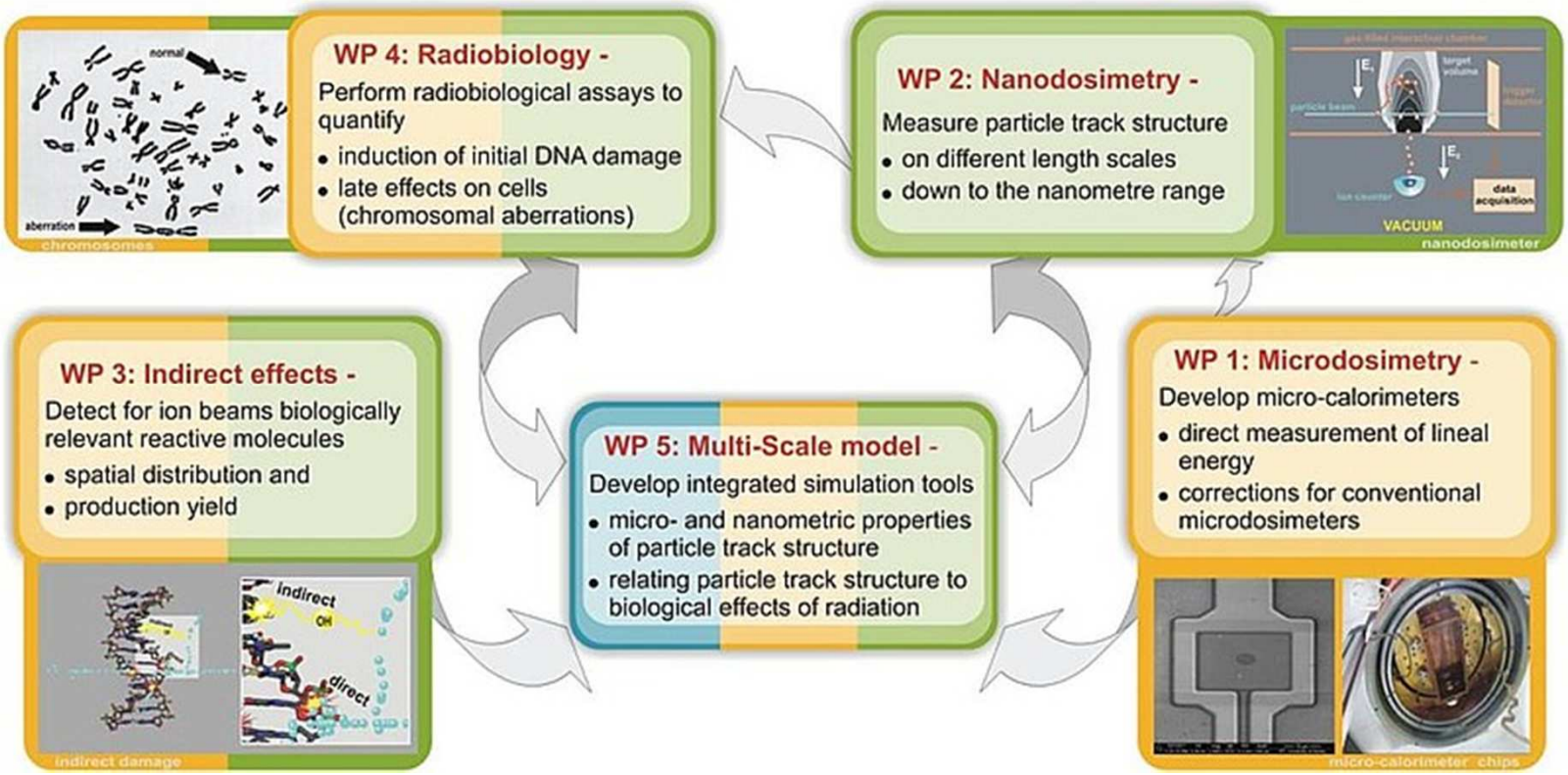
WP 5: Developing a multi-scale simulation model for charged particle track structure and their biological effects at cellular level



BioQuaRT

Goal of the work-package 5

Developing a multi-scale simulation tool able to determine, for a given radiation quality:

- **The track structure at nanometric level (defined by a series of characterization parameters)**
- **The microdosimetric spectra**
- **The total number of DNA clustered damages by direct and indirect effects**
- **The expected number of double strand breaks (DSB)**
- **It's consequence in terms of late effects (dicentrics chromosomes and « micronuclei » block assay)**

In order to identify the parameters in the radiation quality allowing a biological weight for different radiotherapy techniques (focused in hadrontherapy).

To this end, WP5 receives results from all other WP :

- **WP1: Experimental microdosimetric spectra**
- **WP2 : Experimental nanometric cluster size data in coincidence with microdosimetric spectra**
- **WP3: Experimental data on spatial distribution and production rate of particular radicals and ROS (reactive oxygen species) , to be used in the indirect effects simulation**
- **WP4: Experimental data on early and late radioinduced damages obtained with the characterized radiation qualities in the other WP**

Work division on WP5

Work in WP5 is divided in three tasks:

Task 5.1 Cross-section data sets for DNA constituents (June 2012-Sept 2014)

To provide evaluated data set of interaction cross-sections for model molecules representing DNA constituents that should be used by the track structure simulation tool

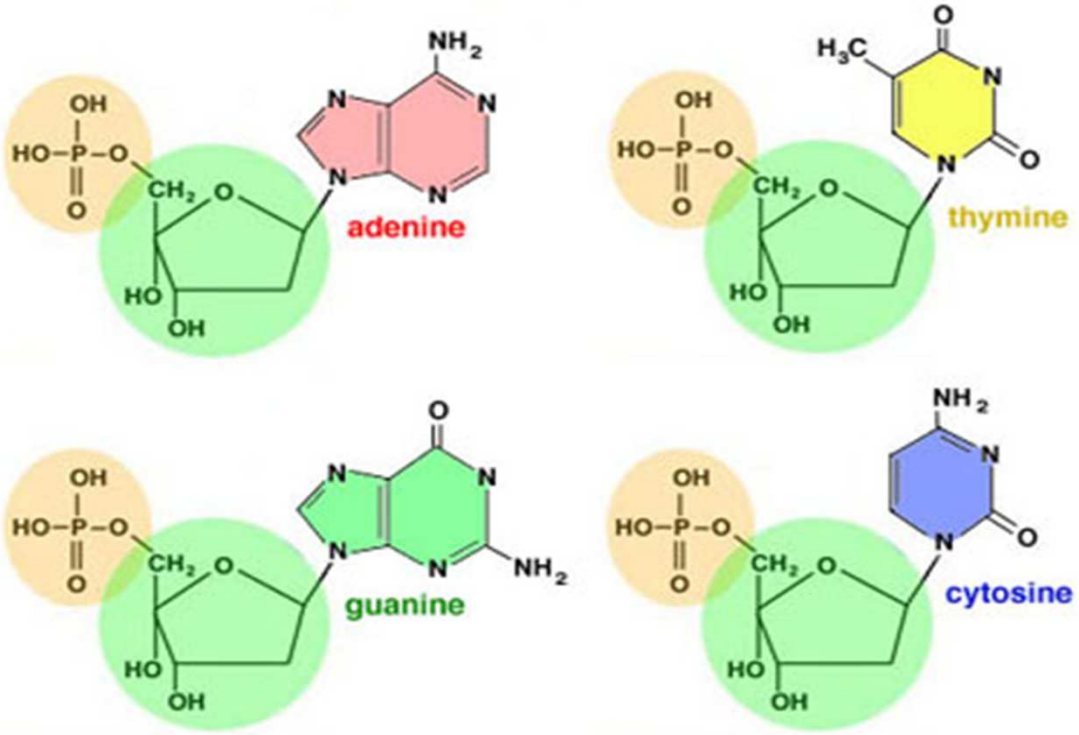
Task 5.2 Development of a multi-scale track-structure simulation tool (June 2012-Apr 2015)

Allowing to calculate the spatial distribution of the energy deposited by ionizing radiation at nanometric level within a DNA geometrical model. These results will be validated with experimental data from WP2 and will be used to determine the parameters in the track structure characterizing the interaction within the target

Task 5.3 Linking track structure with biology (Nov 2013-Apr 2015)

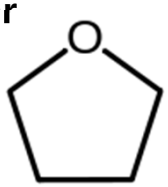
Extension of the multi-scale tool using a mechanistic approach to include indirect effects from the chemical stage and allowing to predict the early effects (DSB) and late effect data obtained in WP4

Task 5.1 Cross section data set for DNA constituents

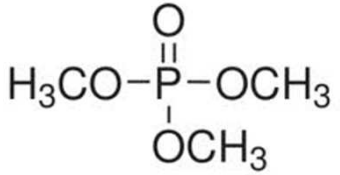


DNA constituents to be investigated:

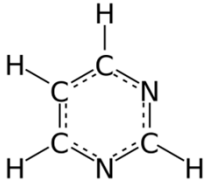
Tetrahydrofuran (THF) -> sugar



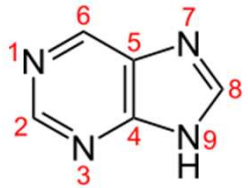
Trimethylphosphate (TMP) -> phosphate group



Pyrimidine (PY) -> cytosine & thymine



Purine (PU) -> adenine & guanine



Task 5.1 Cross section data set for DNA constituents

Cross-sections measurements at PTB for primary particles and secondary electrons.

Ions (proton, helium and carbon, for Bragg Peak energies)

- **Total ionisation cross-sections**
- **Charge transfert cross-sections**
- **Energy and angular distribution of secondary electrons**
- **DNA fragmentation cross-sections**

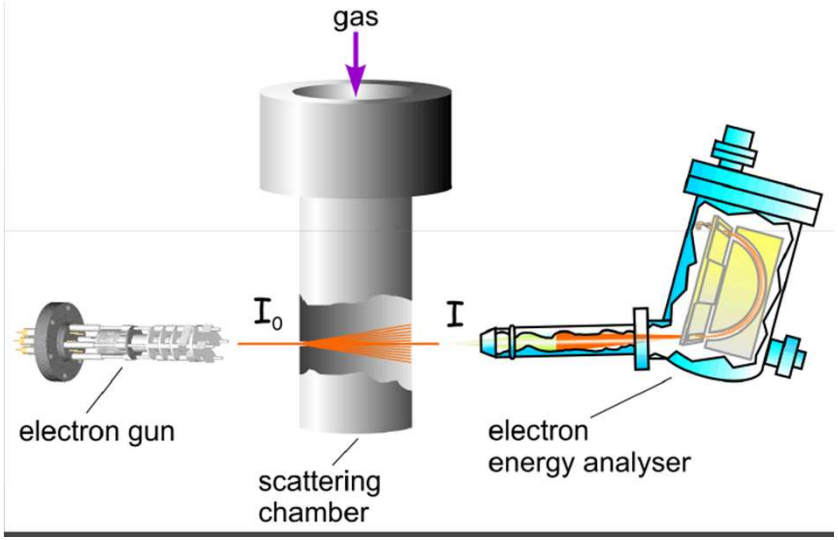
electrons (20 eV-1 keV)

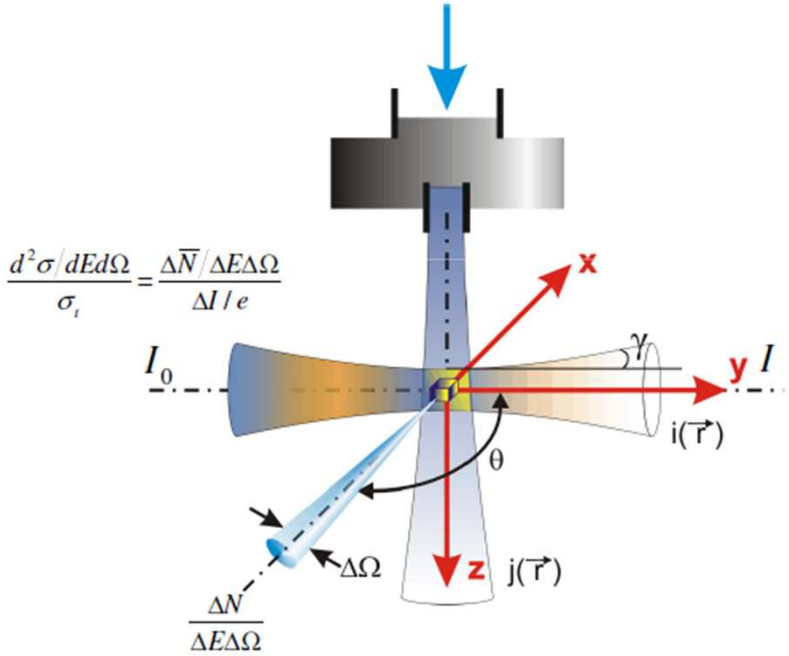
- **Total scattering cross-sections**
- **Differential elastic scattering cross-sections**
- **Double-differential inelastic scattering cross-sections (E, Ω) (Ω :5°-135°extrap. 0°-180°)**
- **DNA fragmentation cross-sections**

Task 5.1 Cross section data set for DNA constituents

Differential elastic scattering cross sections in the gas phase are measured absolutely by means of the current loss ΔI of the primary beam and the measured total interaction cross-section.

*For experimental details see : W. Y. Baek et al., Phys. Rev. A **86**, 032702 (2012) and W. Y. Baek and B. Grosswendt, J. Phys. B **36**, 731 (2003)*





TCS apparatus (beam attenuation)

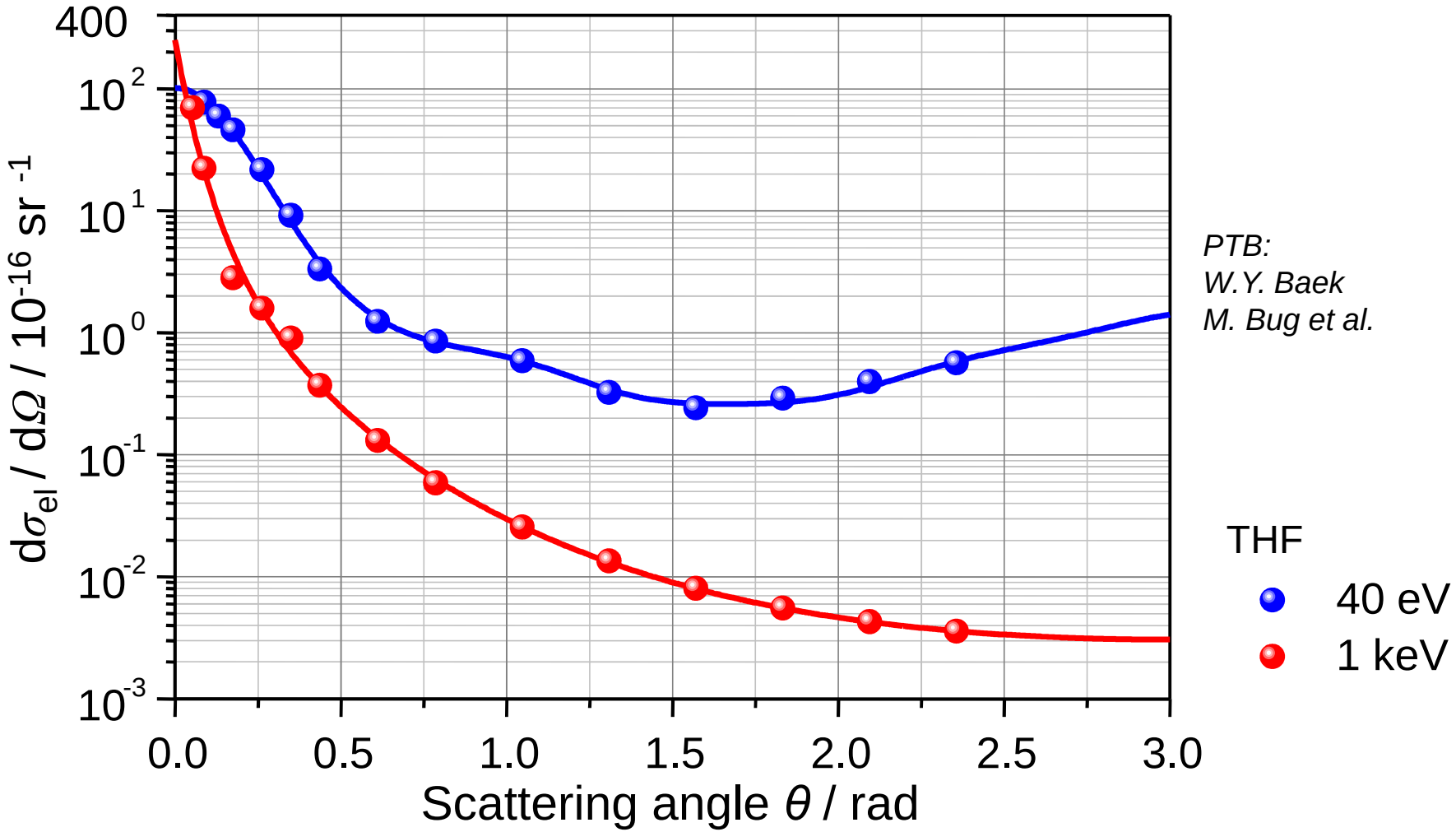
Electron energy analyzer discriminates electrons undergoing scattering processes and ejected in the forward direction. TCS is derived from the electron counting rates and corrected from experimental considerations

Crossed beam experiment for DCS

$$\frac{d\sigma(\theta,T)}{d\Omega} = \frac{e}{\eta(T)}\frac{\Delta N(\dot{\theta},T)}{\Delta\Omega}\frac{\sigma_t(T)}{\Delta I}$$

Task 5.1 Differential elastic cross-sections

Experimental results and fitted models for electron differential elastic cross-sections in THF

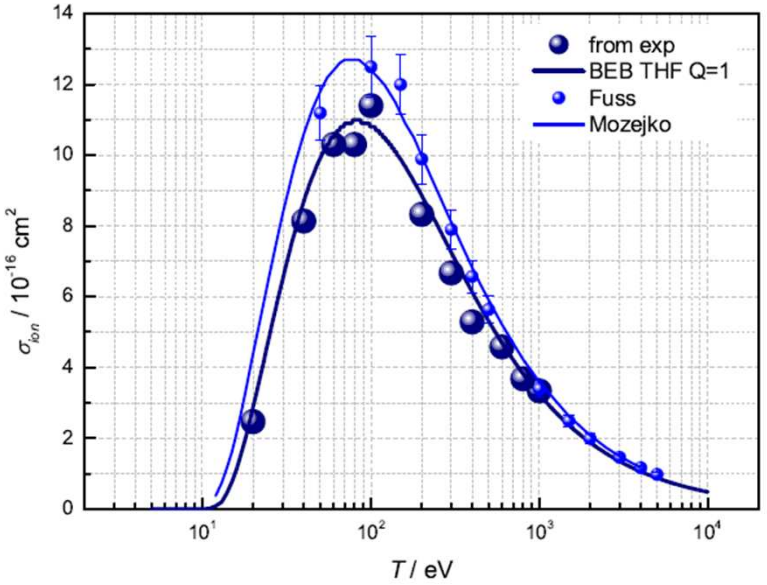


Task 5.1 Ionization cross-section

PTB:
W.Y. Baek
M. Bug et al.

Experimental data of double differential inelastic cross-sections for electrons have been determined by measuring the number of electrons ΔN of energy between E and E+ΔE per time interval into the solid angle segment ΔΩ.

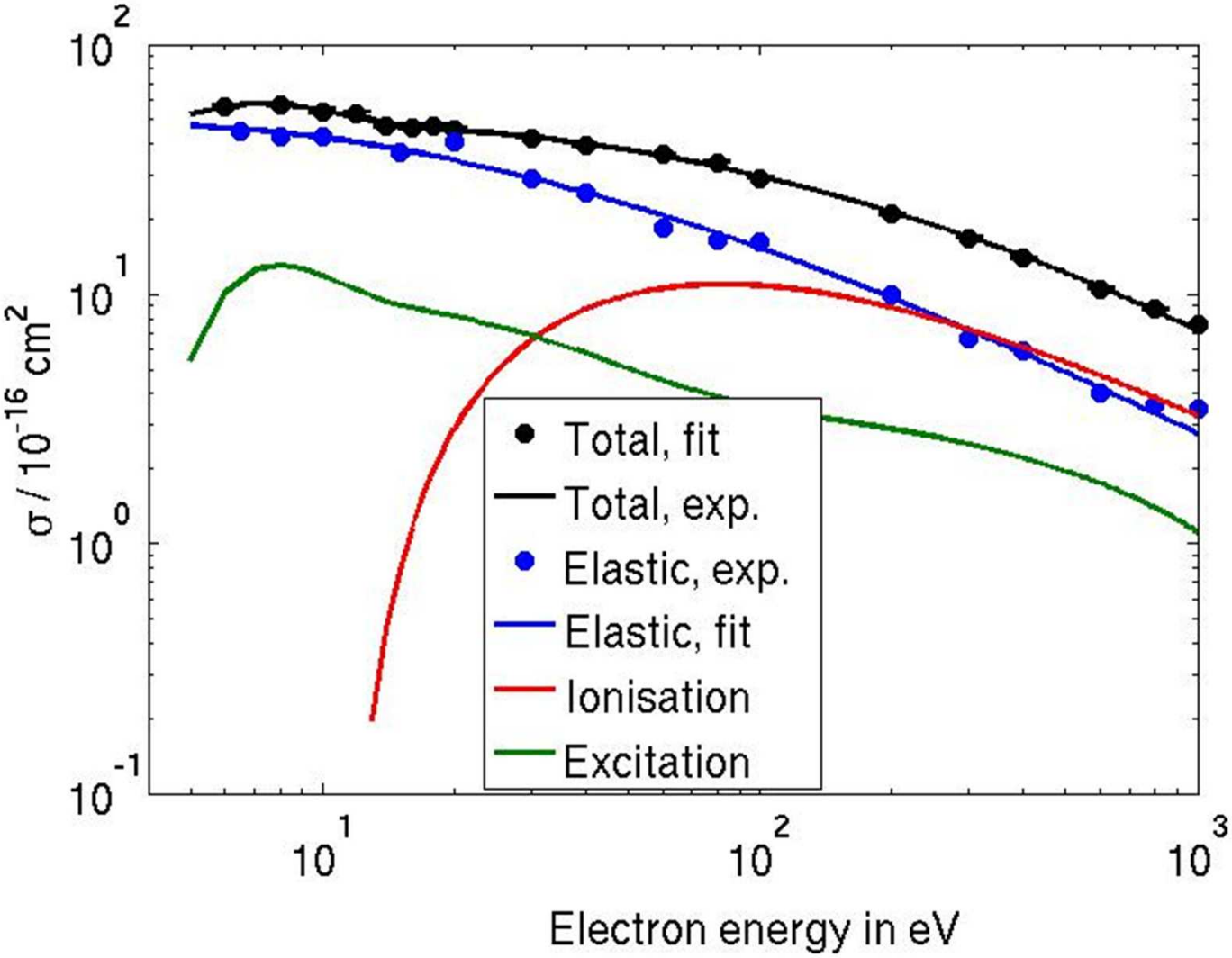
An analytical description for the DDCS is necessary to facilitate their use in the Monte Carlo track structure codes, allowing then the split of these cross sections in terms of partial differential cross-setions for the i-th molecular orbital-> Model fit



Total ionization cross-section obtained integrating the measured DDCS and by the BEB model.
M. Bug , internal report 16/11/2012

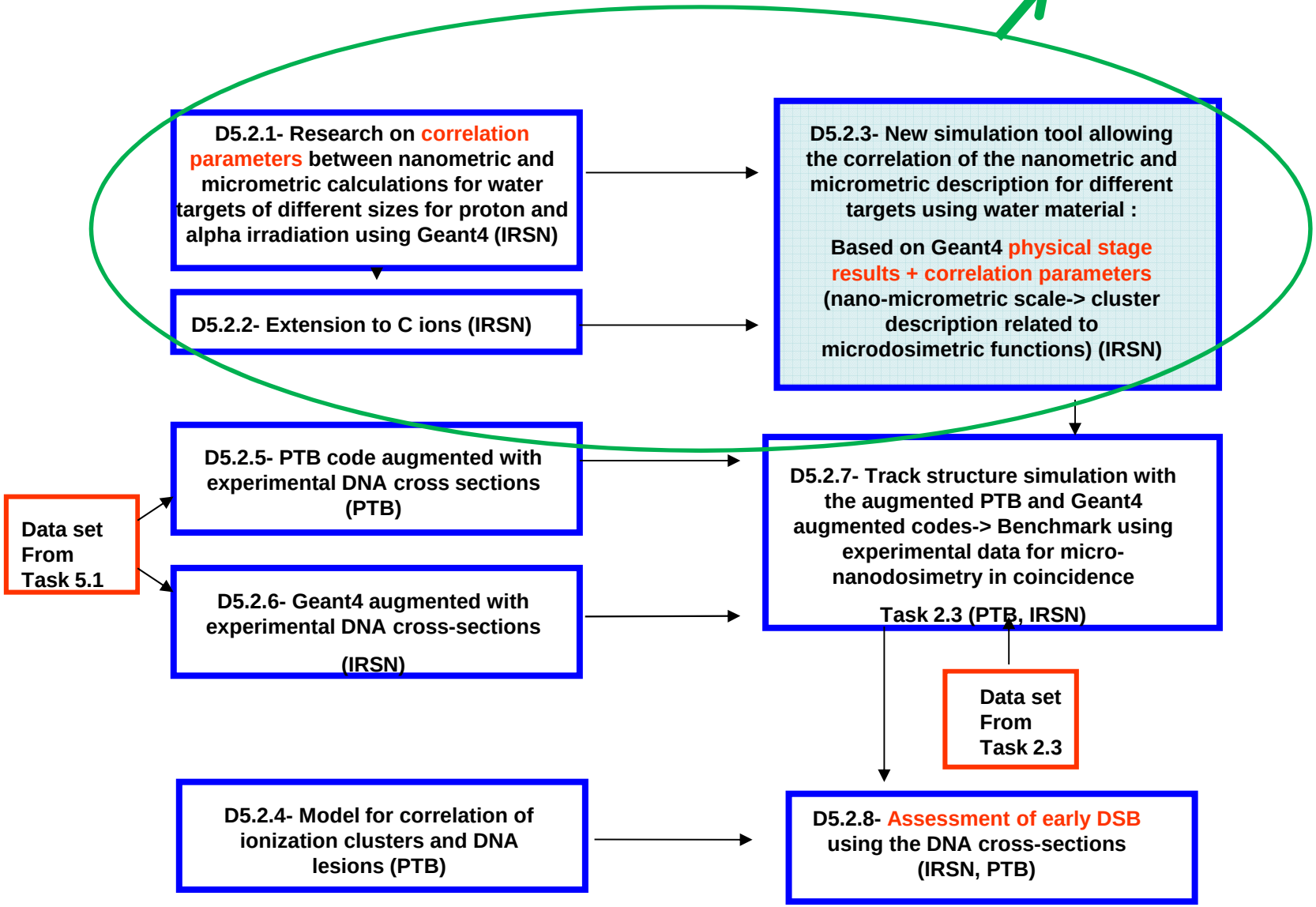
Task 5.1 Experimental and fitted models used in the Monte Carlo simulation (ex. THF in the Ptra code)

Total CS – Models in simulations (THF)
M. Bug internal report 05/2013



Task 5.2 Development of a multi-scale track-structure simulation tool

Davide Bianco
presentation this morning



Task 5.2 Development of a multi-scale track-structure simulation tool

Study of the relations between microdosimetric and nanodosimetric results for protons, alphas and carbon ions

Materials and Methods:

- **Firstly using liquid water cross-sections for ions and secondary electrons transport for the Monte Carlo simulation :**

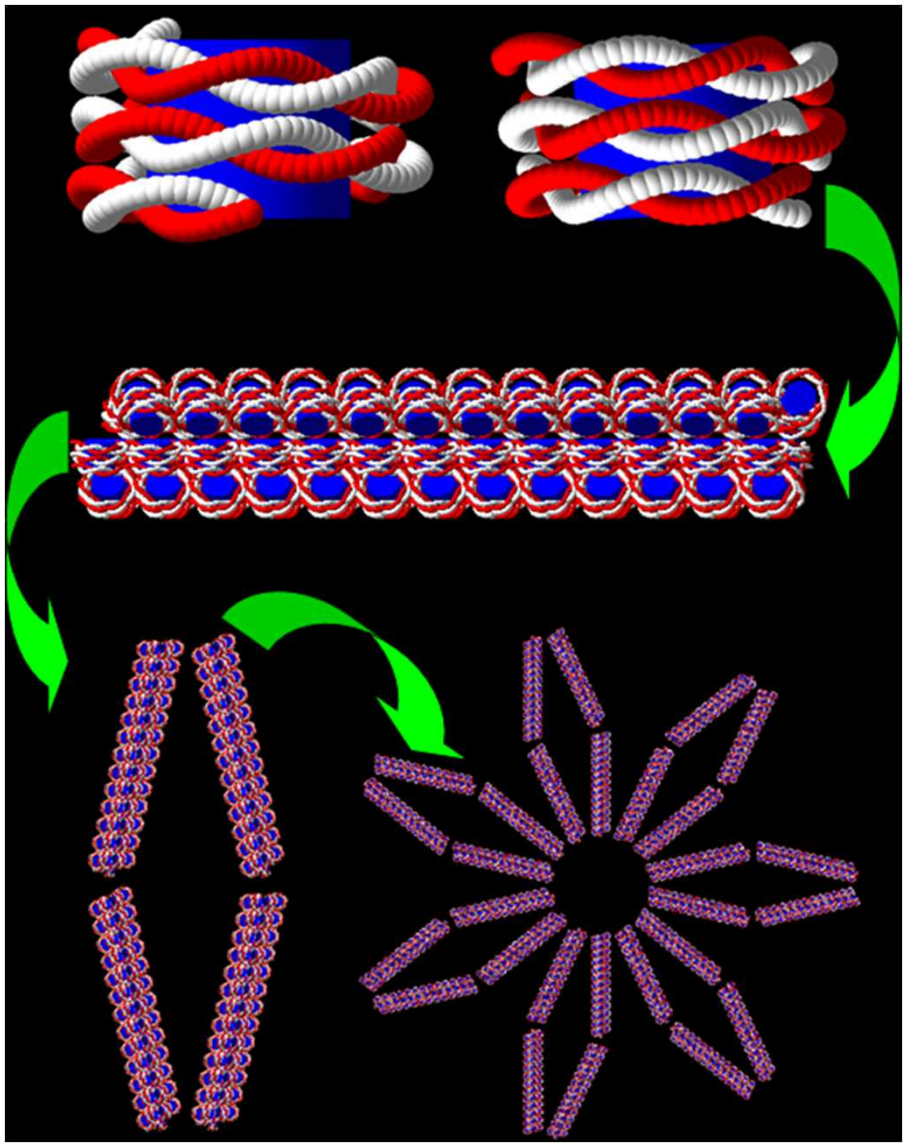
Geant4-DNA processes *(http://geant4-dna.org/ See full details in Med. Phys. 37 (2010) 4692-4708 and Appl. Radiat. Isot. 69 (2011) 220-226))*

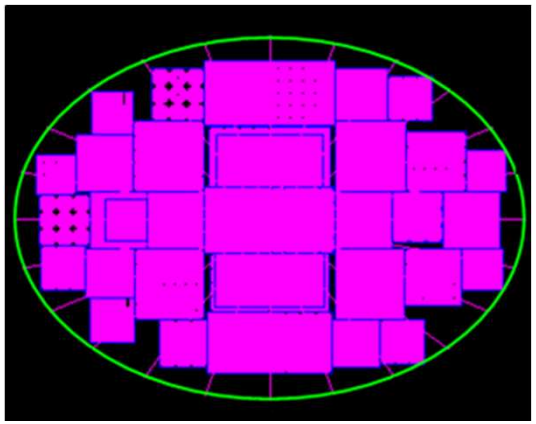
- **DNA geometrical model implemented in the simulation to select energy deposits related to direct damages** *M. Dos Santos et al. NIM B 298 (2013) 47-54*

- **DBSCAN clustering algorithm to reveal clustered damages** *(Density Based Spatial Clustering of Applications with Noise. 2nd Int. Conf. On Knowledge Discovery and Data Mining (Martin Ester et al. – 1998))*

Task 5.2 DNA Geometry model used

M. Dos Santos et al. NIM B 298 (2013) 47-54





Per nucleus:
- 23 pairs of chromosomes
- 11875 flowers or 83125 loops
- 332 500 chromatin fibers
- 29 925 000 nucleosomes
- ~ 6 Gbp

The actual DNA distribution within the nucleus has then been simulated using a nearly uniform distribution of the chromatin, as in the G0/G1 phase (WP4 the cell irradiations)

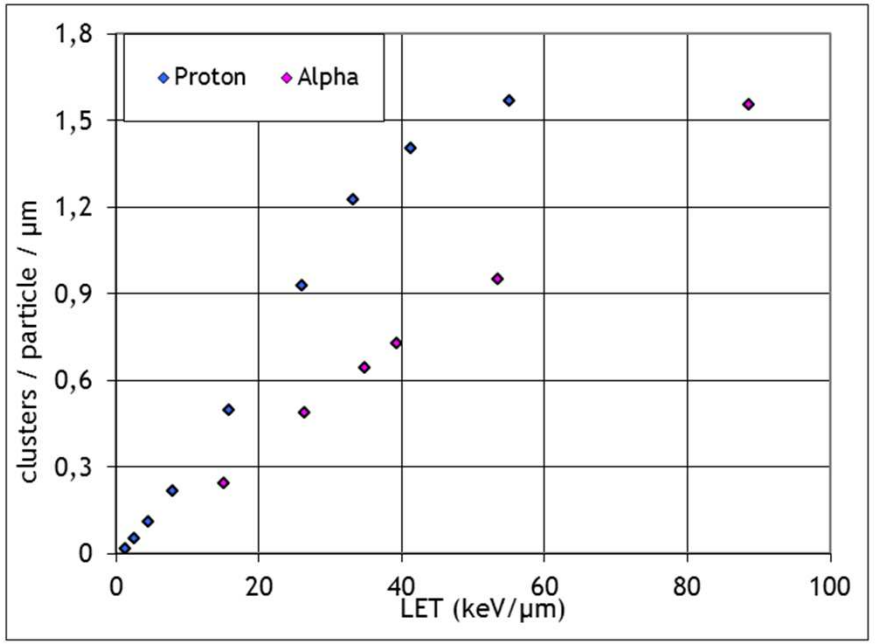
All the ionizations or excitations of the water molecule by the incident ion or secondary electrons are taking into account for the clustering analysis

Task 5.2 Obtained results

- **Microdosimetry spectra :**
  - f(y) and f(z) spectra for protons, alphas and carbon ions
  - covering a wide range in LET
  - with and without the DNA geometrical model

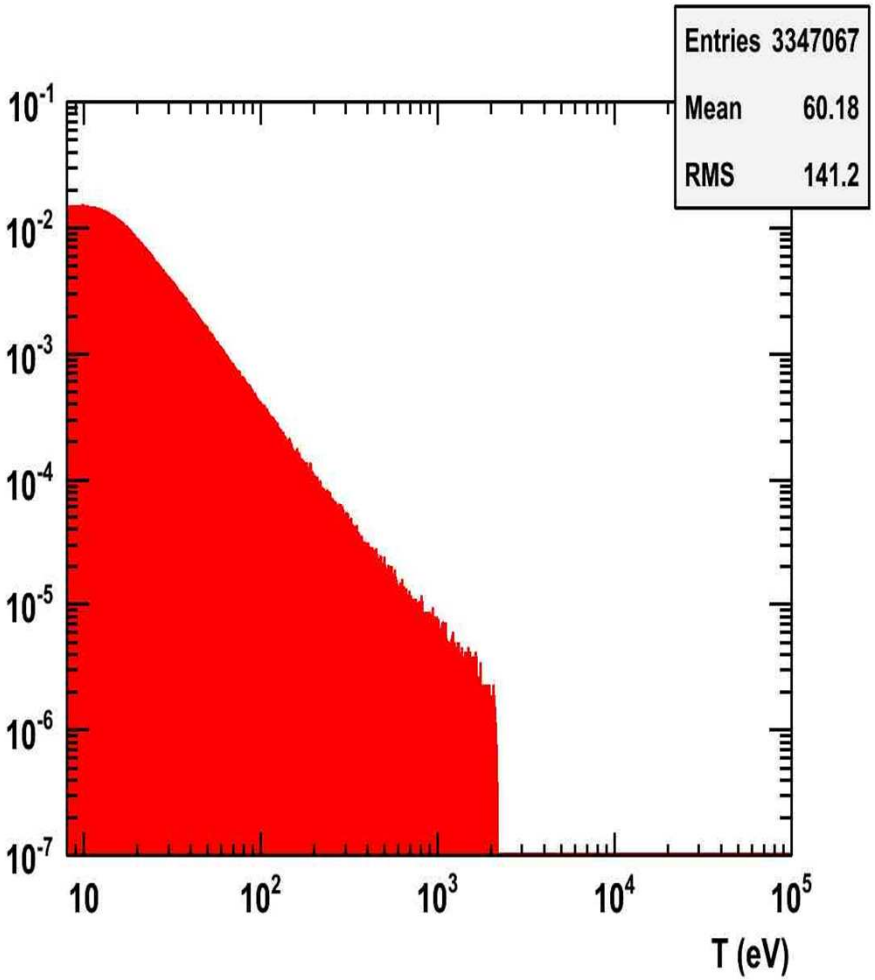
- **Secondary electron spectra calculation**

- **Clustered damage results (nanometric scale) :**
  - Number of direct clustered damages
  - Cluster size distribution
  - Cluster energy distribution

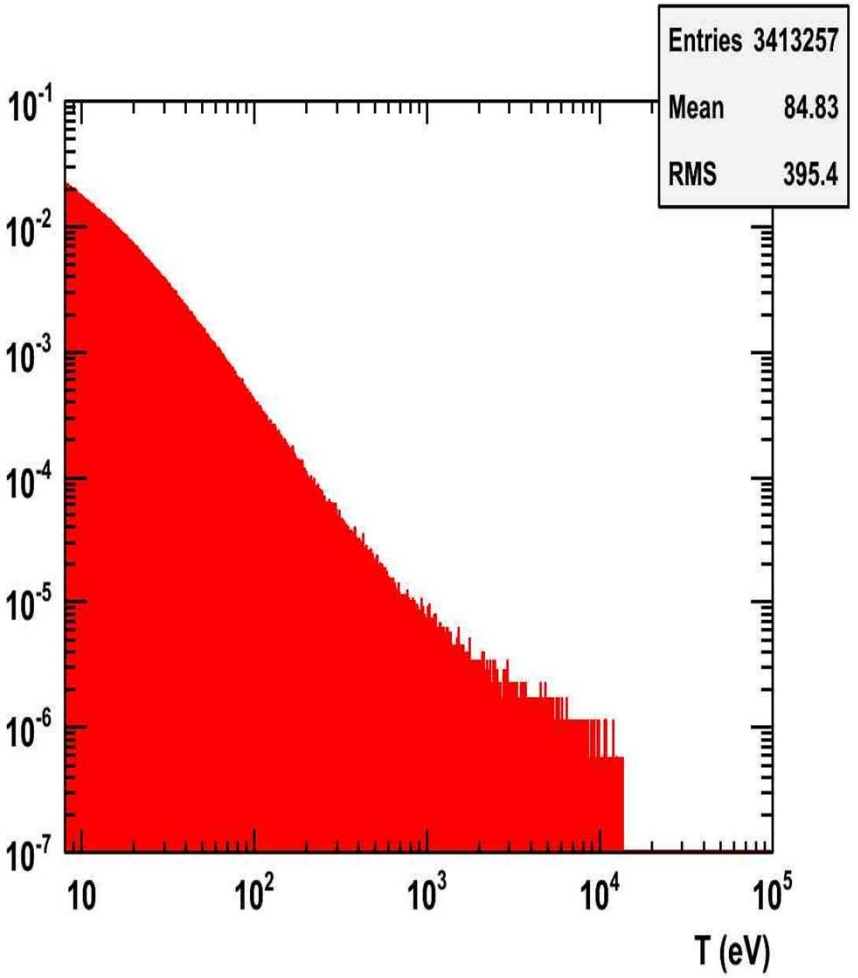


Task 5.2 secondary electron spectra

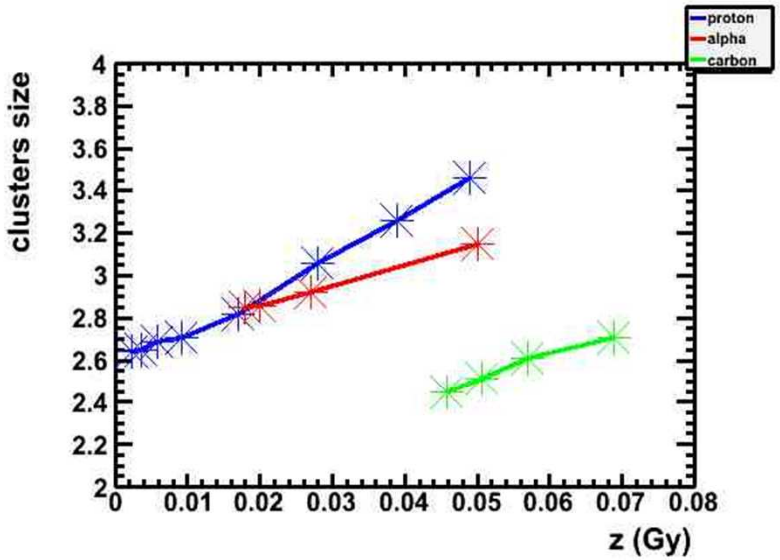
Proton 1 MeV – LET = 29 keV/µm

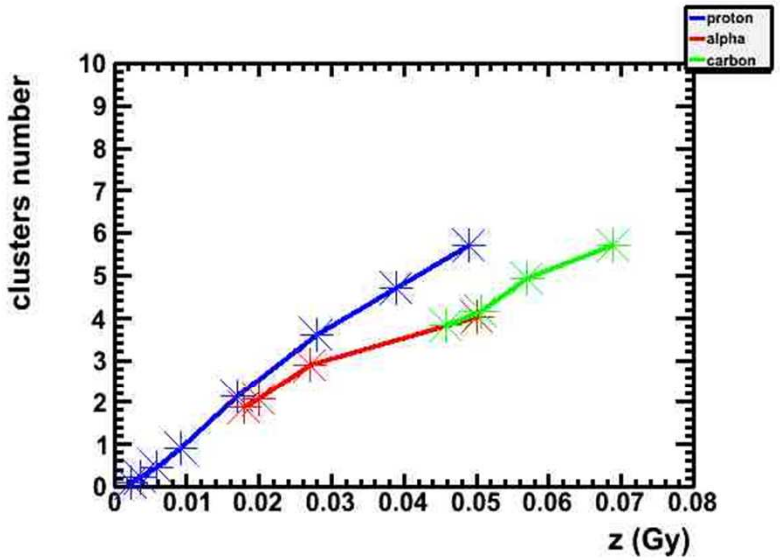


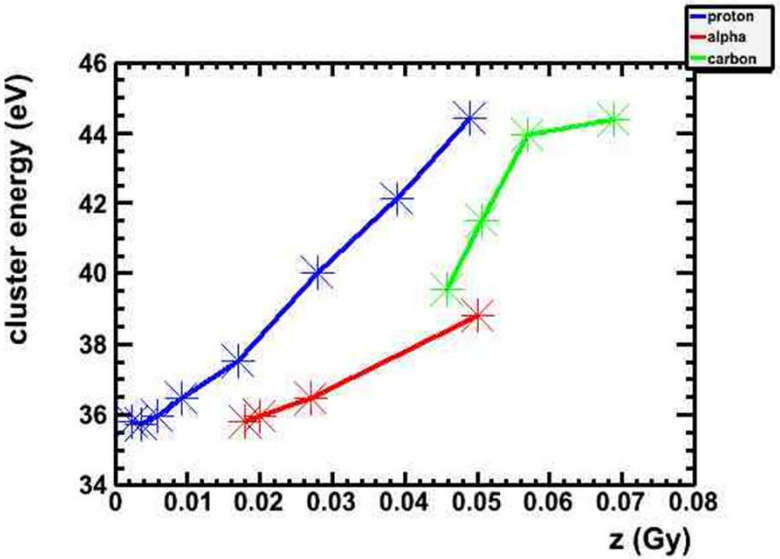
Alpha 25 MeV – LET= 23 keV/µm

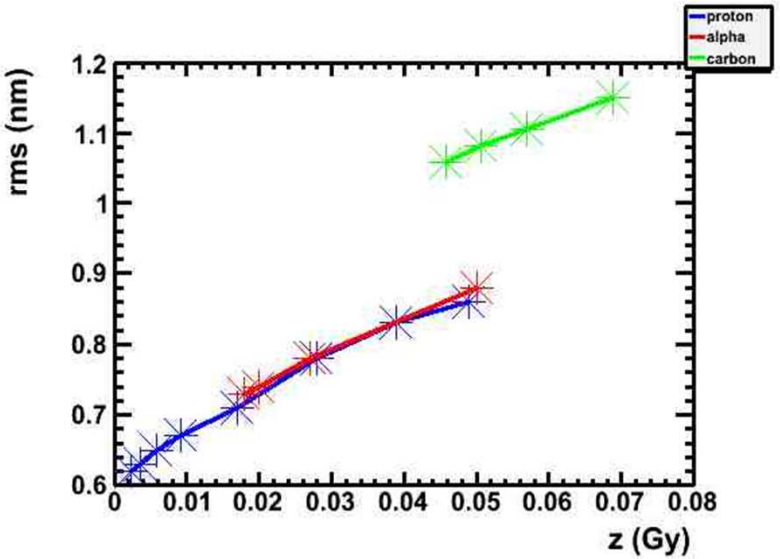


Task 5.2 Micro-nanodosimetry results relation.



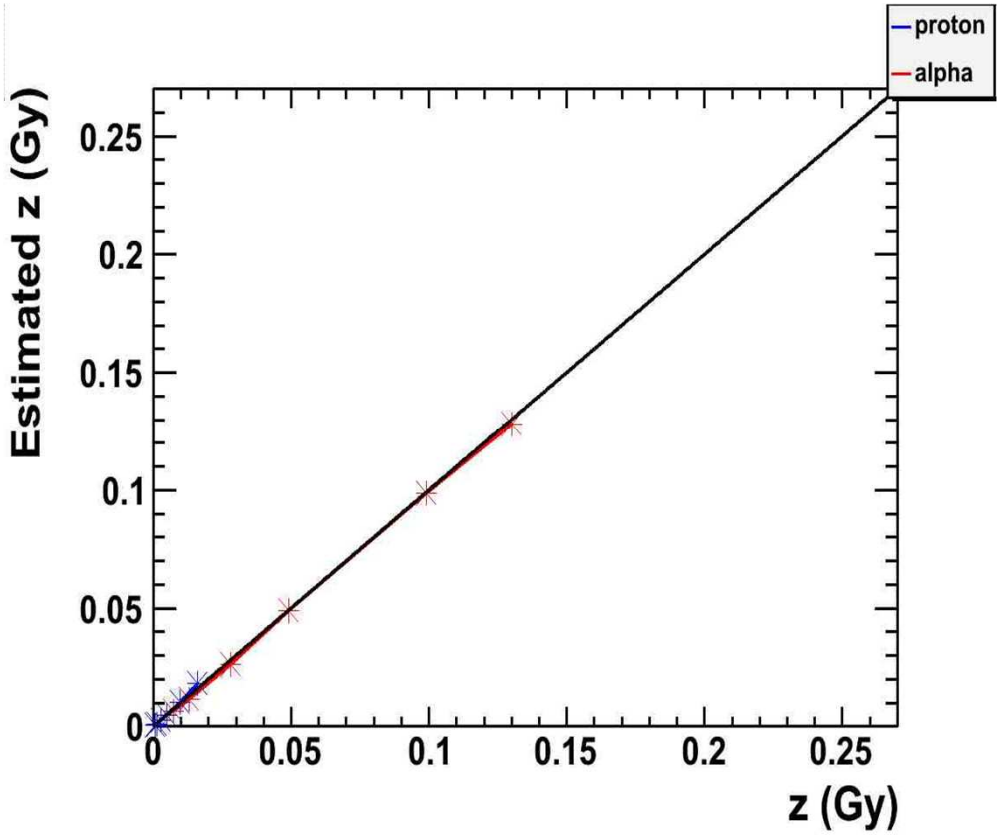






Task 5.2 Multiscale approach on-going work

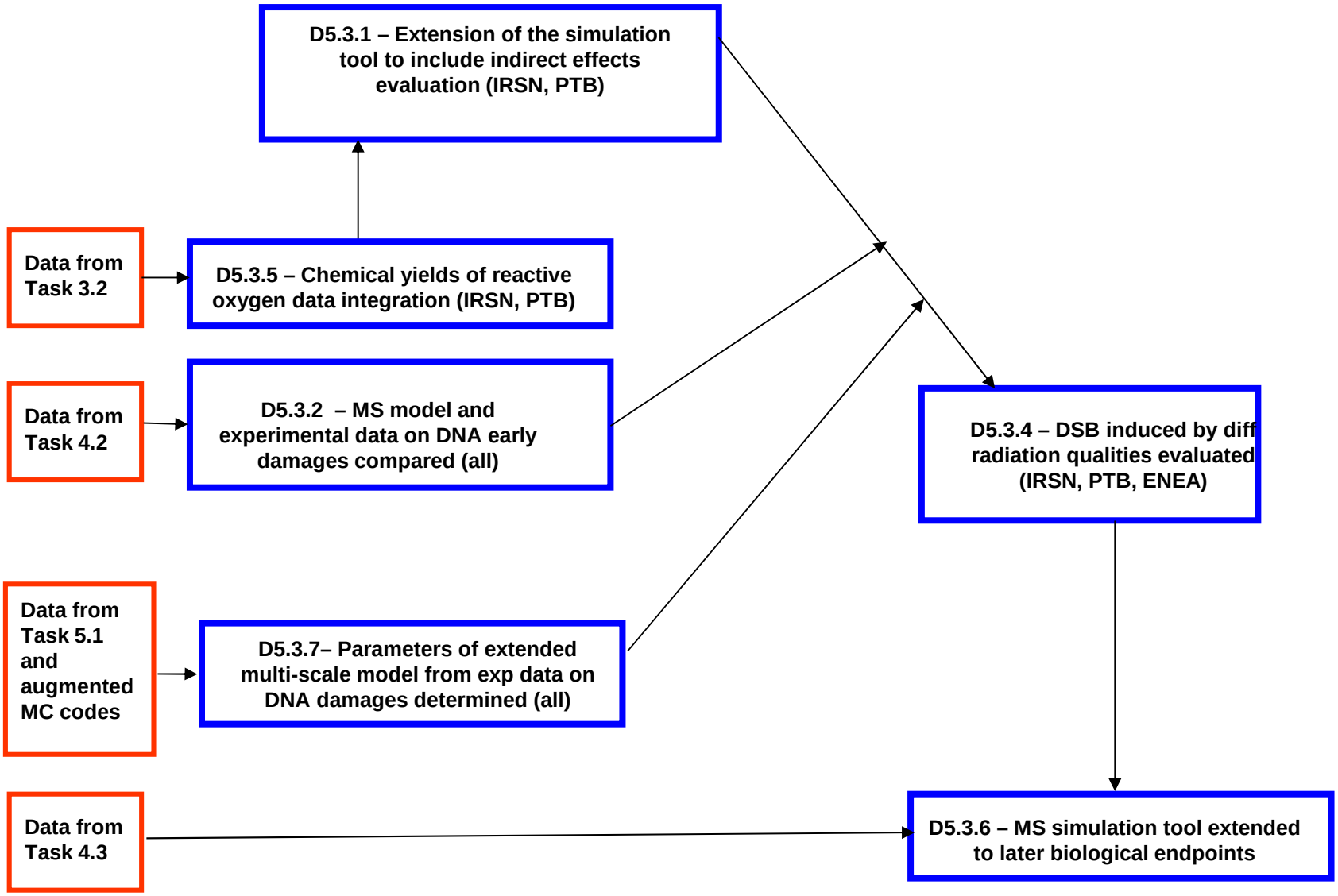
$$E(z) = \overline{k}E(\epsilon_e)E(n_e)(1-p)(1-q)+\overline{k}E(ion)+\overline{k}E(therm)p+q\overline{k}E(\epsilon_{iso})E(n_{iso})$$

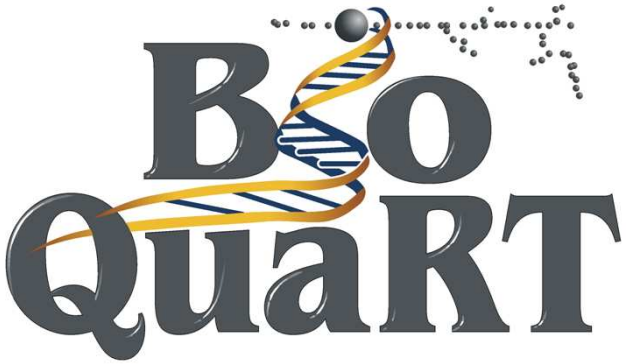


- "p" is the probability to have a secondary electron with a kinetic energy T below the ionization threshold
- "q" is the probability that an electron, with T above the ionization threshold, deposits all the energy in a single interaction ("isolated point")
- "k" is the mean number of ionization made by the primary particles.

Davide Bianco
presentation this morning

5.3 Linking Track structure with biology .





Thank you for your attention