Monte Carlo Simulation of Proton Induced DNA Damage in a Realistic Chromosomal Geometry and Subsequent Repair through the Non-Homologous End Joining Mechanism as Described by Brownian Bridge Interactions.

Nicholas Henthorn and John Warmenhoven

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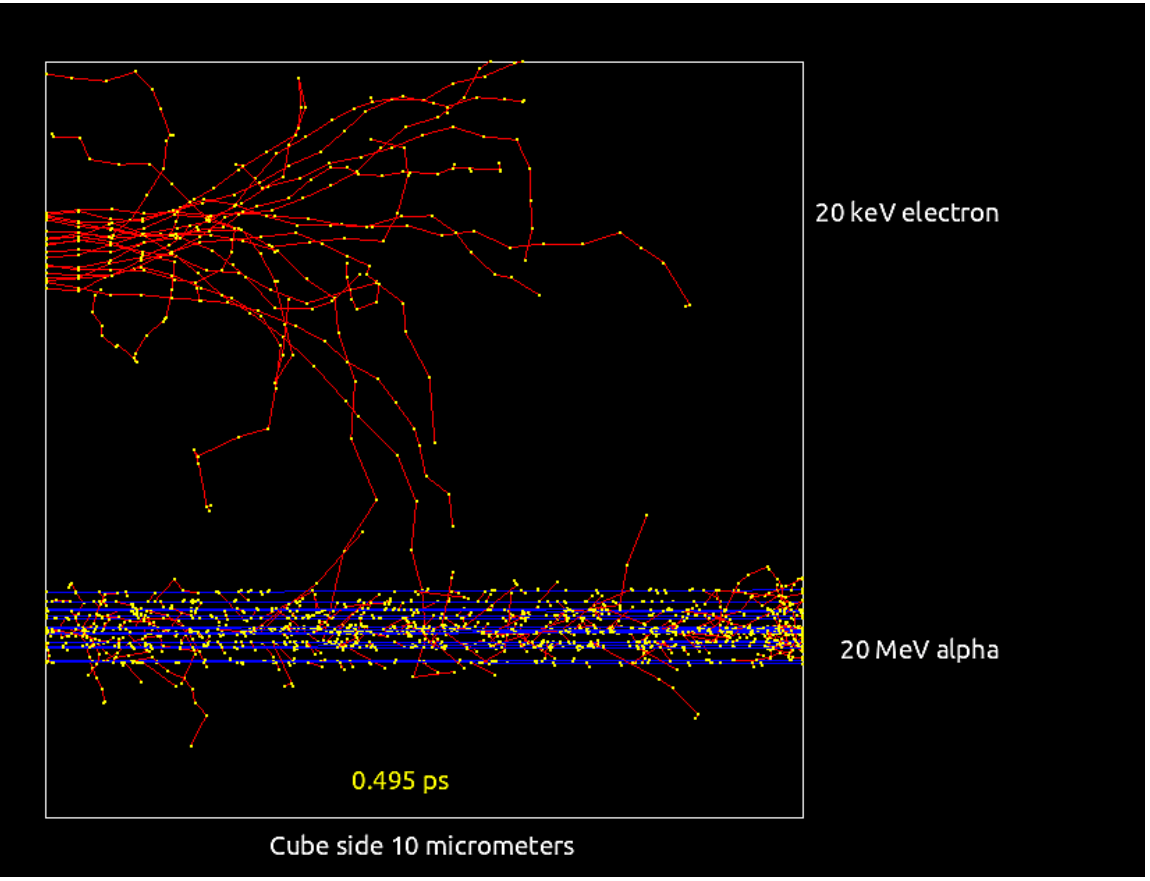
Introduction

- Investigation of physical processes leading to DNA damage from proton irradiation
- Difficult to investigate due to small size scales
- Simulation of proton-DNA interactions through Monte Carlo Code
- Realistic geometry of DNA crucial (cell model - peripheral blood lymphocyte)
- Tracking of energy deposition in DNA regions (Geant4-DNA)
- Calculation of Double Strand Breaks
- Difficult to validate
- Experimental analysis through DSB markers

Geant4 - DNA



- Monte Carlo simulation toolkit part of Geant4
- Particle step with probability of interaction (based on cross section tables)
- Extended physics list to enable tracking of electrons at low energy
  - Electron: 0 eV -> 1 MeV
  - Proton: 10 eV -> 100 MeV
  - H, He, He+, He++, Li, Be, B, C, N, O, Si, Fe
- Validated for liquid water
  - *(S. Incerti, et al, Med. Phys., vol. 37, no. 9, pp. 4692–4708, 2010.)*

V. Štěpán, http://dx.doi.org/10.6084/m9.figshare.1152683

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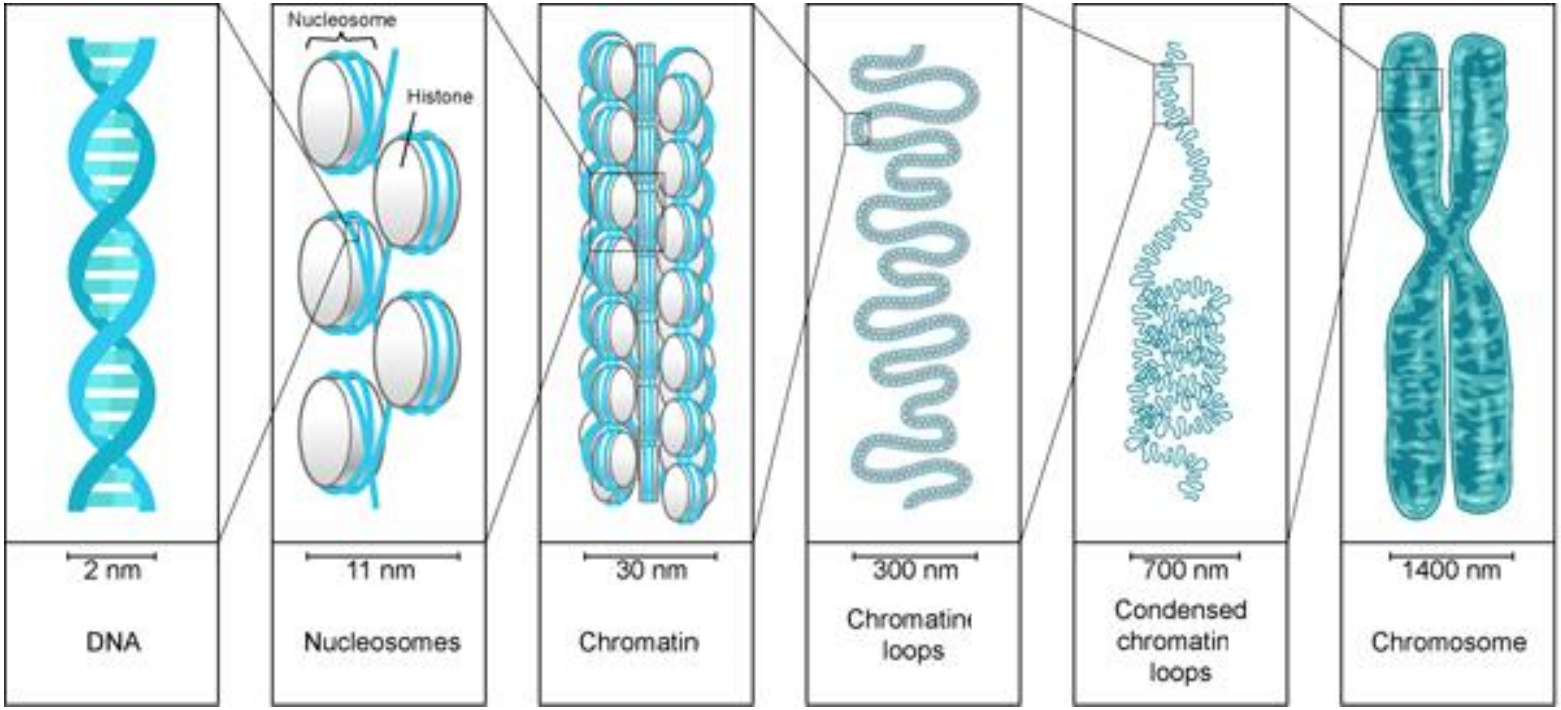
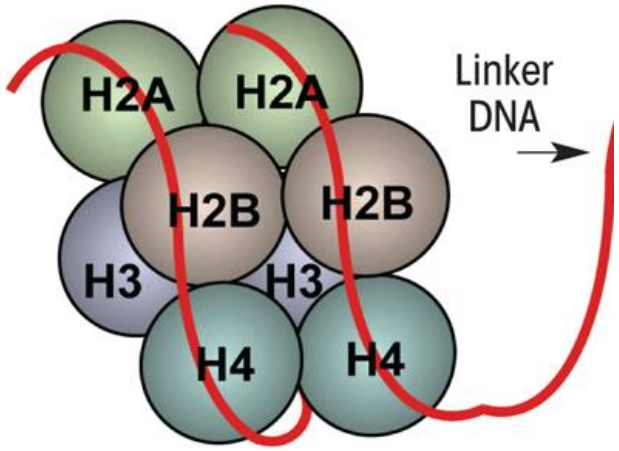
Geometry – *DNA Packaging*

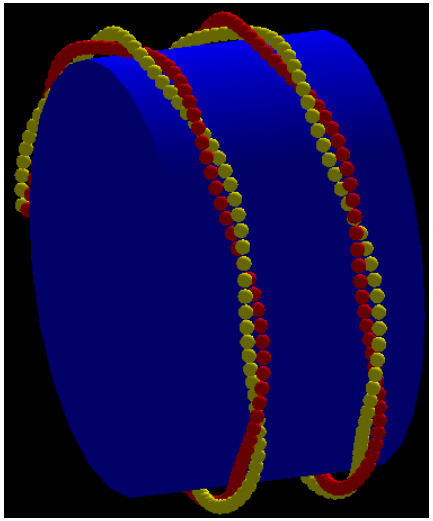


Shmoop.com

Geometry - *Nucleosome*

*





- Histone octamer (modeled as cylinder)
- ≈2 coils of double helix DNA (modeled as B-DNA)
- DNA turns every 10 bp
- Histone + coiled DNA = Nucleosome
- Linker DNA connecting nucleosomes

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** G. Bela et al, Alcohol Research: Current Reviews, vol. 34, 3, (2012), 293-305*

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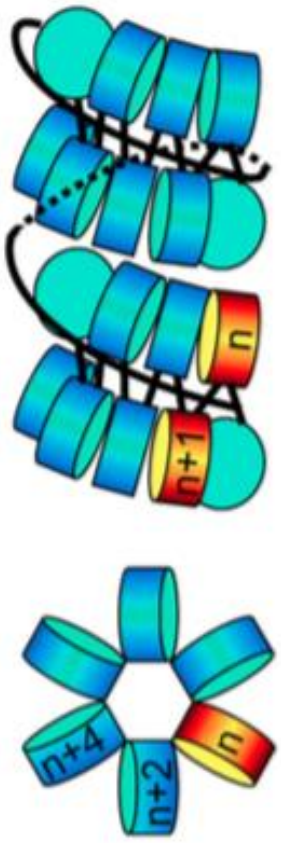
Geometry - *Chromatin*

1)

2)

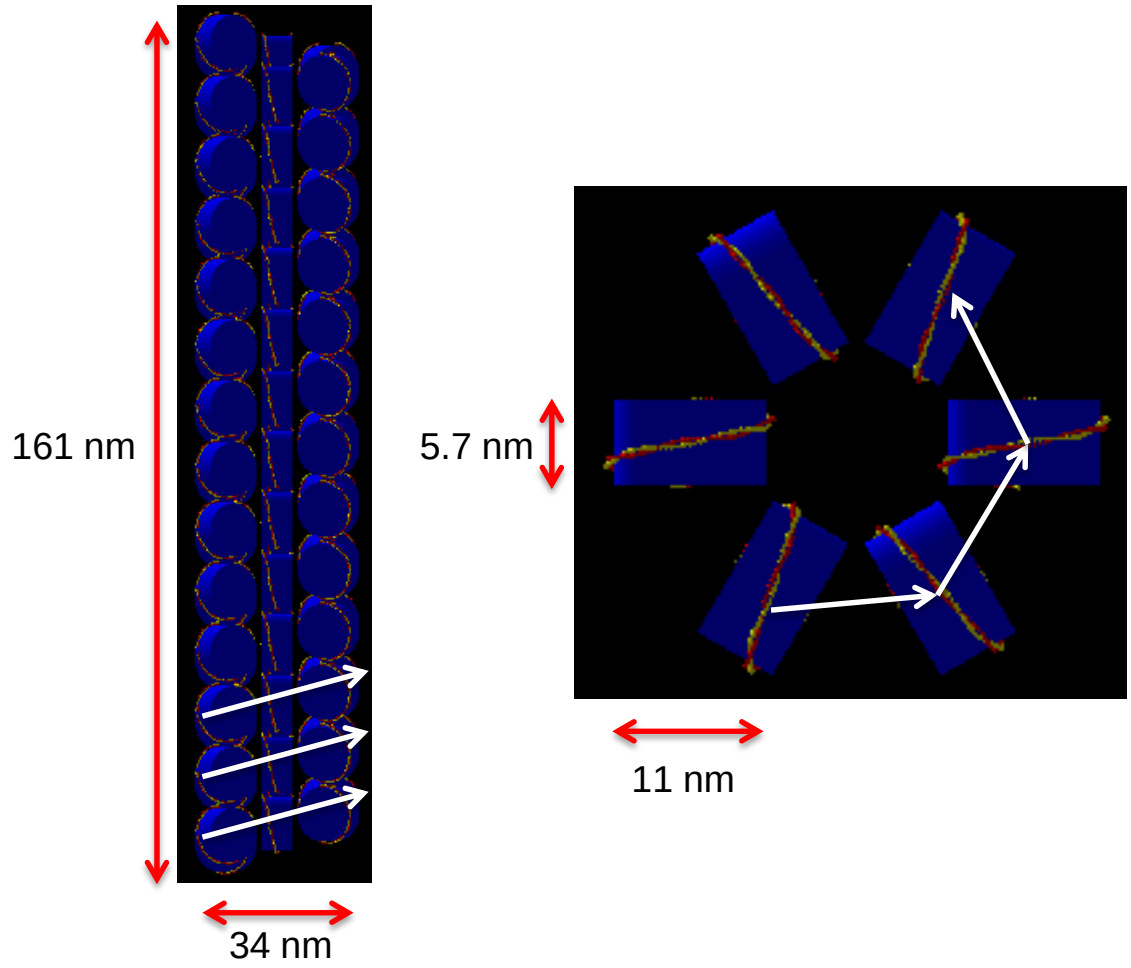


K. Van Holde, J. Zlatanova, Seminars in Cell & Developmental Biology, 18, (2007), 651-658

- Variety of Chromatin geometry models
- Two main classes
  1. One start helix (solenoid)
  2. Two start helix (cross linked double helix)
- Both models assume regular internucleosomal spacing (heterochromatin)
- Both seen experimentally (under different conditions)
- Solenoid favoured model in most work (simpler)

"There is no clear function for a uniform morphology, except to make life easier for biophysicicsts" – K. Van Holde & J. Zlatanova

Initial Simulation – *Solenoid "30nm Fibre"*



- Single chromatin fibre
- Right handed solenoid
- No linker DNA
- 80 nucleosomes -> 14.72 kbp
- Set up 'DNA' as sensitive detector
- Irradiated with 3 MeV protons in a random xy distribution
- For a hit to sensitive detector record base-pair number, energy deposition, number of particle interactions by type, xyz of hit

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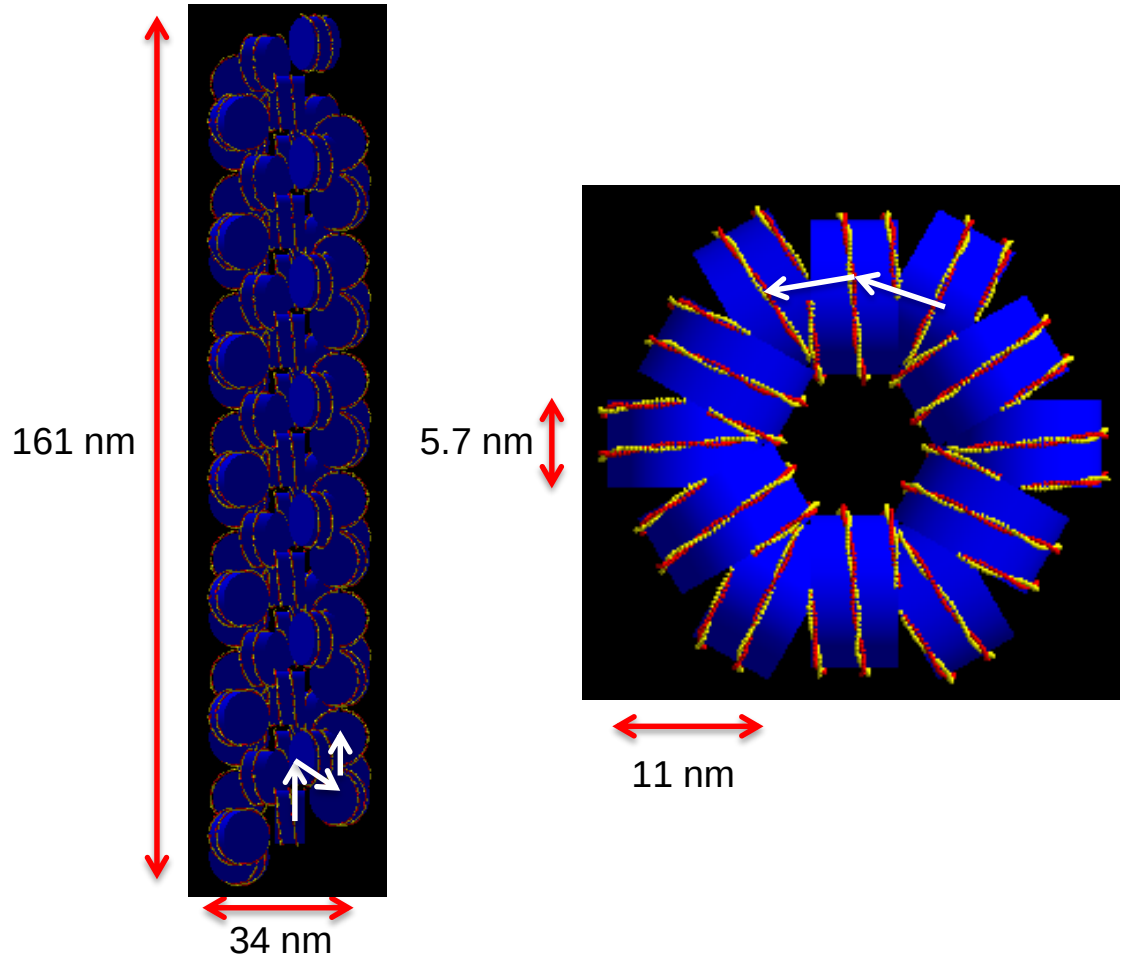
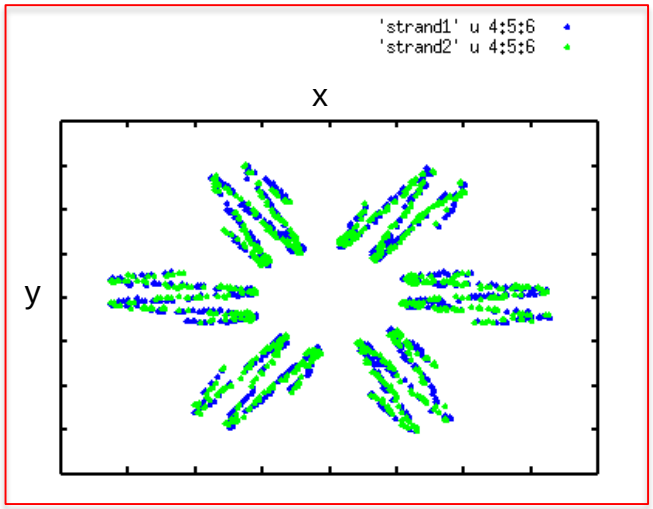
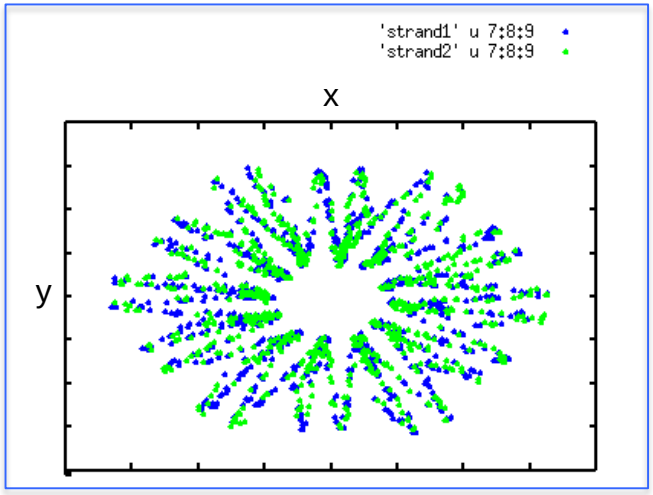
Initial Simulation – *Two Start Helix*



- Single chromatin fibre
- Right handed helix
- No linker DNA
- 74 nucleosomes -> 13.62 kbp
- Set up ‘DNA’ as sensitive detector
- Irradiated with 3 MeV protons in a random xy distribution
- For a hit to sensitive detector record base-pair number, energy deposition, number of particle interactions by type, xyz of hit

Initial Results - *Ionisations*





- Irradiation with 10, 000 protons
- Reject all energy depositions below 7.8 eV – *energy required to excite water molecule*
- Figures show hit positions of all ionisations
  - **Blue = strand 1**
  - **Green = strand 2**

Solenoid – 14.72 kbp

- Total of 1800 ± 30 ionisations
  - Avg. of 4.33 ± 0.11 e- per ionisation
  - Avg. of 0.56 ± 0.02 p+ per ionisation
  - *0.18 ionisations per primary*

Two start helix – 13.62 kbp

- Total of 2000 ± 50 ionisations
  - Avg. of 3.91 ± 0.08 e- per ionisation
  - Avg. of 0.50 ± 0.02 p+ per ionisation
  - *0.20 ionisations per primary*

- Cluster analysis to give number of DSBs

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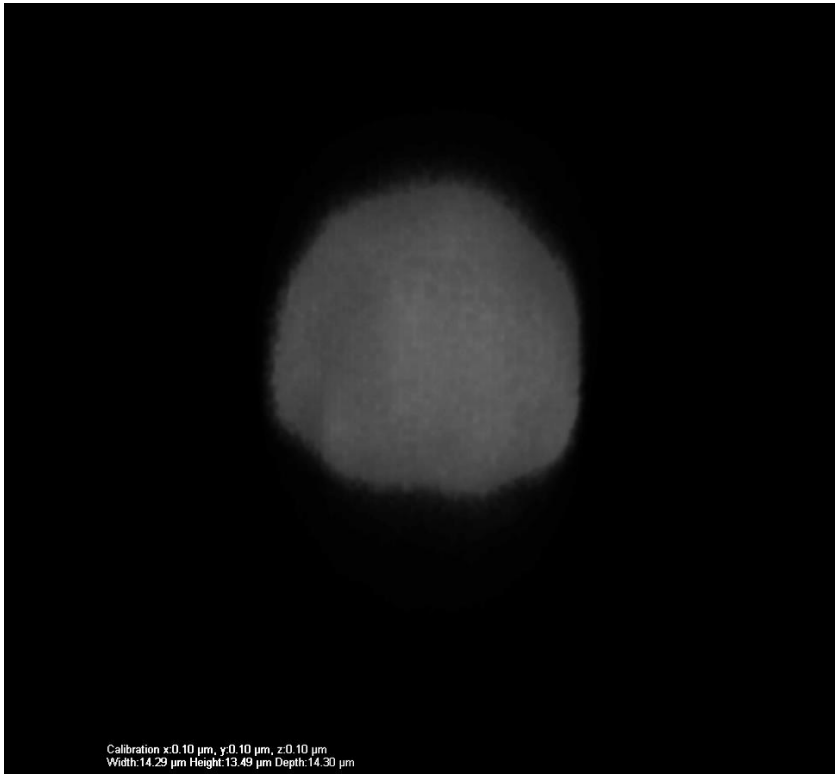
Future Work



- Import confocal scan of PBL nucleus
- Set up chromosome territories
- Replicate chromatin fibre into territories
- Build whole DNA

- Comparison of different chromatin fibre geometries
- Euchromatin and Heterochromatin (effect of chromatin compaction)
- Investigation of dose enhancers, e.g. Gold Nano Particles

- Experimental validation / Refinement of simulation

- Extend to investigate free radical DNA damage?

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Applications

- Physical model to estimate DSBs
- Incorporation into Geant4 DNA release as an example application
- Cell irradiation planning
- Effect of dose enhancers on secondary electron production and DNA damage
- Combination with multi scale cell modeling
- REQUIRES VALIDATION

- Geometry required to model DSB repair…

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> **Cell Survival** -> Patient Survival

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> **Dose Deposited** -> Cell Survival -> Patient Survival

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> **Dose Deposited** -> Cell Survival -> Patient Survival

RBE

"RBE is a simple concept but its clinical application is complex because it is a function of particle type, energy, dose, dose per fraction, fraction number, cell or tissue type, and varies between early and late reactions following therapy." – *IAEA Technical Report 461 on Relative Biological Effectiveness in Ion Beam Therapy (2008)*

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> Dose -> **DNA Breaks Induced** -> Cell Survival -> Patient Survival

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> Dose -> Breaks -> **DNA Repair** -> Cell Survival -> Patient Survival

The DNA Damage Repair Process

The Need for More In Depth Modelling

Radiation in -> Patient Survival out

Radiation -> Dose -> Breaks -> **DNA Repair** -> Cell Survival -> Patient Survival

Effects of Inhibitors

New cytotoxic drugs?

Low Dose Effect

Low dose hypersensitivity?
Low dose radiation hardening?

The DNA Damage Repair Process

Current Work in the Field

Numeric Methods

$$\frac{dn_0}{d\tau} = \alpha(L)\frac{dD}{dt}N_{ir} - n_0(k_1x_1 + p_1y_1) + k_{-1}x_2 + p_{-1}y_2,$$

$$\frac{dx_2}{d\tau} = k_1N_0x_1 - x_2(k_{-1} + k_2x_3) + k_{-2}x_4,$$

$$\frac{dx_4}{d\tau} = k_2x_2x_3 - x_4(k_3 + k_{-2}),$$

$$\frac{dx_5}{d\tau} = k_3x_4 - k_4x_5^2 + k_{-4}x_6,$$

$$\frac{dx_6}{d\tau} = k_4x_5^2 - x_6(k_{-4} + k_5x_7) + k_{-5}x_8,$$

$$\frac{dx_8}{d\tau} = k_{-6}x_{10} + k_5x_6x_7 - x_8(k_{-5} + k_6x_9),$$

$$\frac{dx_{10}}{d\tau} = k_{-7}x_{12} + k_6x_8x_9 - x_{10}(k_{-6} + k_7x_{11}),$$

$$\frac{dx_{12}}{d\tau} = k_7x_{10}x_{11} - x_{12}(k_8 + k_{-7}),$$

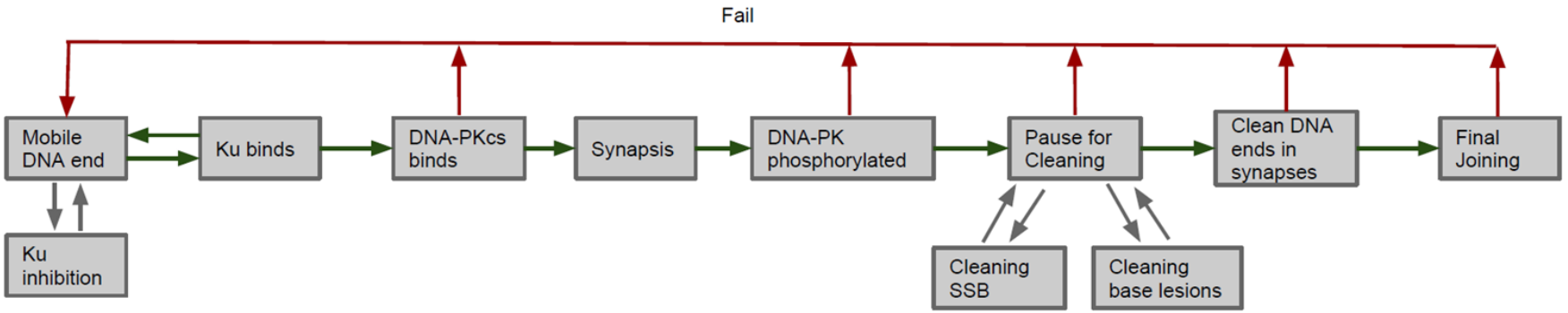
Belov O., 2015. *A quantitative model of the major pathways for radiation-induced DNA double-strand break repair,* Journal of Theoretical Biology 366, 115-130.

The DNA Damage Repair Process

Current Work in the Field

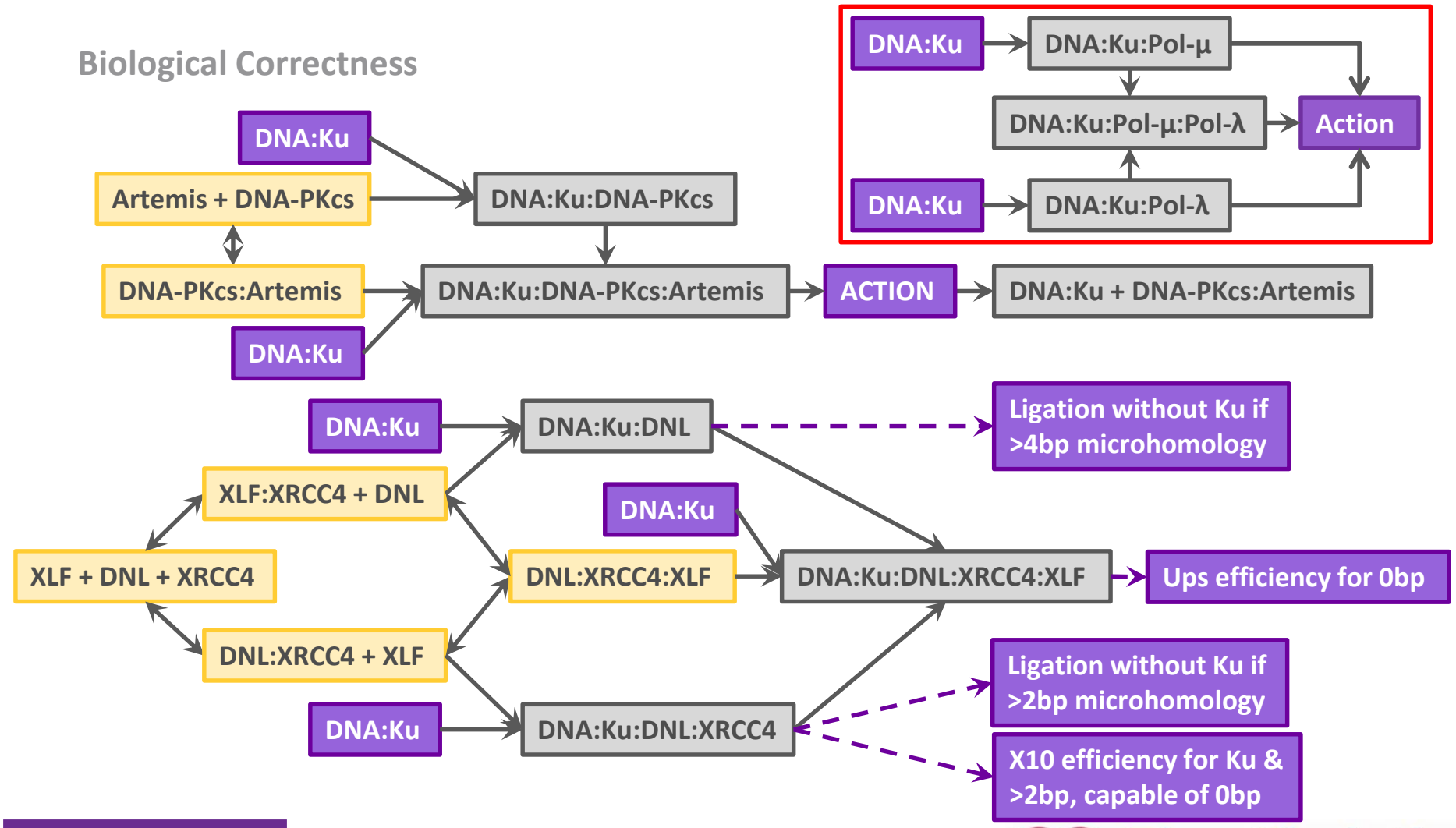
PARTRACK

Friedland W. *et al.*



The DNA Damage Repair Process

Challenges Still Faced by these Approaches



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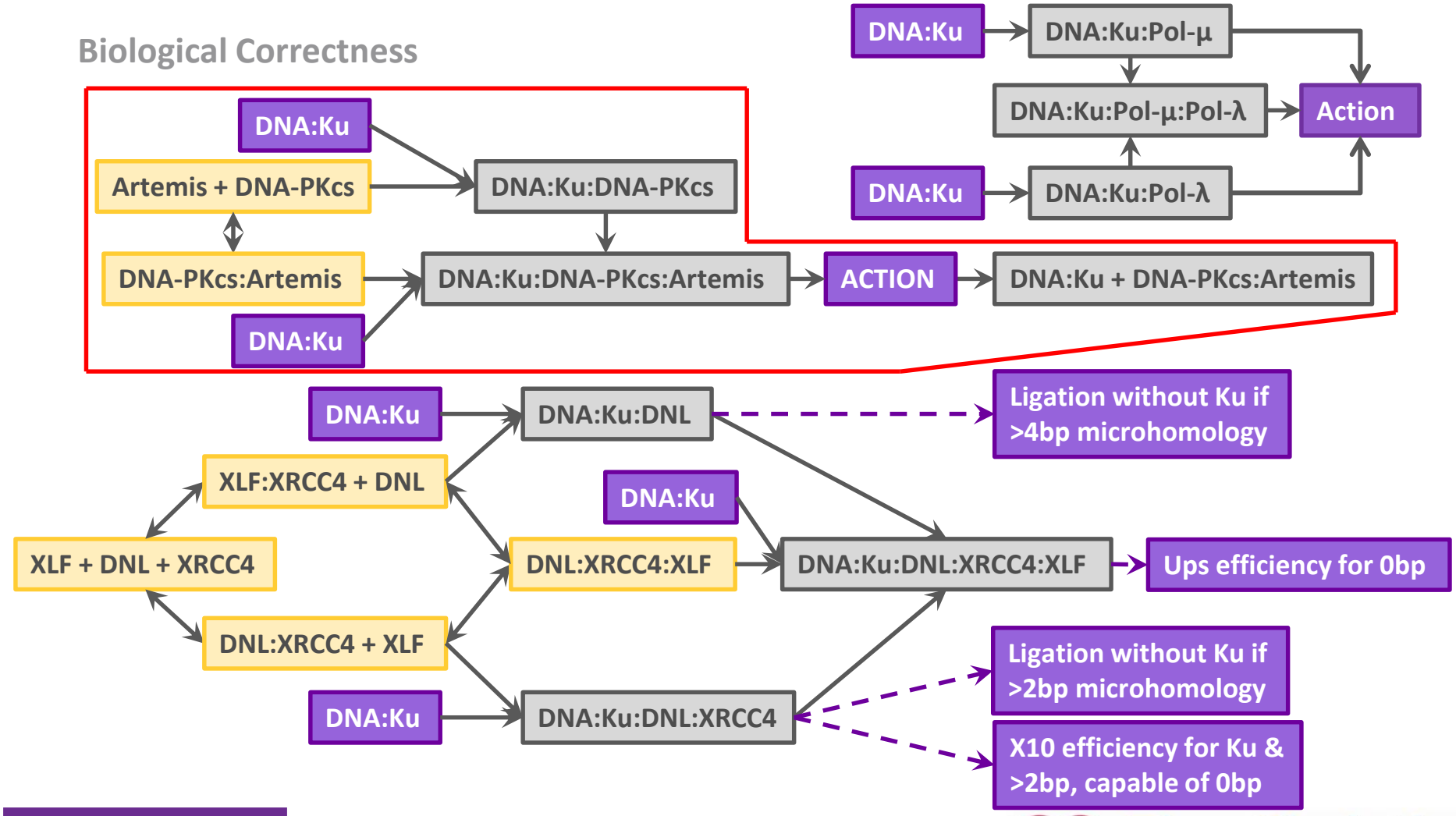

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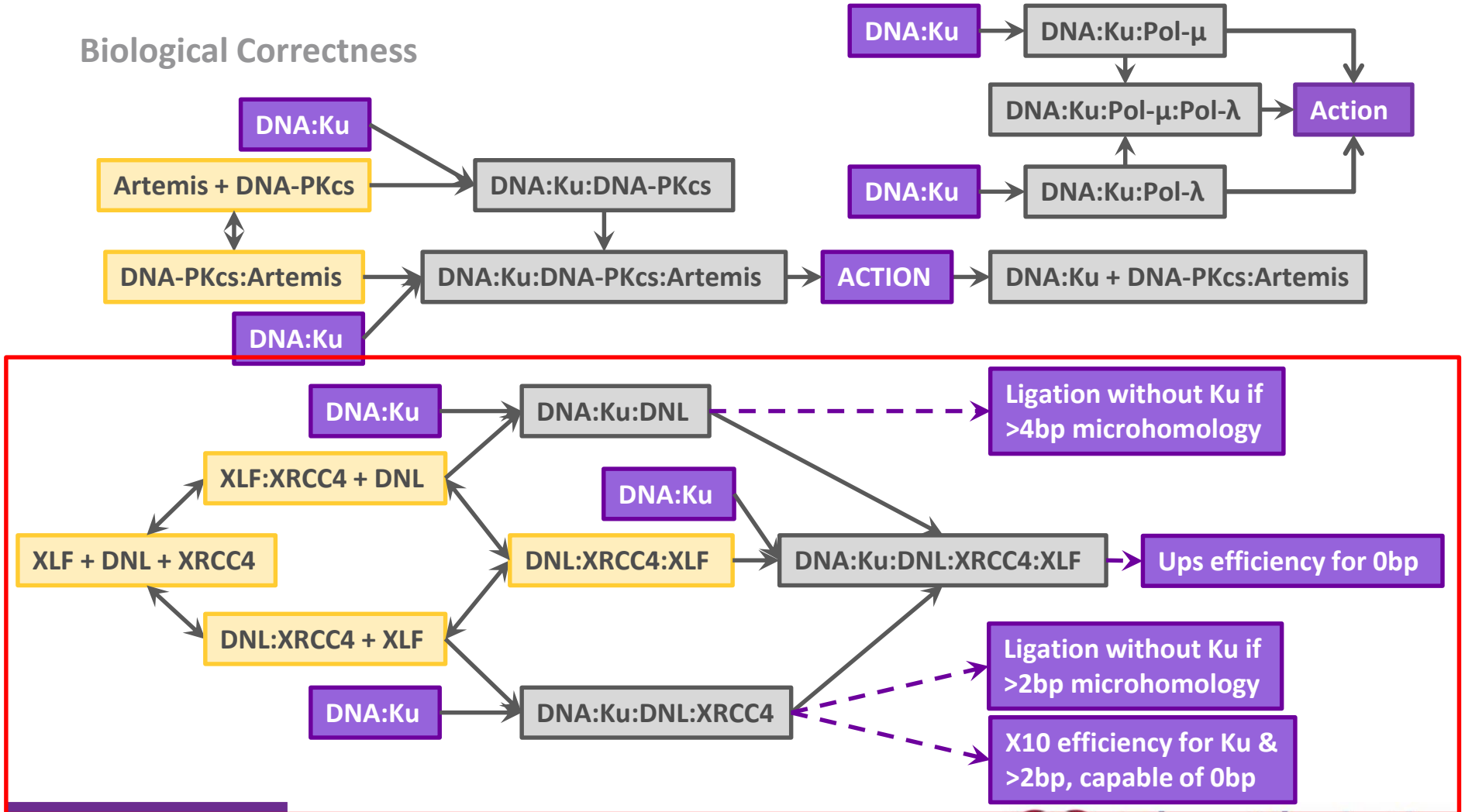
The DNA Damage Repair Process

Challenges Still Faced by these Approaches



The DNA Damage Repair Process

Challenges Still Faced by these Approaches

Fitting of Survival Curves

Altered parameter set has very good agreement with early repair kinetics

Slightly underestimates the number of residual DSBs at time approaching 24h

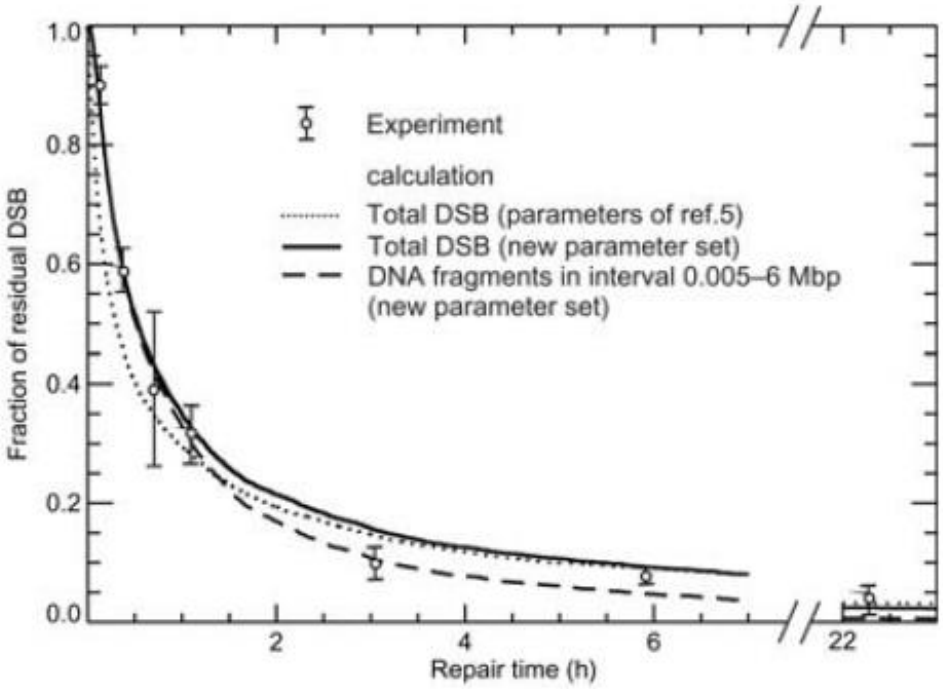


Figure 3. DSB repair kinetics after 100 Gy ^{60}Co gamma irradiation. Model predictions for total DSB numbers and the detectable fraction (0.005–6 Mbp fragments) compared with measured data[(6)].

Friedland W., 2010. *Mechanistic Simulation of Radiation Damage to DNA and its Repair: On the Track Towards Systems Radiation Biology Modelling*, Radiation Protection Dosimetry 143(2-4) , 542-548.

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The DNA Damage Repair Process

Challenges Still Faced by these Approaches

Fitting of Survival Curves

Agreement with measured early repair kinetics decreases with higher LET radiation

Underestimation of residual DSB increases for higher LET radiation

Cannot recreate the dose dependent nature of residual DSBs at long time periods

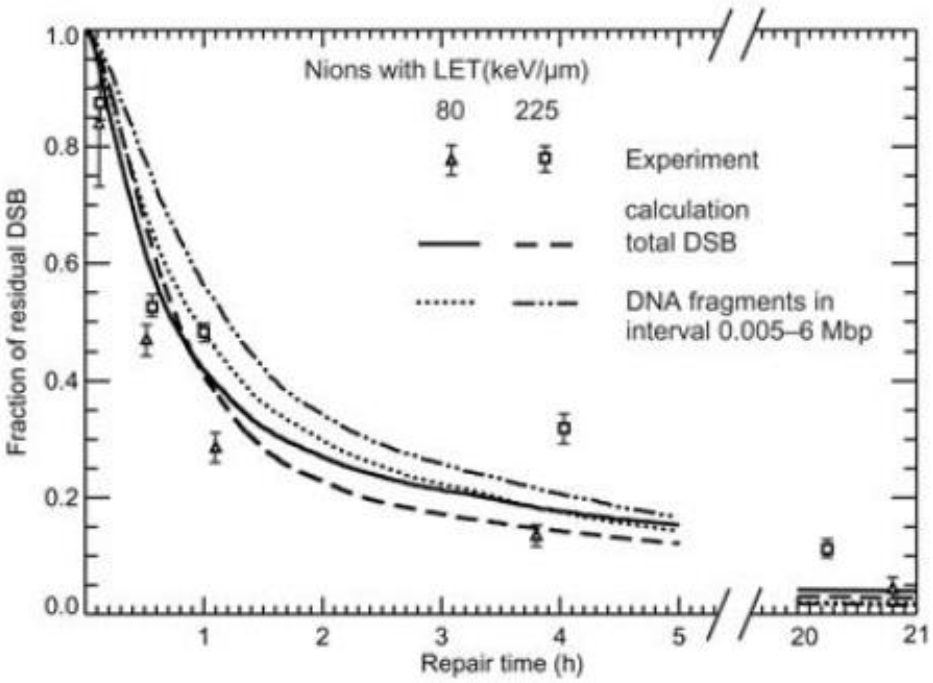

Figure 4. Predicted DSB repair kinetics in terms of total DSB numbers and their detectable fraction (0.005–6 Mbp fragments) after 100 Gy irradiation with nitrogen ions of 80 or 225 keV μm^{-1} LET, compared with measured data[6].

Friedland W., 2010. *Mechanistic Simulation of Radiation Damage to DNA and its Repair: On the Track Towards Systems Radiation Biology Modelling*, Radiation Protection Dosimetry 143(2-4) , 542-548.

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The DNA Damage Repair Process

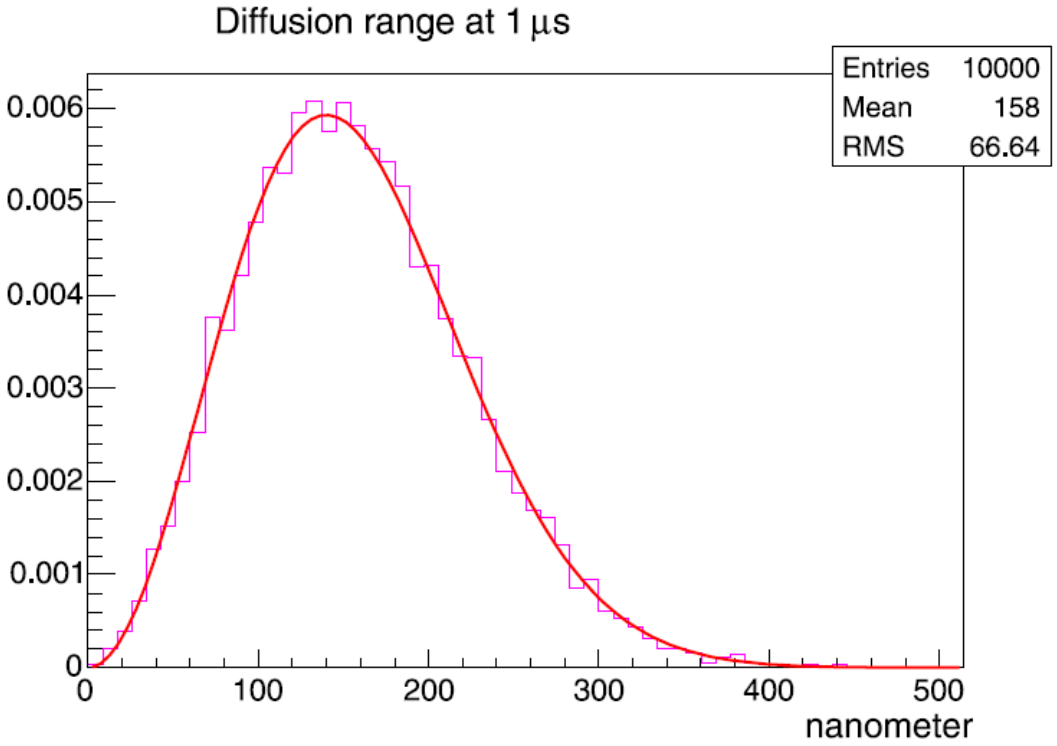
Geant4-DNA as an Environment to Build Models For

Geant4-DNA Chemistry Module

Models the system as simple interactions between discreet parts instead of trying to pin down rules for the complex dynamics which arises from them.

Smoluchowski Equation

Used to calculate the probability density for Brownian diffusion of the discrete particles of interest in the continuous cell medium.



Karamitros M., 2014. *Diffusion-controlled Reactions Modelling in Geant4-DNA*, Journal of Computational Physics 247, 841-882.

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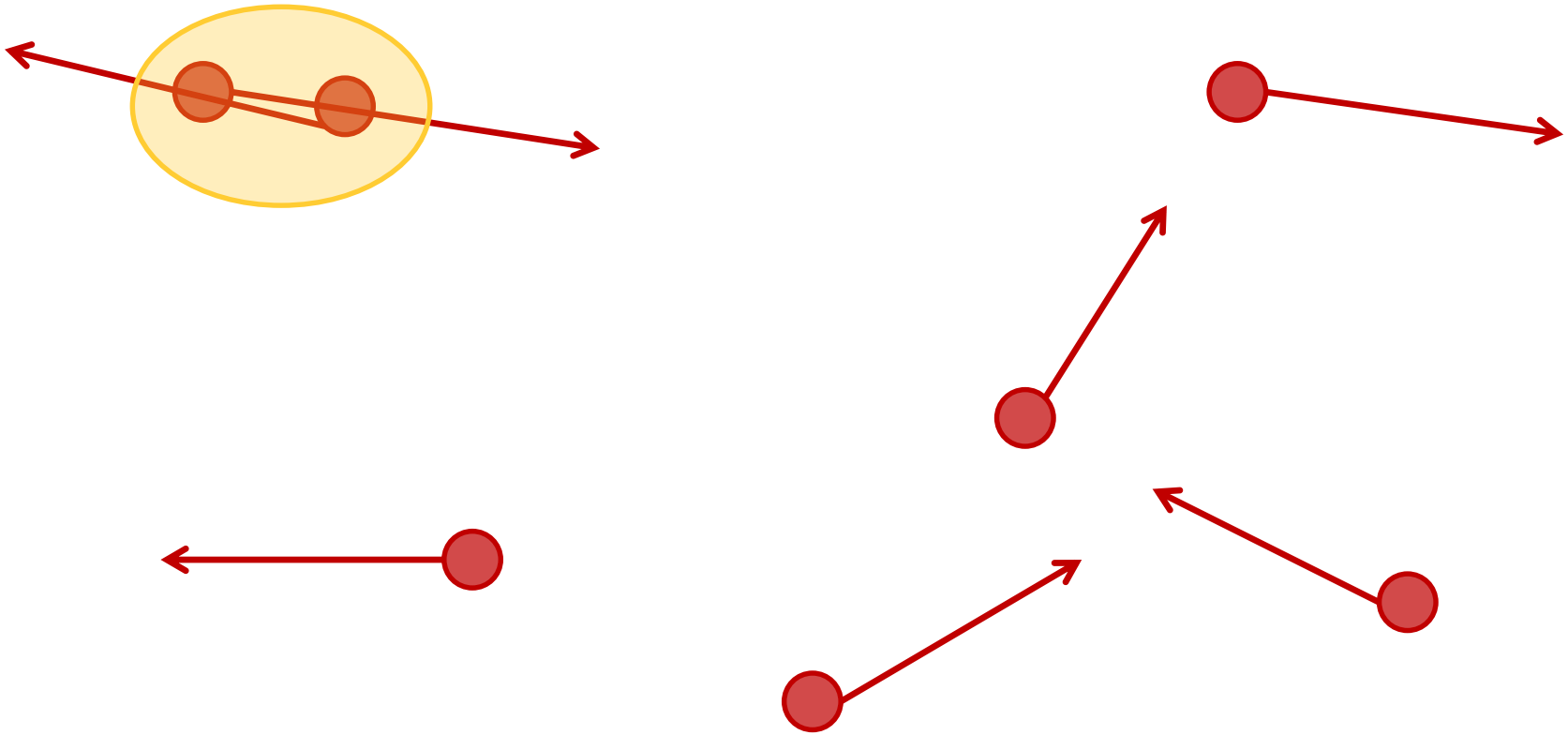
The DNA Damage Repair Process

Geant4-DNA as an Environment to Build Models For

Dynamical Time Step Method

Particles within reaction radius considered to react
Requires small time step to avoid passing by
Very time consuming, $O(N_M^2 N_t)$



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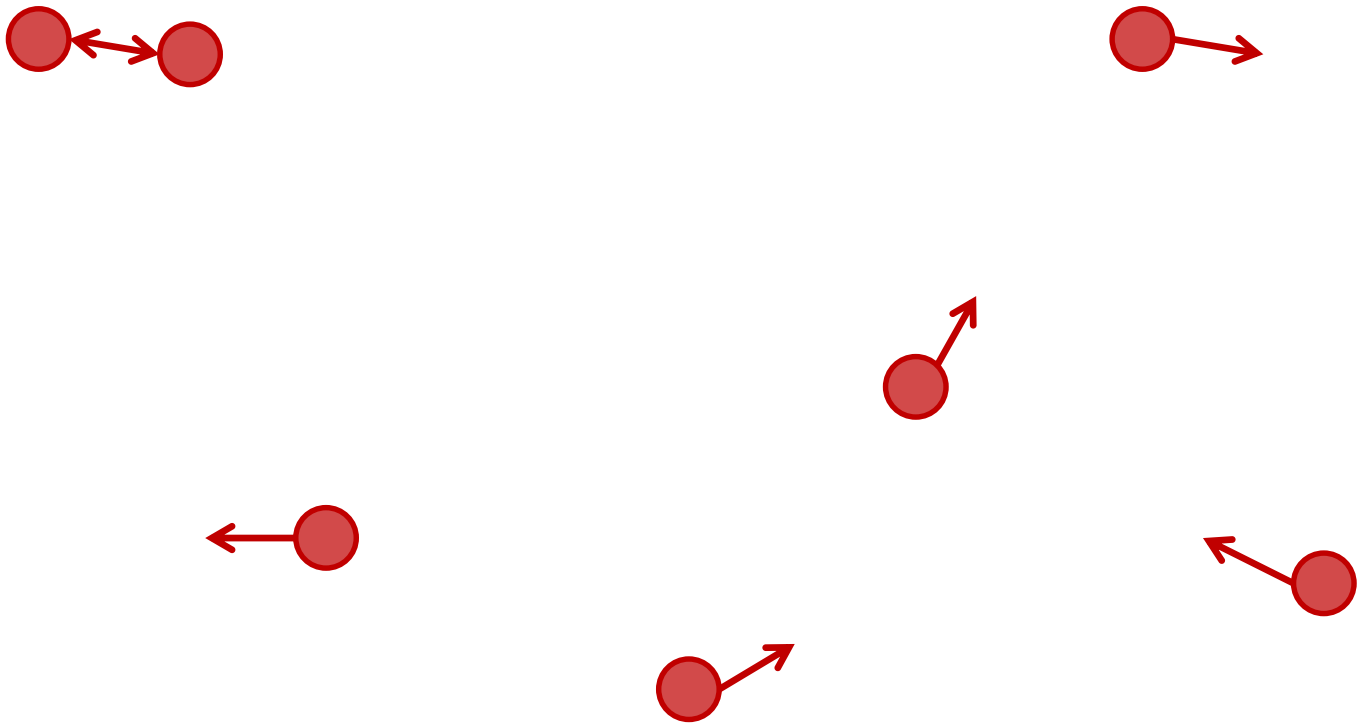

The DNA Damage Repair Process

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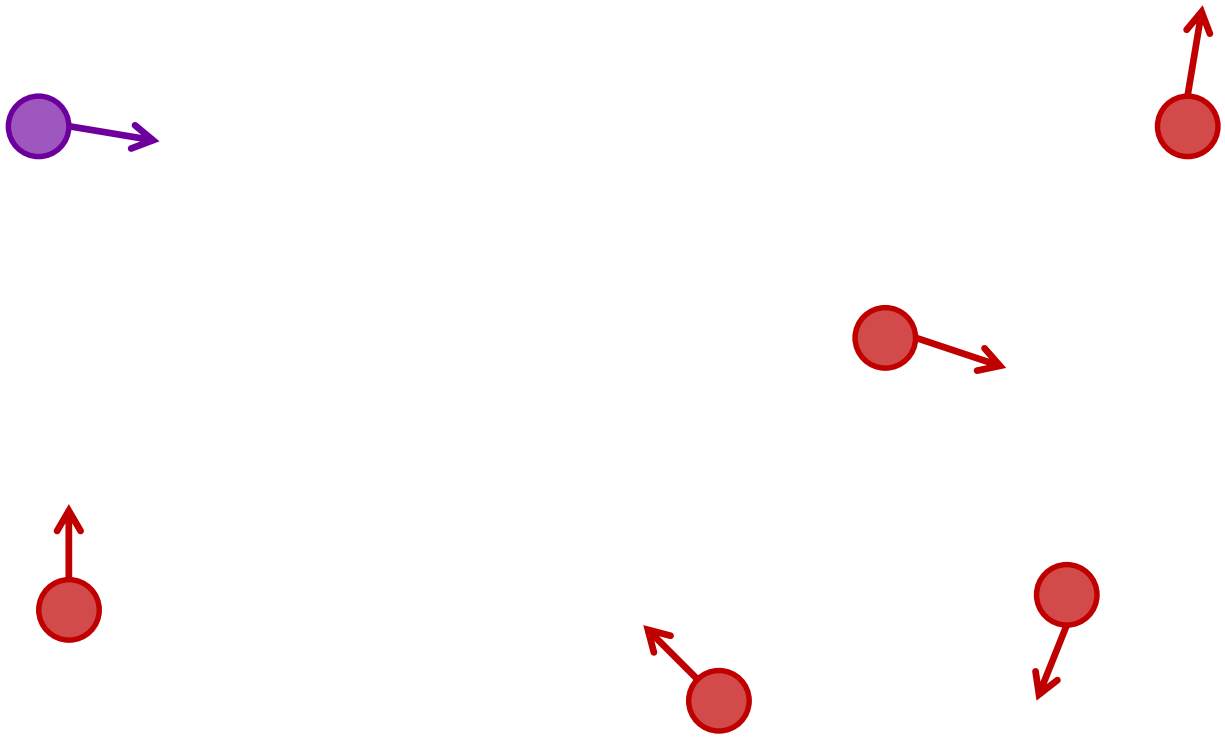


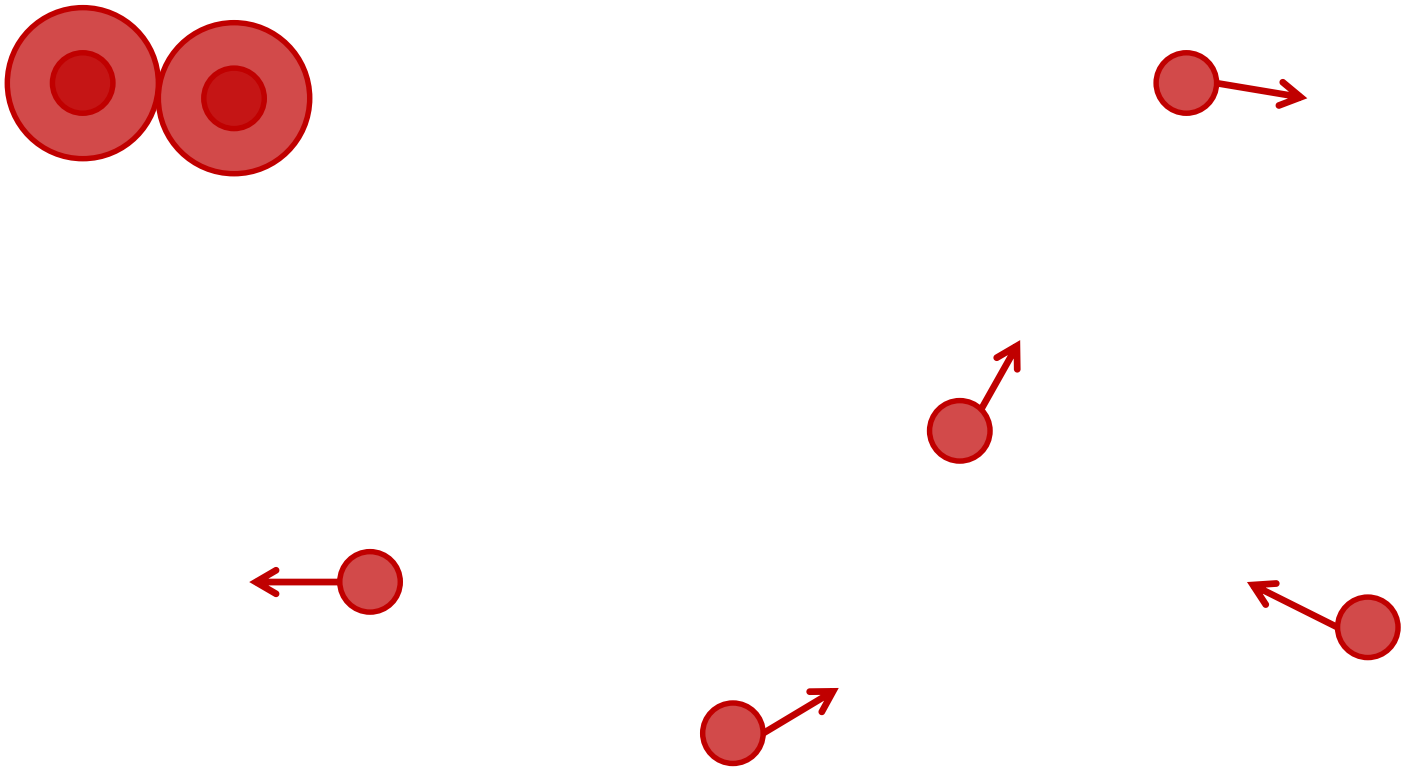
The DNA Damage Repair Process

Geant4-DNA as an Environment to Build Models For

Dynamical Time Step Method

To avoid this obtain closest pair of reactants (k-d tree)

Calculate minimum time of encounter to 95% confidence (1D-Smoluchowski)



The DNA Damage Repair Process

Geant4-DNA as an Environment to Build Models For

Dynamical Time Step Method

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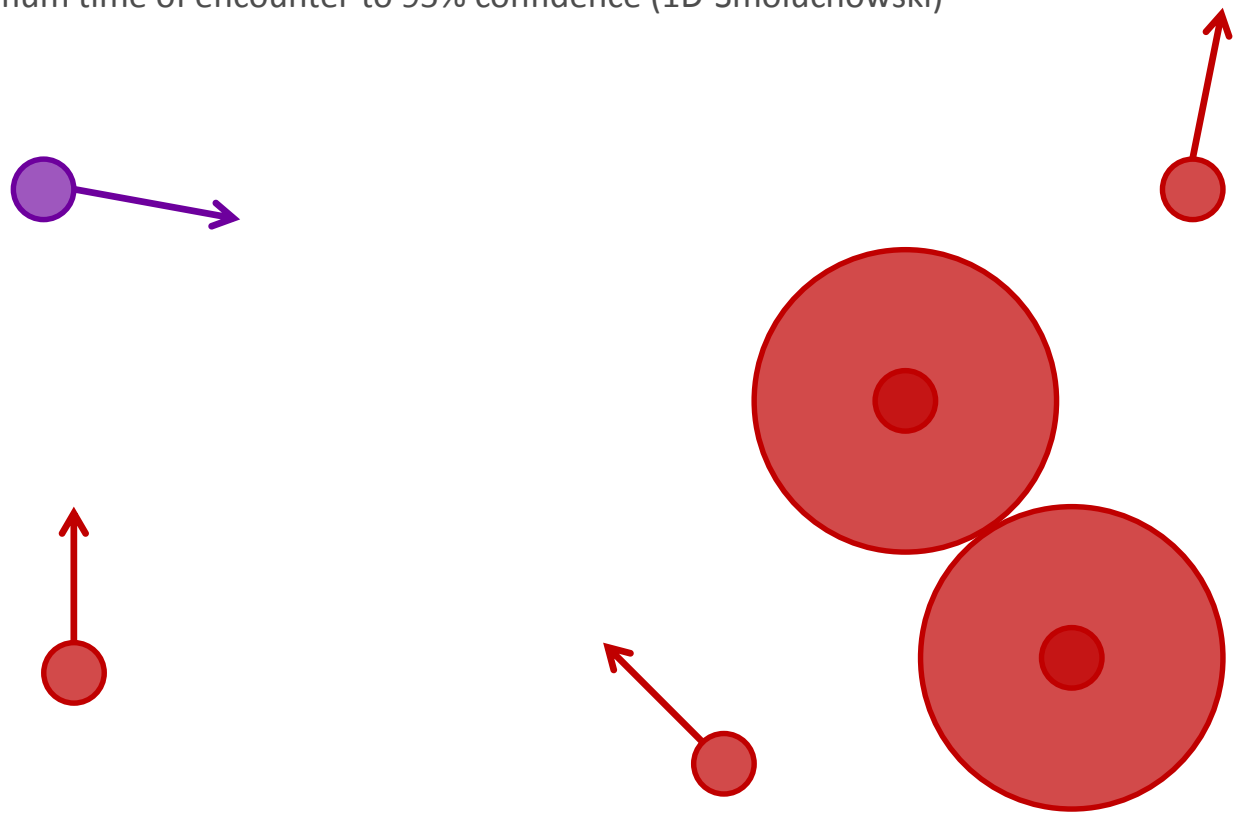
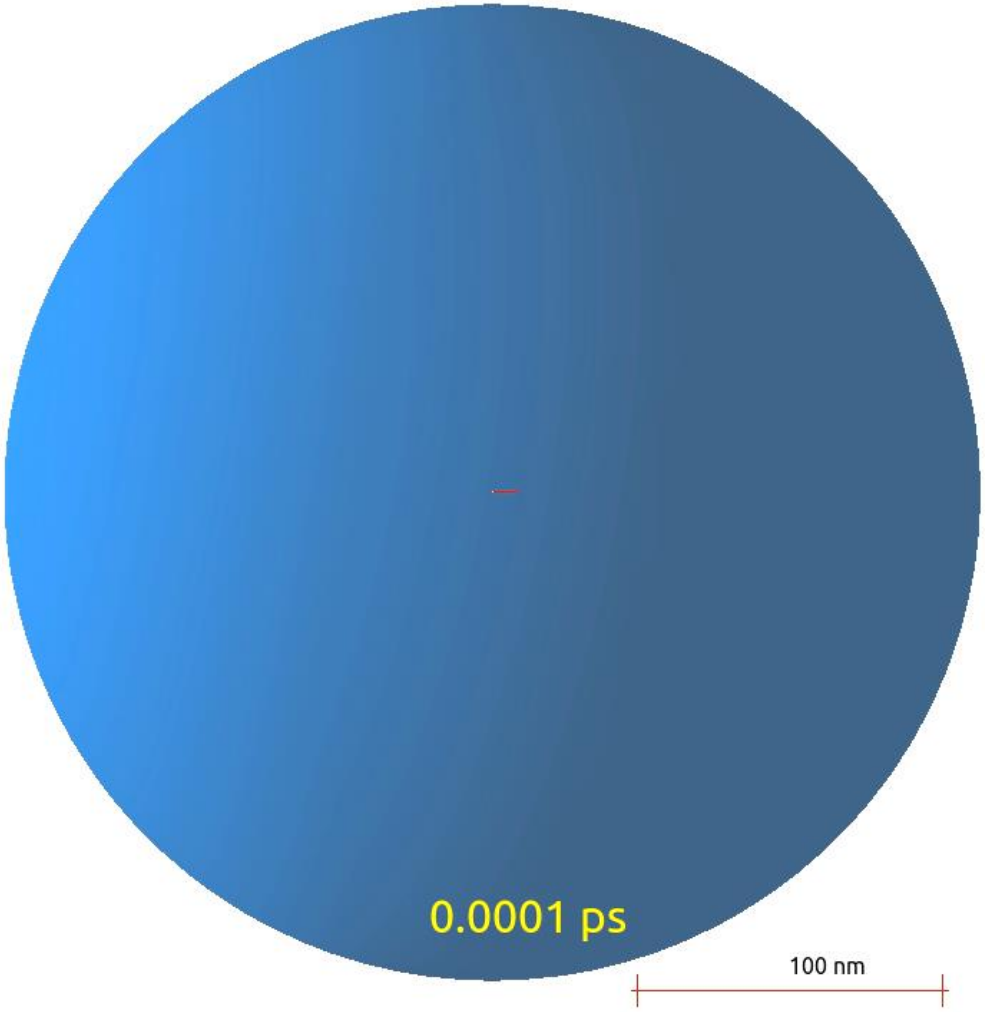


The Chemistry Module



The DNA Damage Repair Process

Geant4-DNA as an Environment to Build Models For

Current Work: A Molecular Reaction Based Model for Repair after proton irradiation through the NHEJ pathway

Model is being developed to simulate the **repair of DNA** at a **molecular scale**.

The aim is to include all relevant **repair proteins** and the **DNA DSBs** as **individual molecules** diffusing in the continuous medium of the cell.

These will then **react** according to **reaction kinetics** taken **from literature**.

Success of the model will be **judged by comparison** with **survival curves** from **biological experiments**.

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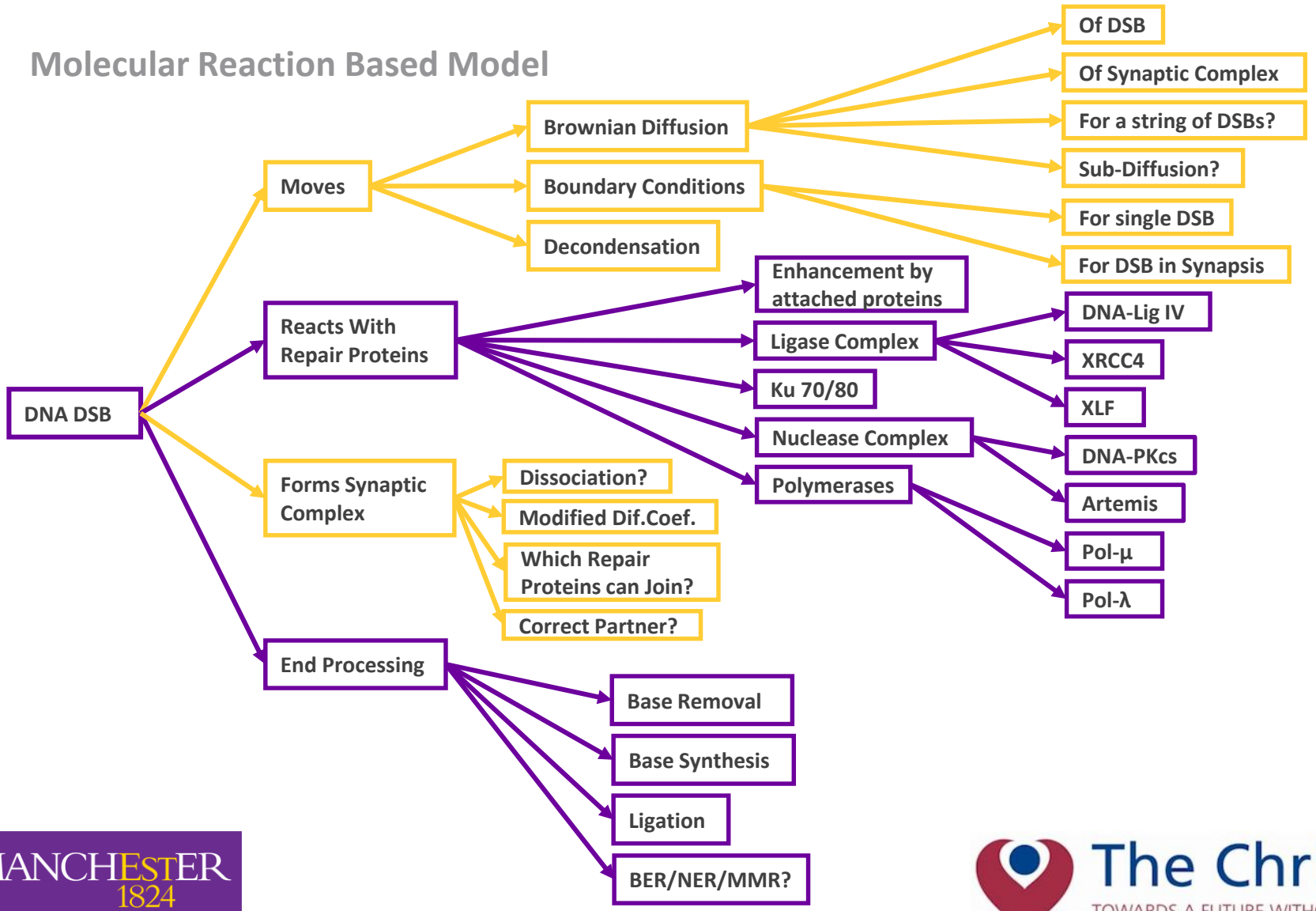
Geant4-DNA as an Environment to Build Models For

Molecular Reaction Based Model



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The DNA Damage Repair Process

Future Goals

Future Work: Development of model to include all available pathways

Initial effort will then be **further developed** to include **Single Strand Break repair** pathways and the more complex **Homologous Recombination repair** pathway. **SSB repair** is important for **"cleaning"** of DNA DSB ends and will allow us to simulate **repair after X-ray radiation** for **comparison** purposes.

Taking it Further: Full cell repair simulation through all available pathways

Once complete this work would **link up** with the **DNA structure model (Nick)**, **gold nano-particle radiosensitisation model (Marios)**, and **cell cycle model (Prof. Norman)** being developed by the team. This complete package could be used to better inform the use of parameters in actual treatment planning software, through parameters such as the **RBE of protons in different tissues**.

Acknowledgements

- Karen Kirkby
- Mike Merchant
- Marios Sotiropoulos
- Norman Kirkby
- Geant4-DNA Collaboration

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Any Questions?

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