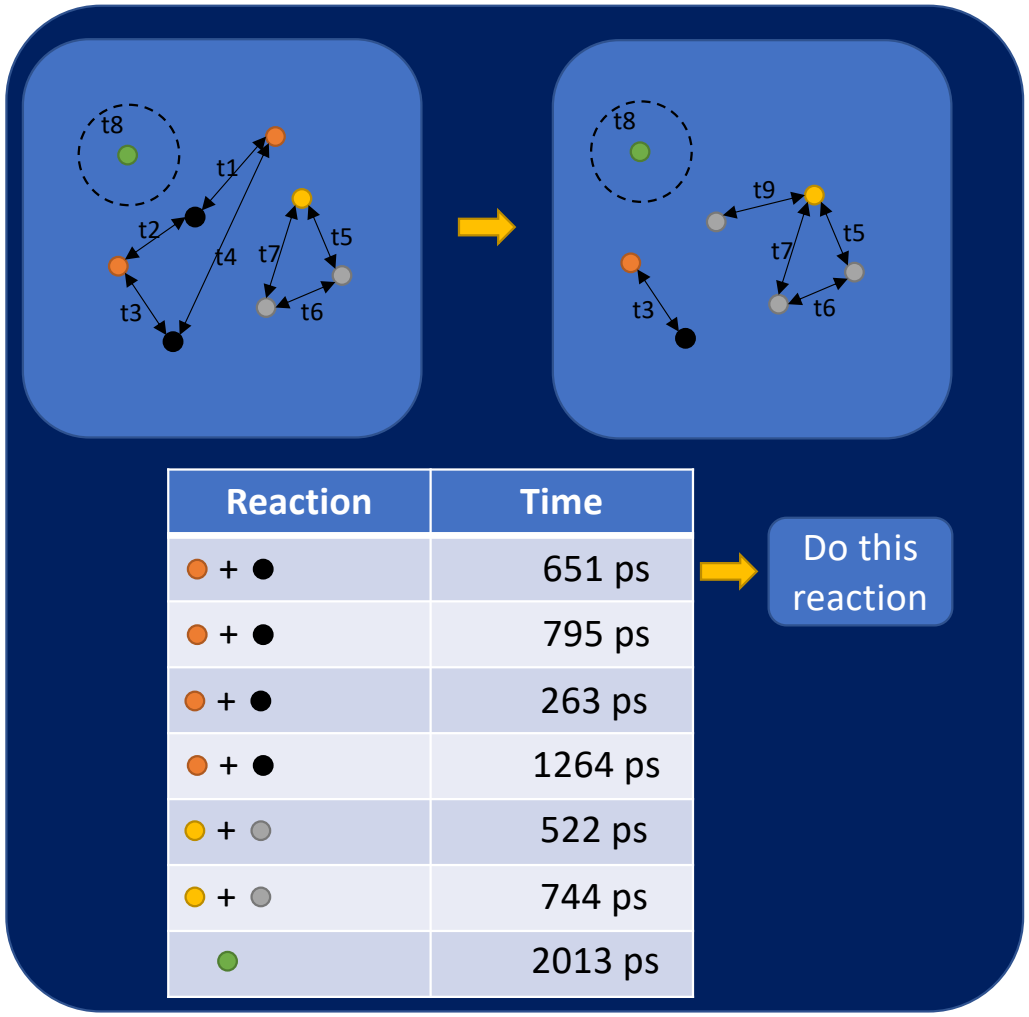




TOPAS-nBio NUCLEUS MODEL



TOPAS-nBio CHEMISTRY



- INDEPENDENT REACTION TIMES (IRT):
- The IRT algorithm doesn't rely on the explicit transport of chemical species.
- Instead, an Independent Time is sampled for every pair of reactives.
- This time is stored into a table and ordered in and ascending manner.
- The first reaction on the table is then executed.
  - Its products placed and resampled.
- This process is repeated till the first reaction in the table exceeds a certain time.

TOPAS-nBio CHEMISTRY CAPABILITIES

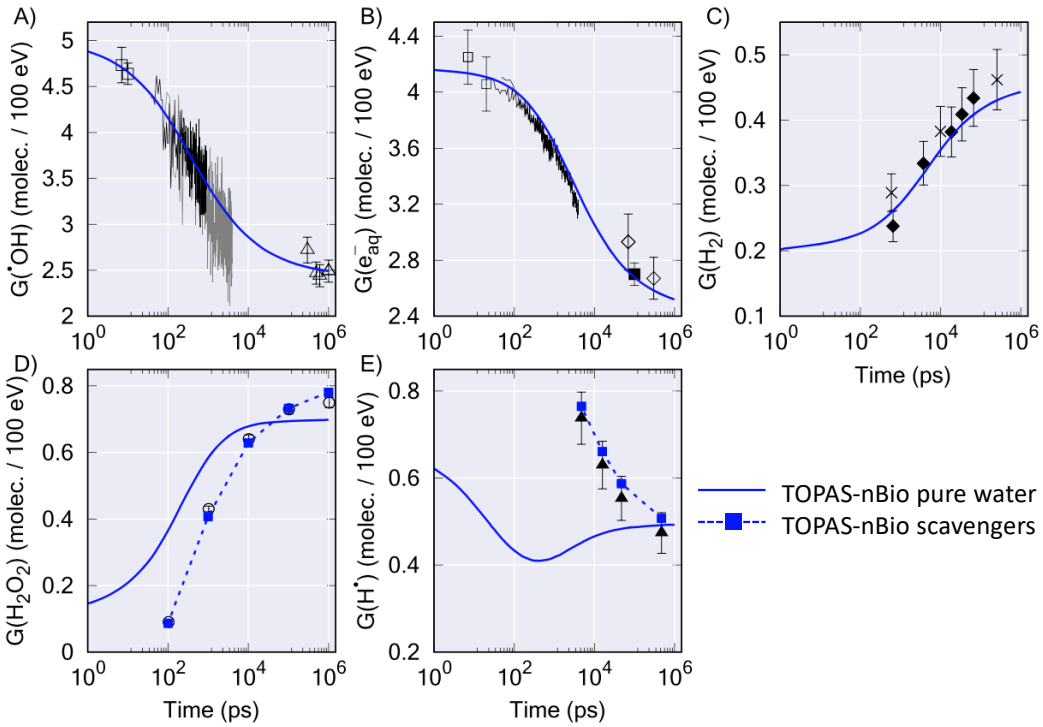


Figure 2. Time-dependent *G* values for fast electrons (1 molec./100 eV = 1.036 × 10^{-7} mol J^{-1}). TOPAS-nBio/Geant4-DNA simulated data: (solid line) pure liquid water calculations; (blue squares connected with dashed lines) simulations of scavenger systems for H_2O_2 and $H^{\cdot}$ as shown in table 1. Error bars represent statistical uncertainties, one standard deviation. Measured data: black and grey solid lines (Ma *et al* 2015); □ (Wang *et al* 2018); △ (Laverne 2000); ■ (Bartels *et al* 2000); ◇ (Shiraishi *et al* 1988); × and ◆ (Pastina *et al* 1999); ○ (Hiroki *et al* 2002); ▲ (Huerta Parajon *et al* 2008).

- Thanks to the flexibility and efficiency of the IRT in TOPAS-nBio, the following simulations can be/has been done:
  - Accurate G-values calculations.
  - Dose dependent G-values.
    - Radiation pulses.
    - Intertrack effects.
  - Automatic pH scalation of reaction rates.
    - Fricke Dosimeter.
  - DNA damage simulations.
    - Using plasmids.
  - Temperature changes to chemistry parameters.

Ramos-Mendez, JA et al (2021). PMB, *66*, 1–12. https://doi.org/10.1088/1361-6560/ac1f39

TOPAS-nBio CHEMISTRY CAPABILITIES

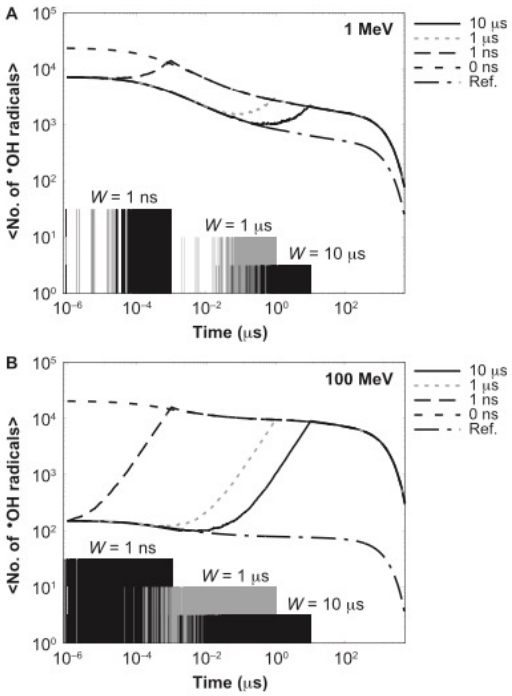
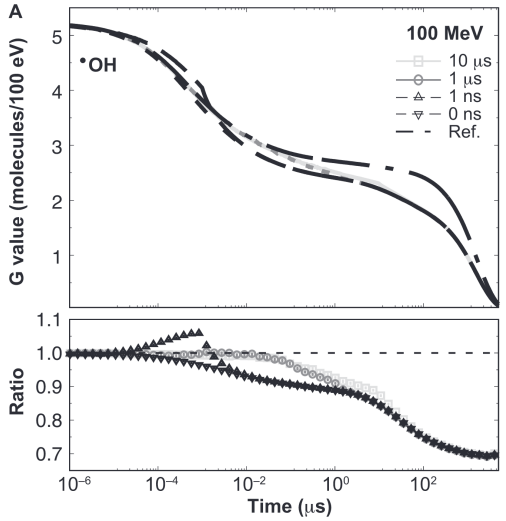


FIG. 2. Time evolution of the mean number of •OH radicals for irradiations with 1 MeV (left) and 100 MeV (right) protons for a dose of 50 cGy. Results for different pulse widths are shown: 0 ns (dashed), 1 ns (long dashed), 1 μs (dotted) and 10 μs (solid). Reference results calculated with protons delivered independently of each other are indicated by dashed-dotted lines. The times when a new history was generated are shown with impulse lines at the bottom; different amplitudes are shown to distinguish each option.



(In liquid water)

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Ramos-Méndez, JA et al. (2020). *Radiation Research*, *194*(4), 351–362. https://doi.org/10.1667/RADE-20-00084.1

TOPAS-nBio CHEMISTRY CAPABILITIES

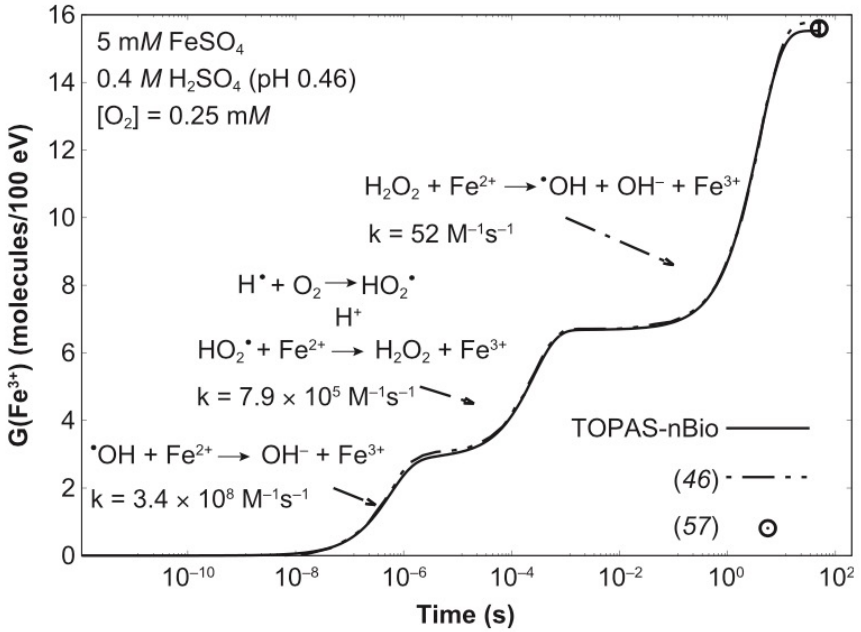

FIG. 1. Time evolution of the G value of Fe^{3+} from ^{60}Co irradiation of a Fricke solution, calculated using TOPAS-nBio (solid line). The reactions between $^{\bullet}OH$, $HO_2^{\bullet}$, and H_2O_2 with Fe^{2+} that leads to Fe^{3+}, and their reaction rate coefficients, are also shown. The arrows indicate the time stages when these reactions contribute to the G value. Simulated data from Plante (*46*) and accepted measured value from ICRU Report 34 (*57*) for ^{60}Co are shown as the dot-dashed line and the open circle, respectively.

- Thanks to the flexibility and efficiency of the IRT in TOPAS-nBio, the following simulations can be/has been done:
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Ramos-Mendez, JA et al (2021). PMB, *66*, 1–12. https://doi.org/10.1088/1361-6560/ac1f39

TOPAS-nBio CHEMISTRY CAPABILITIES

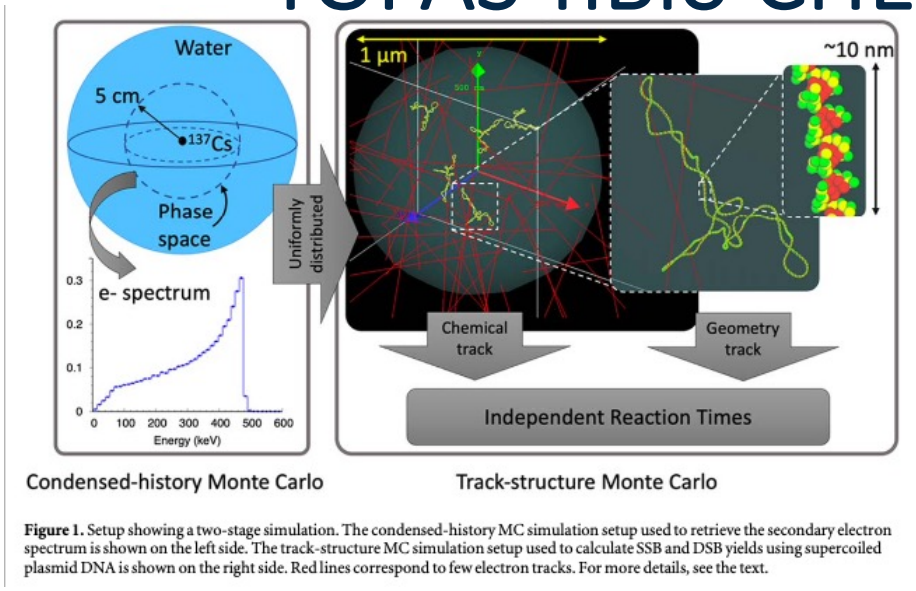
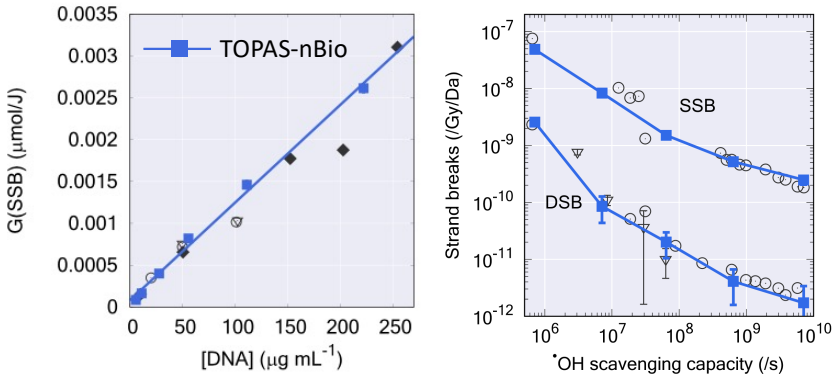


Figure 1. Setup showing a two-stage simulation. The condensed-history MC simulation setup used to retrieve the secondary electron spectrum is shown on the left side. The track-structure MC simulation setup used to calculate SSB and DSB yields using supercoiled plasmid DNA is shown on the right side. Red lines correspond to few electron tracks. For more details, see the text.



Measured data is from Milligan et al (1993), Klimczak et al (1993) and Tomita et al (1995)

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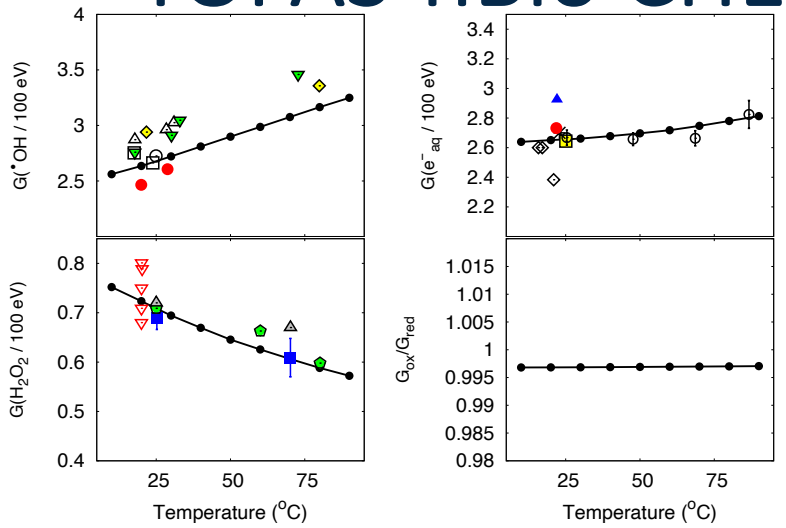
TOPAS-nBio CHEMISTRY CAPABILITIES

In water.



In plasmids

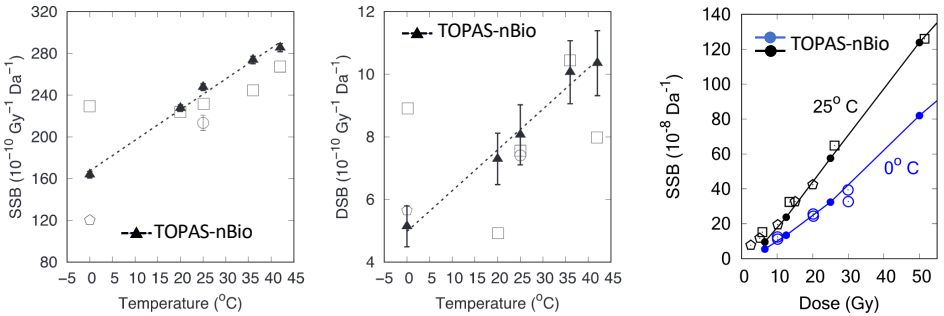


Figure 7. Temperature dependent SSB (left), DSB (center) and SSB/DSB ratio (right) in supercoiled plasmids for an absorbed dose of 50 Gy. Experimental data from Tomita (1995) connected squares (□), Kassis (1999) circle (○) and Sahu (1997) polygon (⬠) are also shown. Monte Carlo data are shown with filled triangles. The Monte Carlo data set is fitted with a least-mean-square straight line with slope $(2.94 \pm 0.11) \times 10^{-10}\,\mathrm{Gy^{-1}\,Da^{-1}\,°C^{-1}}$ ($R^2 = 0.99$), $(0.13 \pm 0.01) \times 10^{-10}\,\mathrm{Gy^{-1}Da^{-1}\,°C^{-1}}$ ($R^2 = 0.99$) and $(-0.12 \pm 0.04)\,\mathrm{°C^{-1}}$ ($R^2 = 0.78$) for SSB, DSB and SSB/DSB ratio, respectively. Fits are shown with the dotted lines.

- Thanks to the flexibility and efficiency of the IRT in TOPAS-nBio, the following simulations can be/has been done:
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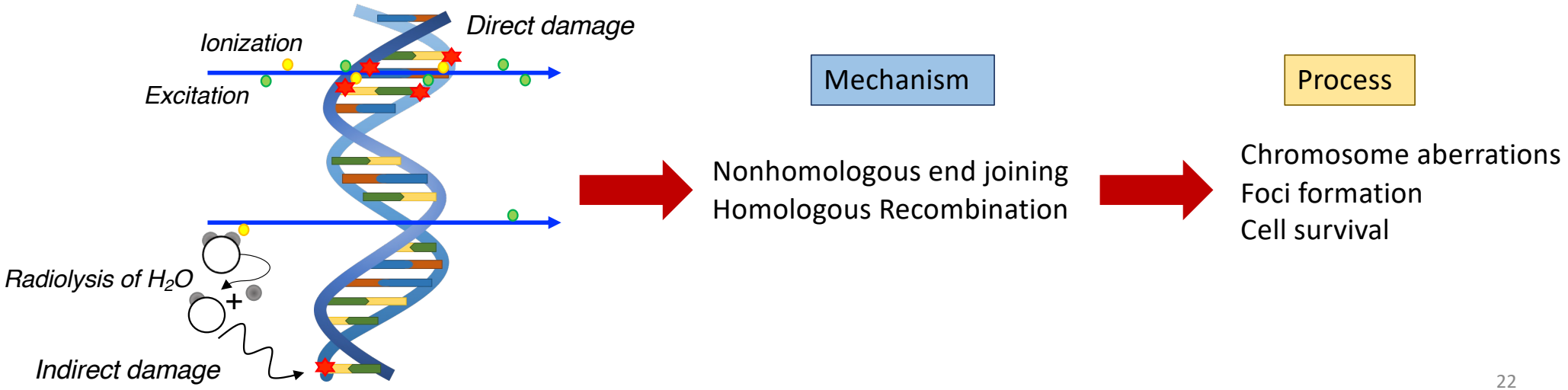
Ramos-Mendez, JA et al (2022). PMB, *67*, 1–13. https://doi.org/10.1088/1361-6560/ac79f9

DNA REPAIR MODELS

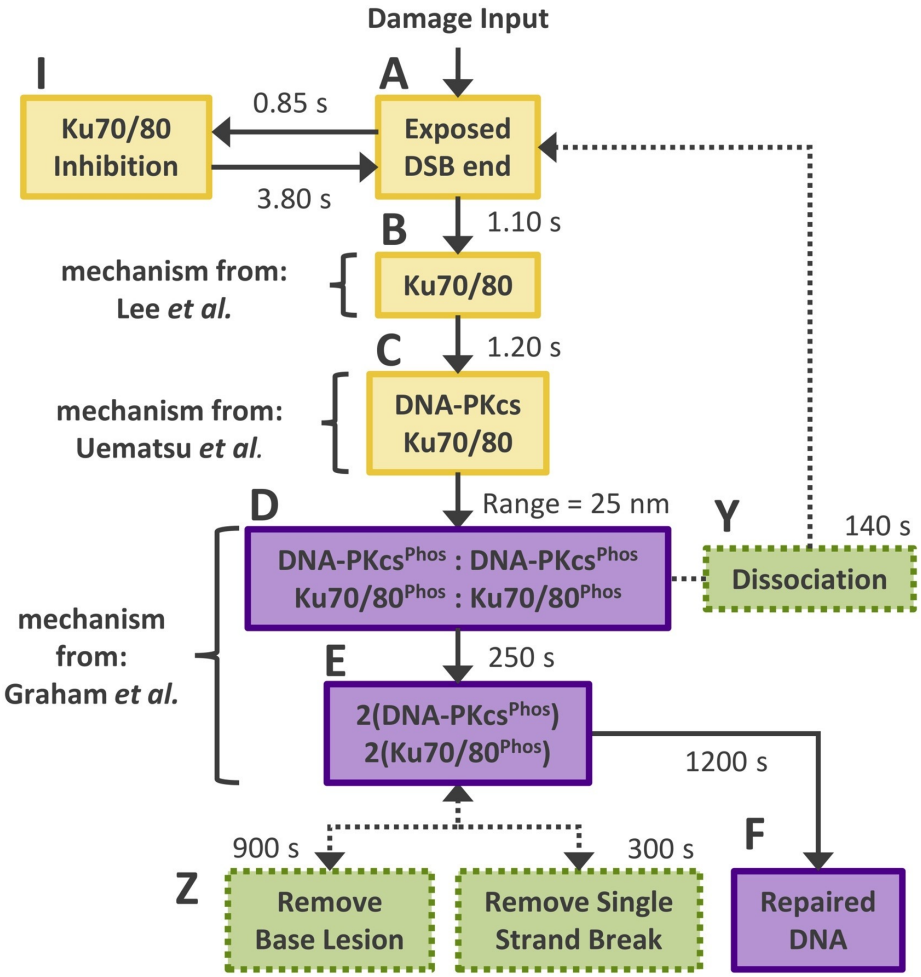
DNA repair models

- Analytic models: Lethal-Potentially Lethal lesion or Repair-Misrepair models.
- Many limited since they focus on a single pathway or endpoint.
- Active area of model development (e.g. McMahon et al. (2016), Warmenhoven et al. (2020))
- DAMARIS (University of Manchester) is a Monte Carlo based framework developed Geant4-DNA for event-by-event tracking of individual DSB ends. Includes multiple endpoints.



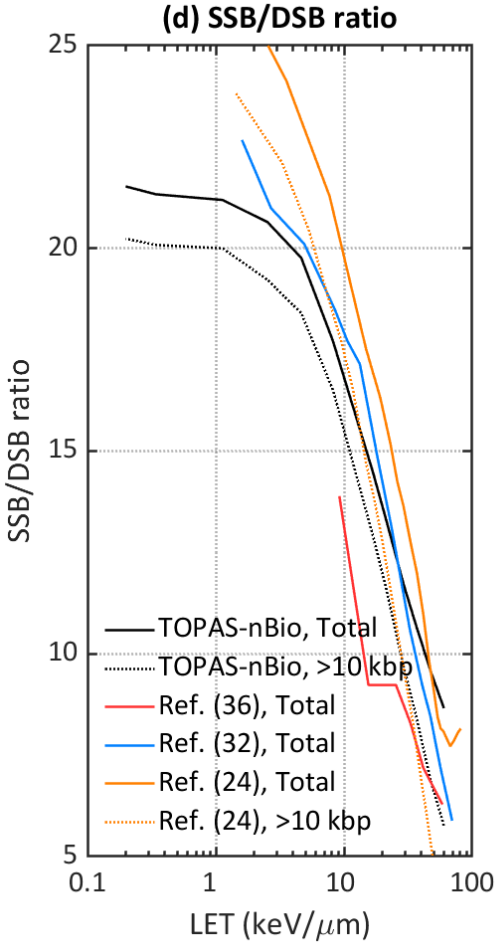
DNA REPAIR MODELS

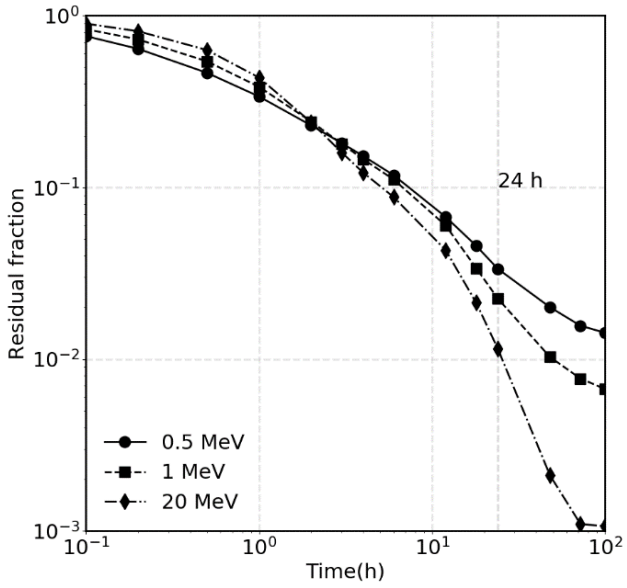
- DNA Mechanistic Repair Simulator (DaMaRiS) – University of Manchester
- Model of the c-NHEJ pathway
- A mechanistic, Monte Carlo based framework that was developed within the Geant4-DNA tool-kit and allows for event-by-event tracking of individual DSB ends.
- Available within Topas-nBio



Warmenhoven et al. (2020) DNA Repair, 85,102743,

DNA DAMAGE AND REPAIR MODELING





Friedland W, Jacob P, Bernhardt P, Paretzke HG, Dingfelder M. Simulation of DNA damage after proton irradiation. Radiat Res 2003; 159:401–10.

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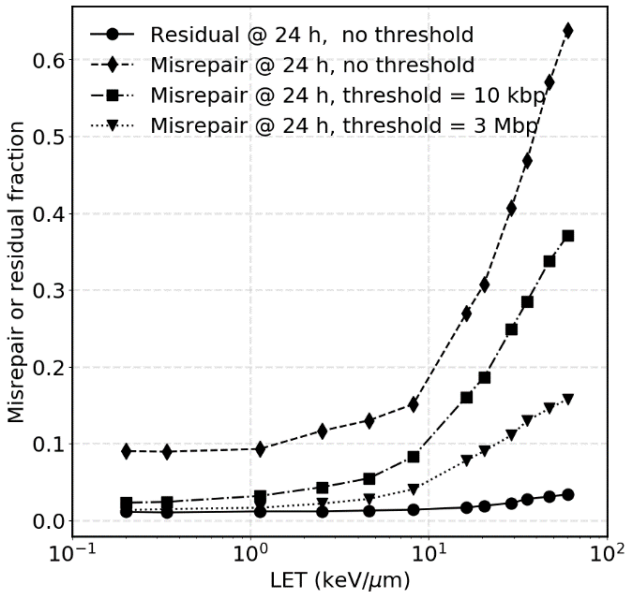
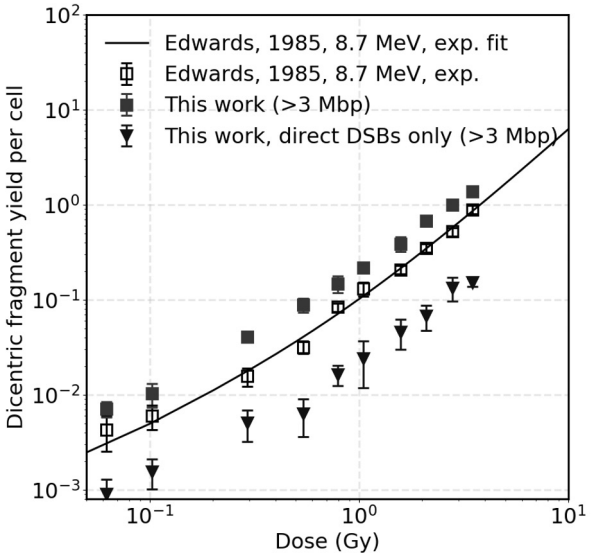
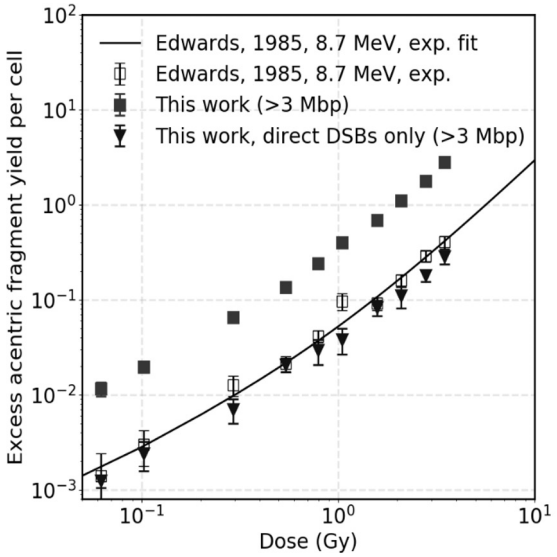


Zhu et al. (2020) Radiat. Res 194, 9.

DNA DAMAGE AND REPAIR MODELING





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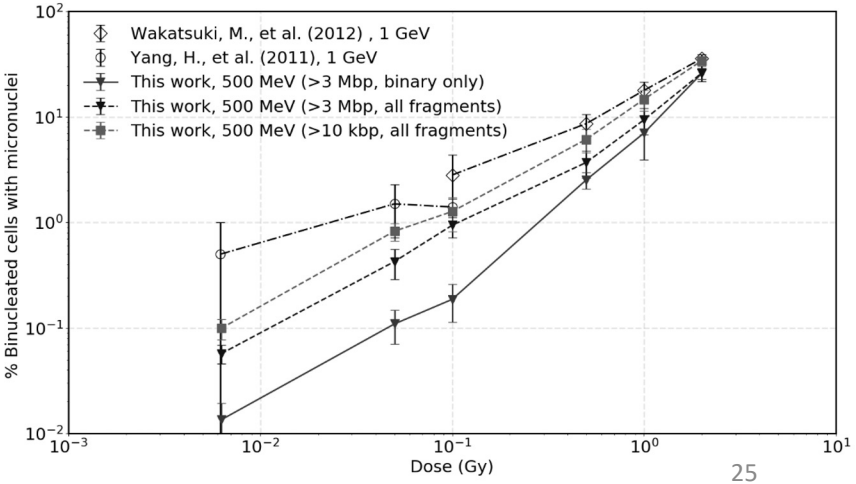

SUMMARY

- Geometry Developments: DNA models incorporating Hi-C data and mixed levels of euchromatin and heterochromatin.
  - Goal: capture cell line specificity.
- Chemistry: Implementation of IRT.
  - Goal: improve efficiency, accuracy and usability of chemistry models.
- DNA Repair Models: Incorporate DNA repair to better predict outcomes.
  - Goal: include more DNA repair pathways.
- Challenges: uncertainty in parameters, approximations, lack of experimental data.

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