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In-silico calculations of DNA damage induced by DaRT for a better understanding of the radiobiological effectiveness of this treatment

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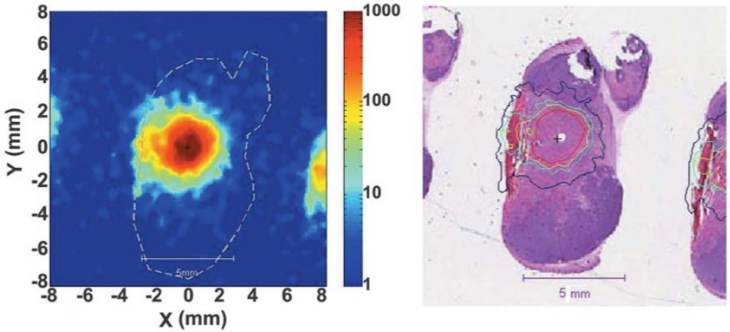
Overview

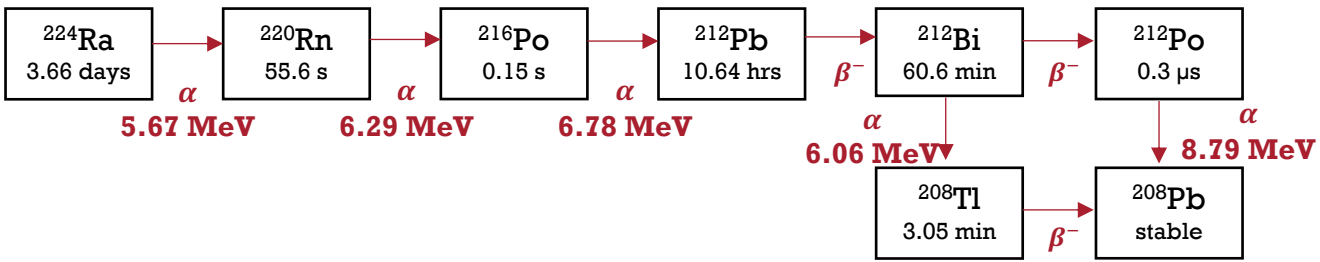
- DaRT
- Aims
- Simulation
- Results
  - DNA damage due to α-particles with kinetic energies in the DaRT decay chain
  - Impact of DNA density on DNA damage
- Summary

Diffusing alpha-emitters Radiation Therapy (DaRT)

- Interstitial brachytherapy technique
- Clinical trials ongoing
  - Skin, oral cavity and prostate cancer
  - Israel, USA, Japan, Italy, France
- Radium-224 seeds
- Diffusion increases the range over which dose is delivered
- Complex decay chain with several α-particles with different kinetic energies



(left) dose distribution calculated from autoradiography and (right) histological section of a human solid tumour treated with 224Ra wires in a human solid tumour[1]



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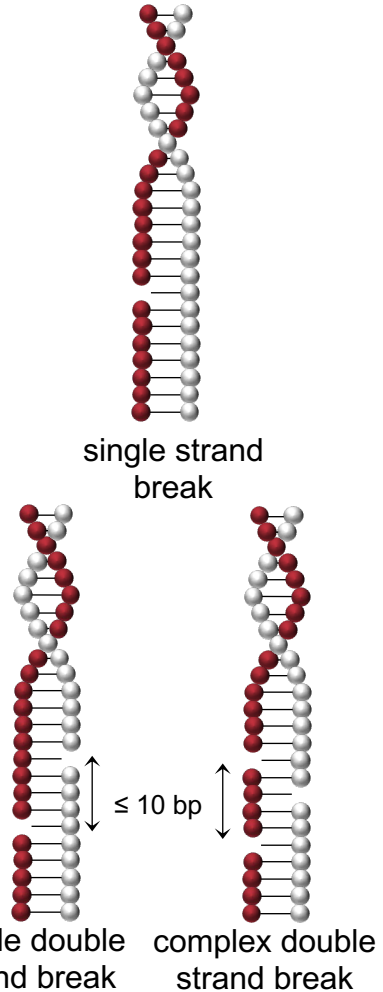
[1] Cooks et al. Anticancer Research, 32: 5315-5322 (2012)

Aims

To simulate the DNA damage induced by DaRT for a better understanding of the radiobiological effectiveness.

- Calculate DNA damage due to α-particles with kinetic energies in the DaRT decay chain
  - How does the distribution vary with LET (linear energy transfer)?
  - What is the distribution of simple and complex damages[1]?
- Calculate impact of DNA density on DNA damage
  - DNA density varies between cell types and during the cell cycle
  - Can simulation time be reduced by increasing the simulation density?

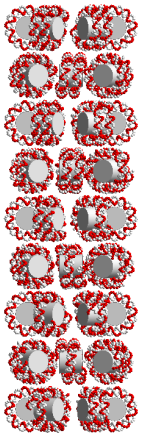


[1] Based on Nikjoo et. al., Int J Radiat Biol, 71(5), (1997)

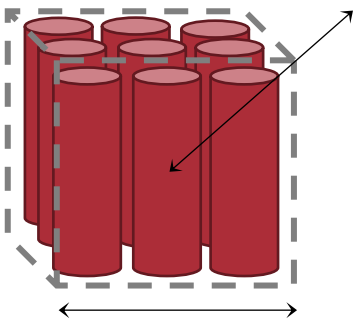
Simulation

- Geant4 11.0
- Simplified cell nucleus with straight strands of chromatin fibre to reduce simulation time
  - ~21,000 base pairs per chromatin fibre
  - Number and position of chromatin fibre strands can be varied
- Primary source spherical surface 1 μm radius centred on the nucleus
- G4EmDNAPhysics_option2 inside the nucleus and G4EmStandard_option4 outside
- Direct damage
  - Direct damage radius 0.35 nm
  - Linear damage model[1] 5 – 37.5 eV
- Indirect damage
  - IRT model
  - 40.5% probability of $OH^{\bullet}$ radical causing an indirect strand break
  - Cut off time 5 ns
  - Radicals removed > 9 nm from DNA

Chromatin Fibre



Simplified Cell Nucleus

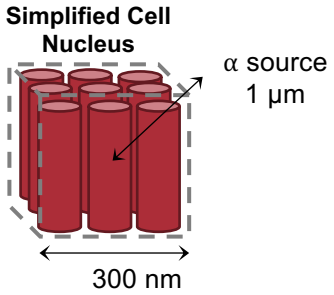


Number and spacing simulation dependant
275 – 750 nm

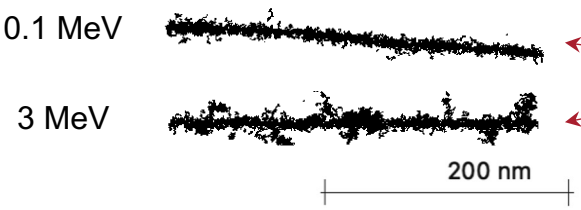
[1] W. Friedland et al., Radiat. Res., 159 (2003), 401–410

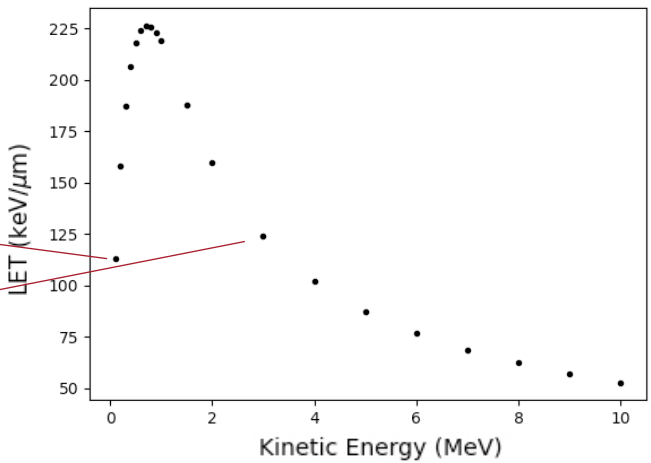
Aim 1: Calculate DNA damage from α-particles with kinetic energies in the DaRT decay chain

- To understand the radiobiological effectiveness of DaRT an understanding of DNA damage for the relevant kinetic energies is required
- Incident α-particles with kinetic energy in range 0.1 - 9 MeV, to cover DaRT range
- Track structure is dependant on the kinetic energy however two particles with different kinetic energy can have the same LET



Position of OH• radicals up to 1ns, ~120 keV/μm



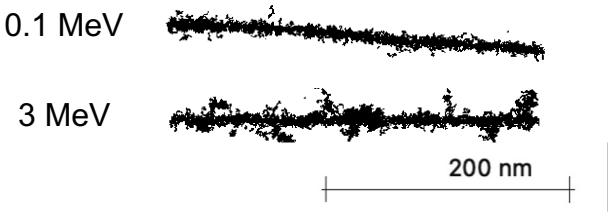


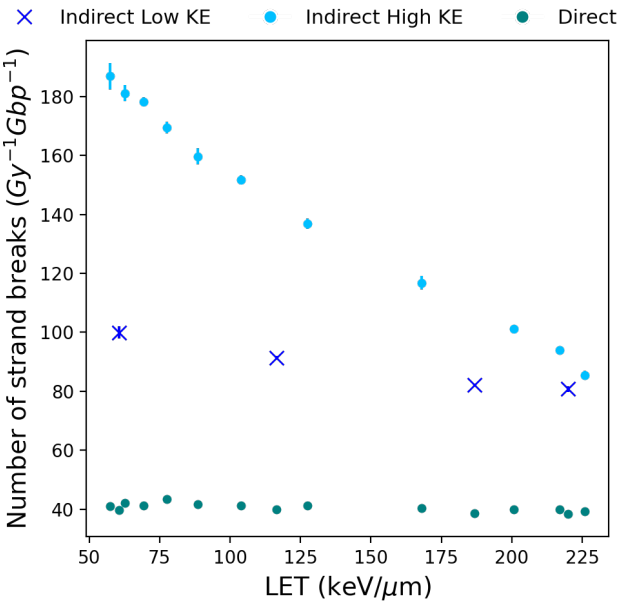
Individual Strand Break Results

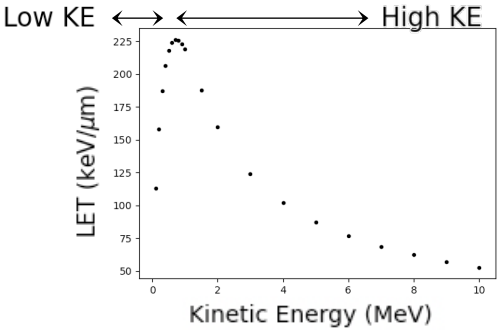
- Direct damage is constant
- Higher kinetic energy α-particles (above maximum LET)
  - Indirect damage decreases with increasing LET
- Lower kinetic energy α-particles (below maximum LET)
  - Indirect damage is lower for an α-particle with kinetic energy below the maximum LET

Indirect damage is more significant than direct damage at low LET

Position of OH• radicals up to 1 ns, ~120 keV/μm



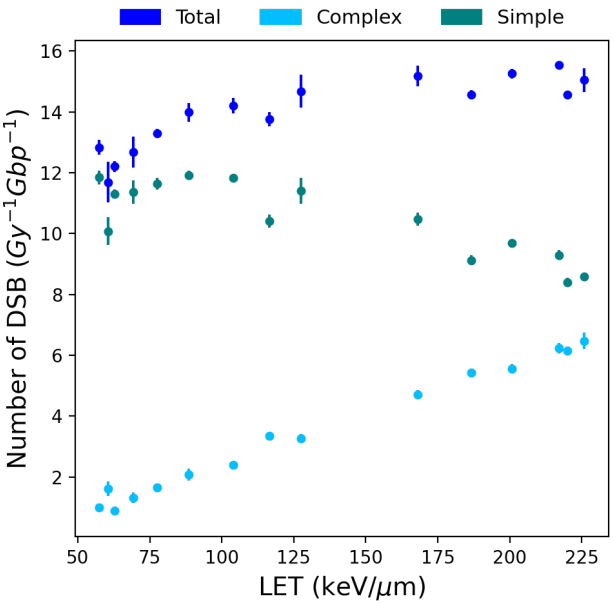




Double Strand Break Results

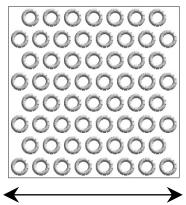
- Number of total DSB increases with increasing LET
- Complexity of DSB increases with increasing LET
- Number of complex DSB increases approximately linearly with LET

DSB complexity increases with LET therefore more detrimental damage to the cell is done at higher LET

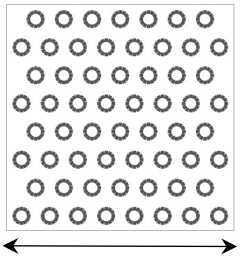


Aim 2: Calculate impact of DNA density on DNA damage

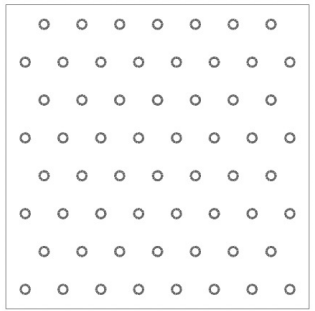
- Base pair density in human cells varies in the range[1] 0.007 - 0.058 bp/nm^3
- Fix number of base pairs, vary volume and chromatin fibre spacing
- 1.3 million base pairs
- Primary source spherical surface 1 μm radius centred on the nucleus
  - Incident α-particles with kinetic energy in range 3 – 8 MeV
  - Maximum variation in kinetic energy across the target 5% of mean kinetic energy



275 nm
0.056 bp/nm^3



350 nm
0.035 bp/nm^3



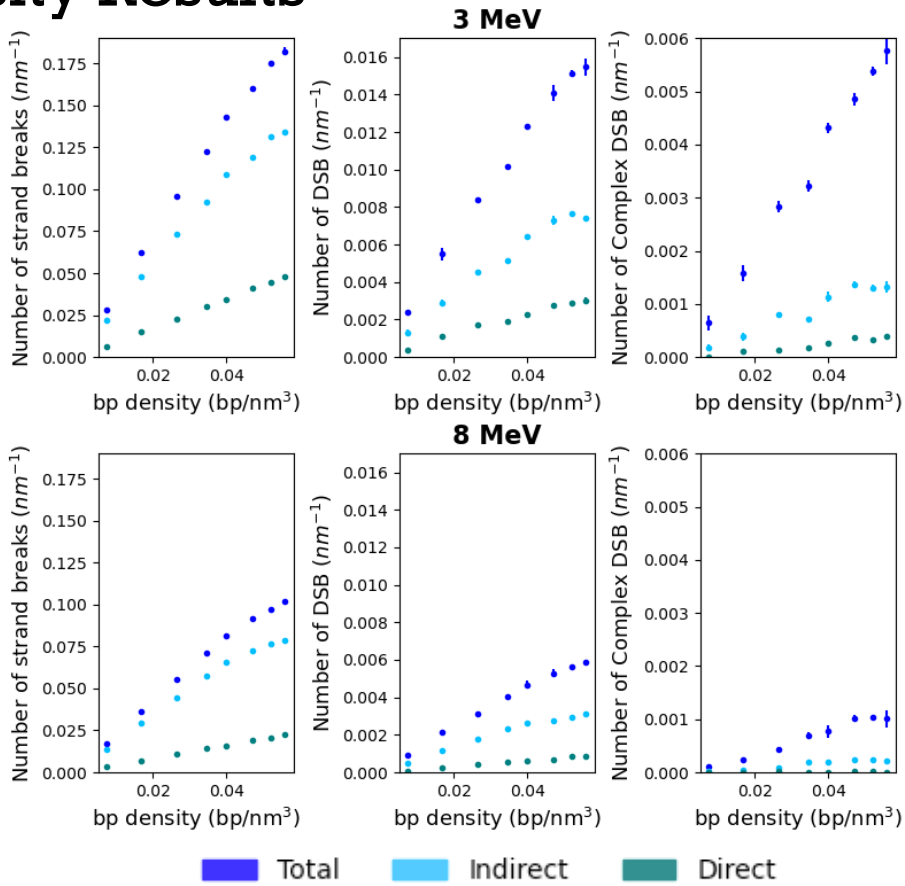
750 nm
0.008 bp/nm^3

[1] *Rep. Prog. Phys.77(2014)*

Base Pair Density Results

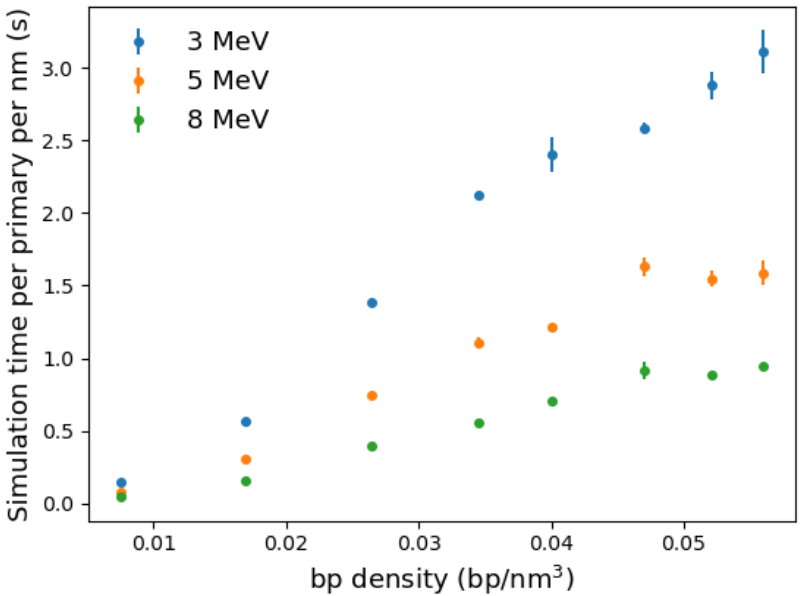
- The number of strand breaks increases approximately linearly with base pair density
- LET of a 3 MeV α-particle is higher than at 8 MeV, therefore more energy is deposited per unit distance and more strand breaks occur.

Base pair density significantly affects the amount of DNA damage



Base Pair Density Simulation Time

- Aim to see if simulation time could be reduced by using higher density geometries as less primary particles are required
- However the simulation is significantly longer for higher density geometries
  - Due to larger number of molecules to track for the chemical simulation
- For all energies there is approximately a 6 times increase of total strand breaks for a 20 times increase in simulation time



Summary and Future Work

- Aim 1: Calculate DNA damage due to α-particles with kinetic energies in the DaRT decay chain
  - Number of individual damages per Gy caused by direct damage is constant
  - Number of individual damages per Gy caused by indirect damage decreases
  - Indirect damage differs for kinetic energies above and below the maximum LET
  - More complex DSB at higher LET
- Aim 2: Calculate impact of DNA density on DNA damage
  - More DNA damage occurs for a denser DNA geometry
  - Approximately linear
  - Simulation time increases significantly for higher density geometries
- Future work:
  - Compare to a more realistic cell geometry
  - Calculate cell survival
  - Calculate the DNA damage distribution for DaRT taking into account the whole decay chain and diffusion of radon
  - Compare to photon simulations for a better understanding of the radiobiological effectiveness of DaRT
- Initial results are promising for simulating the full DaRT process and assessing the radiobiological effectiveness of this treatment

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Thank you

Any questions?

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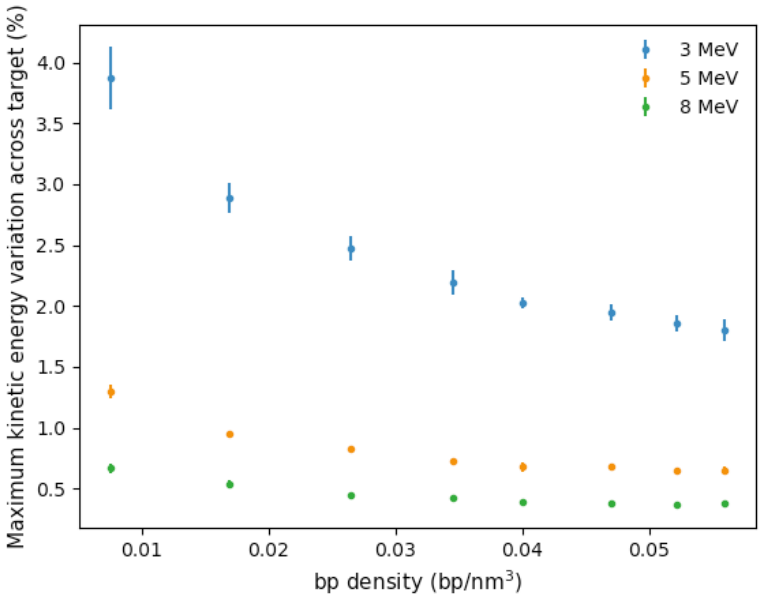
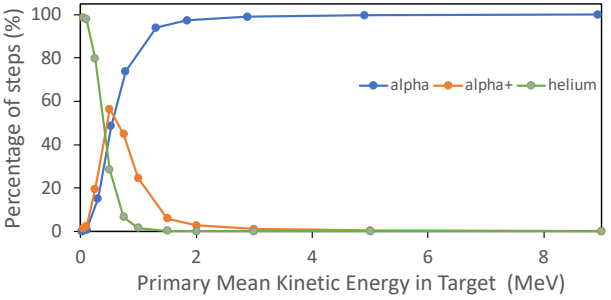
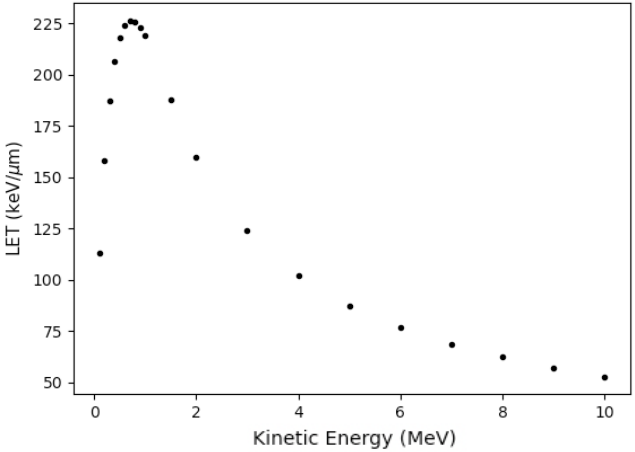
Kinetic energy variation across the target

- Maximum kinetic energy variation across the target as a percentage of the mean kinetic energy
- Maximum variation 5%



Charge decrease at low kinetic energies





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