HelmholtzZentrum münchen
German Research Center for Environmental Health

Track structure and initial DNA damage simulation for ion energies around the Bragg peak

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Outline

Introduction to PARTRAC modules and principal results

Ion cross section basis in PARTRAC (Dingfelder)

New pragmatic approach for slow light ion cross sections

LET, range and radial dose values compared to other data

Calculation of DNA single and double-strand breaks for C ions between 2 and 800 MeV

Conclusion

Scheme of PARTRAC tools

Friedland et al 2011 Mutat Res 711:28

Modelling of radiation track structures

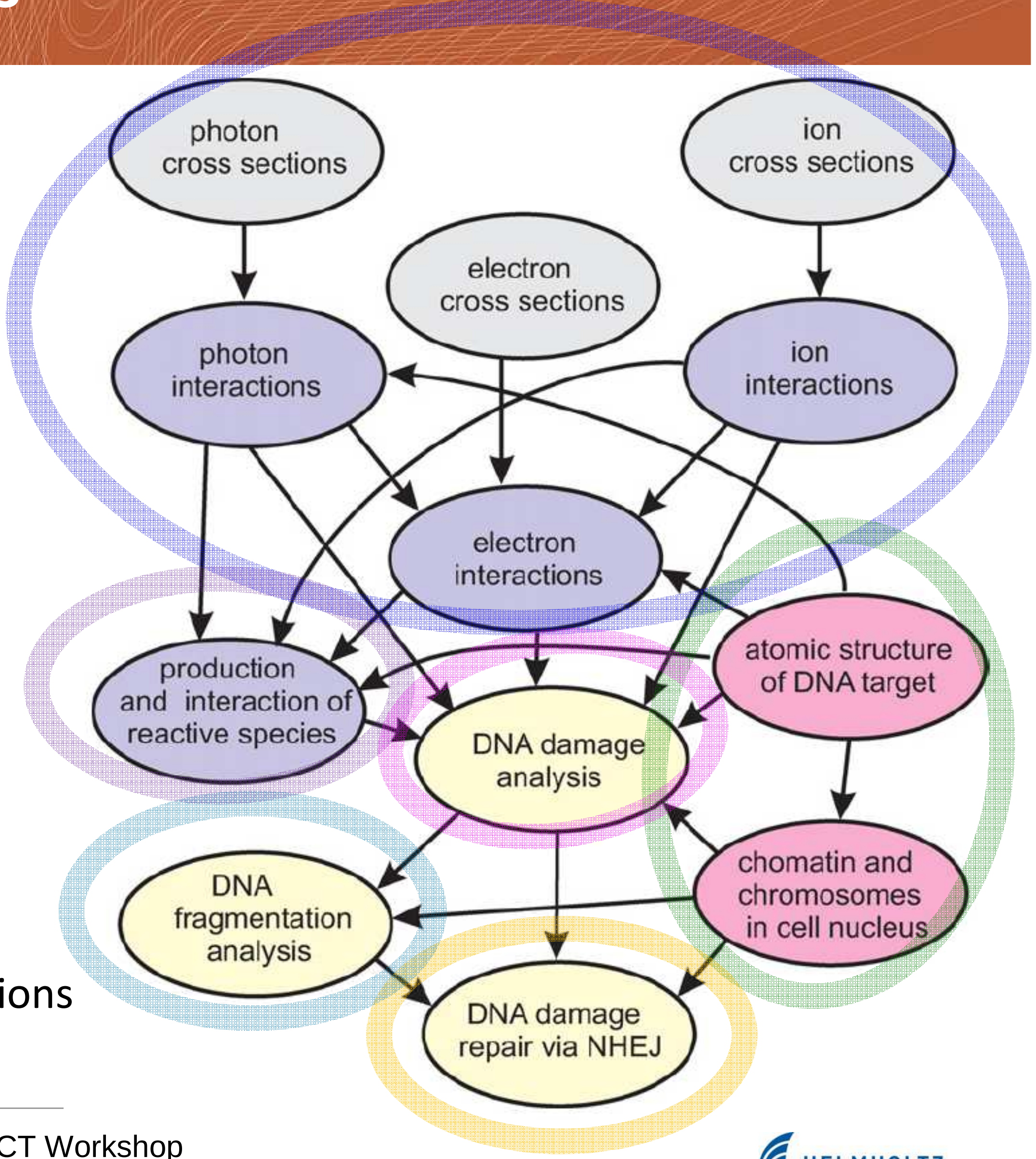
Track structure development during
pre-chemical and chemical stage

DNA target models for
biological effect calculation

Modelling of DNA damage:
SSB, DSB, base lesions, clusters

Analysis of dose-dependent DNA
fragmentation

Modelling of DNA damage repair and
formation of chromosomal aberrations



Physico-chemical and chemical stage in PARTRAC: OH radicals are completely consumed in High-LET tracks

physical stage → $10^{-15} – 10^{-12}$ s → physiochemical → $10^{-12} – 10^{-6}$ s → chemical stage

- relax
- auto-ionize
- dissociate

- diffuse
- react

e_{sub}, H_2O^+
A^1B_1, B^1A_1
Ryd, db, de

e_{aq}, •OH, H•, H_2
H_3O^+, OH^- , H_2O_2

diffusion coefficients D

reaction rate constants k

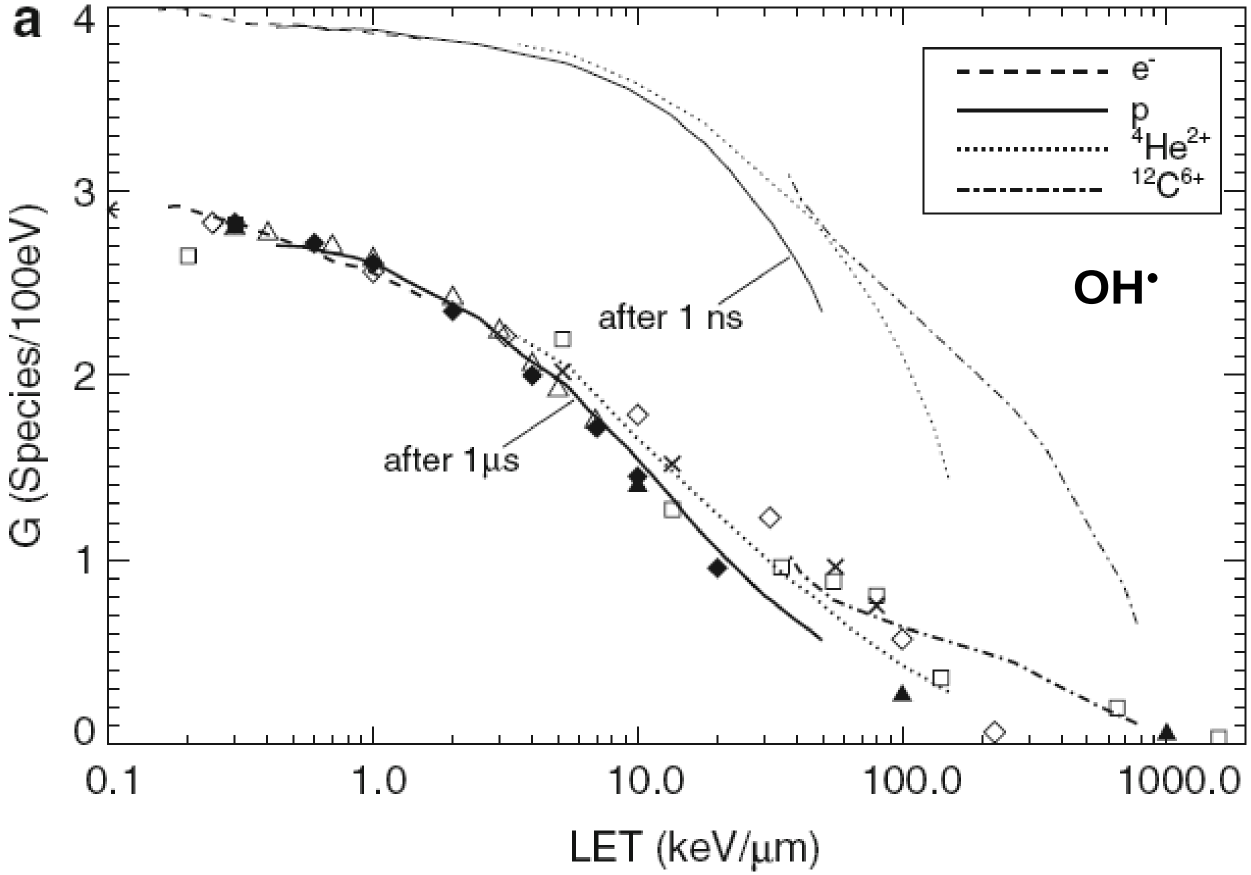
$H_2O^+ + H_2O \rightarrow H_3O^+ + \bullet OH$

A^1B_1	→	H_2O + DE	35%
		H• + •OH	65%
B^1A_1	→	H_2O + DE	30%
		$H_3O^+ + \bullet OH + e_{aq}$	55%
		$H_2 + \bullet OH + \bullet OH$	15%
Ryd,db	→	H_2O + DE	50%
		$H_3O^+ + \bullet OH + e_{aq}$	50%

$e_{aq} + e_{aq} + 2H_2O \rightarrow H_2 + 2OH^-$
$e_{aq} + \bullet OH \rightarrow OH^-$
$e_{aq} + H\bullet + H_2O \rightarrow H_2 + OH^-$
$e_{aq} + H_3O^+ \rightarrow H\bullet + H_2O$
$e_{aq} + H_2O_2 \rightarrow OH^- + \bullet OH$
$\bullet OH + \bullet OH \rightarrow H_2O_2$
$\bullet OH + H\bullet \rightarrow H_2O$
$H\bullet + H\bullet \rightarrow H_2$
$H_3O^+ + OH^- \rightarrow 2H_2O$

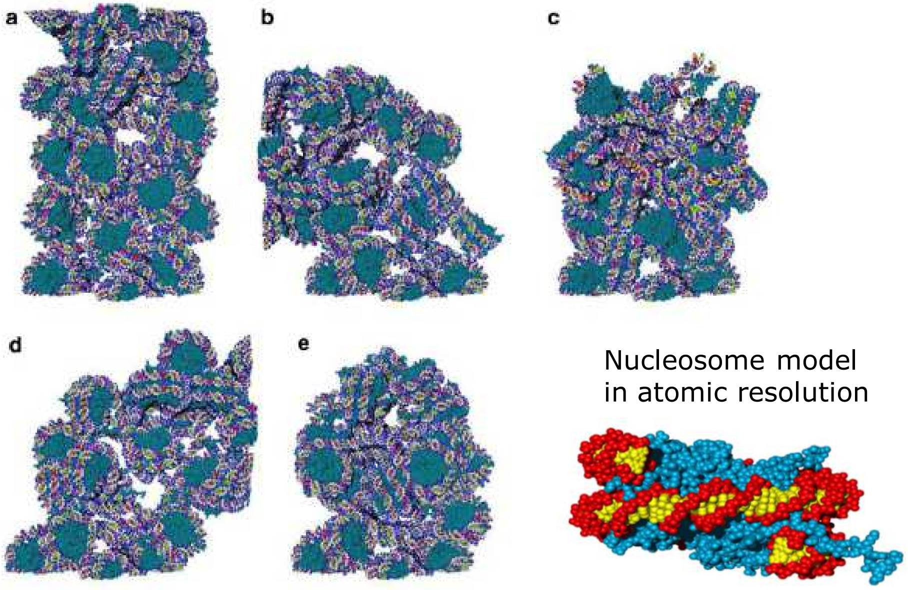
LET dependent yield of OH˙ during (after 1 ns) and at the end of the chemical stage (after 1 µs) without additional scavengers

Kreipl et al. 2009 Radiat Environ Biophys 48:11



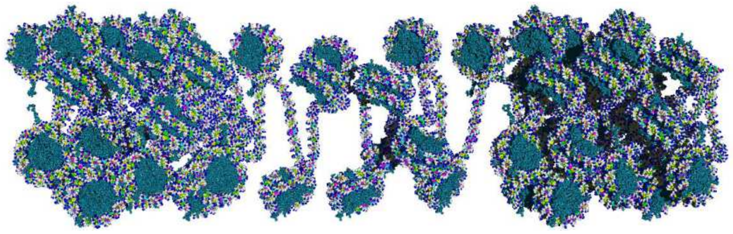
PARTRAC: Modelling of chromatin (nuclear DNA) in G0/G1 phase

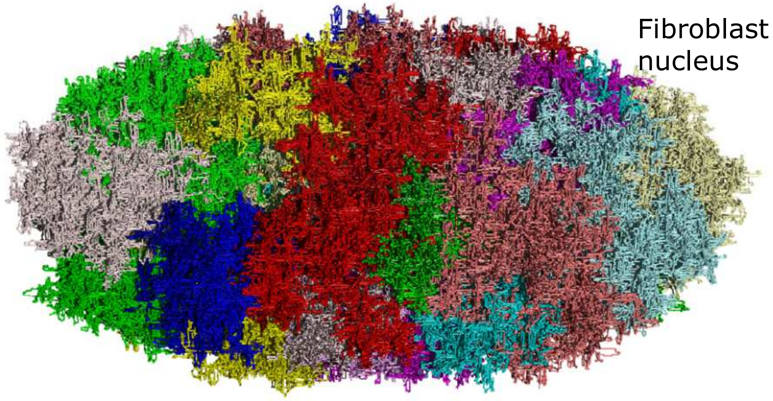
- DNA double-helix
- Nucleosome
- Chromatin fibre
- Chromatin loops, domains, chromosome territories: SCD model – KIP Heidelberg
- Hetero-/euchromatin structure and regions in nucleus
- Centromeres & chromosome origin of joined fragments for CA analysis



Nucleosome model in atomic resolution

Chromatin fibre elements (boxes: straight & bent) building up the random-walk fibre model

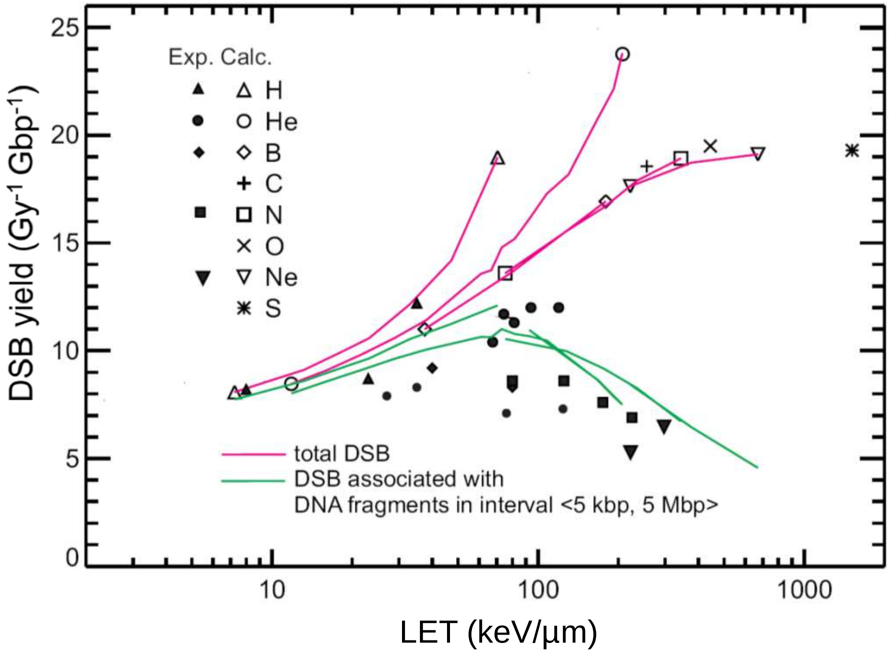




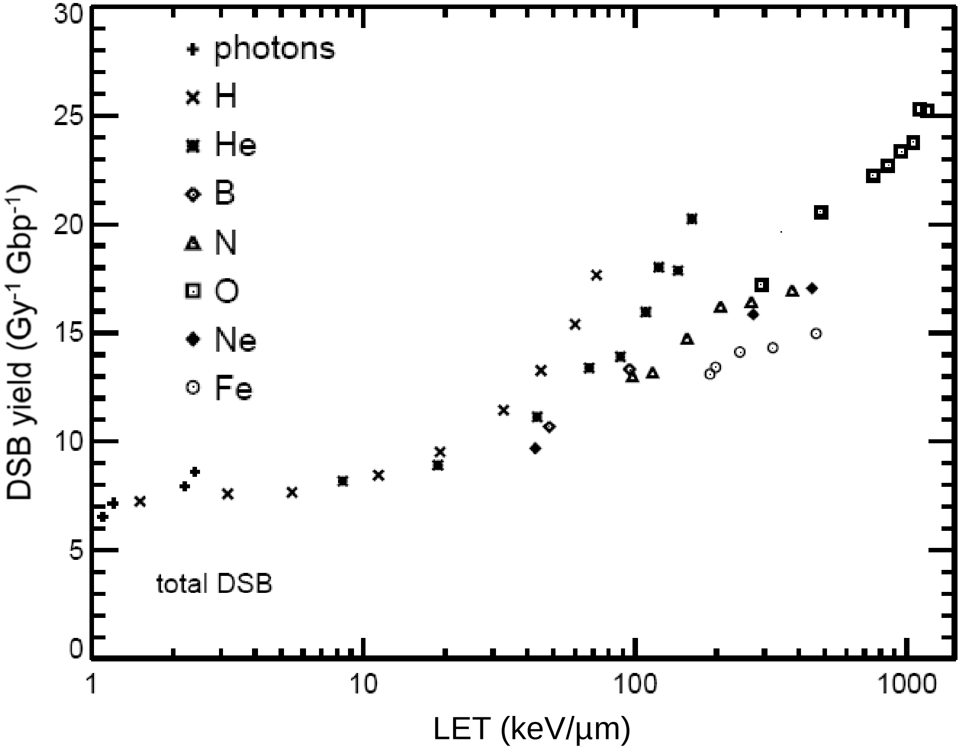
Fibroblast nucleus

DSB induction in experiment and PARTRAC calculation: neglection of small fragments counteracts LET dependence

Friedland et al 2006 Radiat Prot Dosim 122:116
Experimental results: Frankenberg (H, He),
Rydberg (He), Höglund (B, N, He)

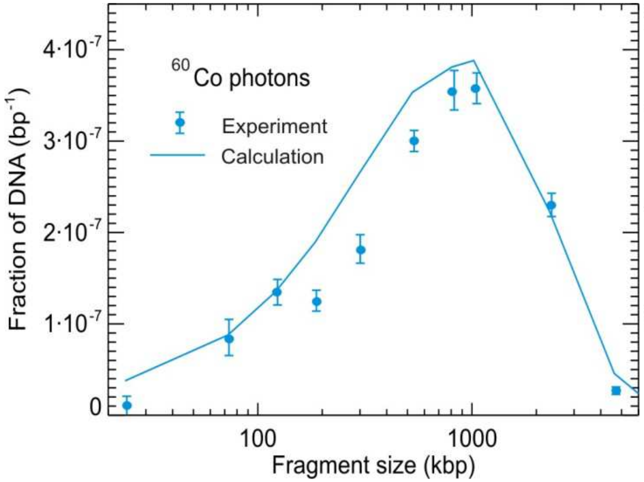


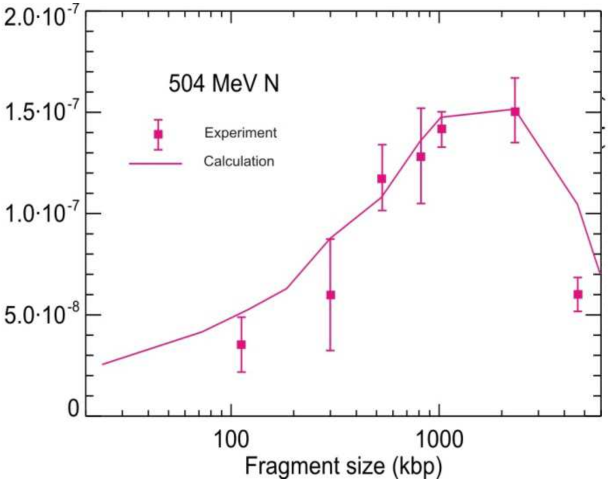
Friedland 2012 unpublished data

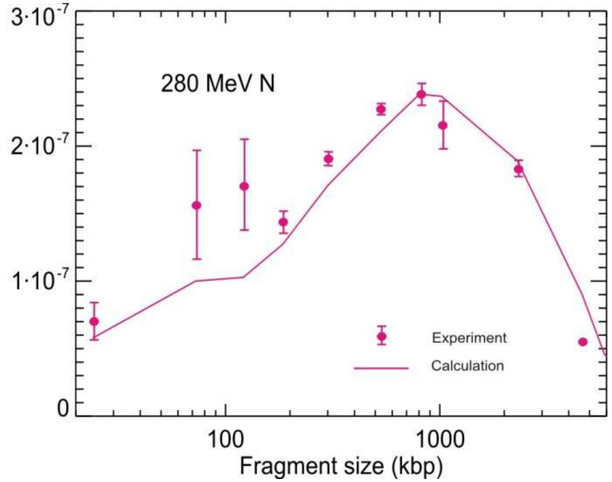


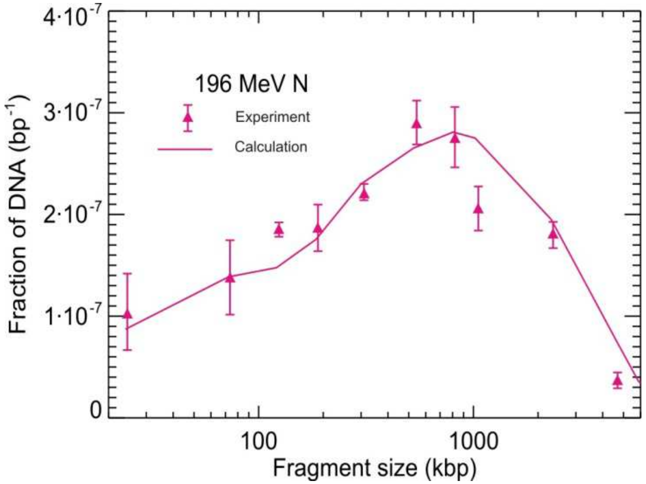
With increasing LET measured and calculated DNA fragment distributions after ^{60}Co γ- and N ion irradiation show increasing non-random breakage

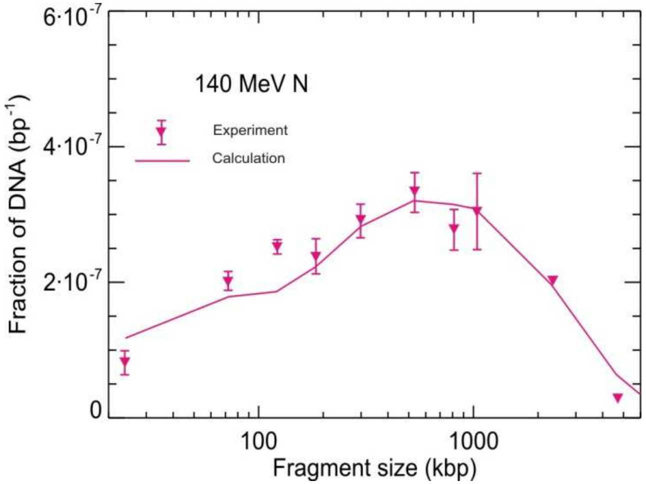
Friedland et al 2011 Mutat Res 711:28; Exp.: Höglund et al 2001 Radiat Res 155:818









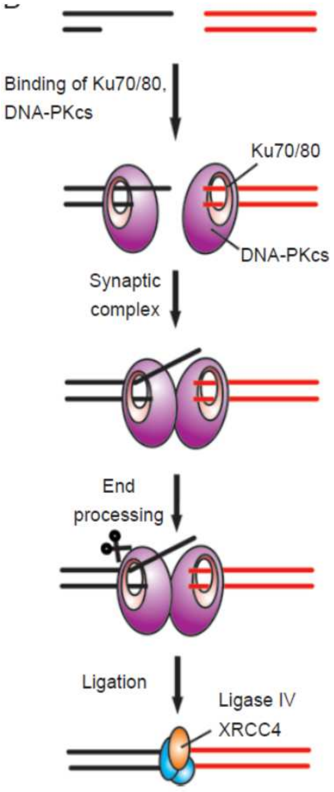


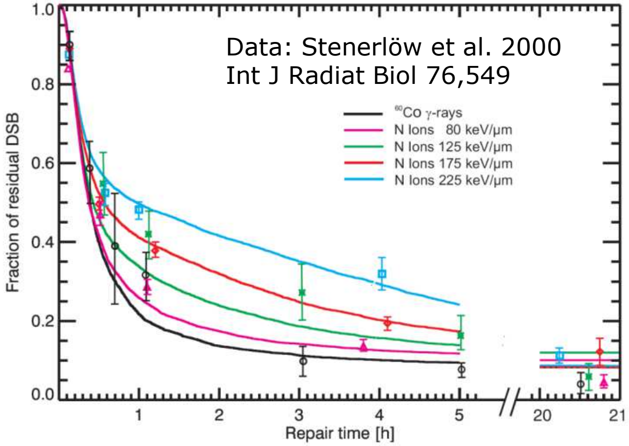
PARTRAC chromosome aberration model

- Bottom-up, 'ab initio' approach
- Spatial & temporal aspects of repair via NHEJ & aberration kinetics

- **Temporal aspects:** DSB repair kinetics

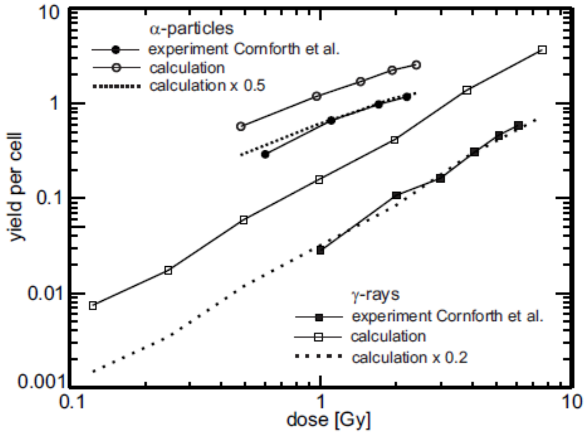
Weterings & Chen
2008 Cell Res 18,114



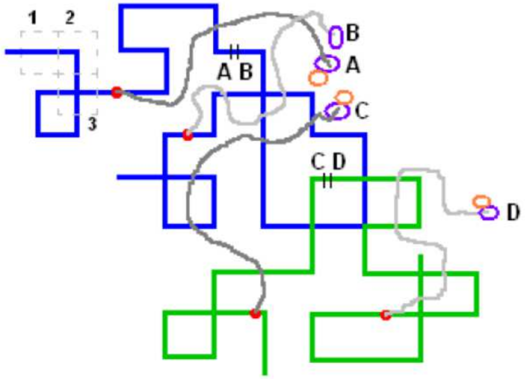


Data: Stenerlöw et al. 2000
Int J Radiat Biol 76,549

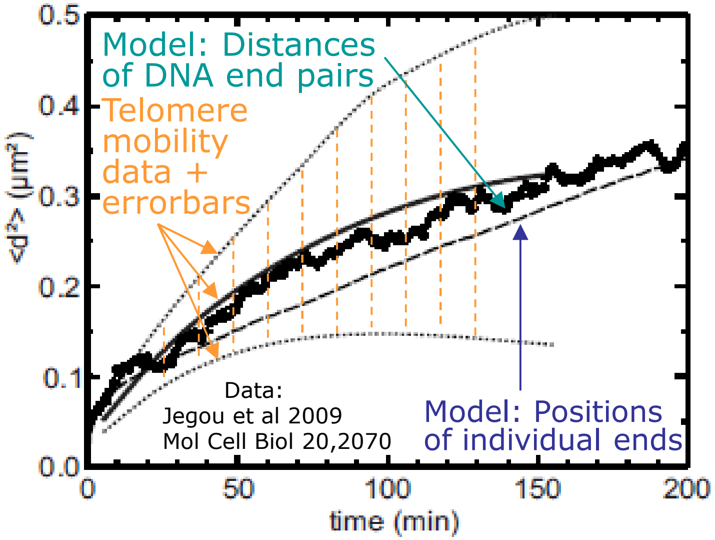
Result: yield of dicentrics



- **Spatial aspects:** mobility of DNA ends
  - Semi-free movement of chromatin fiber



  - Reproduces apparent mobility of chromatin



Model: Distances of DNA end pairs

Telomere mobility data + errorbars

Data:
Jegou et al 2009
Mol Cell Biol 20,2070

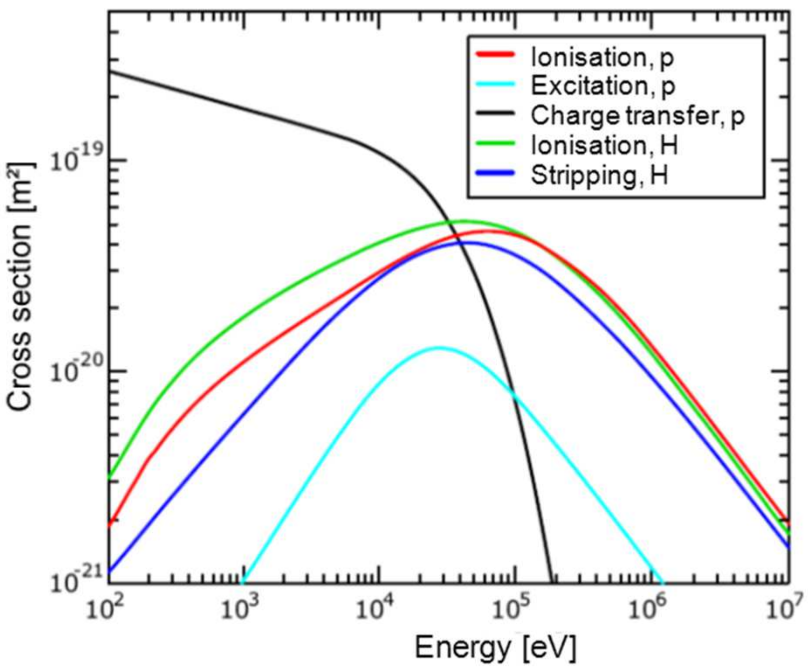
Model: Positions of individual ends

PARTRAC: Running projects and cooperations

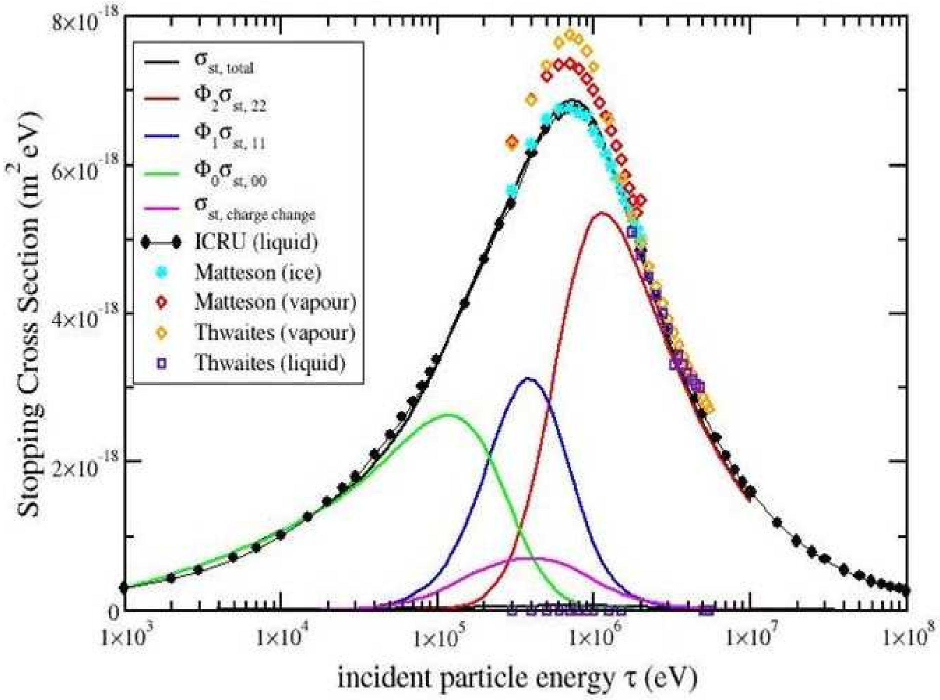
- **DoReMi task ‚INITIUM‘: Cross sections and DNA damage for slow light ions (C, N, O, P, Ca)**
- DoReMi task ‚INITIUM‘: Radiation effects on mitochondria
- German KVSF Project ‚LET-Verbund‘ (FKZ 02NUK031) :
  Radiation effects of focused bunches of low-LET ions (e.g. 117 20 MeV-protons)
  compared to single high-LET ions (e.g. 55 MeV C ion)
  and to quasi-homogeneously distributed low-LET ions
- Dose enhancement and cellular radiation effects due to gold nanoparticles (Wenzhang Xie, Tsinghua University, Beijing)
- Relation between cellular radiation effects and ionization cluster size distribution (Ana Belchior, IST-ID, Lisbon)

Cross sections for H and He in PARTRAC (Dingfelder)

Cross sections for proton and neutral hydrogen interactions in liquid water
(log scale)
Dingfelder et al 2000 Radiat Phys Chem 59:255



Stopping cross sections for charge state dependent interactions of He in liquid water
(linear scale)
Friedland et al 2005 Radiat Phys Chem 72:279



Cross sections for ions heavier than He are scaled from proton data according to the Barkas formula

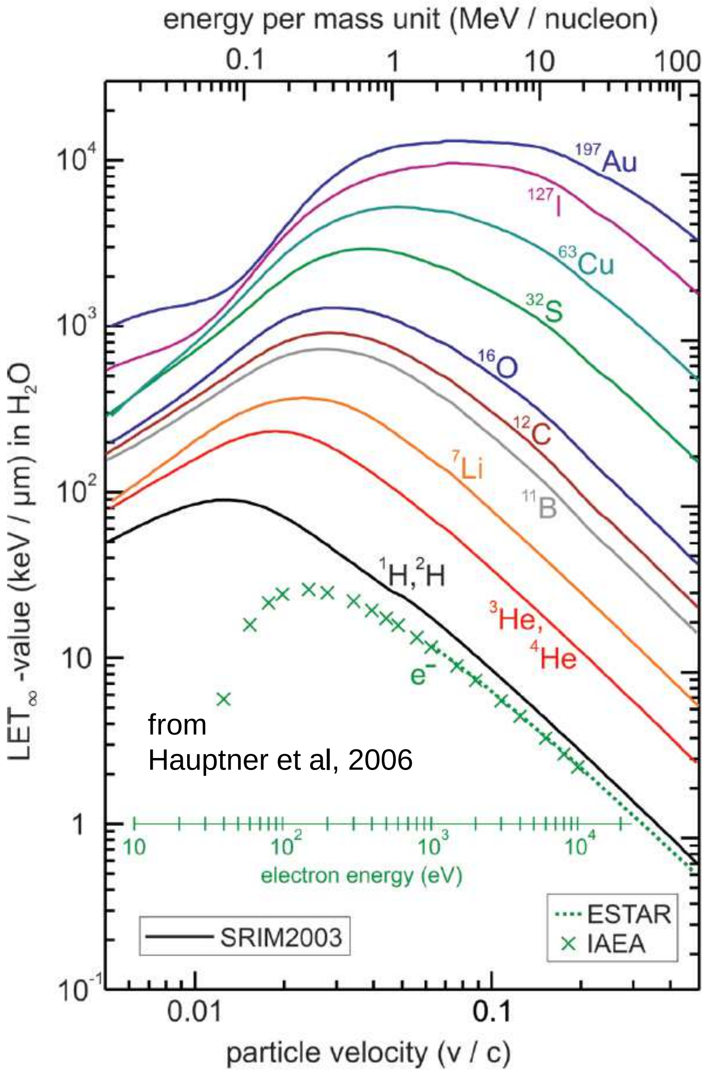
Cross sections of ions with high energy (many MeV/nucleon) scale with Z²
on the basis of specific energy (velocity)

$\sigma_Z(v) = \sigma_p(v) \cdot Z^2$

$\sigma_Z(E) = \sigma_p(E/A) \cdot Z^2$

This scaling law has been extended down to around 1 MeV/nucleon by replacing Z with an effective charge Z_{eff} given by the so-called Barkas formula

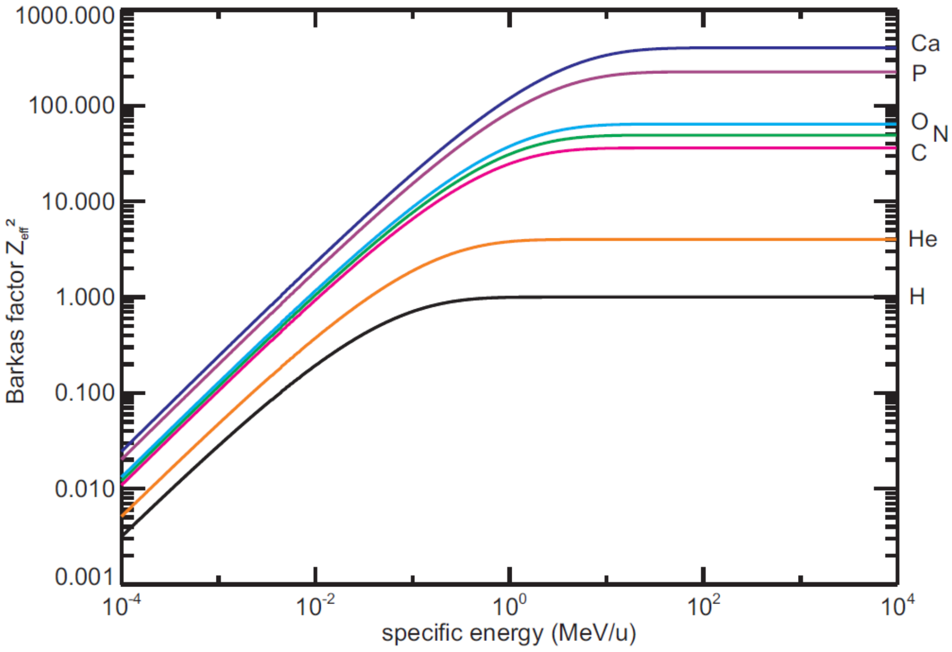
$$\boxed{\begin{aligned} &\sigma_Z(v) = \sigma_p(v) \cdot Z^2_{eff}(v) \\ &Z_{eff}(v) = Z \cdot (1-\exp(-125(v/c) \cdot Z^{-2/3})) \end{aligned}}$$



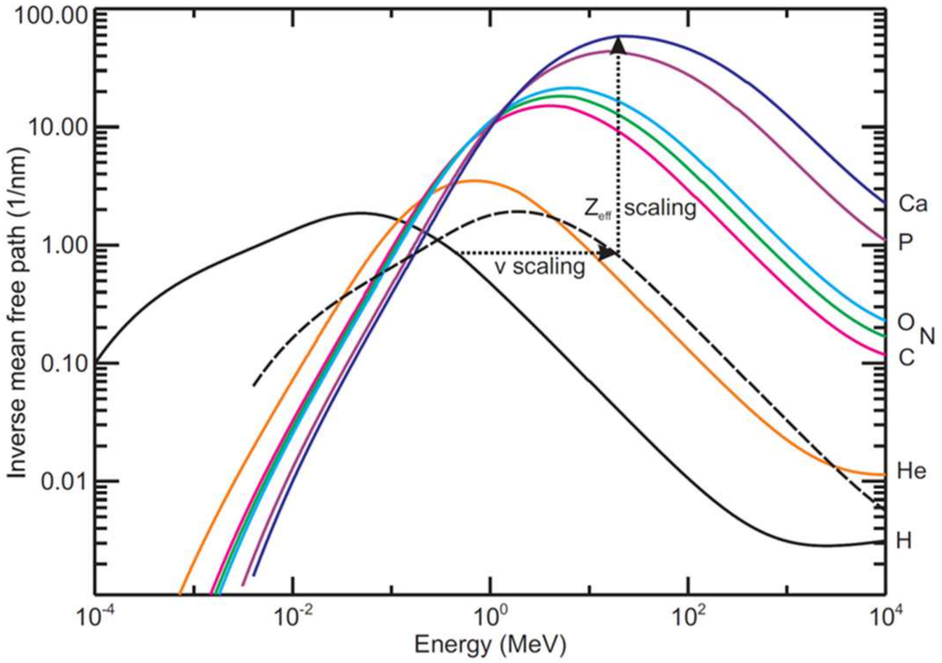
from
Hauptner et al, 2006

Z_{eff}^2 according to the Barkas formula for light ions obviously underestimates cross sections at low energies

Barkas factor for light ions as function of specific energy



Resulting inverse mean free path (macroscopic cross section) for light ions as function of energy



Ion cross sections applicable for ‘full’ slowing down with the objective: a pragmatic solution for track simulations (I)

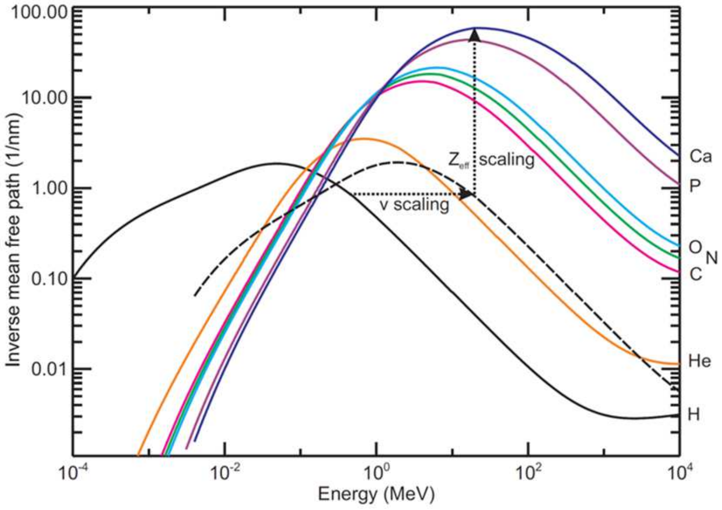
Idea: Scaling procedure should give reasonable results when applied to hydrogen/protons

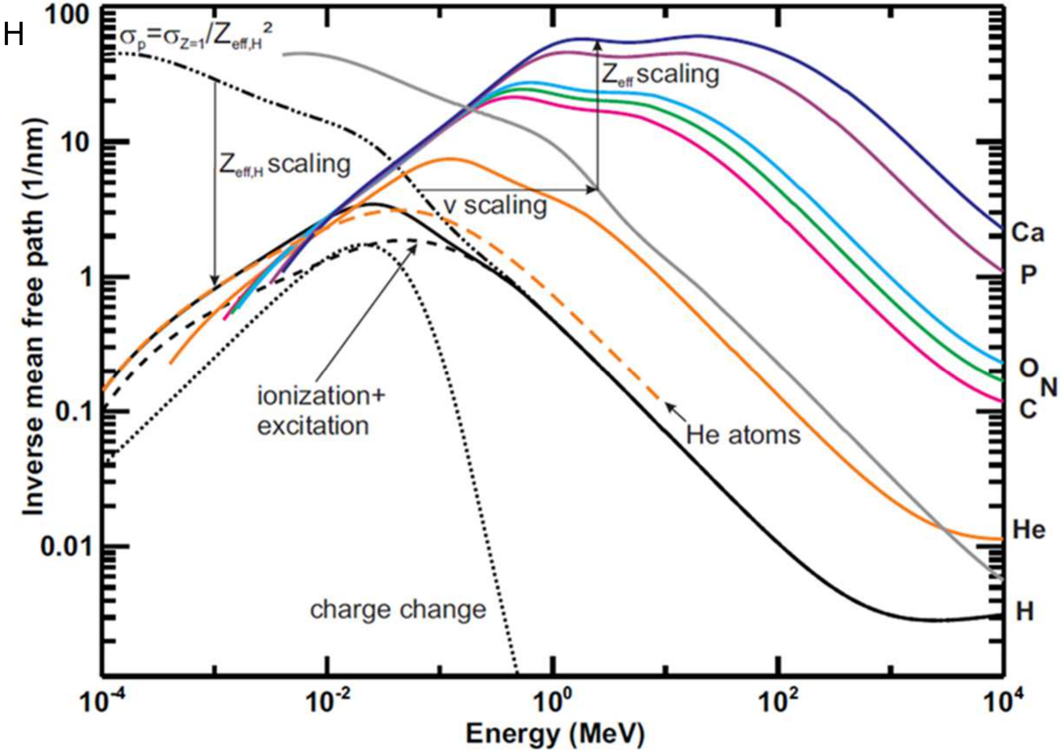
Two views: Scaling *modified cross sections* according to Barkas or
adopting a *modified scaling function* for proton/hydrogen cross sections

Modified cross sections for scaling corresponding to the ‚idea‘ are (dash-dot-dot-dotted)

$$\sigma^*_p=(\sigma_{H+}\cdot Z_{eff,H}+\sigma_{H0}\cdot(1-Z_{eff,H}))/Z^2_{eff,H}$$

where $Z_{eff,H}$ is taken as probability
for a hydrogen being ionized





Ion cross sections applicable for ‘full’ slowing down with the objective: a pragmatic solution for track simulations (II)

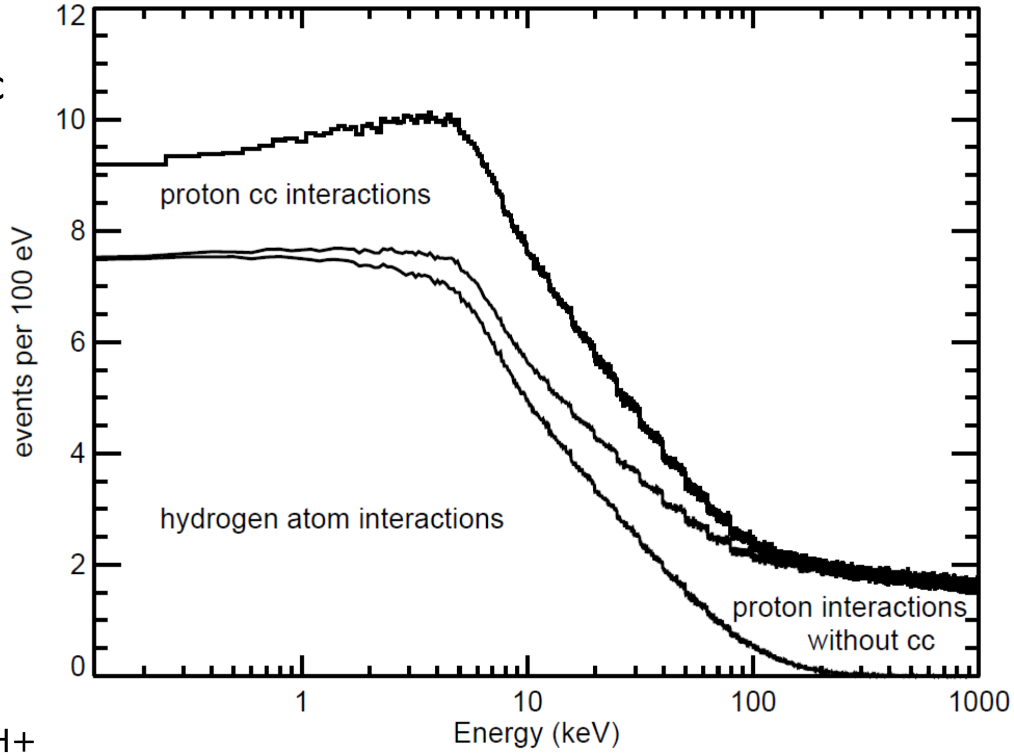
Modified cross sections for scaling are $\sigma^*_p=(\sigma_{H+}\cdot Z_{eff,H}+\sigma_{H0}\cdot(1-Z_{eff,H}))/Z^2_{eff,H}$ where $Z_{eff,H}$ is taken as probability for a hydrogen being ionized

In a refined calculation the energy dependent fractions p_{H+} of protons from full Monte Carlo slowing down calculations are used $\sigma^*_p=(\sigma_{H+}\cdot p_{H+}+\sigma_{H0}\cdot(1-p_{H+}))/Z^2_{eff,H}$

At low energies charge changing processes still contribute considerably to the inelastic interactions

Typical process is the electron loss of hydrogen with immediately followed by electron pick-up by the proton

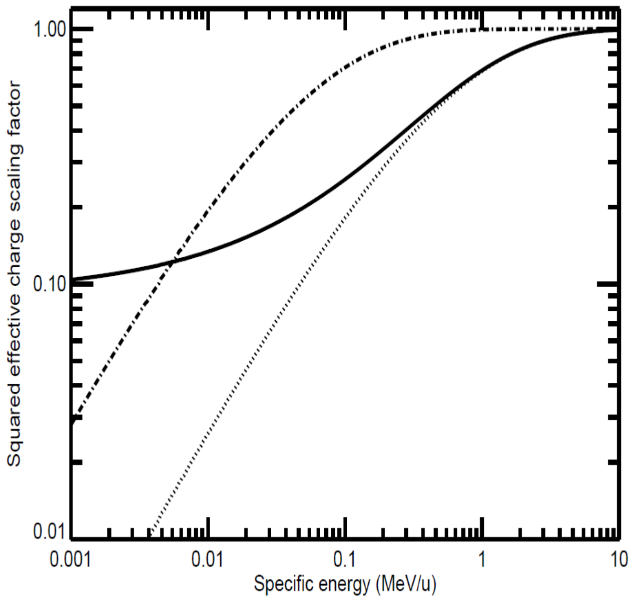
Both processes are considered as single ionization event with electron emission in forward direction with an energy corresponding to the speed of the ion for each charge change event of hydrogen and neglecting cc of protons in σ_{H+} and p_{H+}



Ion cross sections applicable for ‘full’ slowing down with the objective: a pragmatic solution for track simulations (III)

Two views: Scaling *modified cross sections* according to Barkas or adopting a *modified scaling function* for proton/hydrogen cross sections

The *modified scaling function* for ions with charge Z is given by the relation between Barkas functions for Z and for Z=1; for higher energies it approaches the usual Barkas function



Effective-charge factor for carbon with hydrogen in charge equilibrium taken as reference ion

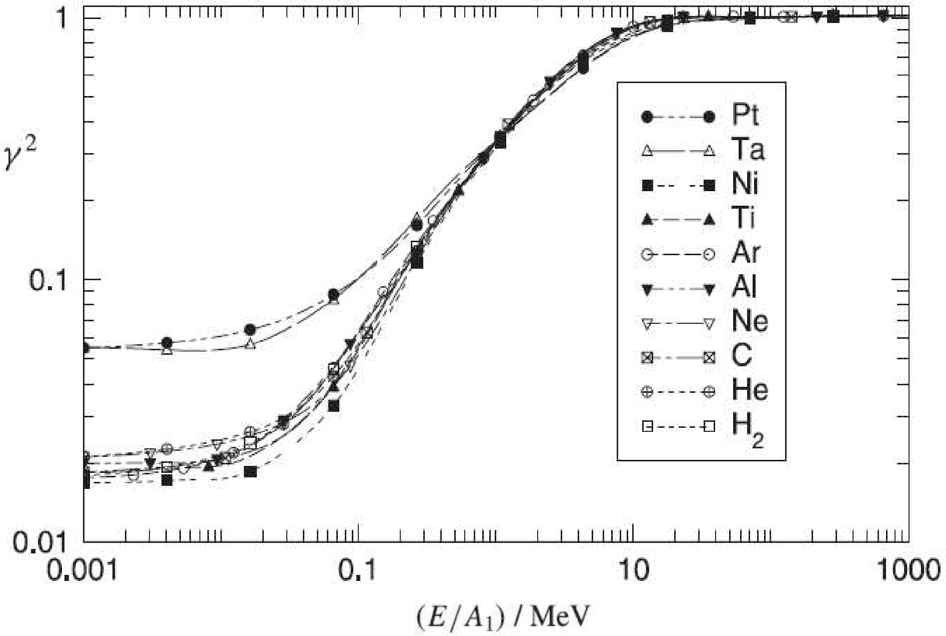
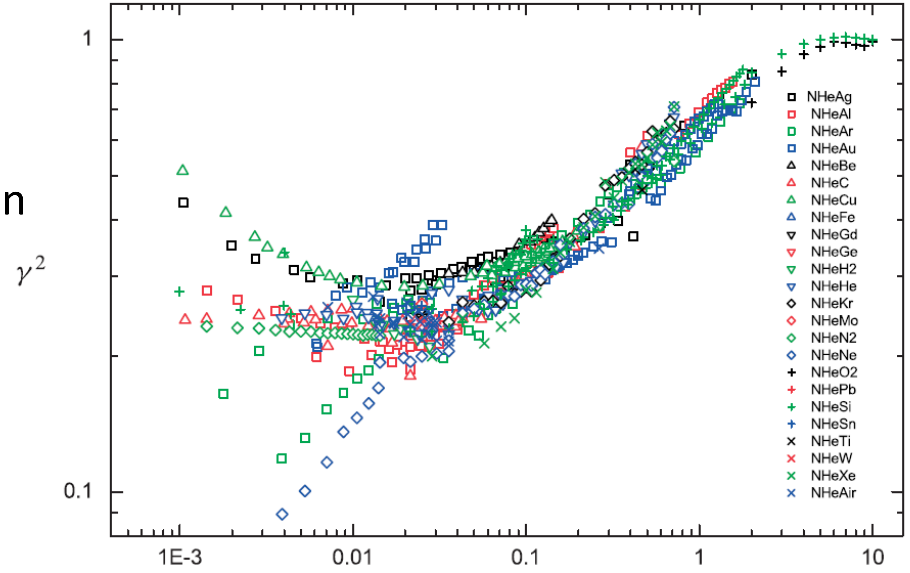


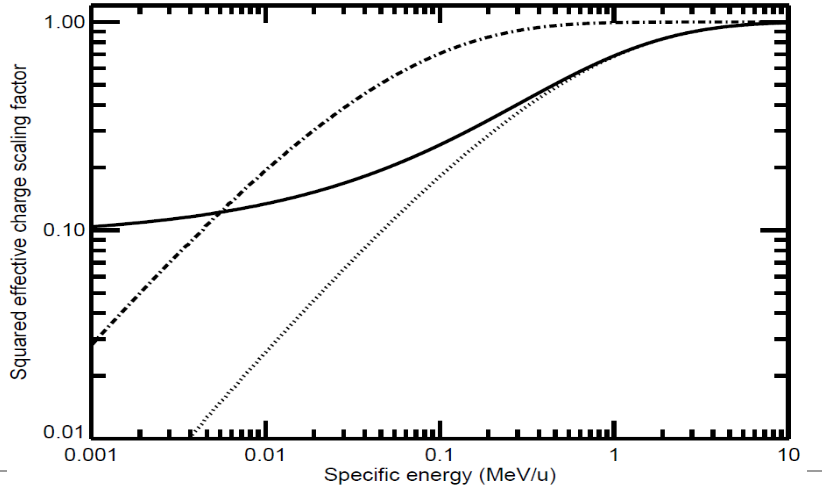
Figure 5.3. Effective-charge factor γ^2, Eq. (5.1), for argon with hydrogen in charge equilibrium taken as reference ion calculated from PASS.

Ion cross sections applicable for 'full' slowing down with the objective: a pragmatic solution for track simulations (IV)

The *modified scaling function* for ions with charge Z is given by the relation between Barkas functions for Z and for Z=1; for higher energies it approaches the usual Barkas function

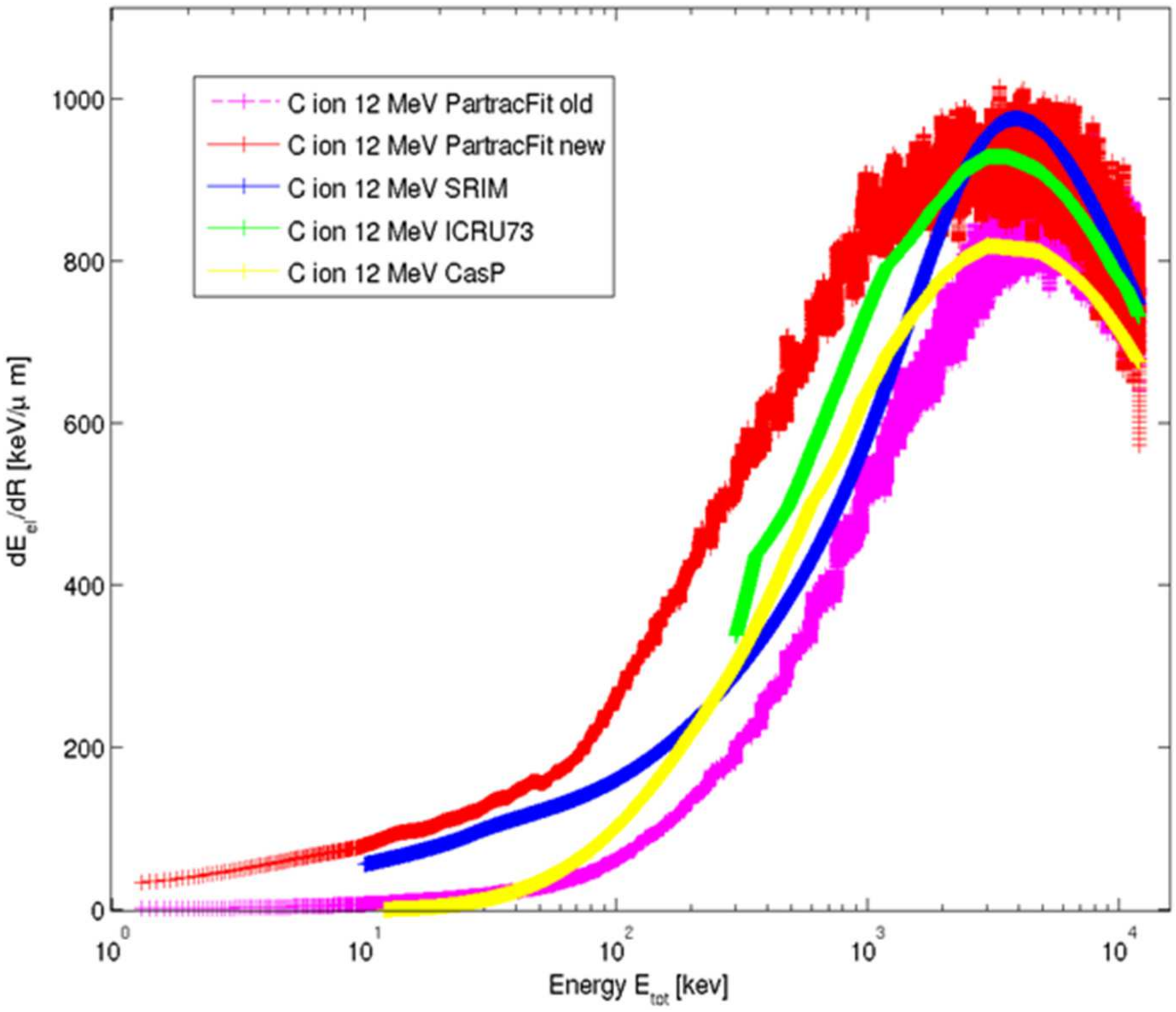


Effective-charge factor extracted from measured stopping powers for **nitrogen** with **helium** in charge equilibrium taken as reference ion (ICRU73), Data compilation by Paul

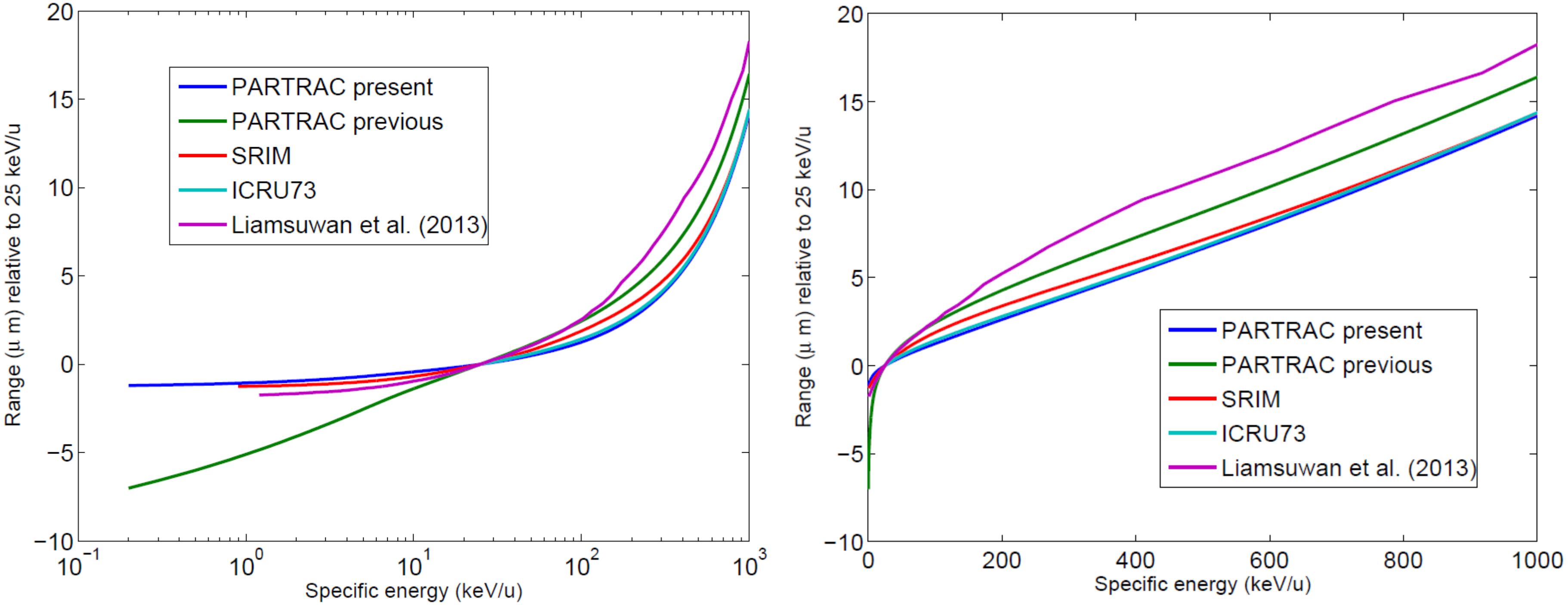


Effective-charge factor for **carbon** with **hydrogen** in charge equilibrium taken as reference ion

LET of carbon ions below 1 MeV/u according to PARTRAC, SRIM, ICRU73 and CasP

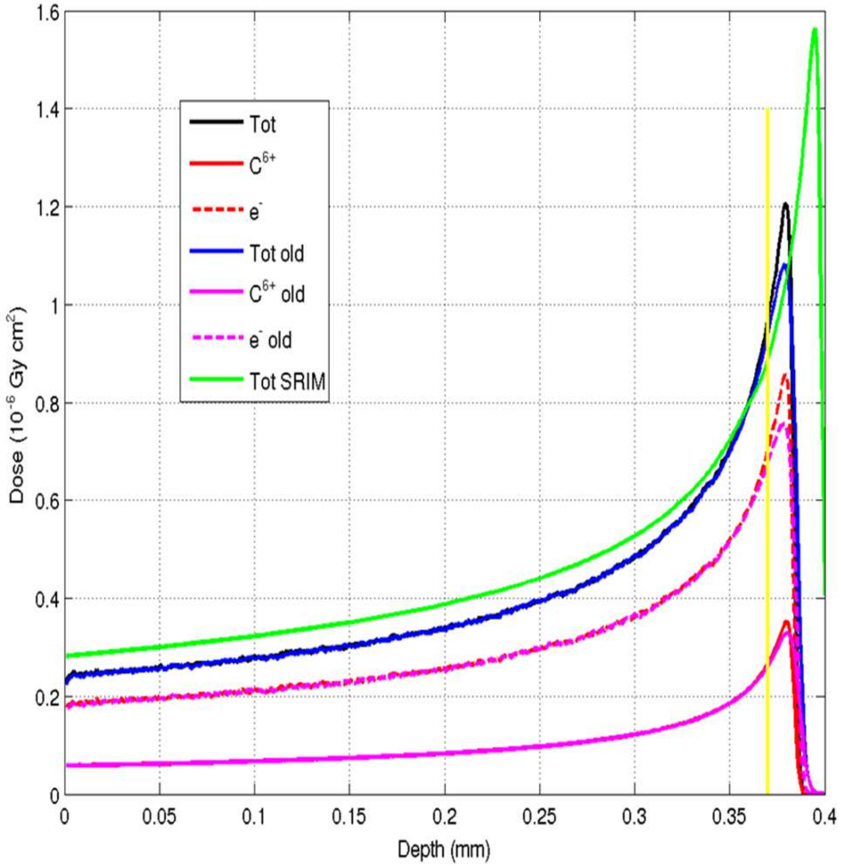


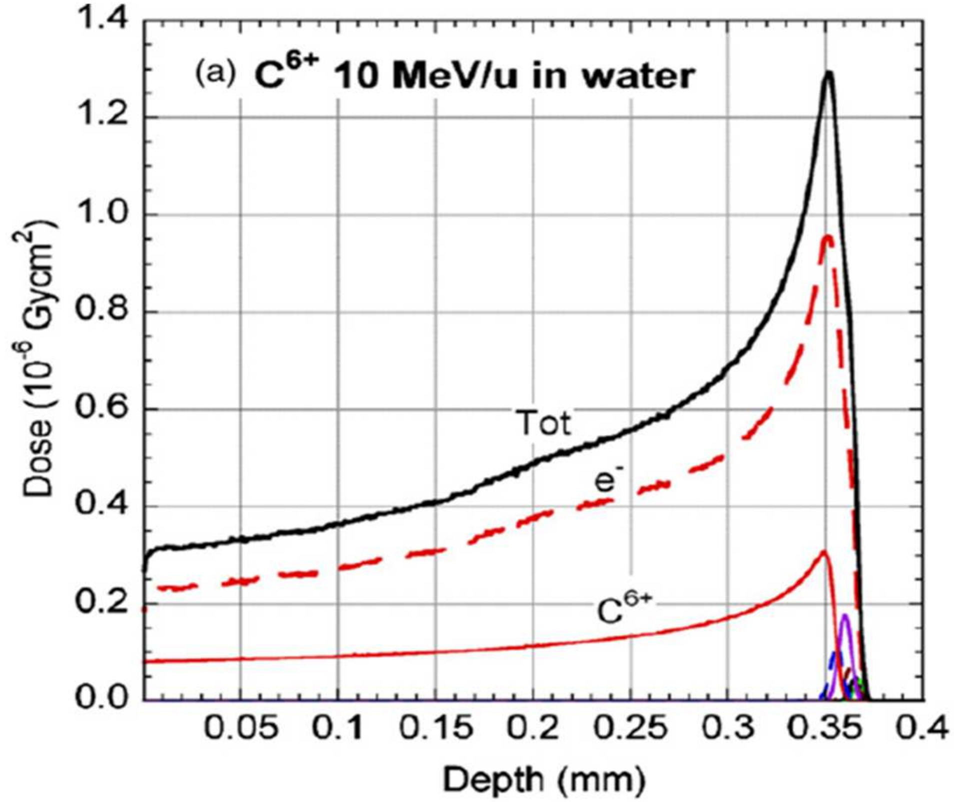
Range of carbon ions below 1 MeV/u according to PARTRAC, SRIM, ICRU73 and KURBUC_carbon on log and linear energy scale



Area integrated dose for C ions (10 MeV/u) according to PARTRAC (left) and KURBUC_carbon* (right)

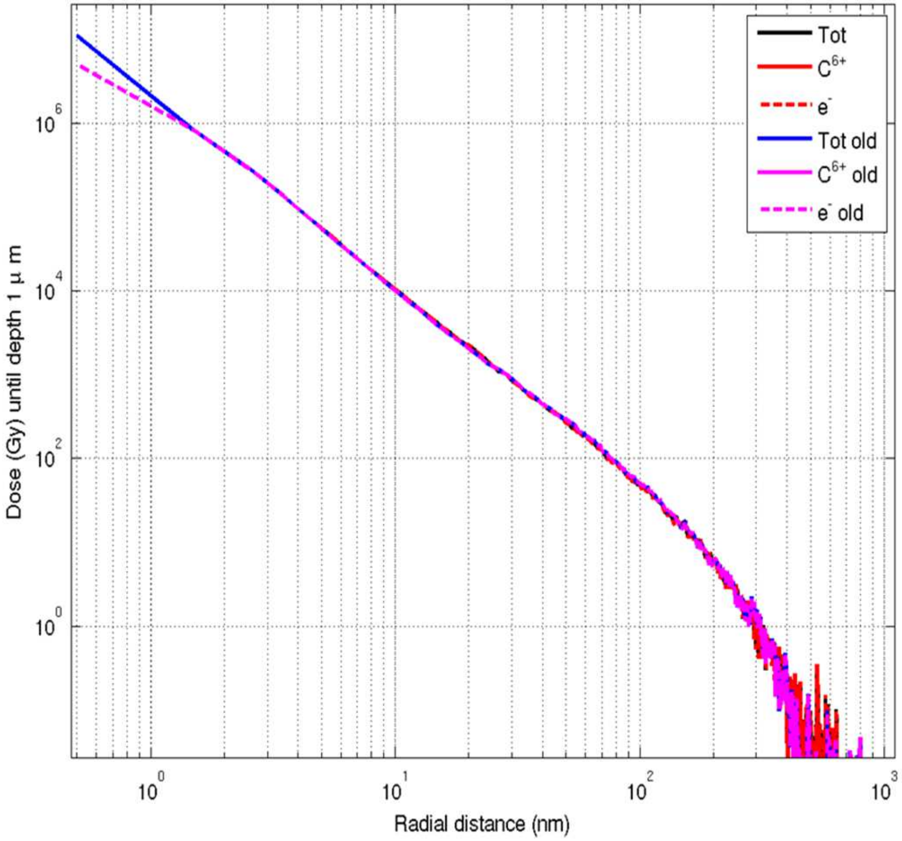
*Liamsuwan et al 2013 Phys Med Biol 58:673

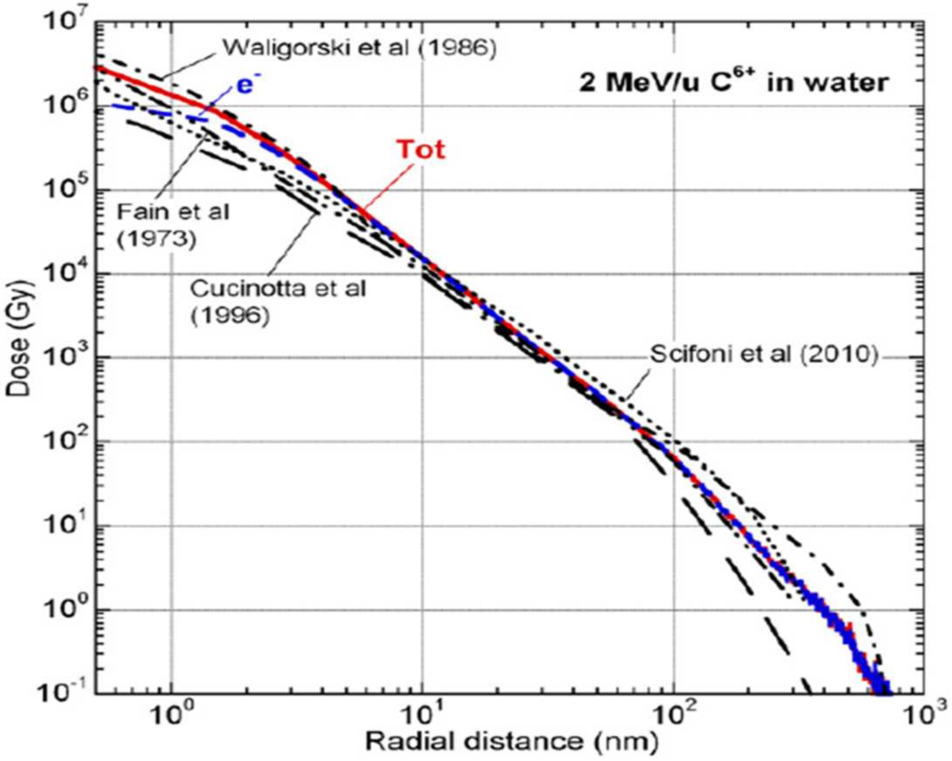




Radial dose distribution for C ions (2 MeV/u) according to PARTRAC (left), KURBUC_carbon* and other model calculations (right)

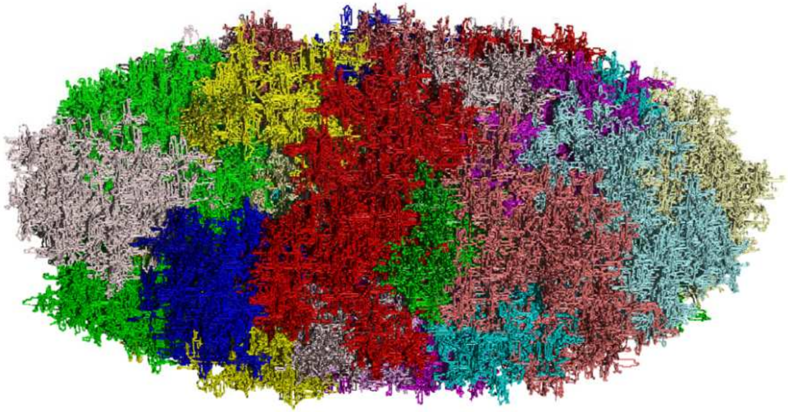
*Liamsuwan et al 2013 Phys Med Biol 58:673





Setup for DNA damage calculations

Carbon ions with initial energies 2, 4, 6, 8, 10, 12, 24, 50, 100, 200, 400, 800 MeV



started 3 µm below central layer of an
ellipsoidal fibroblast cell
(20 µm × 11 µm × 5.4 µm)

irradiated 10 × with fluence $1/\mu m^2$ (in each $1\ \mu m^2$ square 1 randomly located start point)

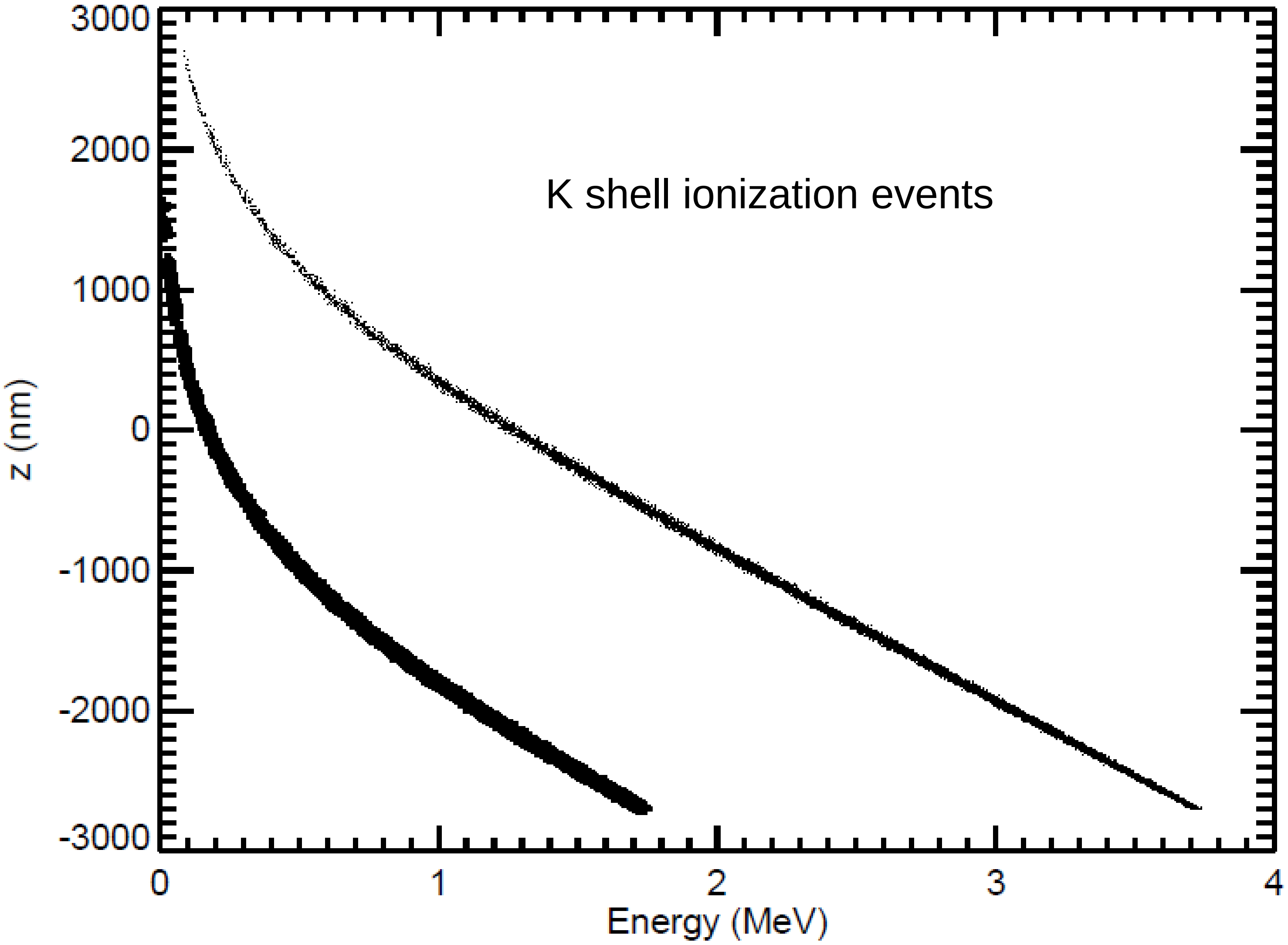
almost in z (short axis) direction with $0.99 < \cos z < 1.00$ (to avoid alignment with DNA structure at exactly $\cos z = 1$.

Energy deposition scored in **cuboid** target volume ($20\ \mu m \times 11\ \mu m \times 5.4\ \mu m = 1188\ \mu m^3$) surrounding the nucleus for dose determination

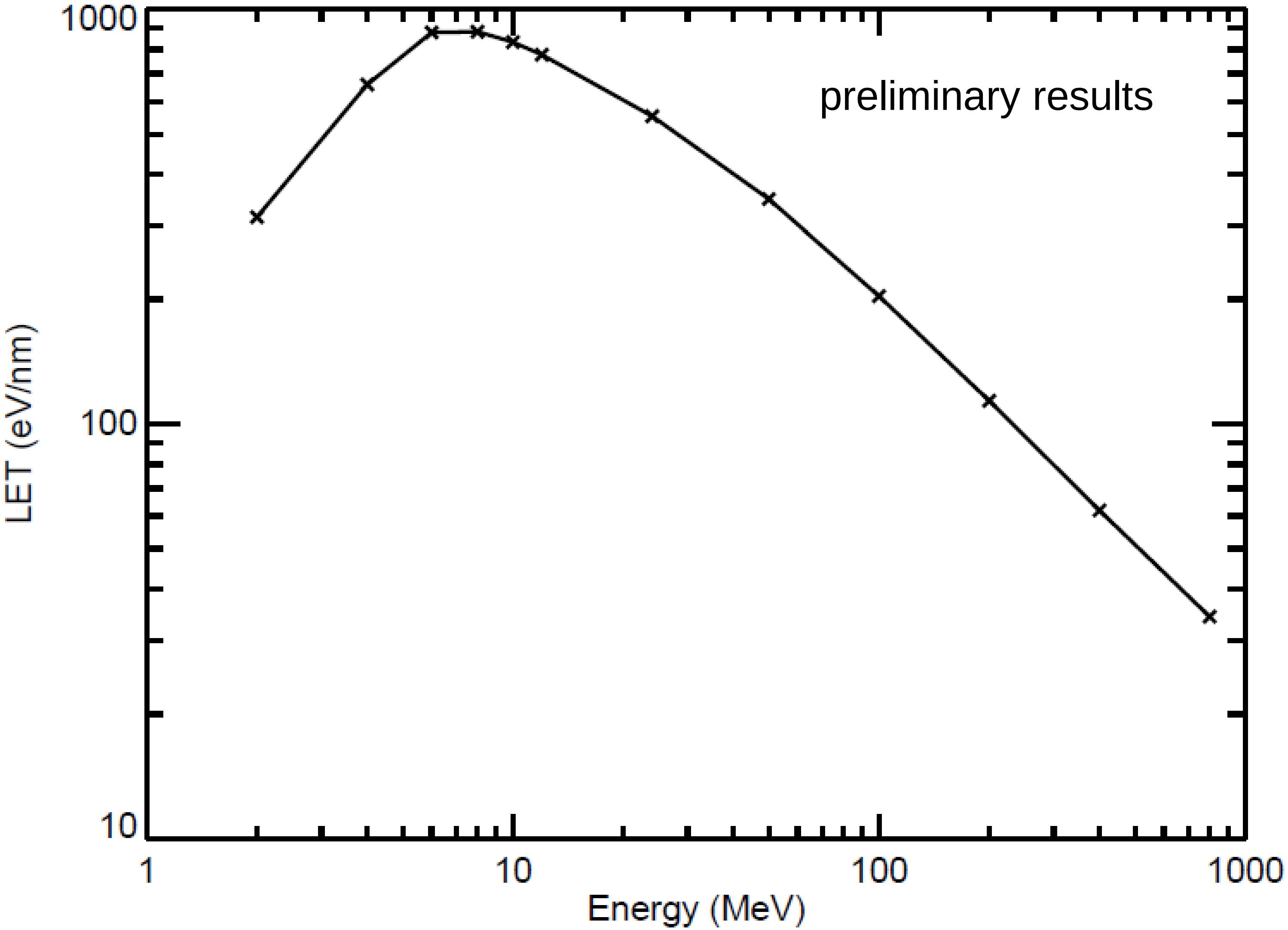
Mean LET calculated from relation between dose D, fluence ϕ and LET

$D\ [Gy] = 0.16 \times \phi\ [1/\mu m^2] \times LET\ [keV/\mu m]$

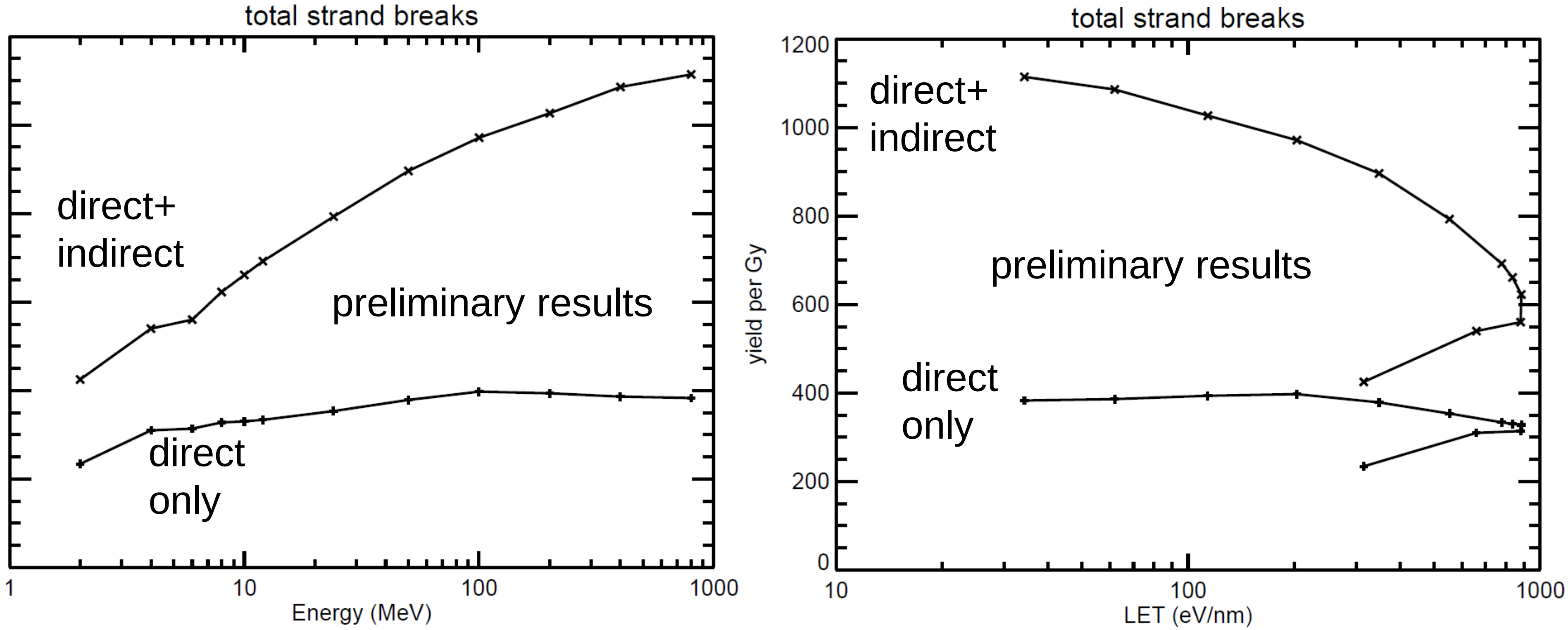
Kinetic energy of 2 and 4 MeV carbon ions when passing through the nucleus: inhomogeneous dose distribution



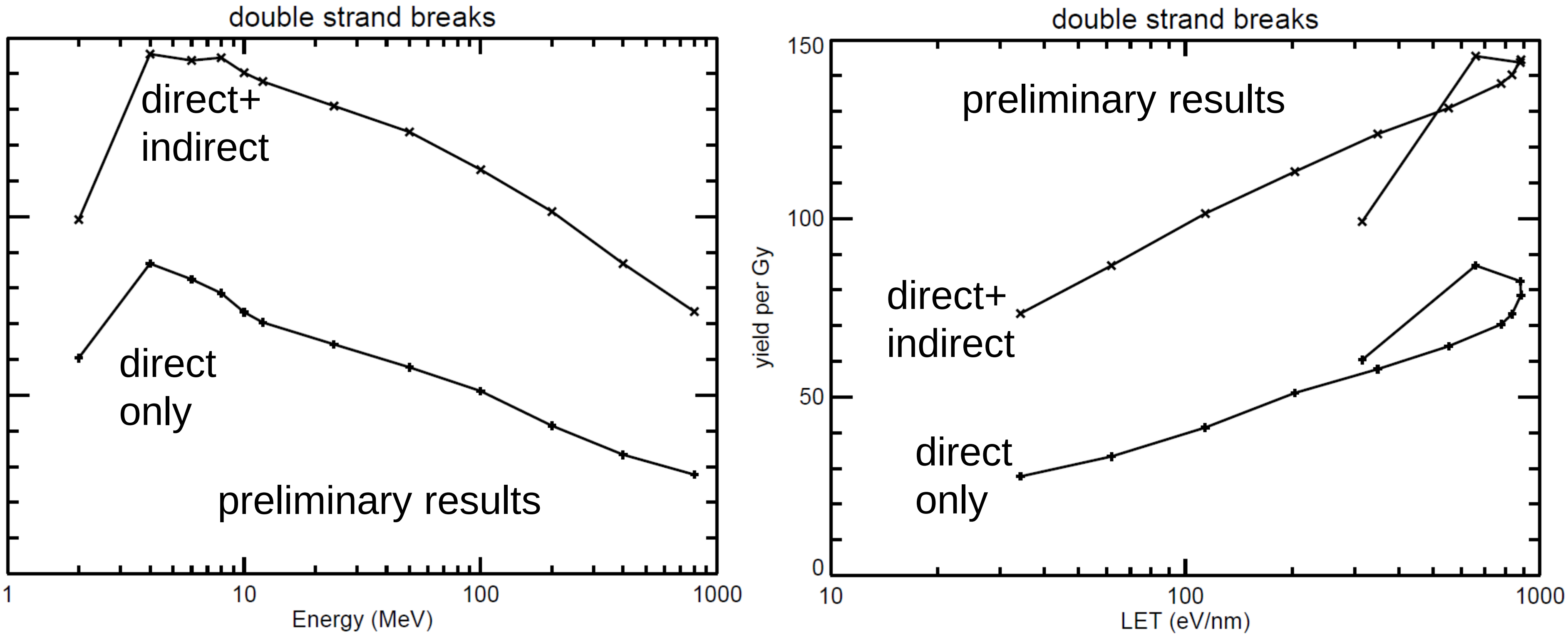
Relation between mean LET and initial carbon ion energy



Yield of total strand breaks (SSB + 2×DSB) per cell and Gy as function of initial energy and mean LET



Yield of double strand breaks per cell and Gy as function of initial energy and mean LET



Conclusion

A pragmatic solution for simulations of light ion tracks down to energies around and below the Bragg peak has been found by modified Barkas scaling of a mixture of proton and neutral hydrogen cross sections

The resulting characteristics of the track structures such as ranges, LET-values and radial dose distributions are in overall accord with other model calculations and literature data

Radiation damage at rather low energies is influenced by the dose inhomogeneity

This inhomogeneous irradiation may be responsible for the decrease in the yield of strand breaks due to direct effects with decreasing particle energy

Yields of DSB in relation to LET exhibit loops with higher yields at the same LET at lower energies after passing through the Bragg peak

Google‘s view on Helmholtz Zentrum München

Funding by DoReMi ‚INITIUM‘ is gratefully acknowledged

Thank you for your attention!