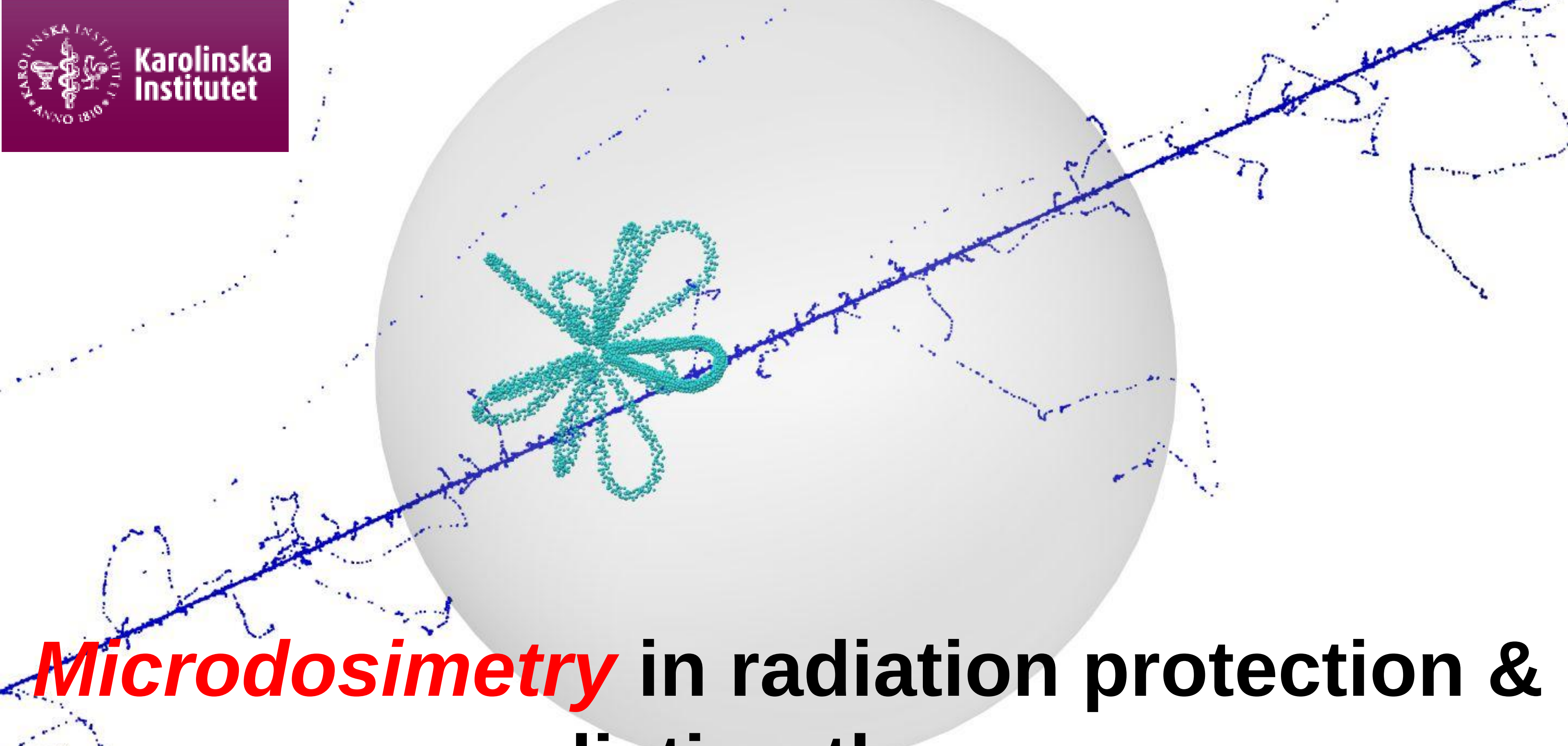


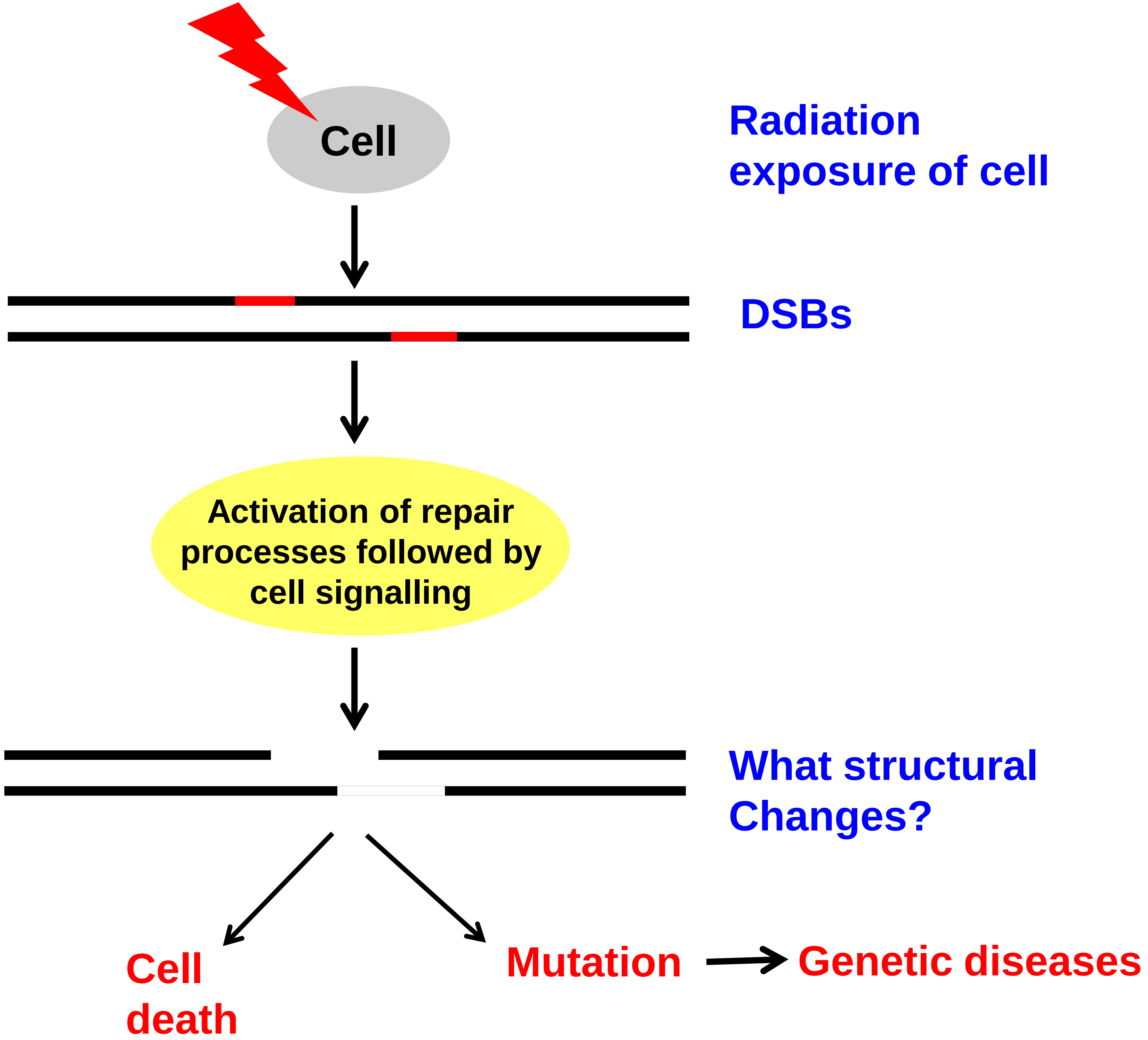
Microdosimetry in radiation protection & radiation therapy

Hooshang Nikjoo, Lennart Linborg, Thiansin Liamsuwan, Reza Taleei, Peter Girard

Radiation Biophysics Group

Department of Oncology-Pathology,

Karolinska Institutet


Cell
Radiation exposure of cell
DSBs
Activation of repair processes followed by cell signalling
What structural Changes?
Cell death
Mutation
Genetic diseases

Some Questions

- In Radiation Physics

    Characterization of radiation field

    Accurate dosimetry

- In Radiation Protection

    Background levels for risk estimation (genetic & cancer)

- In Radiation therapy

Clinical RBE values

- In Radiation Biology

    Mechanism of radiation induced DNA Damage Response & Repair

    What is the relevant type of damage induced by IR?

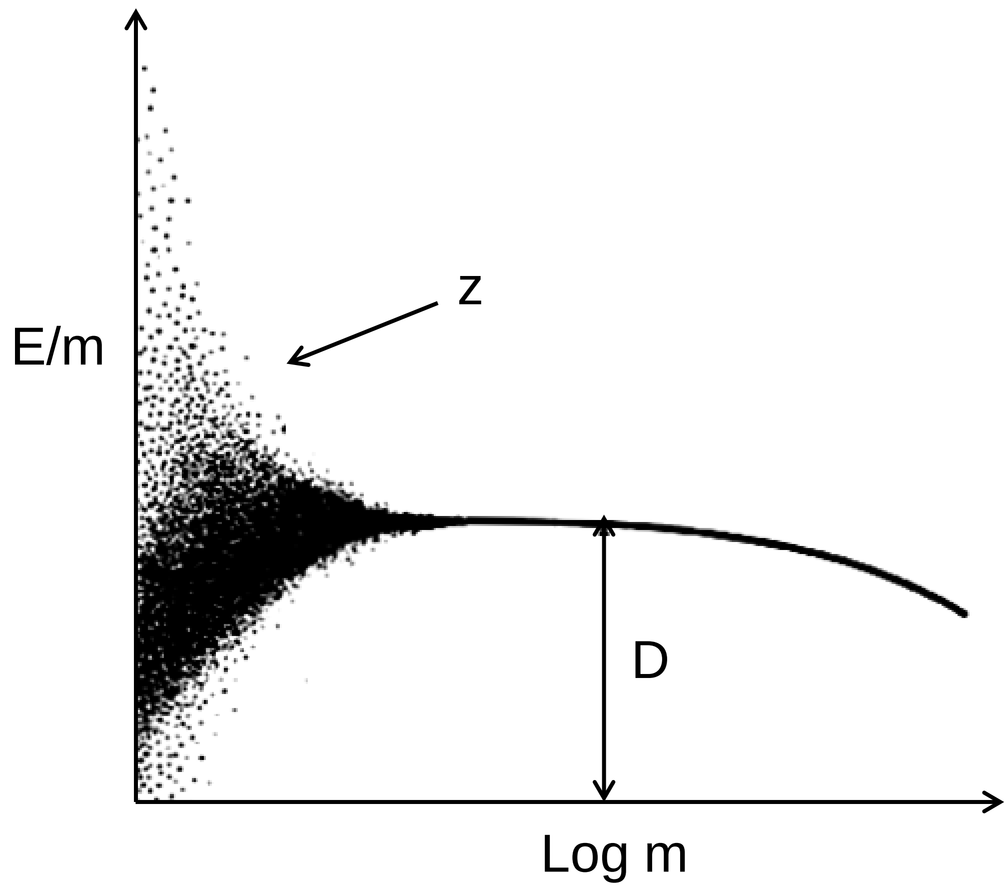
Hypothesis

Progress in radiation risk estimation and cancer therapy in the 21st century will be driven by the integration of genomic knowledge with that of DNA Damage, and DNA-repair mechanism

Most radiation-induced mutations are large multi-gene deletions

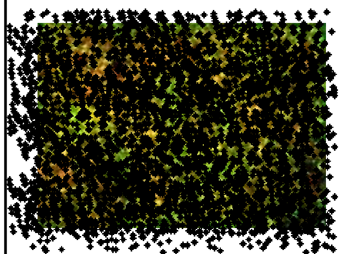
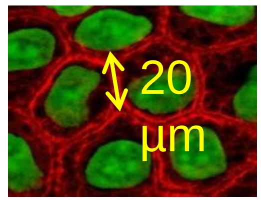
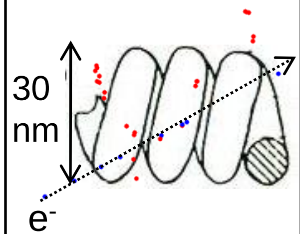
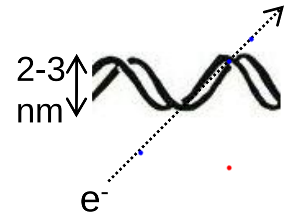
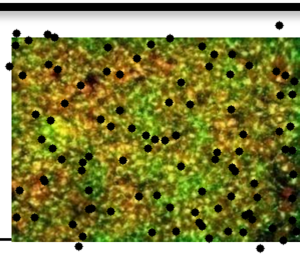
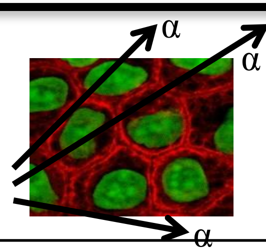
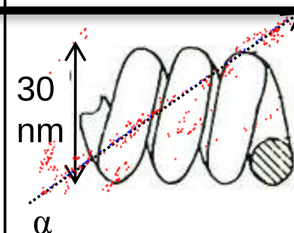
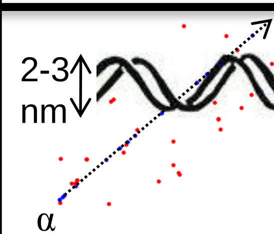
Spontaneous deletions induced in germ cells are more likely to be multi-system developmental abnormalities rather than single gene diseases

Sankaranarayanan & Nikjoo 2010



Energy density as a function of the mass for which energy density is determined. The horizontal line covers the region in which the absorbed dose can be established in a single measurement. Rossi 1968

Microscopic consequences of 1cGy absorbed dose

Radiation	Tissue	Cells	Chromatin fibre	DNA	Mean no. lethal lesions per cell
γ-ray					~0.001
Dose uniformity	Uniform dose=1 cGy	~Uniform dose~1 cGy	very non-uniform	very non-uniform	
Mean no. tracks	~10^{11} gm^{-1}	~5000 $cell^{-1}$	~10^{-6} $segment^{-1}$	~10^{-6} $segment^{-1}$	
^{220}Rn 2-4 α particles					~0.01
Dose uniformity	0 - 2 cGy	0 - ~30cGy	0 - ~10^4 Gy	0-2x10^6 Gy	
Mean no. tracks	~10^7 gm^{-1}	~0.26 $cell^{-1}$ ~ 90% of cells unirradiated	~6x10^{-7} $segment^{-1}$	~10^{-9} $segment^{-1}$	

Adopted from Goodhead 1987

Why Microdosimetry

1. Dosimetry at a microscopic scale
   – Densely ionising radiation → dose inhomogeneity at cellular/subcellular levels
   – Dose calculations based on stopping power are inaccurate at a sub-mm precision.

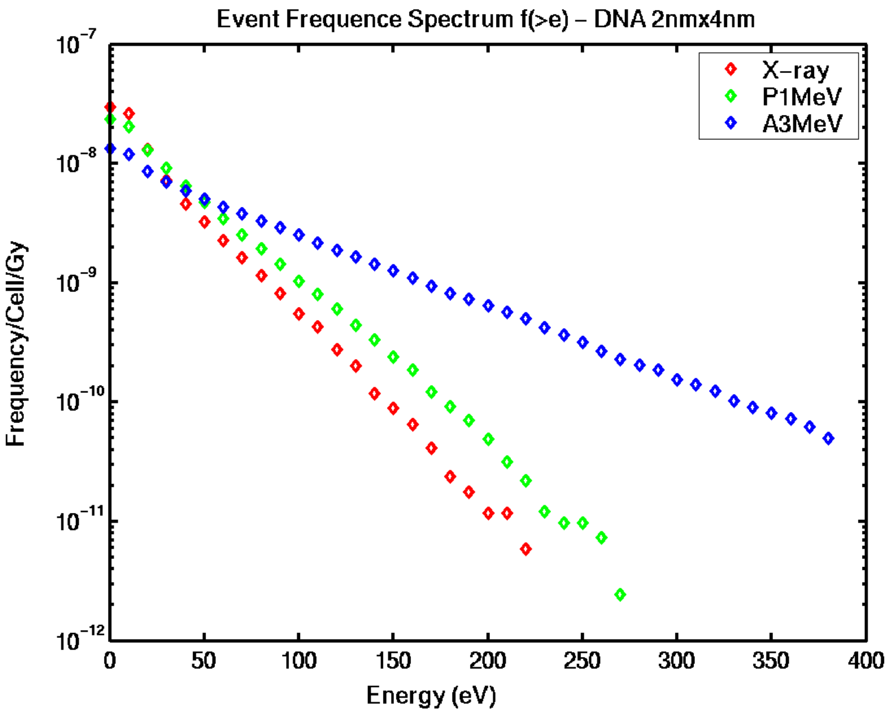
2. Effective method to characterise the radiation quality of ion beams
   – Linear Energy Transfer (LET): average and macroscopic quantity → insufficient as a describtor of biological effectiveness
   – Better alternative: a quantity related to energy depositions at a scale relevant to biological targets → Microdosimetry

Why Microdosimetry

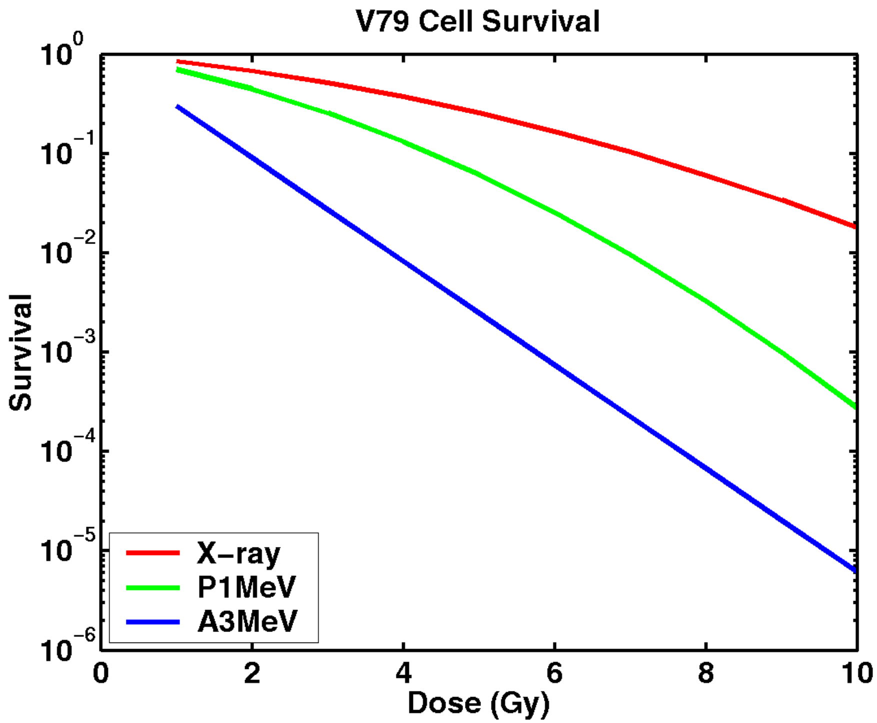
- A better way of characterizing radiation track
- Microdosimetric quantities vary with the size of target volume
- Microdosimetry is a recommended method for characterising radiation quality when biological effectiveness is not well known
- Is there a volume that is most suitable to characterize clinical RBE-values?

Example 1

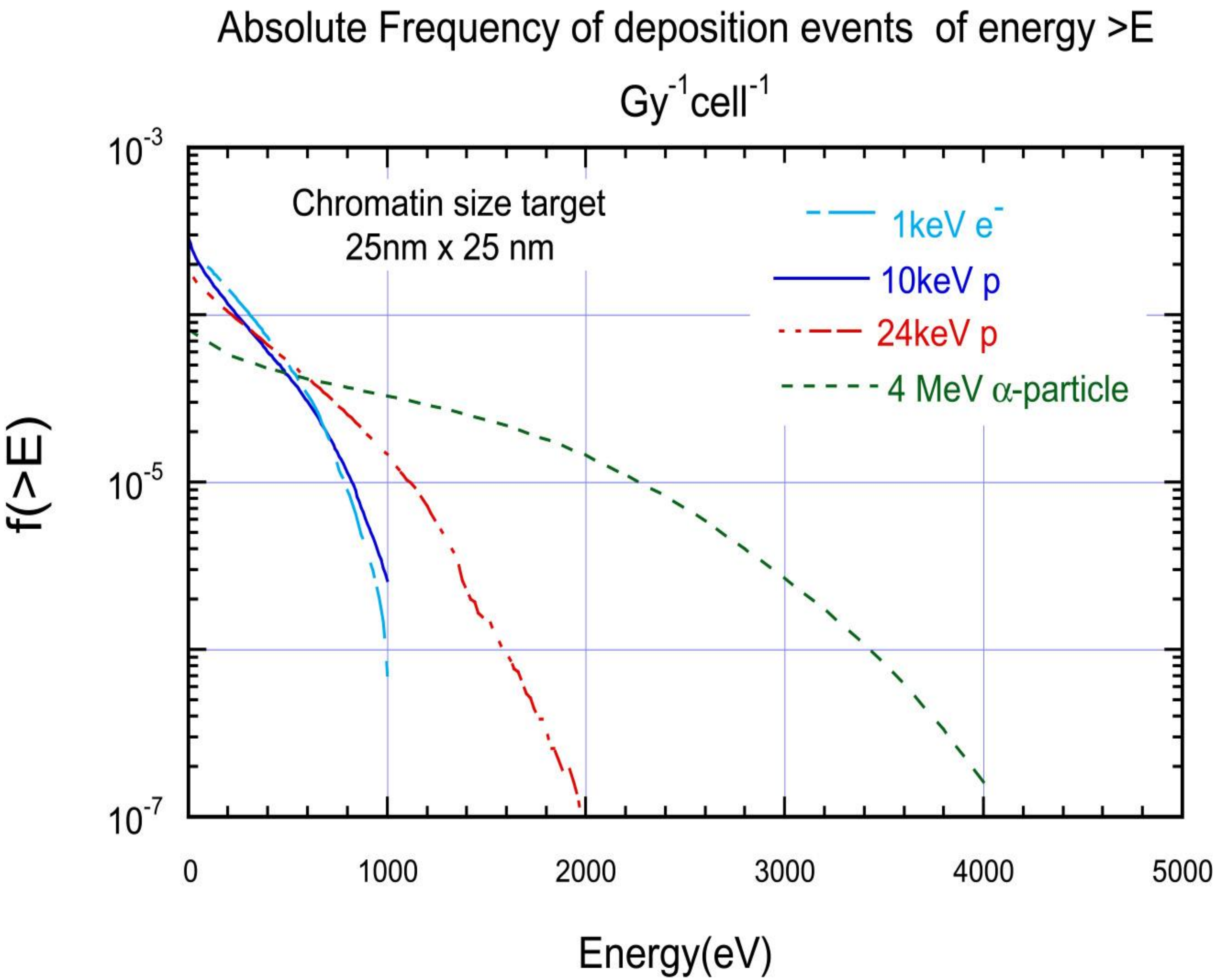
Energy deposition



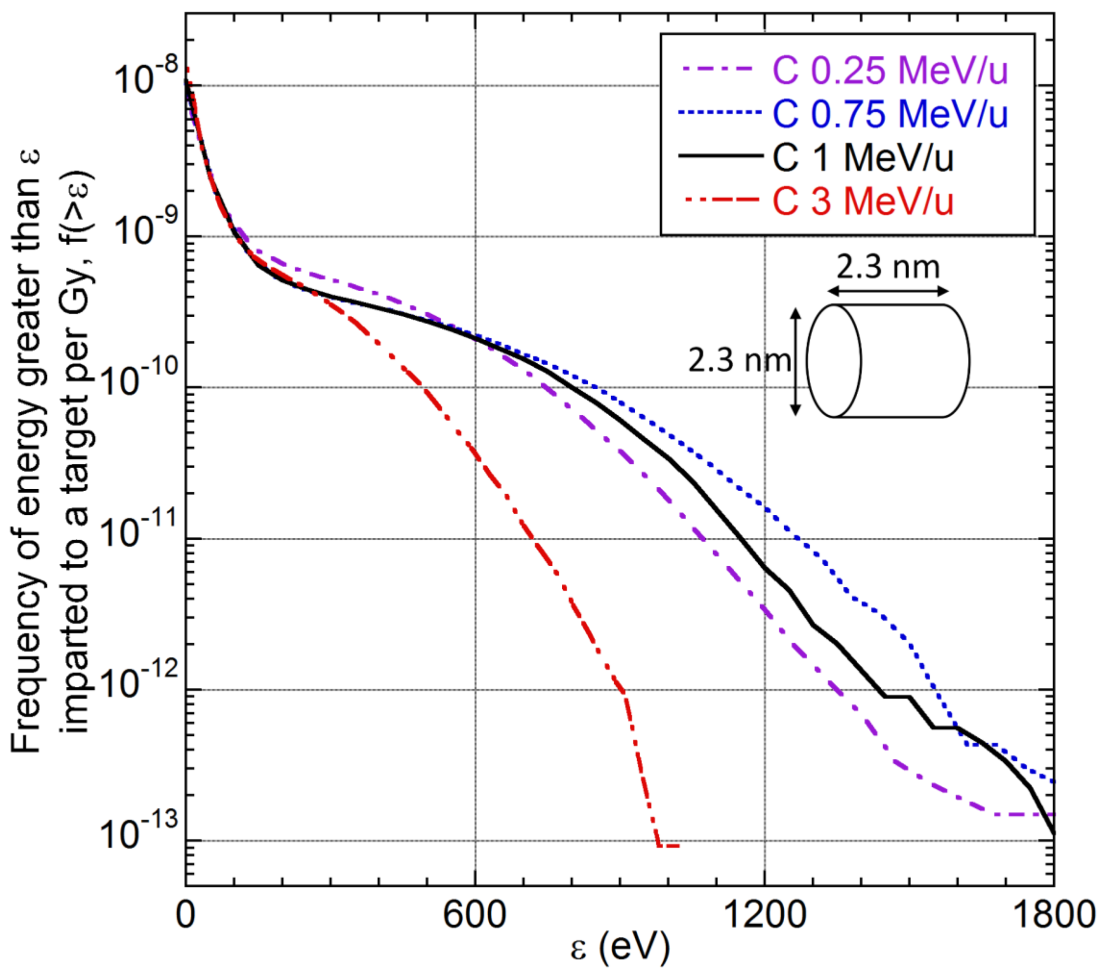
Cell Survival



Nikjoo (unpublished)

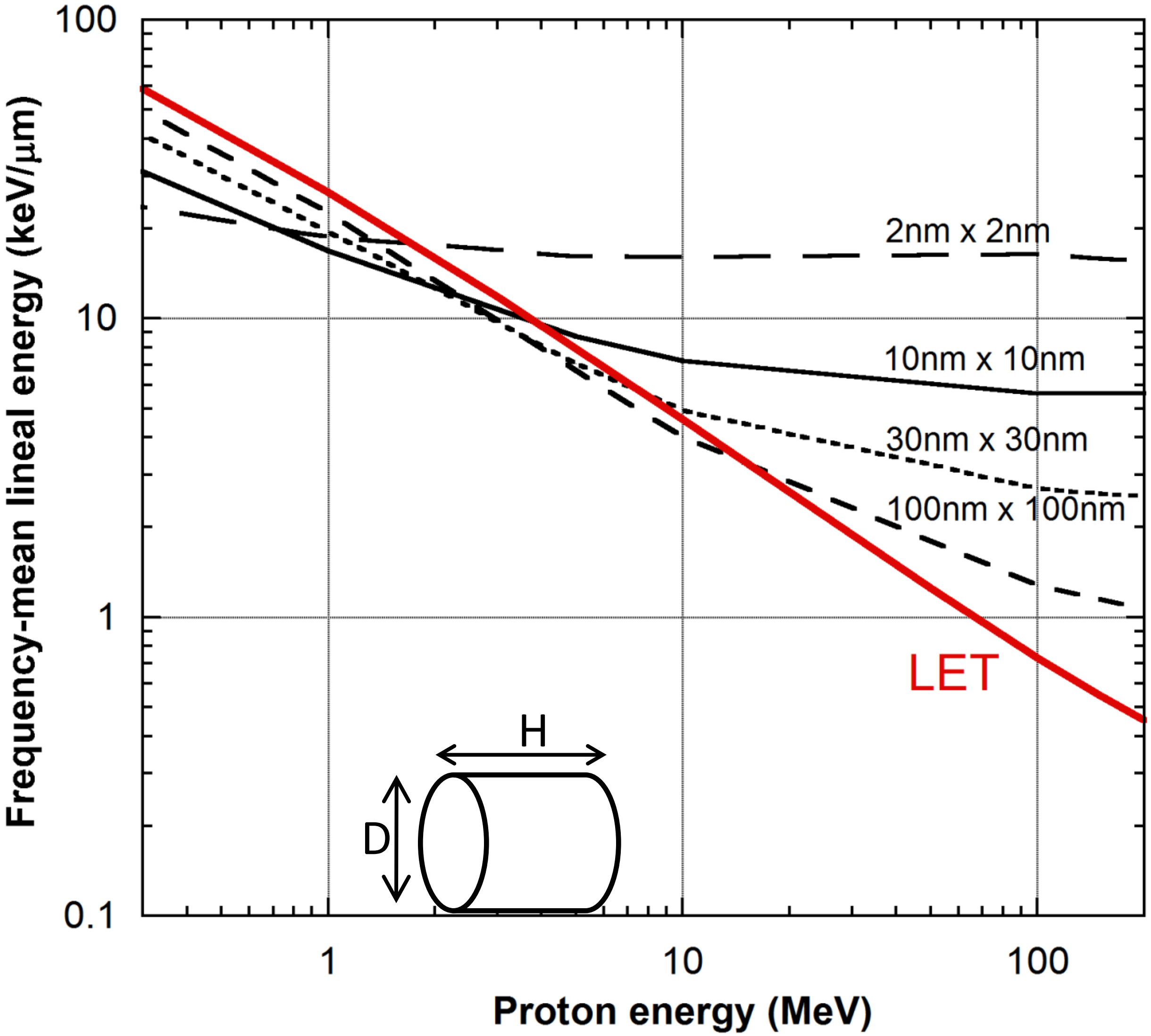


Nikjoo et al various monographs



Liamsuwan 2013 (thesis)

Frequency mean lineal energy (y_F) vs. LET for protons



Lineal energy (*y*) = Ratio of energy imparted by a single track to the mean chord length of the target

LET = Ratio of average energy loss of a particle in its path length

Liamsuwan et al 2011

Example 2

RBE v W values

Can α-ratio and y_D be correlated?

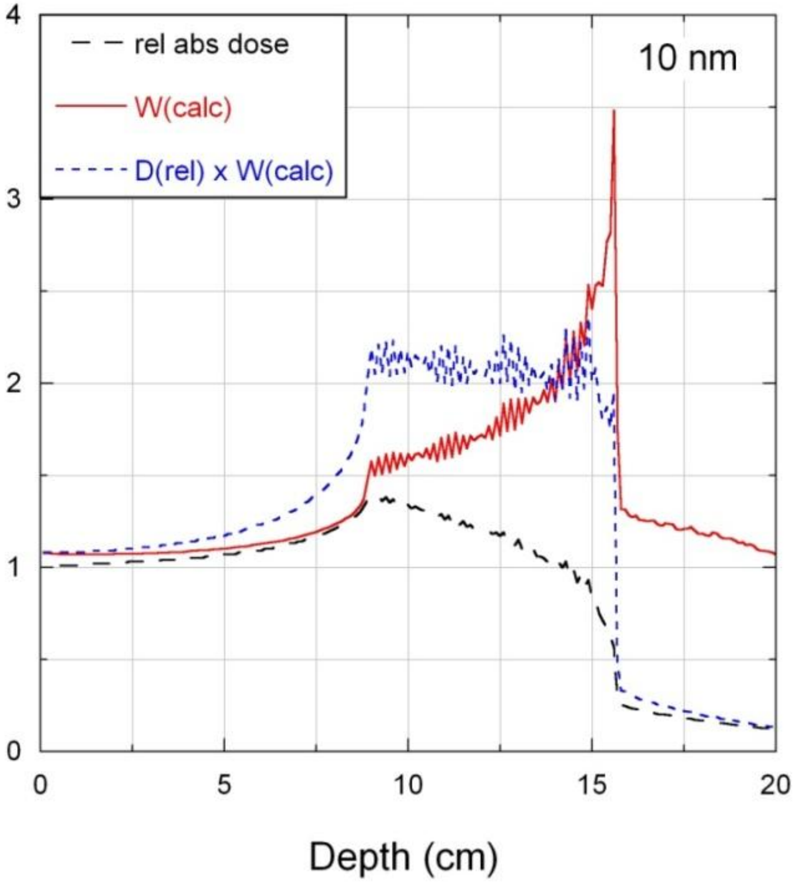
Weighting factors in

Rad. Protection & Radiation Therapy

	w_R	RBE_{clin}
^{60}Co γ/X-rays	**1**	**1.25**
^{60}Co γ /Protons	**2**	**1.1**
^{60}Co γ /Neutrons	**2.5 -21**	**3.2**
^{60}Co γ/ C- ions	**20**	**3.2 ?**

Why are they different?

Lindborg, Hultqvist, Carlsson, Nikjoo, 2013



Radiation quality	α-ratio derived from the LQ relation	y_D Ratio D=10nm
X-ray/ ^{60}Co γ	1.2	1.16
p (175 MeV) /^{60}Co γ in SOBP at 5cm	1.1	1.05
^{12}C SOBP / ^{60}Co γ centre	2.9	2.2
^{12}C SOBP /^{60}Co γ distal end	3.6	3.6
n/^{60}Co γ	3.8	3.7

Lindborg, Hultqvist, Carlsson, Nikjoo, 2013

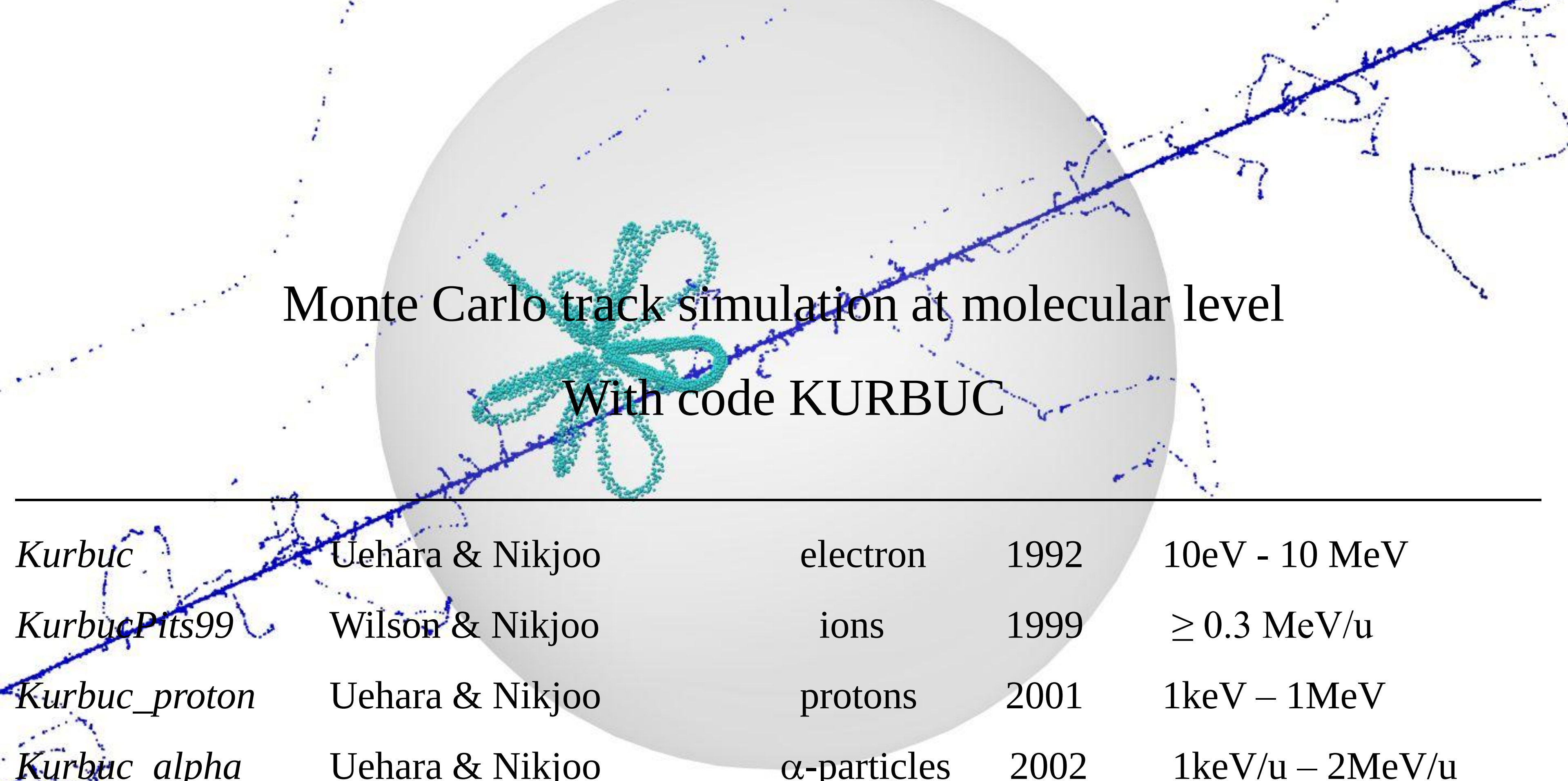
Conclusion1

- All microdosimetry parameters and distributions can be obtained from absolute frequency of energy depositions in the target under consideration.
- We have calculated such data for electrons, and ions in target sizes 2nm – 100nm

Conclusions 2

1. Microdosimetry is a recommended method for characterising radiation quality when biological effectiveness is not well known (IAEA)
2. Size of the simulated target volume influence microdosimetric quantities.
3. For a simulated volume of about 10-15 nm, the α-ratio increases approximately linearly with the $\bar{y}_D$ ratio for all investigated radiation beams. (Lindborg et al 2013)
4. The correlation between y and α provides the evidence for the use of y to charactrerize therapy beam when weighting factors to be estimated
5. Low energy electrons play crucial role in characterizing radiation field

I) 4D DESCRIPTION OF RADIATION TRACK (x, y, z, t)

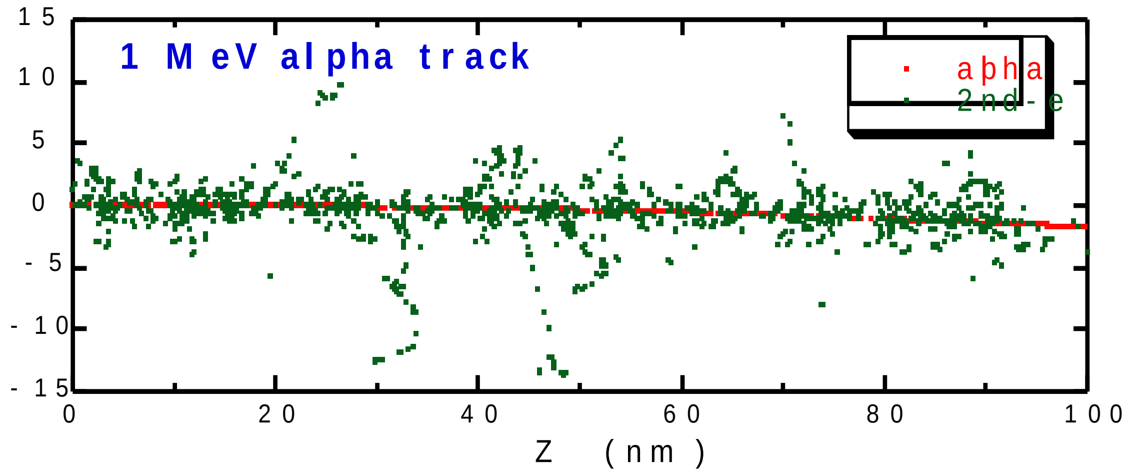


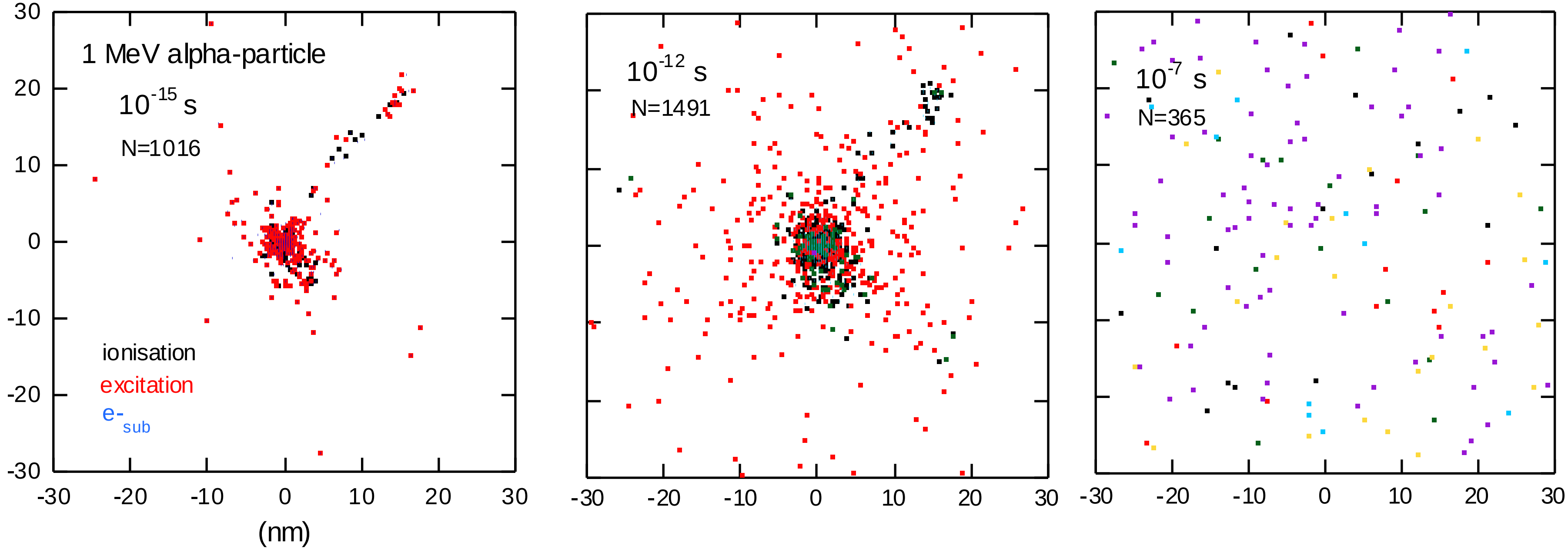
Monte Carlo track simulation at molecular level

With code KURBUC

Kurbuc	Uehara & Nikjoo	electron	1992	10eV - 10 MeV
KurbucPits99	Wilson & Nikjoo	ions	1999	≥ 0.3 MeV/u
Kurbuc_proton	Uehara & Nikjoo	protons	2001	1keV – 1MeV
Kurbuc_alpha	Uehara & Nikjoo	α-particles	2002	1keV/u – 2MeV/u
Kurbuc_Chem	Uehara & Nikjoo	chemistry	2006	$\geq 10^{-12}$ s
Kurbuc_Neutron	Nikjoo & Uehara	neutrons	2007	thermal - 100 MeV
Kurbuc_liq	Emfietzoglou et al	electron	2008	10 eV – 10 keV
Kurbuc_Proton	Liamsuwan et al	protons	2010	1keV – 300 MeV
Kurbuc_Carbon	Liamsuwan & Nikjoo	C-ions	2012	1keV/u – 10MeV/u

Physical and Radical Chemistry Simulation of Radiation Track at Molecular Level

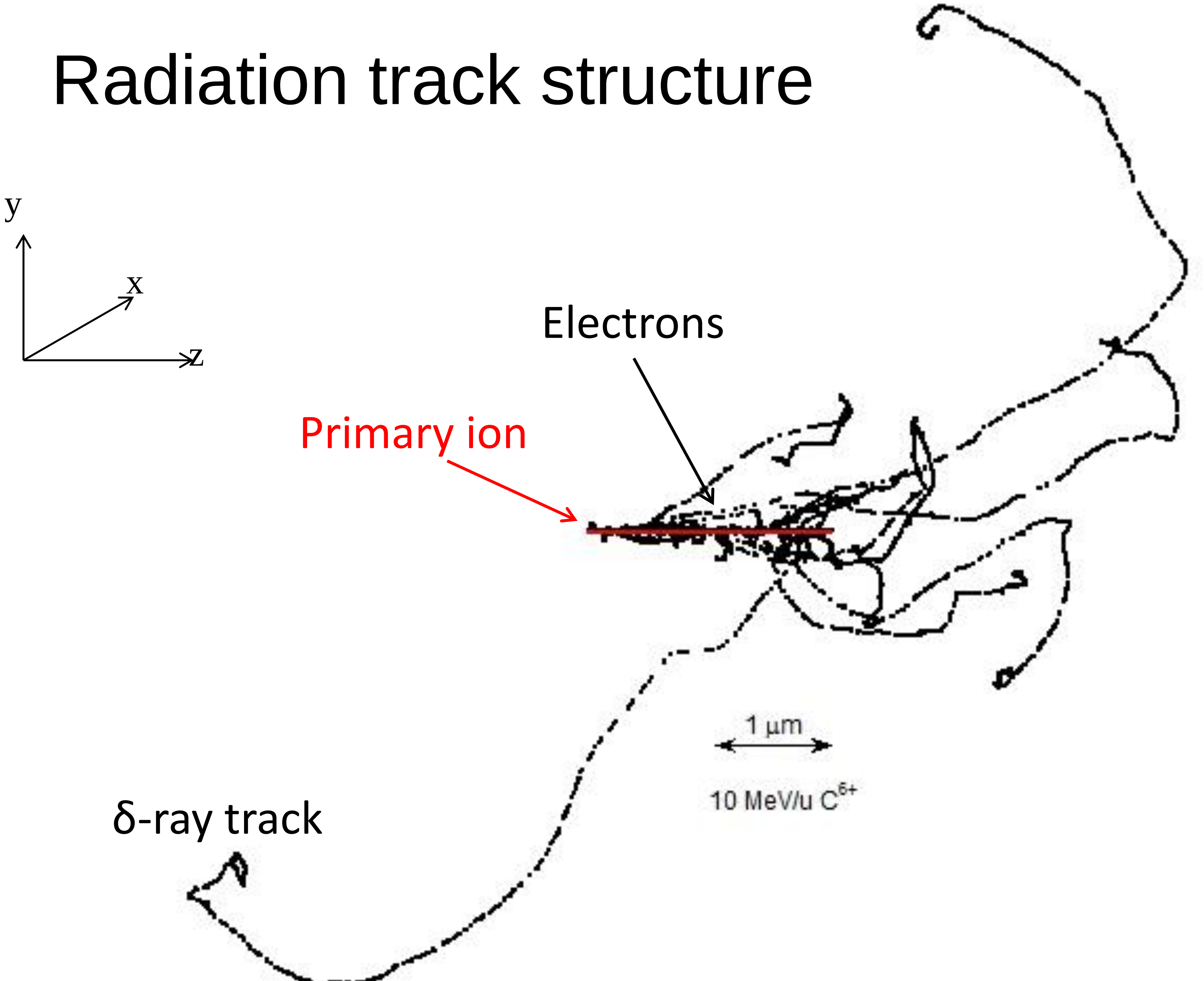




EURODOS 2013 Barcelona

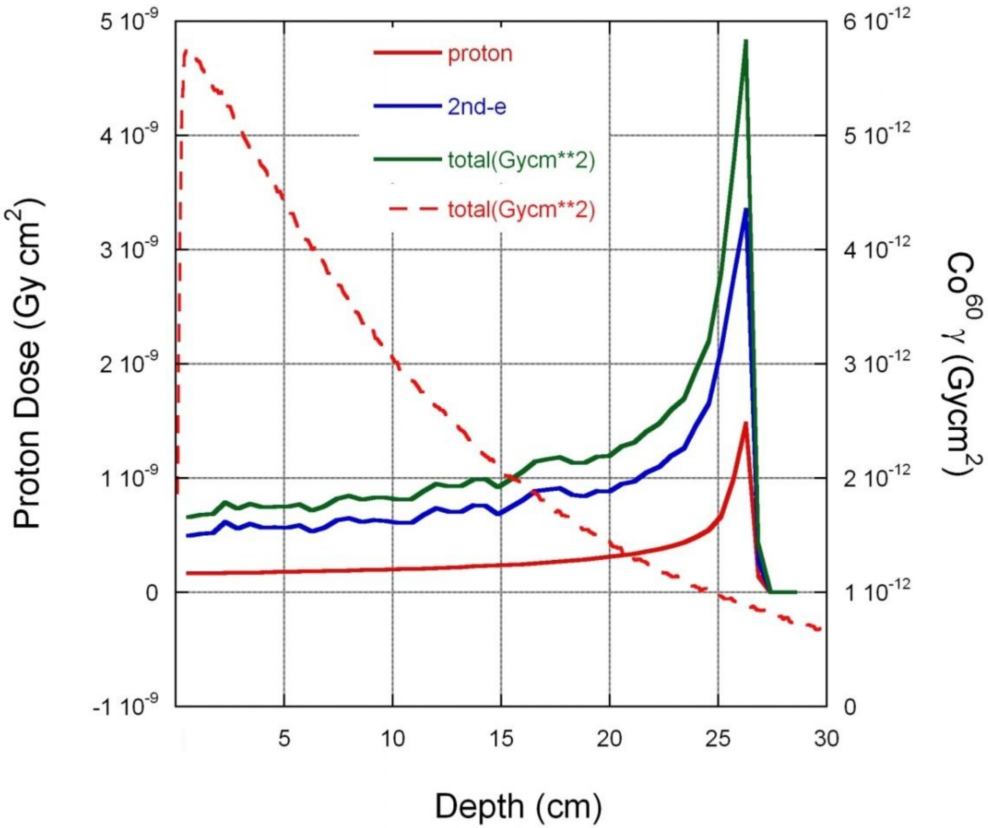
Uehara & Nikjoo 2006

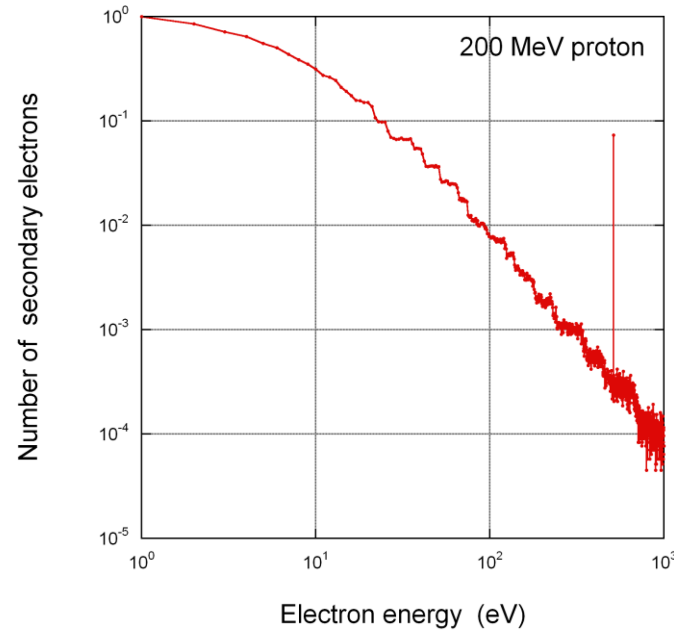
Radiation track structure



Liamsuwan thesis, 2013

MCTS simulation with sensitivity at a single cell level





Liamsuwan et al 2011, 2012
Liamsuwan and Nikjoo, 2013

Radiation	Depth at	Dose Gy cm^2	Fluence for 1 cGy /cm^2	Track # per cell Nucleus
^{60}Co γ rays	5 mm	5.8 x10 $^{-12}$	1.72 x 10^9	6900
200 MeV proton	Bragg peak	4.7 x10^{-9}	2.13x 10^6	8.5
10 MeV/u C ions	Bragg peak	1.3 x10^{-6}	7.69x10^3	0.03

Nikjoo, Uehara, Emfietzoglou, 2012, CRC Press

Number of events in a 200 MeV full slowing down proton track

p	elastic scattering	200,908
p	ionization	1,943,795
p	excitation	1,117,797
p	e-capture	1,294
H	elastic scattering	2,259
H	ionization	1,084
H	excitation	676
H	electron loss	1,293
Secondary electrons		
ionization (12.62 eV)	12.62 eV	1,977,465
ionization (14.75 eV	14.75 eV	1,494,653
ionization (18.51 eV)	18.51 eV	877,941
ionization (32.40 eV)	32.40 eV	20,812
ionization (539.7 eV)	539.7 eV	7,135
excitation	A_1B_1	198,989
excitation	B_1A_1	648,345
excitation	Rydberg A+B	246,620
excitation	Rydberg C+D	347,007
excitation	diffuse band	1,204,030
excitation	H* Lyman a	343,570
excitation	H* Balmer a	67,931
excitation	OH*	836,387
sub-excitation electrons		634,450

Liamsuwan et al 2011
Liamsuwan & Nikjoo 2013

Some physical characteristics of radiation tracks

Particle type	Energy (keV)	primary interactions (%)	secondary electron interactions (%)	dE/dx (keV/µm)	Energy in track by primary %	Energy in track by delta electrons %
e^-	1keV	**25**	**75**	12	**39**	**61**
e^-	10keV	**23**	**77**	2.3	**37**	**63**
e^-	100keV	**22**	**78**	0.42	**34**	**66**
Proton	1MeV	**21**	**79**	27	**30%**	**70%**
Proton	20MeV	**20**	**80**	2.5	**34%**	**66%**
Proton	200MeV	**20**	**80**	0.4	**30%**	**70%**
Carbon	20MeV/u	**20**	**80**	93	**20%**	**80%**

Nikjoo and Lindborg 2010
Nikjoo & Goodhead 1989

Conclusions 3

- Radiation track description in space and time is possible for electrons and ions in homogenous biological media

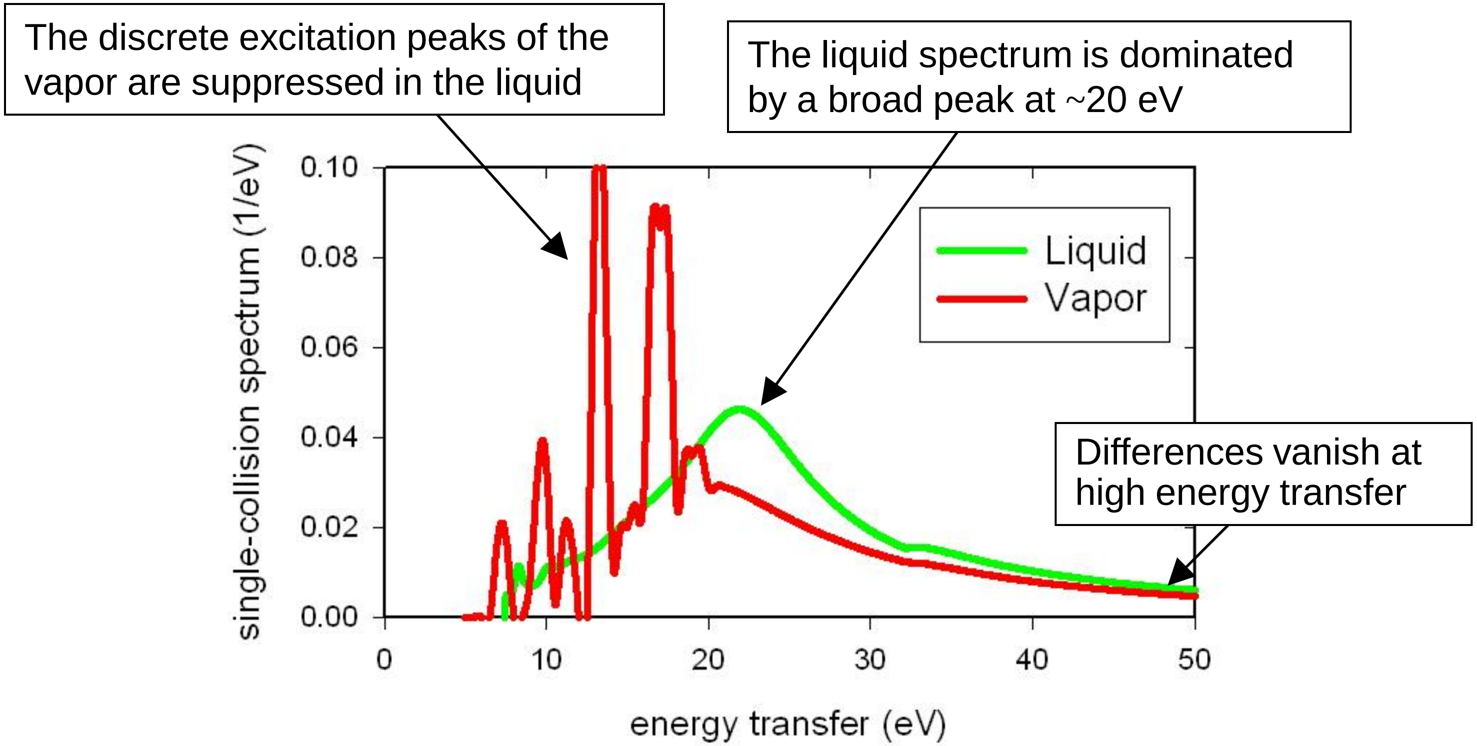
- How good is the technology?

Electron energy loss in condensed matter

- Inelastic interactions with atomic electrons leading to *electronic excitations (including ionizations)* is the most important energy-loss mechanism for electrons at all energies of practical interest.

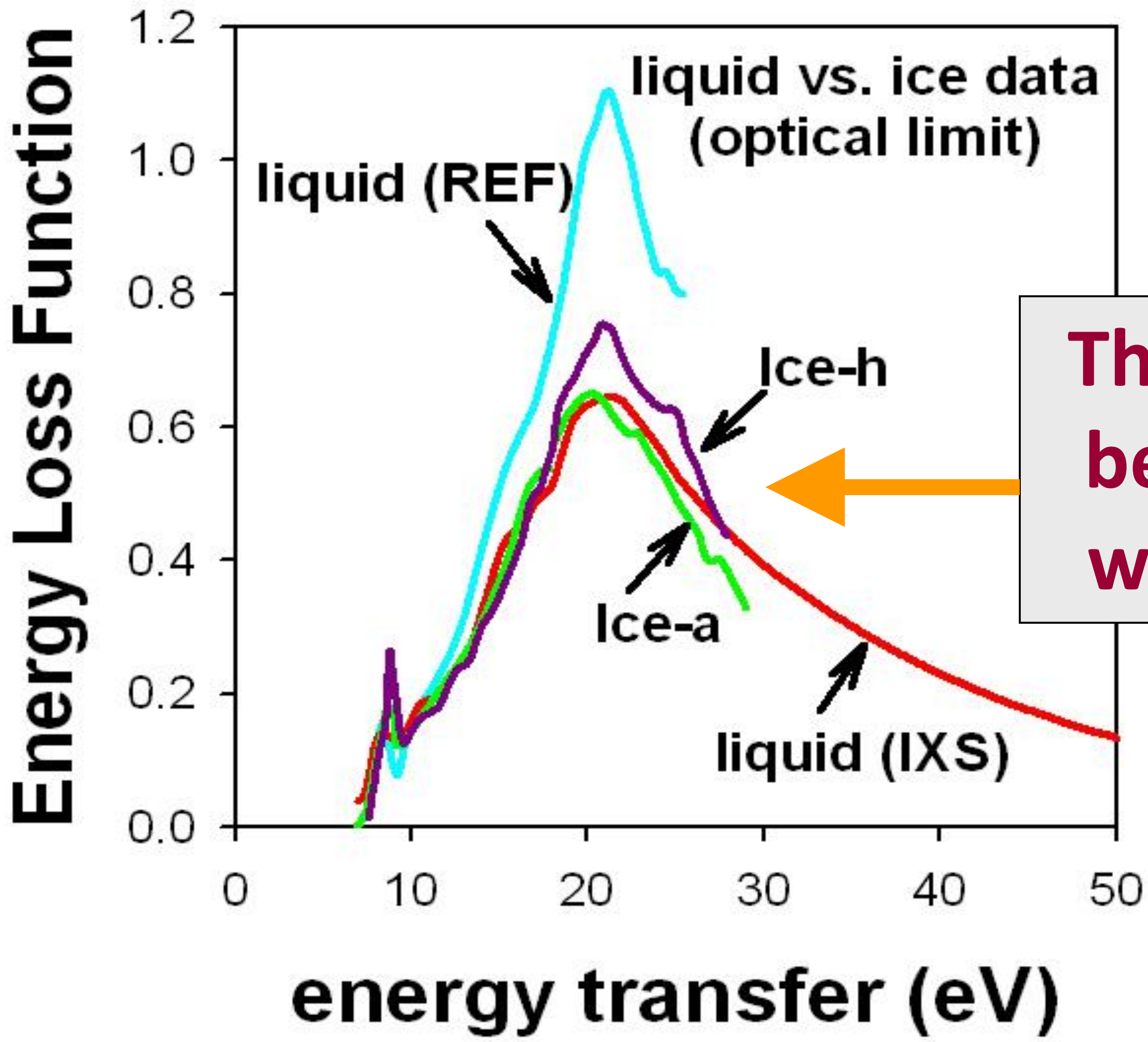
- Electronic excitations depend not only upon the atomic composition of the system but also upon its state of aggregation (gas vs. solid or liquid).

Example: single-collision energy-loss spectrum of vapor vs. liquid water



Emfietzoglou et al Nikjoo, 2012

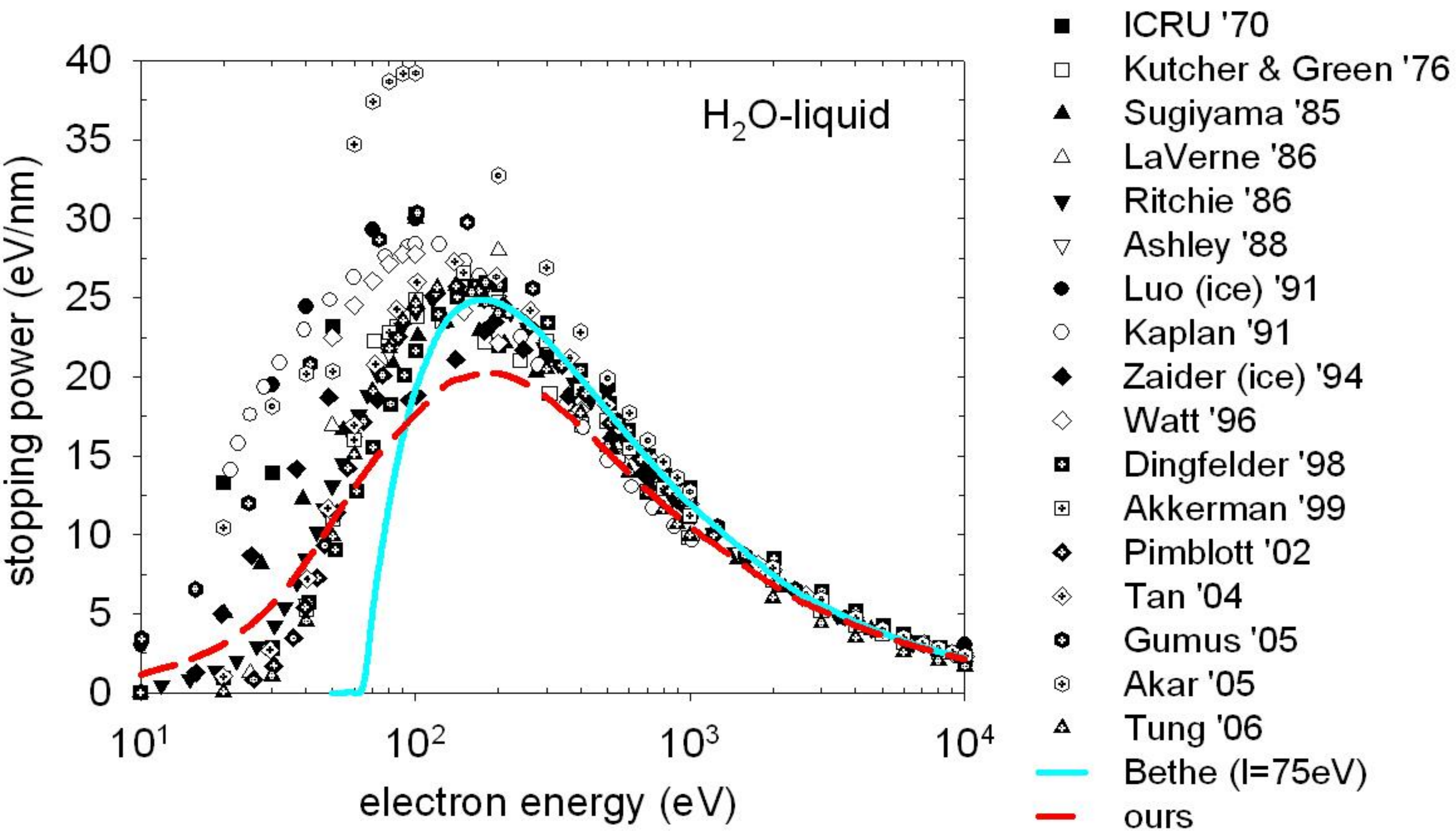
Liquid vs. Ice data



The IXS data are in better agreement with the ice data.

Emfietzoglou et al Nikjoo, 2012

Electron stopping power in liquid water



Emfietzoglou et al 2012

Conclusions 4
physics of electron energy loss in liquid water

- For electrons >200 eV optical-data model calculations for the IMFP are not very sensitive to the choice of the physics model used
  - ➢The differences between models are less than ~10%
- For electrons <200 eV the IMFP is very sensitive to the choice of physics model

Emfietzoglou et al Nikjoo, 2012

Conclusions 4
Is Trajectory Simulation Correct?

An explicit trajectory picture of the transport of low energy (< 1 keV) electrons in liquids and amorphous solids is certainly not valid according to the Heisenberg uncertainty principle. In fact, it does not correspond to physical reality.

But, a trajectory treatment provide a good approximation of multiple quantum scattering down to electron energies in the order of $\sim$ 10 eV, due to the incoherence introduced by a randomlike structure of the medium and to the presence of multiple inelastic scattering.

Liljequist and Nikjoo 2013

Conclusions 5

a. We now have the technology to describe physical and chemical interactions of electrons and ions at molecular level. (track segment and full-slowing down)

b. Low energy electrons <100eV are responsible for most of energy depositions by a track

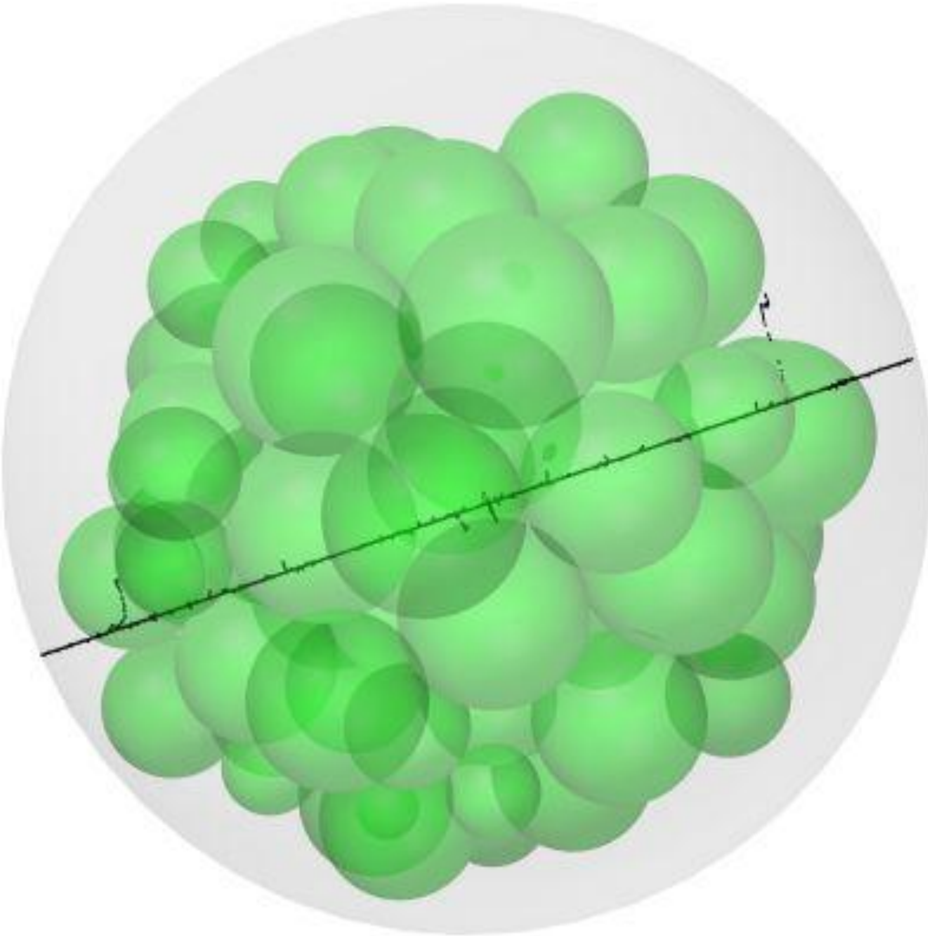
c. Although we know a lot about physics of radiation track but at energies below 100eV our understanding is incomplete and uncertain, especially in condensed matter

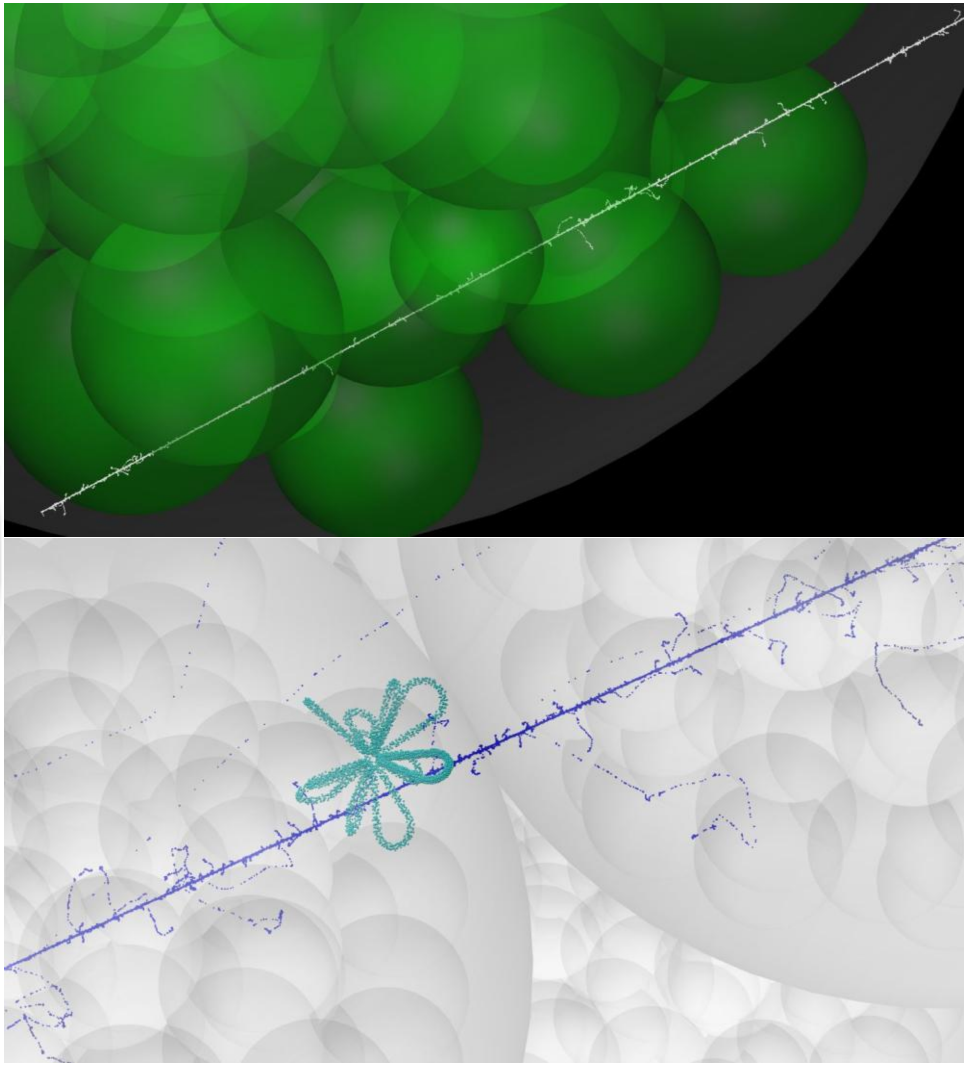
d. Microdosimetry considerations proves LET is not a good parameter for characterising radiation track

II) DNA DAMAGE

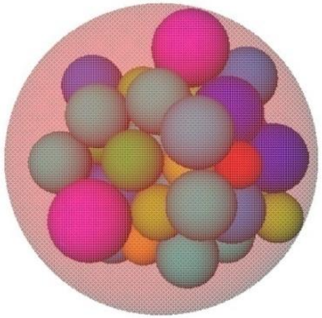
DNA Damage in human genome

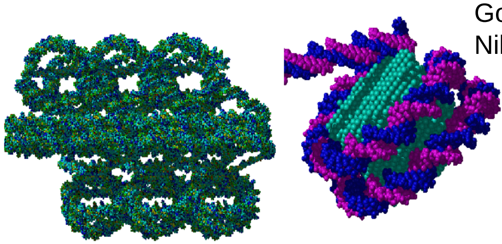
Intersecting domains:
70, 44, 18, 13, 20



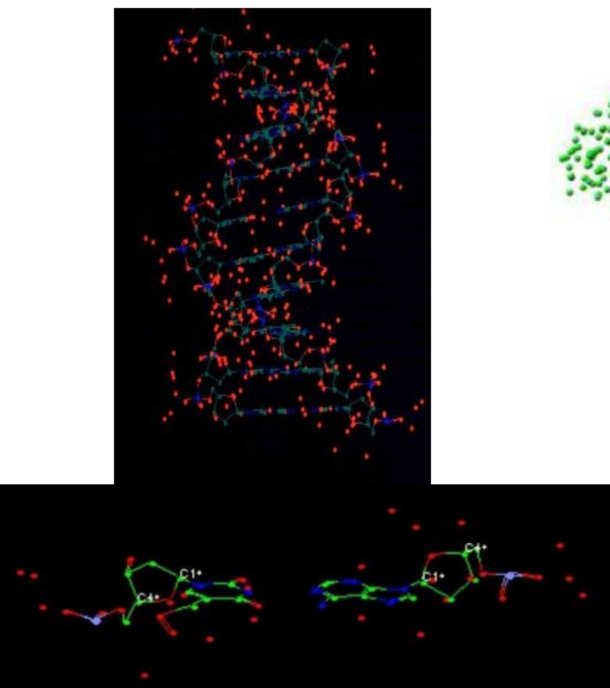


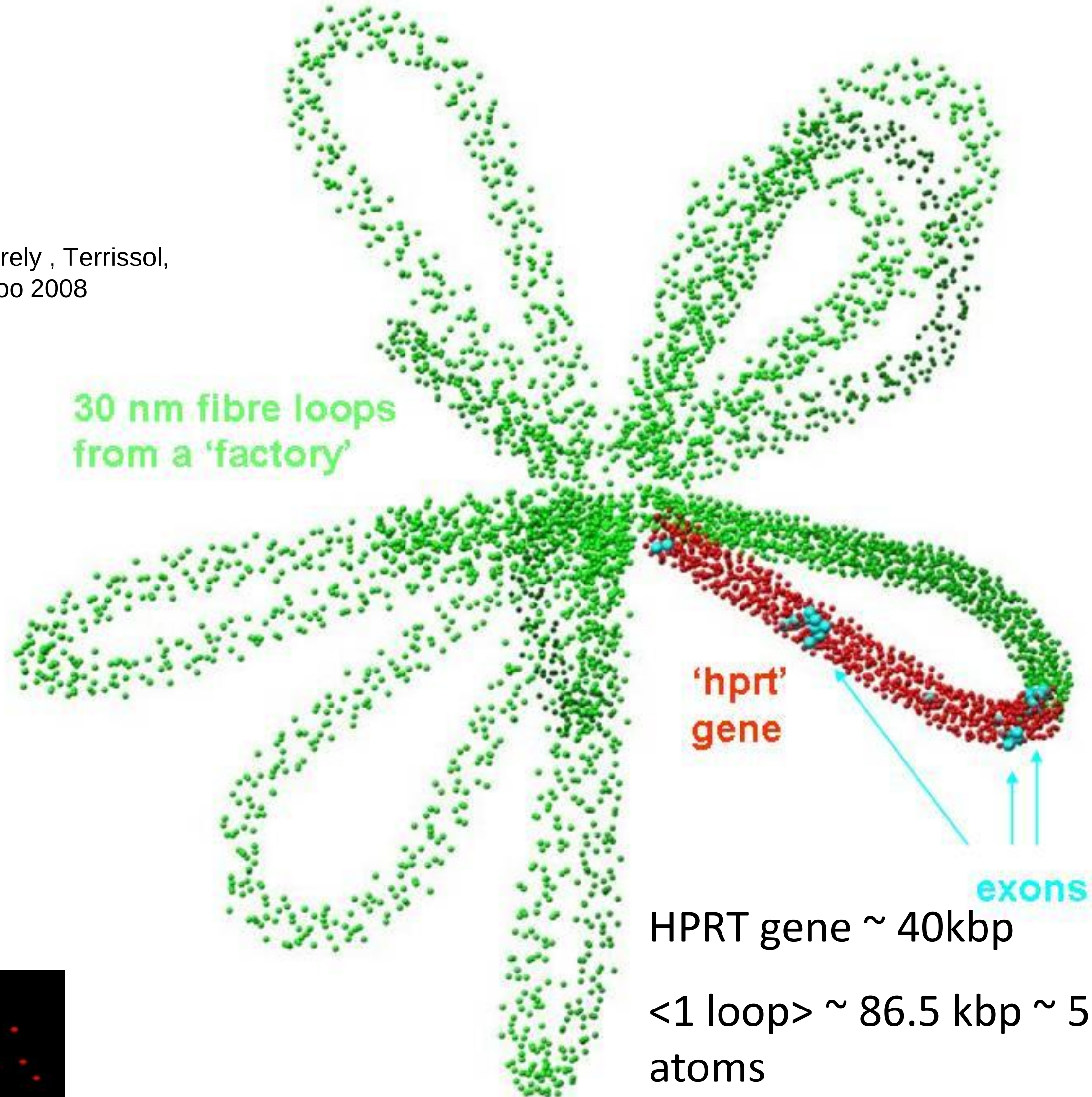
Nikjoo & Girard 2012

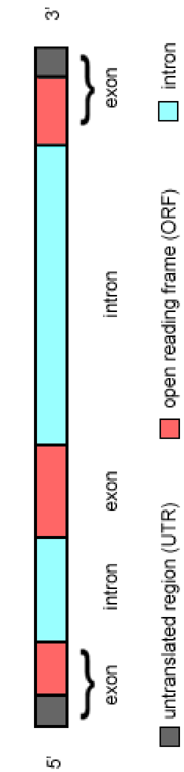




Goorely , Terrissol, Nikjoo 2008







HPRT gene ~ 40kbp

<1 loop> ~ 86.5 kbp ~ 5×10^6 atoms

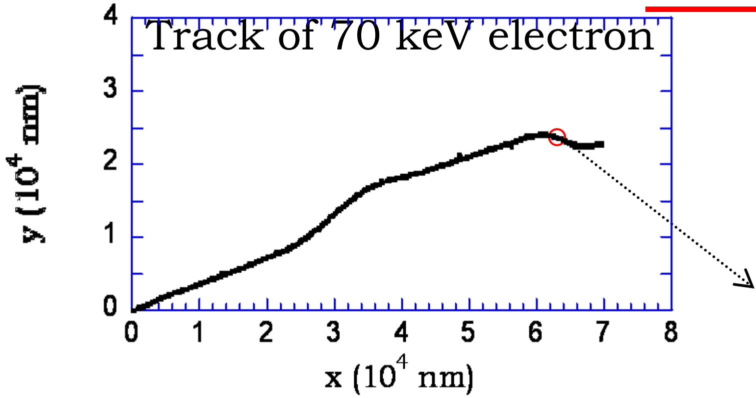
1 factory ~ 50×10^6 atoms

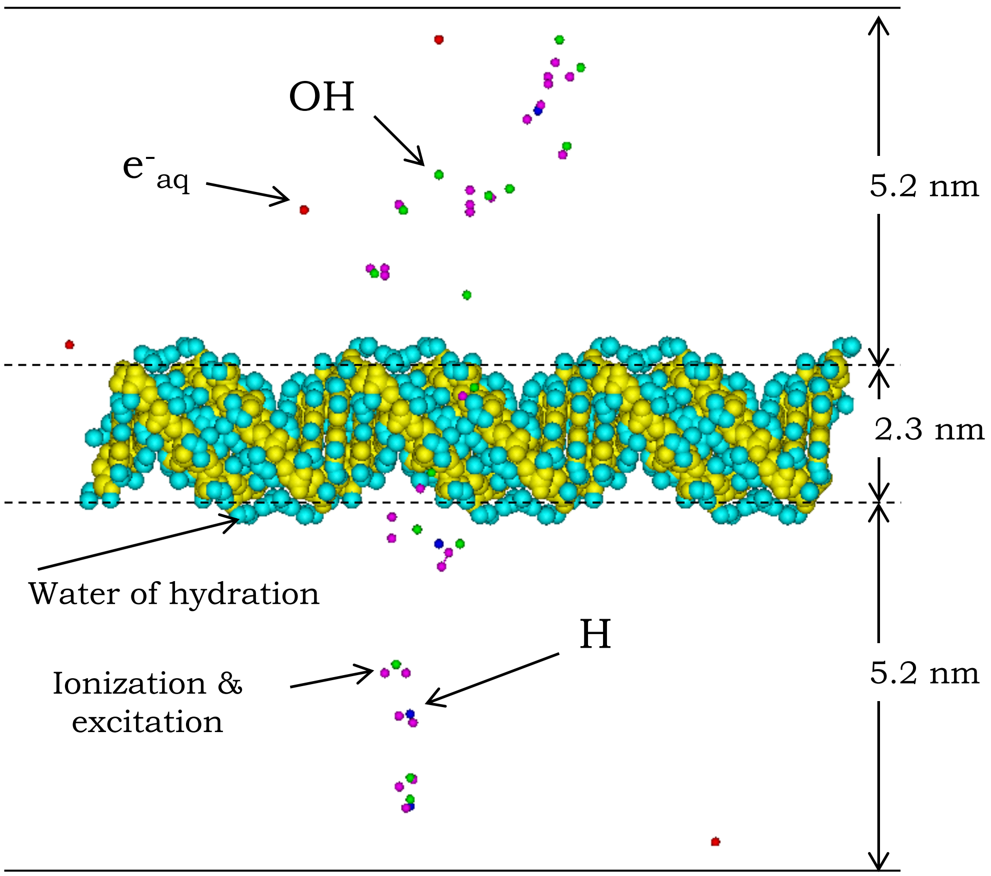
EURODOS 2013 Barcelona

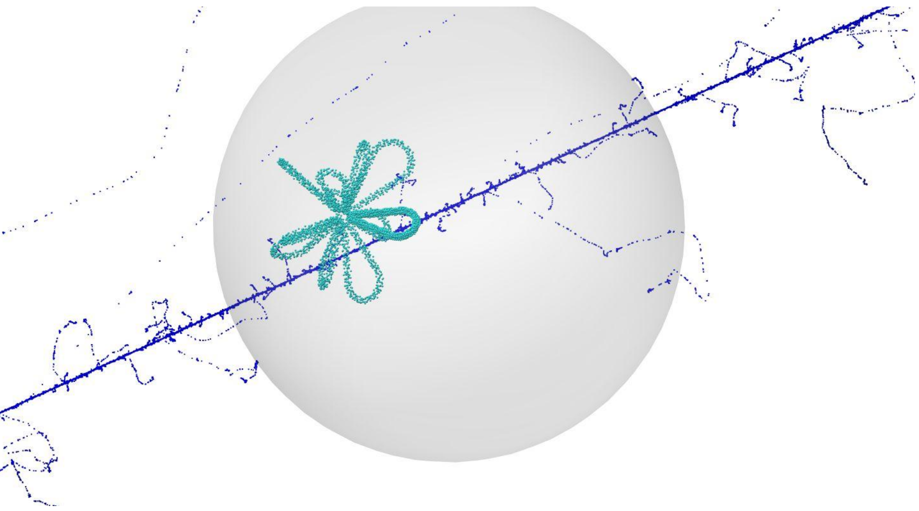
Umrania, Nikjoo, Goodfellow 1995

Nikjoo, Girard, 2012

Cell Response to Radiation: I- track interaction with the genome



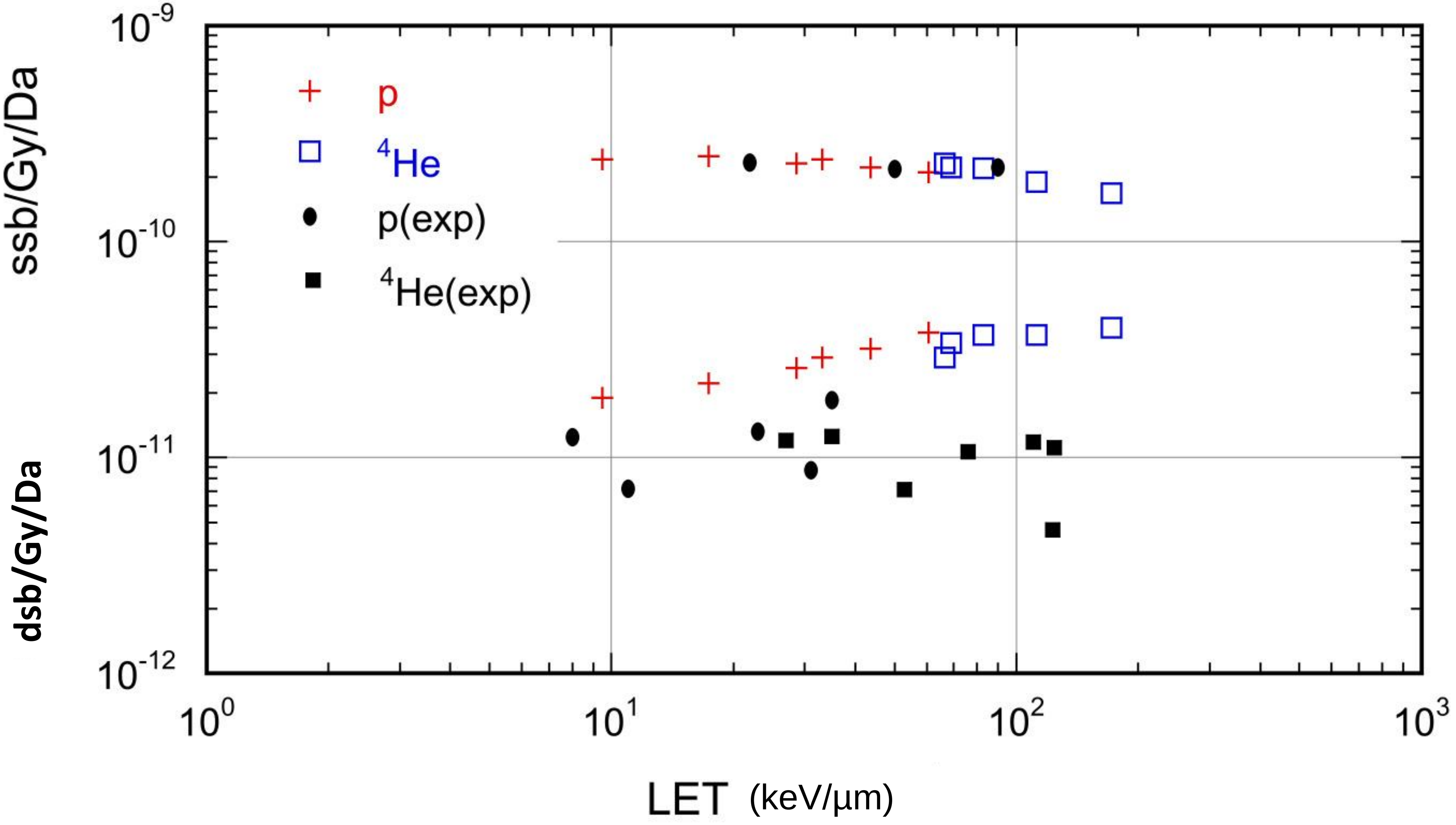




EURODOS 2013 Barcelona

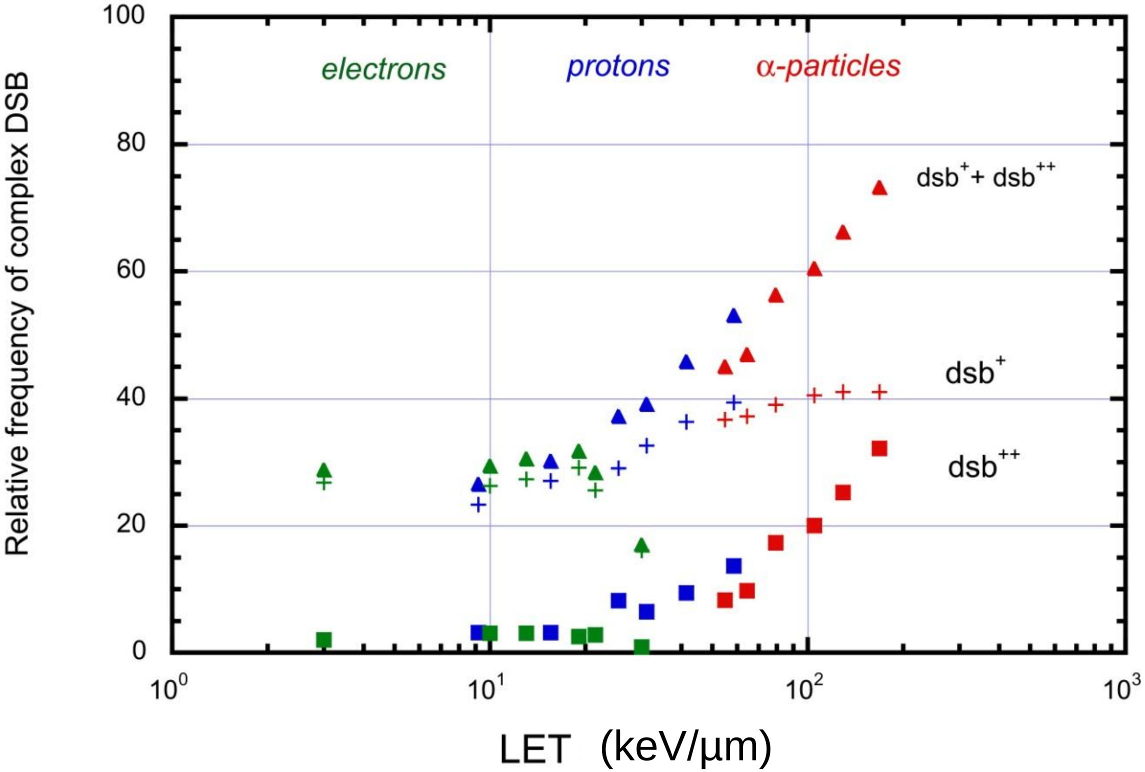
Watanabe & Nikjoo 2002

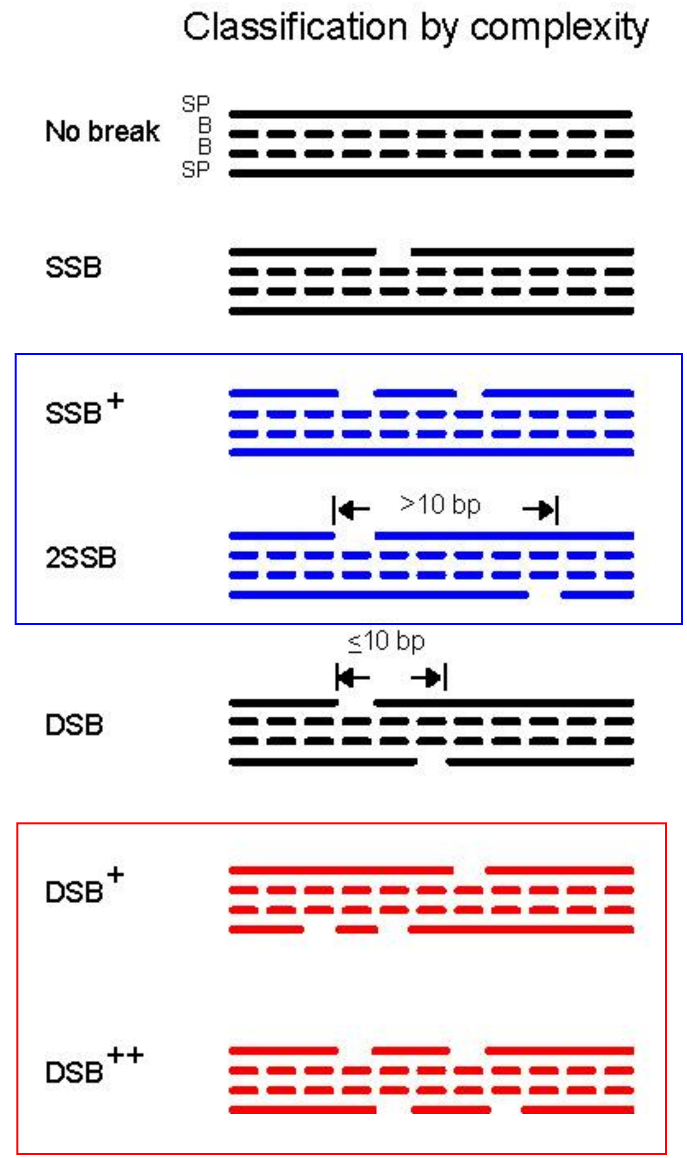
Cell Response to Radiation: Yield of SSB & DSB



Charlton, Humm, Nikjoo, 1989
Nikjoo *et al*, 2001

Cell Response to Radiation: Complexity of DSB





Charlton, Nikjoo, Humm, 1989
Nikjoo *et al* 1999
Nikjoo *et al* 2001
Sankaranaranan & Nikjoo, 2011
Taleei & Nikjoo 2012, 2013

Low-LET
Complex DSB ~20%

High-LET
Complex DSB ~70%

SSB, DSB, & BD in cell nucleus from a single track of 0.5 MeV/u proton

```
TOTAL ENERGY = 178.  TRACK: 1,  DOMAIN: 10,  FACTORY: 115,  LOOP: 6
00276     43609     43642    46495
 .        x....  1       ........................1.-
 .        .....  .       ...........................
 .        .....  .       --.........................
 1        ....1  .       ...x...1x...............-....
```

[x = SSB]
[1 & - not an SSB]

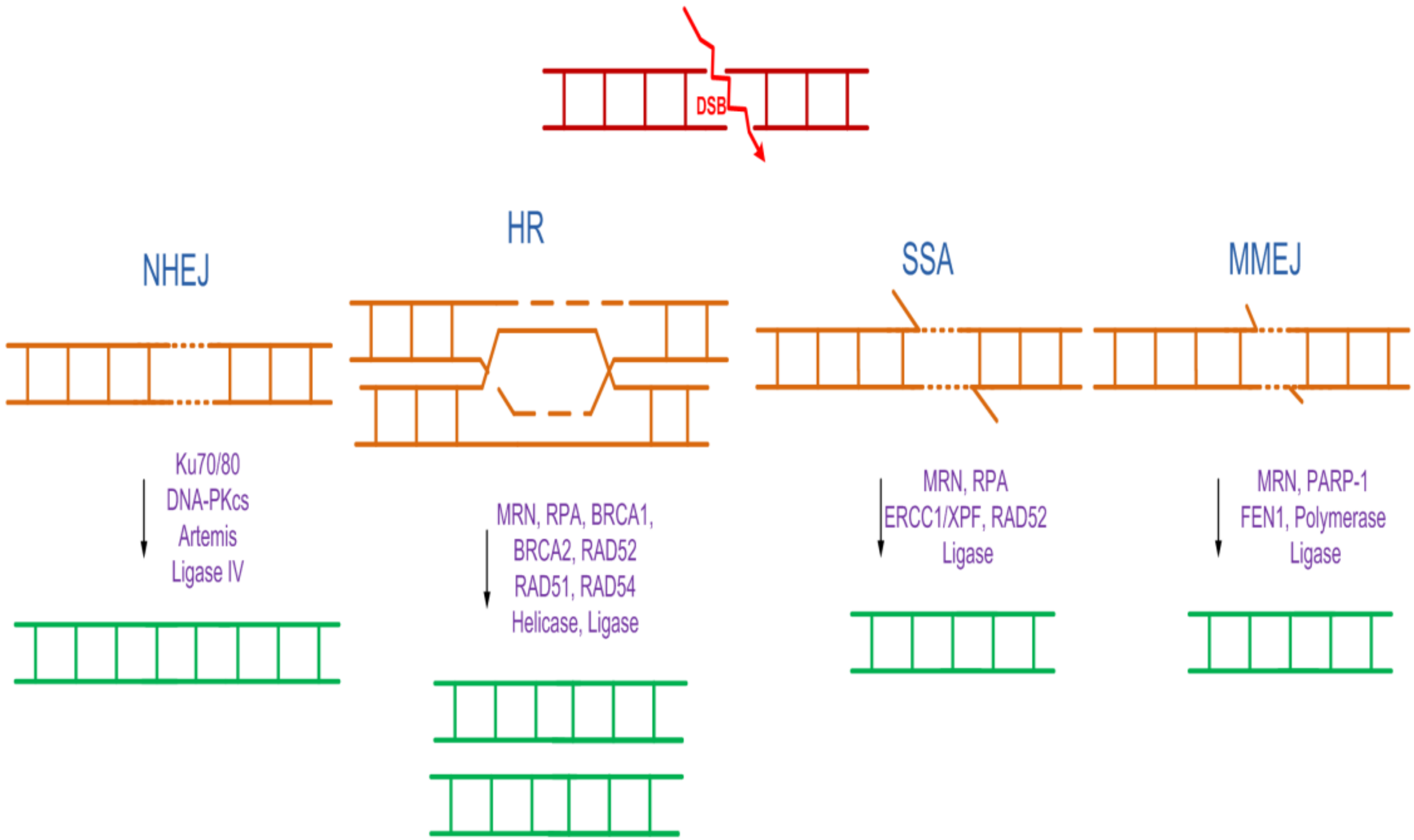
```
TOTAL ENERGY = 331.  TRACK: 1,  DOMAIN: 3,  FACTORY: 124,  LOOP: 9
00394   00480    00529    00575    00604   01426    01513   01610                        79795
 .      x..x      .        .       .....  .         ...    1.....................  1...1
 x       ....     1        1        .....  1        x..     ................x....  .....
 .       ..x.     .        .        .....  .        ...     .....................  .....
 .       .-x.     .        .       1...x  .         .1-     ...................-  .....
```

```
TOTAL ENERGY =  179.  TRACK: 1,  DOMAIN: 3,  FACTORY: 125,  LOOP: 9
 00802   01662  01959                    03089         04140  04172                   05255   05283   06381
 .       .      ................... .........  1      -....1..........  -..     ..     .
 .       .      ................... .........  .      .................-  .-.     ..     1
 .       .      ................... 1......-   .      .........-.......  ...     -.     .
 x       1      1.................-1 .........  .      -................  ..1     .-     .
```

```
TOTAL ENERGY =  94.  TRACK: 1,  DOMAIN: 90,  FACTORY: 28,  LOOP: 11
 01661     01756    02445    02592    02672
 .         -        .        .....  .
 .         .        .        x....  .
 .         .        x        ..-..  .
 1         .        .        ....x  -
```

Nikjoo & Girard 2012

DSB-Repair Kinetics



Taleei , Nikjoo, 2012

Kinetics of Repair by NHEJ (C_K X-ray)

Initial damage spectrum

```
TCGCGCGAATTCGCGCGAATTCGCGCGAATTCGCGCGAATTCGCGCGAATTCGC
..ID...............................I..................
I.I...............I...................................
......D.......I....I...I....II......................I.
..I....................I..............................
```

Biochemical repair of initial damage	Elapsed Time (min)	Elapsed Time (Average DSB_c)
Ku70/80 finds the DSB ends and translocates inward	0.3	0.3
DNA-PKcs is recruited to the damage site	1.3	1.5
First autophosphorylation of DNA-PKcs	4.3	4.4
Second autophosphorylation of DNA-PKcs	7.8	7.6
End processing by Artemis	187.3	184.1
Gap filling by Polymerase λ - µ	339.5	300.9
Ligation of complex DSB	391.9	348.7
Repair time (min) for complex damage	391.9	348.7

Taleei, Nikjoo 2013
Taleei et al 2013

Radiation Biophysics Group (RBG)

Hooshang Nikjoo, Professor, Group Leader

Peter Girard	Radioprobing/Molecular computational studies
Reza Taleei	DNA Damage-Repair
Thiansin Liamsuwan	Physics and track simulation
Lennart Lindborg	Microdosimetry
Alfredo Metere	Genome Technology/IT
Shirin Rahmanian	DNA damage response & repair





Scientific Collaborators

Dimitris Emfietzoglou	Medical Physics, Ioannina Medical School
K. Sankaranarayanan	Toxicogenetics Department, Leiden
Shuzo Uehara	School of Health Sciences, Kyushu