UNIVERSITY OF OXFORD

CANCER RESEARCH UK | OXFORD CENTRE

General Sir John Monash Foundation

Incorporating biological factors
in radiation therapy treatment planning

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Motivation

- PTCOG: as of end of 2014 over 137,000 cancer patients had been treated with particle therapy worldwide, with protons being the chosen modality in 86% of cases [Jermann, 2015]

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- Main therapeutic advantage: *Bragg peak* in energy deposition

- Most of the energy is deposited toward the end of its trajectory in a sharp peak

- Advantageous in IMPT as the energy and intensity of individual pencil beams can be manipulated to deposit a highly conformable dose to the tumour volume, with a low dose on entry and no exit dose

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▶ May be quantified through various biological endpoints

▶ Quantification of radiobiological effects can be incorporated into treatment plan optimization algorithms

▶ Seek a dose distribution that is both <u>physically</u> and <u>biologically</u> favourable

Quantification of biological effects
Relative Biological Effectiveness

Definition

Relative Biological Effectiveness (RBE): the dose delivered using a specific modality and energy that yields the same biological effect as a reference dose in a reference modality;

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▶ In-vitro cell data on its own is unsatisfactory

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Definition

Restricted RBE for complex damage: ratio of the number of DSBs in the modality of interest to the number generated in a reference modality depositing the same dose;

$$\mathrm{RBE_{cd}} = \left(\frac{\#\mathrm{DSB\ induced\ by\ test\ radiation}}{\#\mathrm{DSB\ induced\ by\ test\ radiation}} \right)_{\mathrm{same\ dose}}. \qquad (2)$$

Modeling DNA damage
Linear energy transfer (LET)

▶ Differential loss of kinetic energy over
distance given by stopping power $\langle dE/dl \rangle$

low concentration of
ionisation events

γ-radiation
Low LET tracks

α-radiation
High LET track

high concentration of
ionisation events

30 nm

Figure: Image cropped from Fig 1 in [Lomax et al., 2013].

Modeling DNA damage
Linear energy transfer (LET)

- Differential loss of kinetic energy over distance given by stopping power $\langle dE/dl \rangle$

- Microsimetry: <u>linear energy transfer</u> (LET) is used instead – which is stopping power but with energy delivered to highly energetic knock-on electrons subtracted
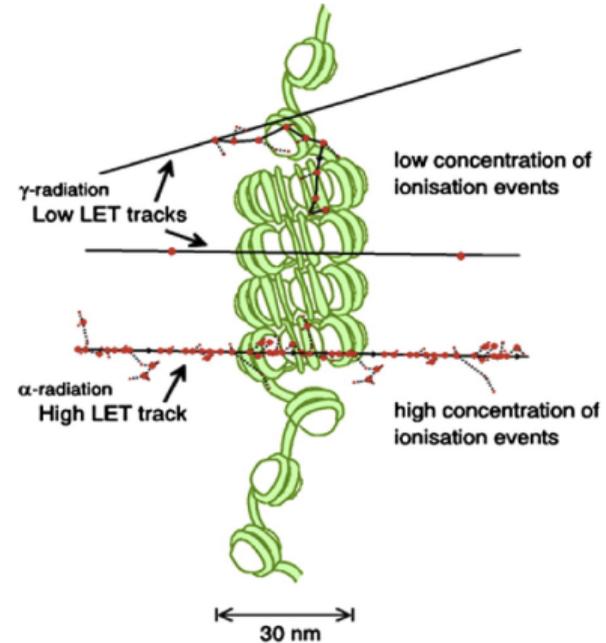
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- Microdosimetry: <u>linear energy transfer</u> (LET) is used instead – which is stopping power but with energy delivered to highly energetic knock-on electrons subtracted

- Density of ionisations along track can therefore be measured using LET and is closely related to the kinetic energy of the particle
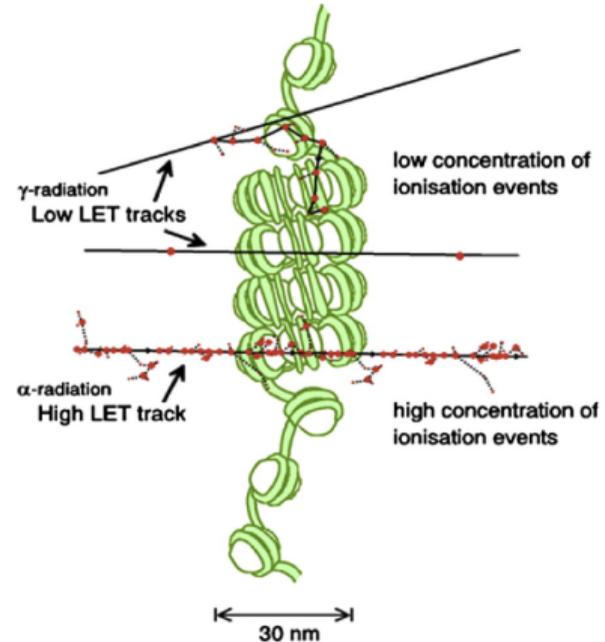
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Modeling DNA damage
Single particle interaction model
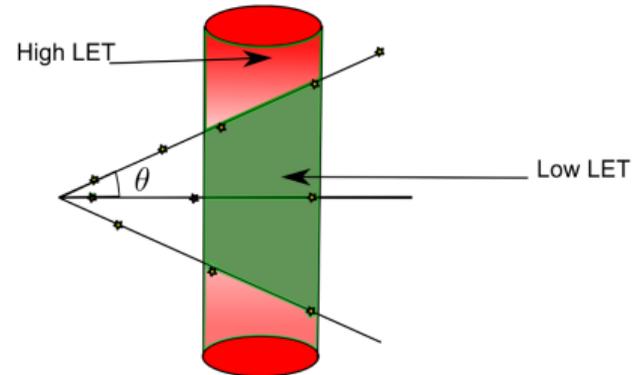
▶ Approximate a section of the DNA as a cylinder
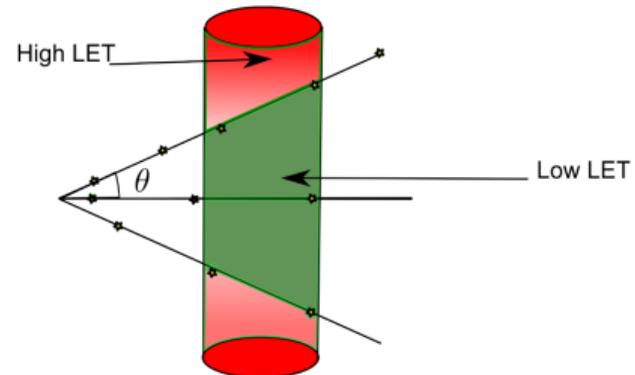
Figure: Image from Figure 1 in [Van den Heuvel, 2014].

Modeling DNA damage
Single particle interaction model

▶ Approximate a section of the DNA as a cylinder

▶ Use the energy dependent mean free path $\lambda(E)$ between successive ionisations to determine the distribution of clustered lesions [Van den Heuvel, 2014]
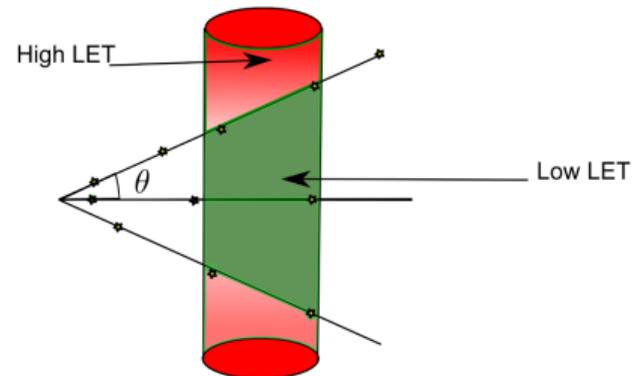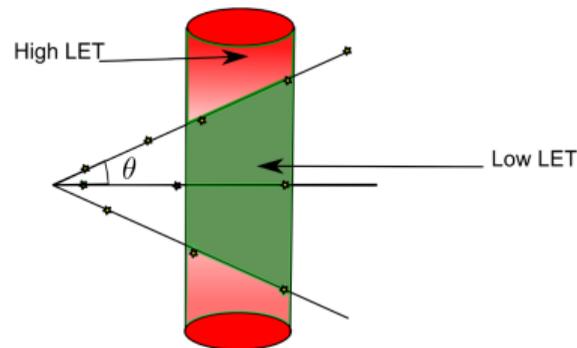

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- Use the energy dependent mean free path $\lambda(E)$ between successive ionisations to determine the distribution of clustered lesions [Van den Heuvel, 2014]

- Angular dependence: larger $\theta \implies$ longer path through DNA $\implies$ higher LET and greater likelihood of inducing clustered damage
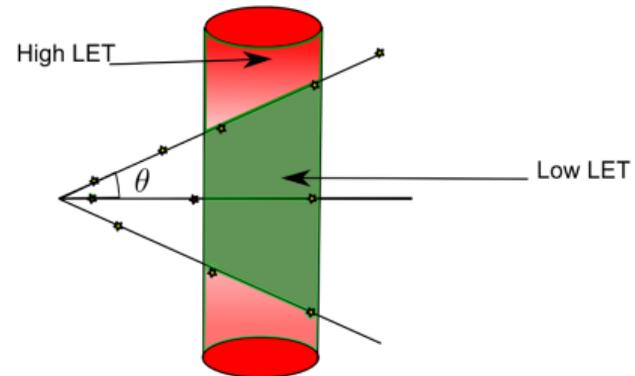
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Modeling DNA damage
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▶ Problem is equivalent to setting an
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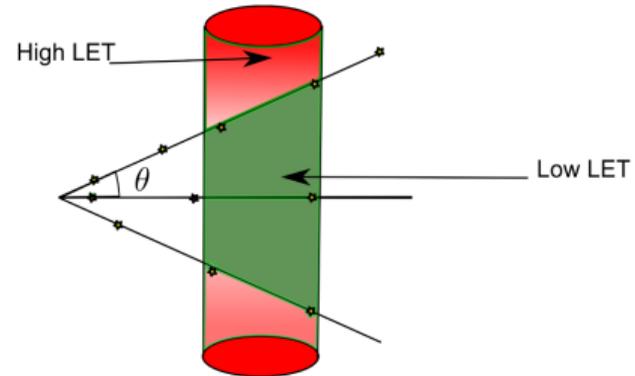
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Modeling DNA damage
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- Problem is equivalent to setting an isotropic point source at the boundary of the cylinder

- Reduces mathematically to that of the distribution of projections of a point source on a line-piece

- Solution: Cauchy distribution
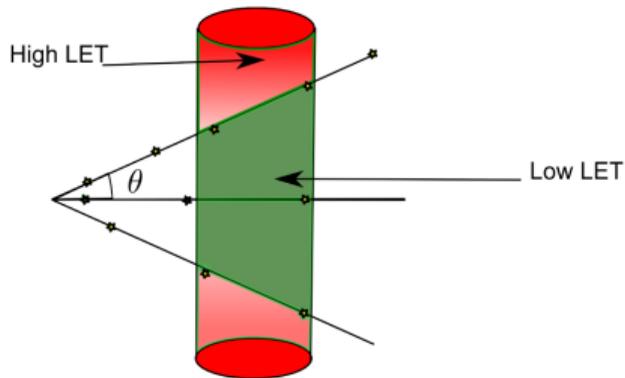
High LET

Low LET

θ

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Modeling DNA damage
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- Using $\lambda(E)$, the distribution of DSBs may be reformulated as a function of E instead of θ

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- Damage response function: expected yield of DSBs given by [Van den Heuvel, 2014]

$$F_{\text{cd}}(E) = (a-b)\frac{2}{\pi}\left[\tan^{-1}\left(\frac{E-E_0}{\Gamma/2}\right)\right] + b \quad (3)$$

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▶ Units: $\mathrm{Gbp}^{-1}\mathrm{Gy}^{-1}$
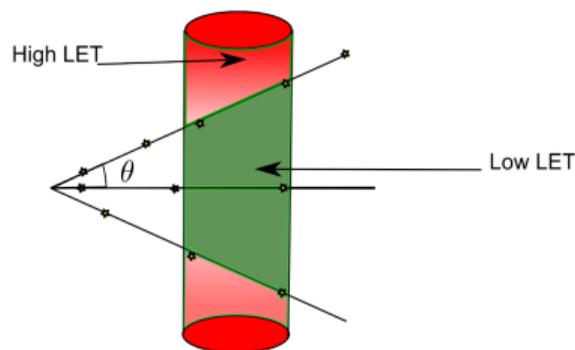
Figure: Image from Figure 1 in [Van den Heuvel, 2014].

Modeling DNA damage
Single particle interaction model

▶ Parameters a, b, Γ, and E_0 fitted through a two-stage χ^2 minimisation

Figure: Images from Figures 3(b) and 4(b) in [Van den Heuvel, 2014].

Modeling DNA damage
Single particle interaction model

- Parameters a, b, Γ, and E_0 fitted through a two-stage χ^2 minimisation

- 1. Differential Lorentz distribution dF_{cd}/dE
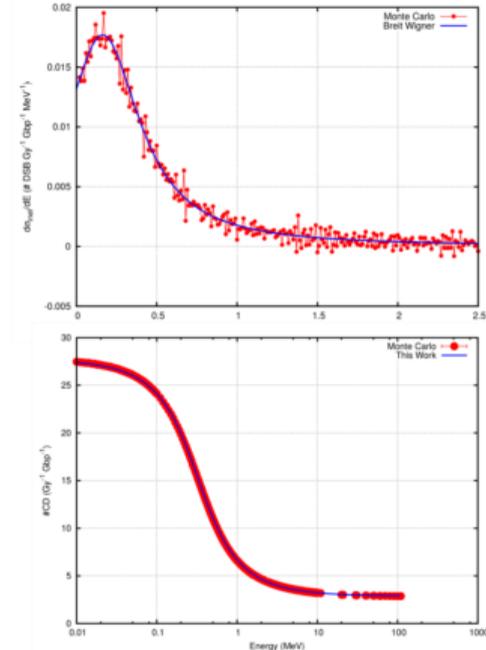
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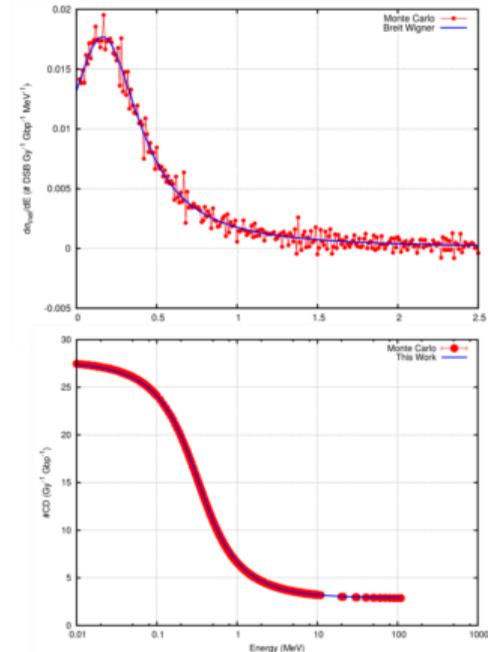
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- Good agreement with microscopic Monte Carlo software MCDS [Semenenko and Stewart, 2004]
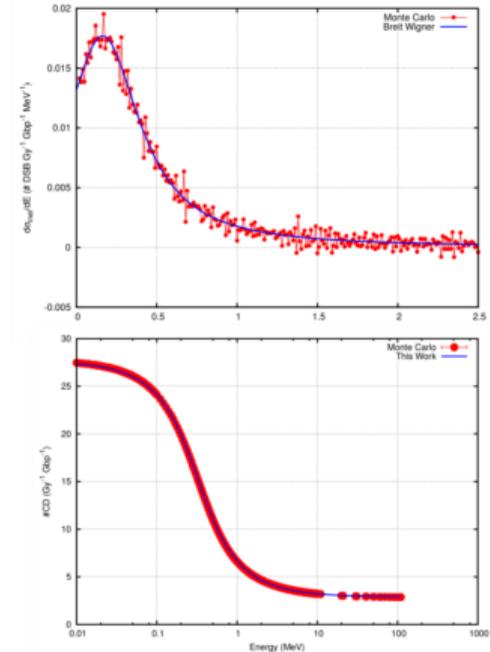
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Voxelised RBE distribution

▶ Dose deposited in each voxel $D[i, j.k]$ of the patient CT
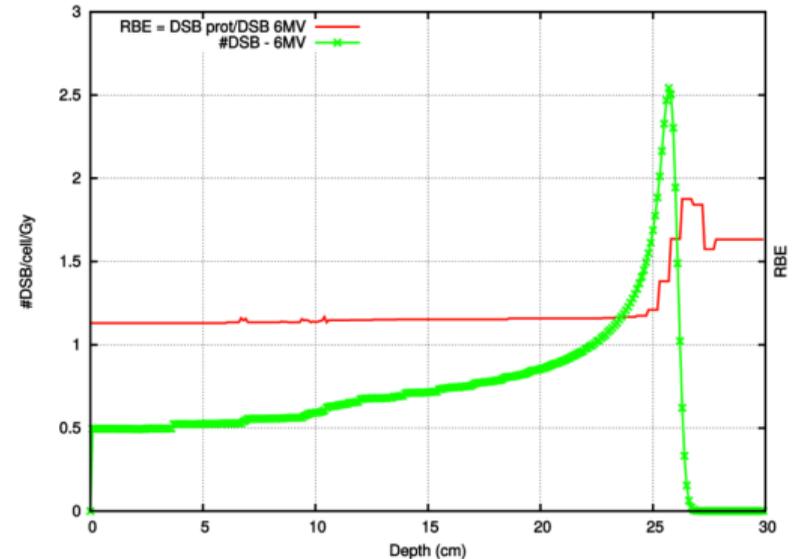
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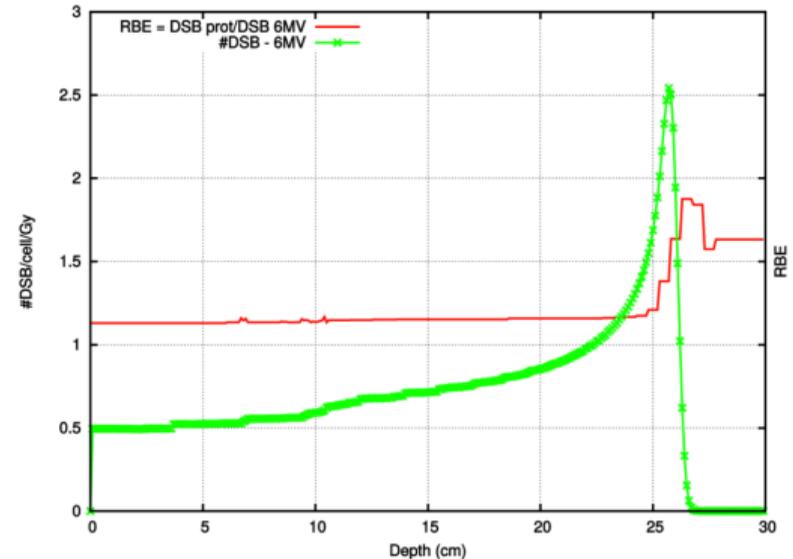
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$$M_{cd}[i, j, k] = D[i, j, k] \times \frac{\int_0^{E_{\max}[i,j,k]} \Psi_{ijk}(E) F_{cd}(E) dE}{\int_0^{E_{\max}[i,j,k]} \Psi_{ijk}(E) dE}$$

(4)
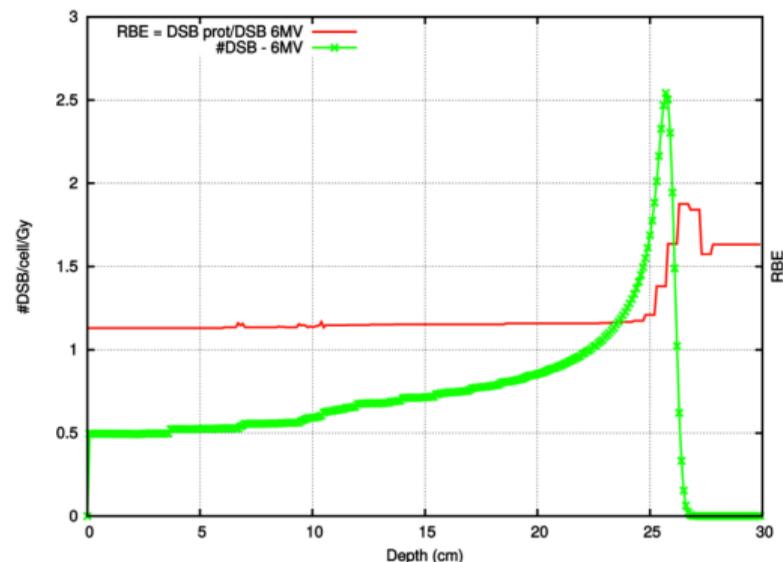
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-

$$\mathrm{RBE}_{cd} = M_{cd,p}/M_{cd,\gamma} \qquad (5)$$
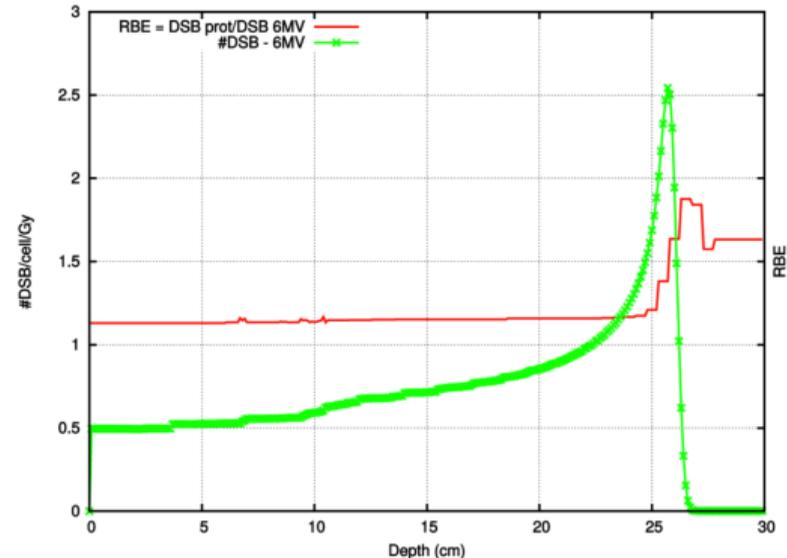
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Further considerations
Oxygen level modeling

- Amount of oxygen binding that can occur has a saturation behaviour
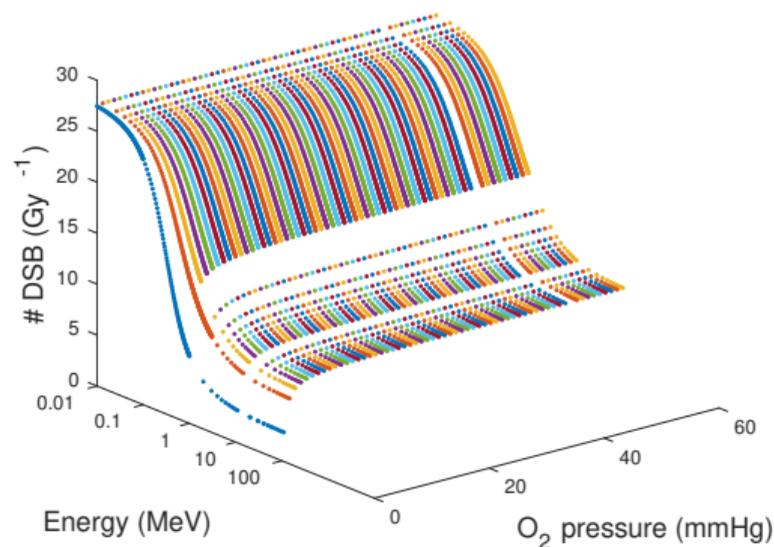
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▶ Can be modeled using second order D.E. [Kepner, 2010; Van den Heuvel, 2014]

$$\frac{(d^2y/dx^2)dx}{(dy/dx)} = N\left(\frac{dy}{y}\right) - M\left(\frac{dx}{x}\right) \quad (6)$$
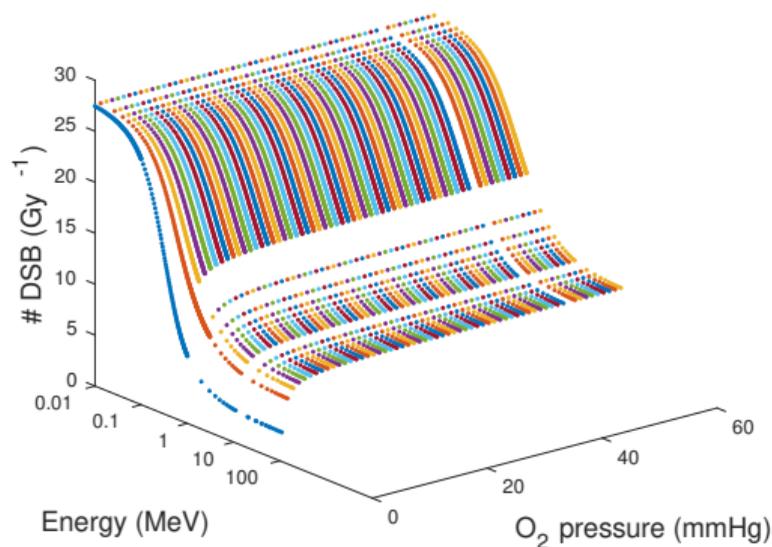
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- In hypoxic conditions, only low-level damage component is reduced
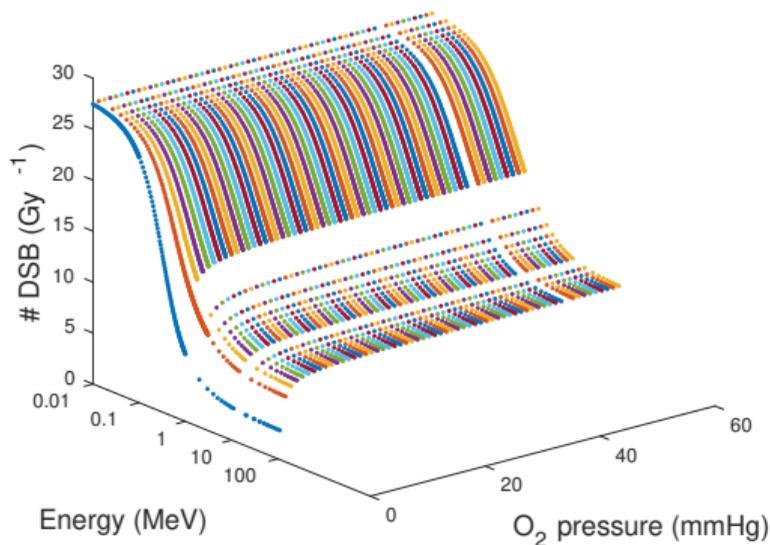
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Simplifying electron spectra

▶ Electronic build-up in entrance channel
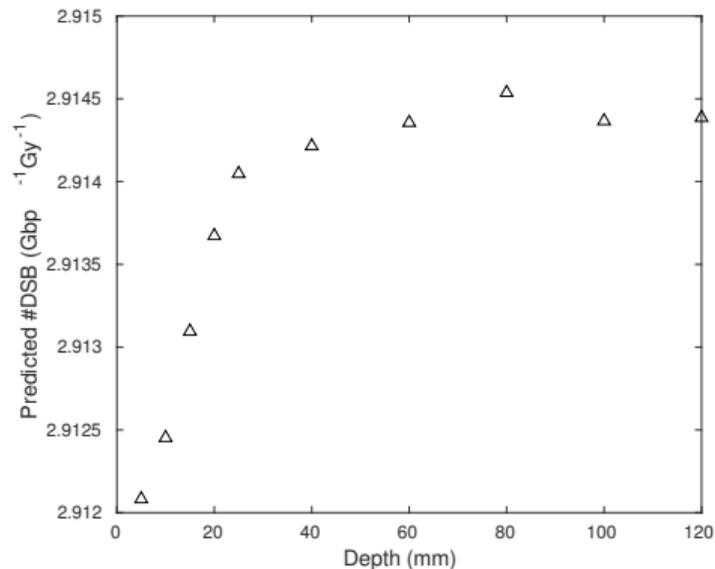
Further considerations
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▶ Electronic build-up in entrance channel

▶ Otherwise, energy spectrum weakly dependent
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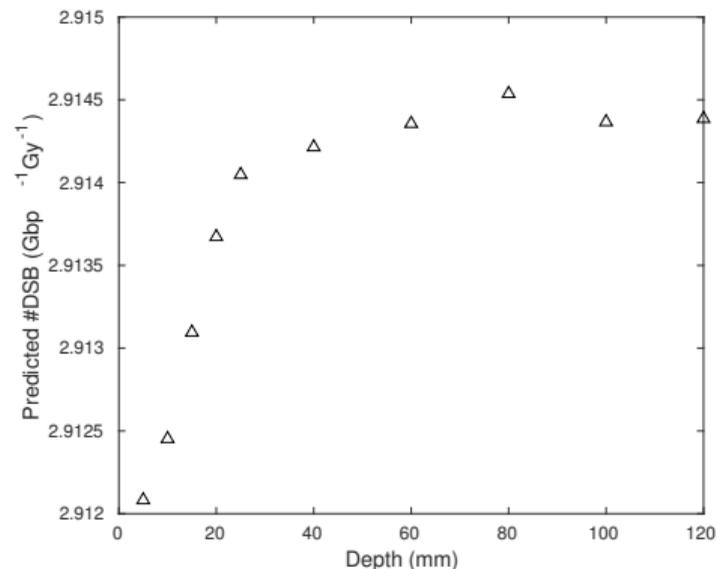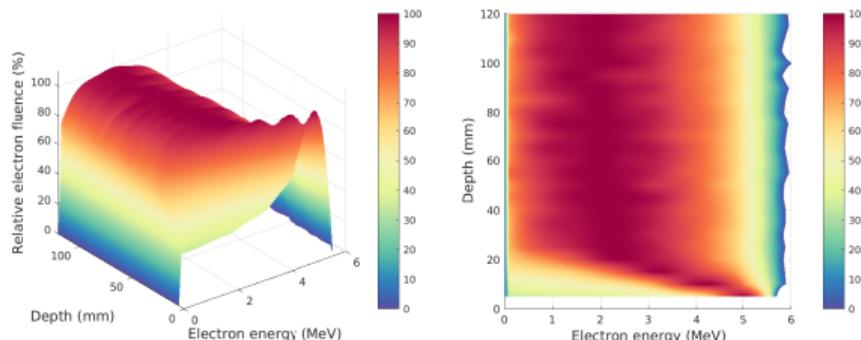
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► Weak depth dependence seen in proton beam
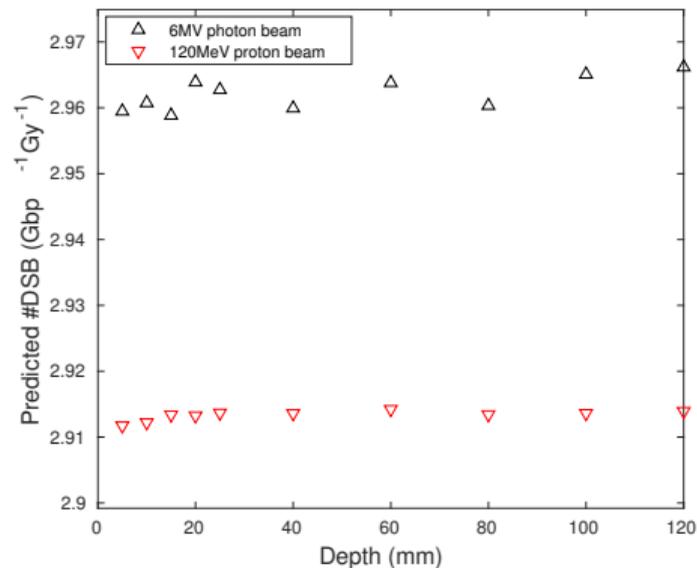
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Simplifying electron spectra

▶ Weak depth dependence seen in proton beam

▶ Resulting difference between electron-induced complex damage yield almost constant
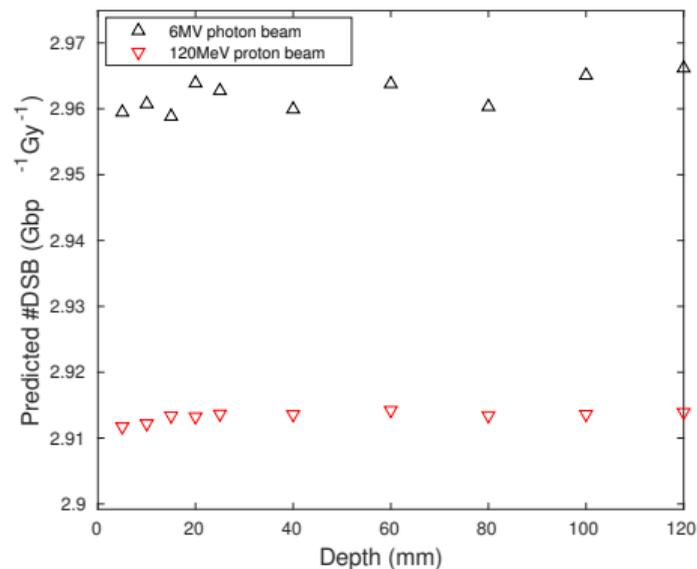
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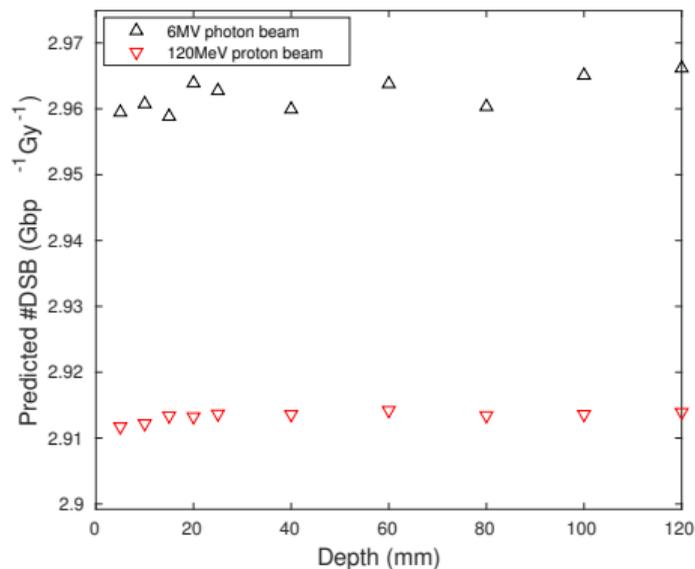
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▶ In Monte Carlo, can calculate $F_{cd}(E)$ on the fly for each history instead of obtaining a spectrum explicitly
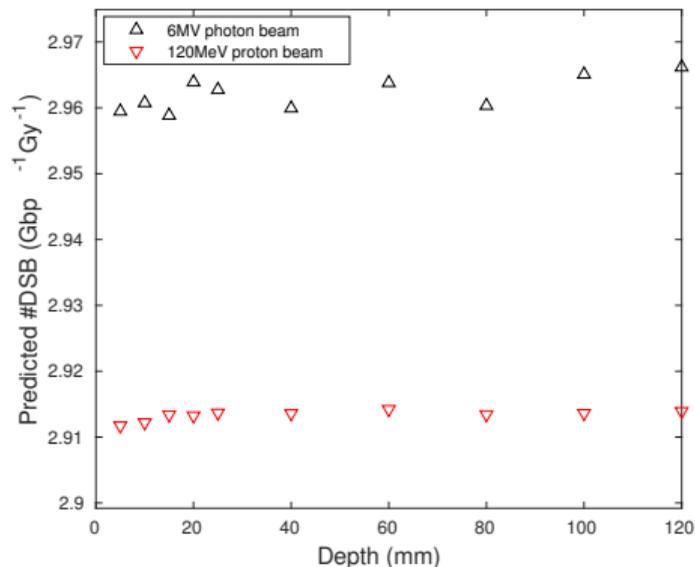
Further considerations
Quantum chemistry and scattering

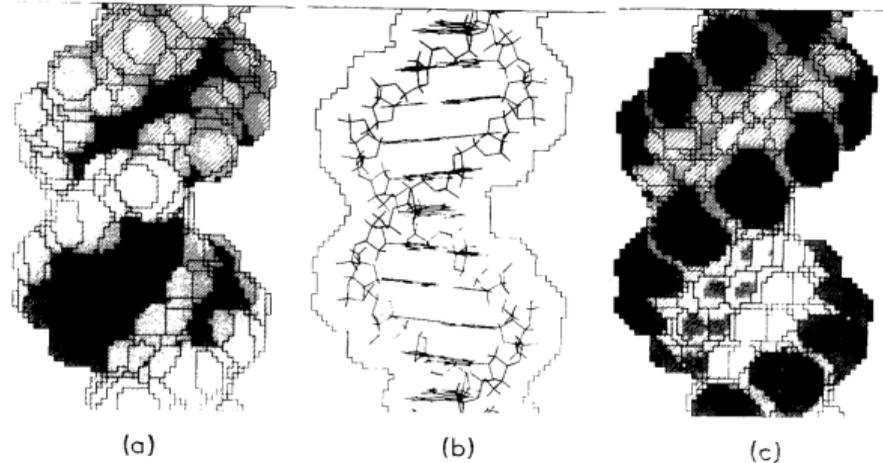▶ Use density functional theory (DFT) to obtain electron distribution in small (10bp) segment of B-DNA
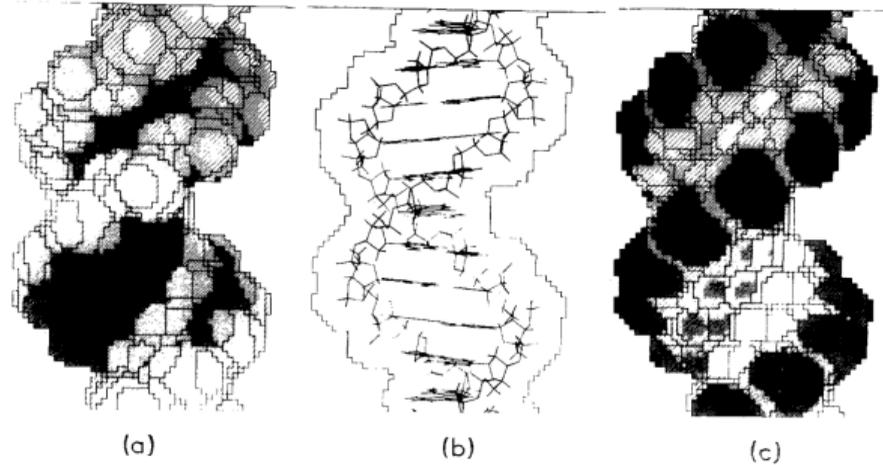
Fig. 2 : Potential (fig. 2a), a diagramatic representation (fig. 2b) and the field (fig. 2c) in a complete turn of a B-DNA double helix, with G-C base sequences. Significance of shadings :
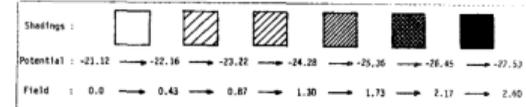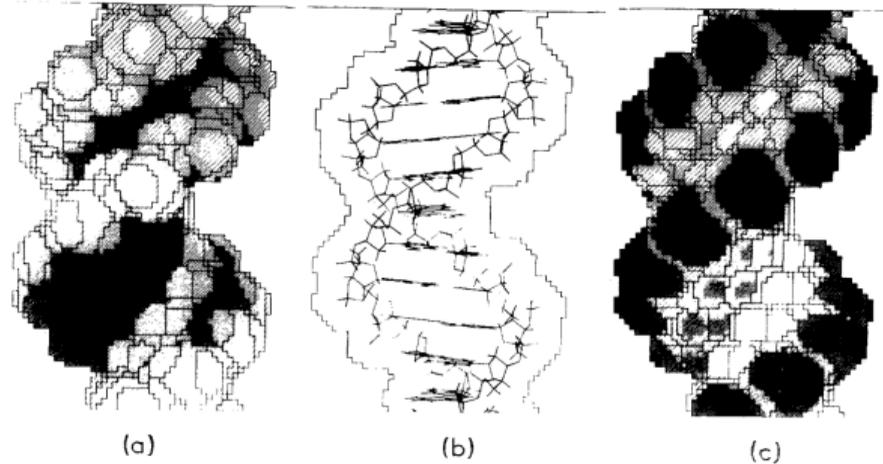
Figure: From [Pullman et al., 1983].

Further considerations
Quantum chemistry and scattering

▶ Use density functional theory (DFT) to obtain electron distribution in small (10bp) segment of B-DNA

▶ Calculate electrostatic potential map

(a)   (b)   (c)

Figure: From [Pullman et al., 1983].

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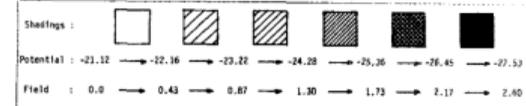▶ Find cross-section from scattering through Born series

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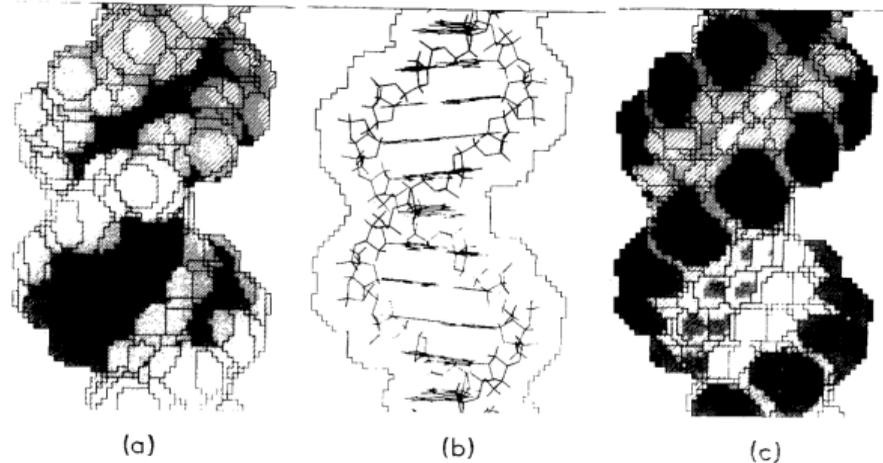▶ Second term in expansion is proportional to probability of two ionisation events within 10bp. This is labelled a DSB
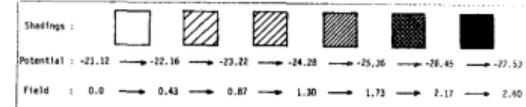

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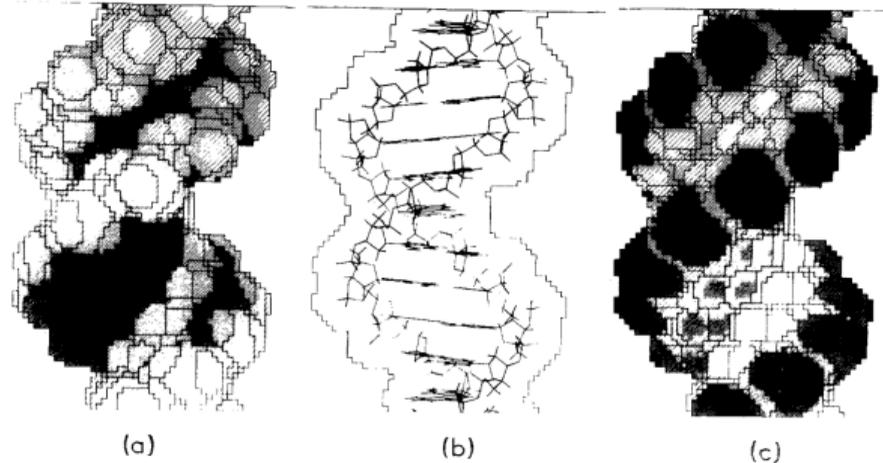
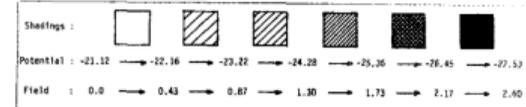▶ Use more terms for more clustered damage

Figure: From [Pullman et al., 1983].

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- Refine physical DNA-damage model

- Incorporate RBE into TPS on a voxel-by-voxel basis for proton and other particle (e.g. helium ion, carbon ion) therapies

- Provide algorithmic framework for fast IMPT optimization (PTV- and robustness-based) which includes constraints on the RBE distribution.

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Radiation Therapy Medical Physics Group: Prof. Frank Van den Heuvel, Dr. Francesca Fiorini, Dr. Suliana Teoh, Dr. Ben George, Mark Brooke.

References

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