Dose modifiers with particle beams,

from track structure to treatment planning:

Oxygen effect and Nanoparticle sensitization

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IOL, NIRS, Chiba

Outline

Introduction: ion beams and dose modifiers

Oxygen effect

- OER modeling for particle therapy
- TPS implementation
- Experimental verification

Nanoparticle sensitization

- Track structure and cross sections analysis
- Protons and Nanoparticles dose enhancement

Summary & MiND challenges

Modifiers of radiation response

- in general a dose enhancement factor (DEF) is defined as a ratio of doses compared to normal conditions (n.c.)

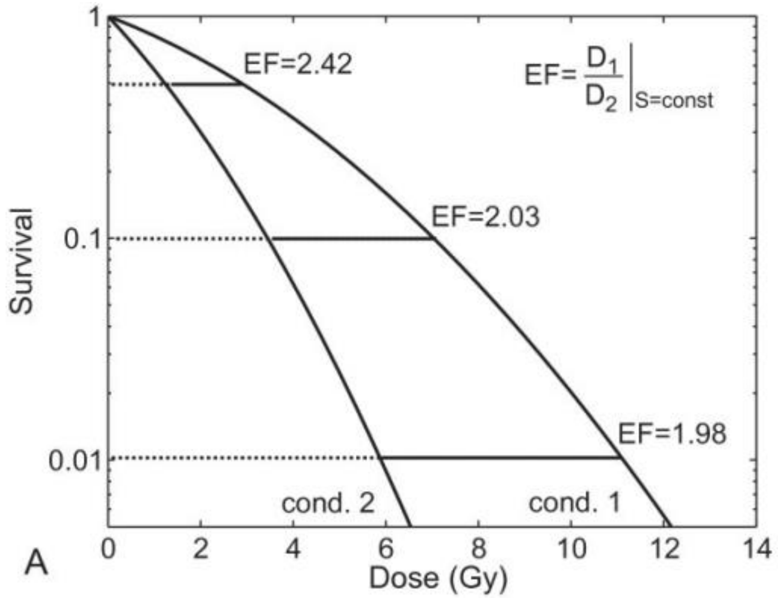
$$DEF = \left. \frac{D_{special\,conditions}}{D_{n.c.}} \right|_{same\,effect(S)} \quad ; \qquad DEF([C]) = \left. \frac{D([C])}{D_{n.c.}} \right|_{same\,effect(S)}$$

- instead of being a radiation quality related feature like RBE, it is more a *target* property.

- it is called a „*dose modifing factor*“ if independent on S (or D)

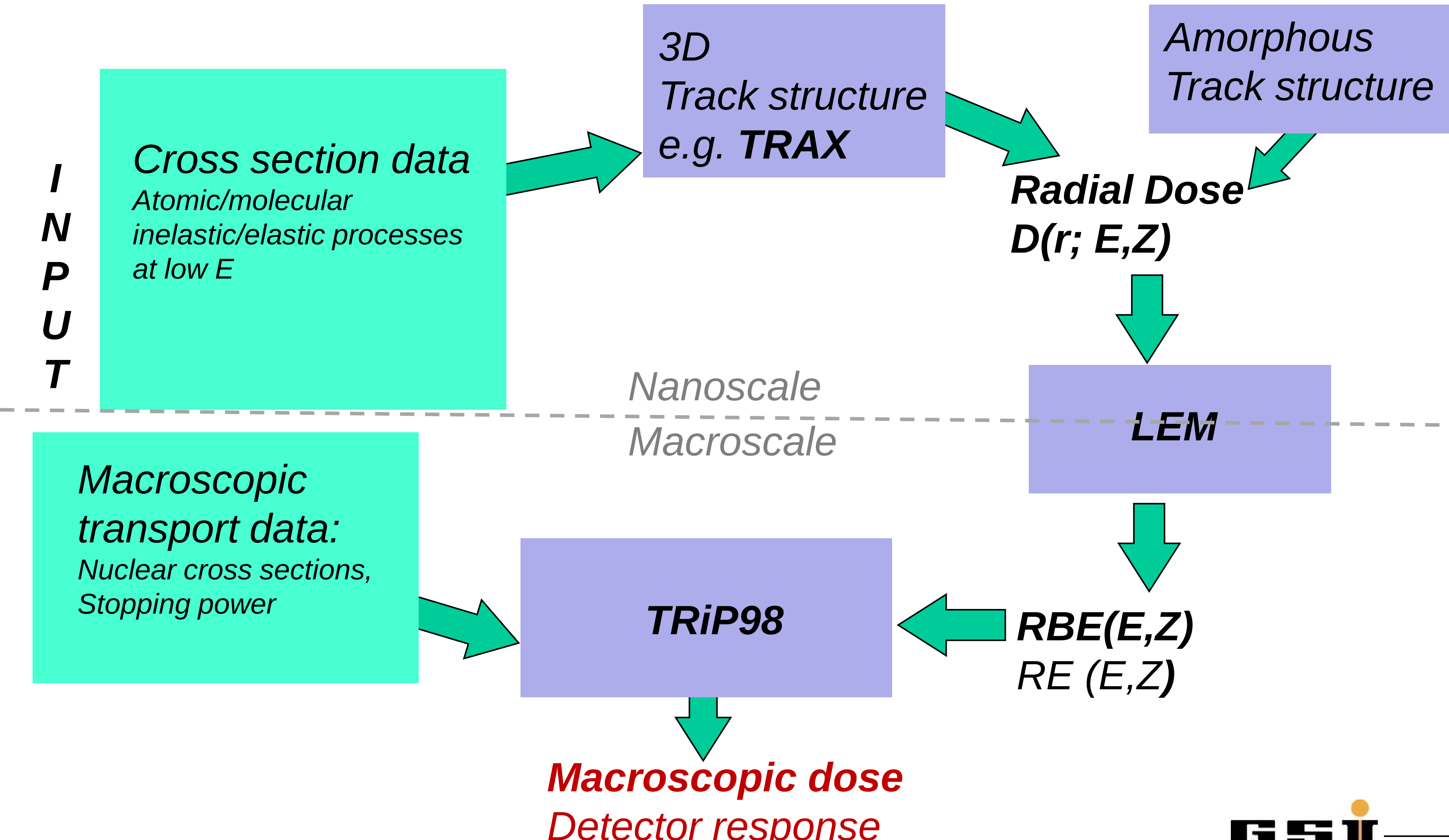
Dramatic effects in low-LET radiation:

what about ions?

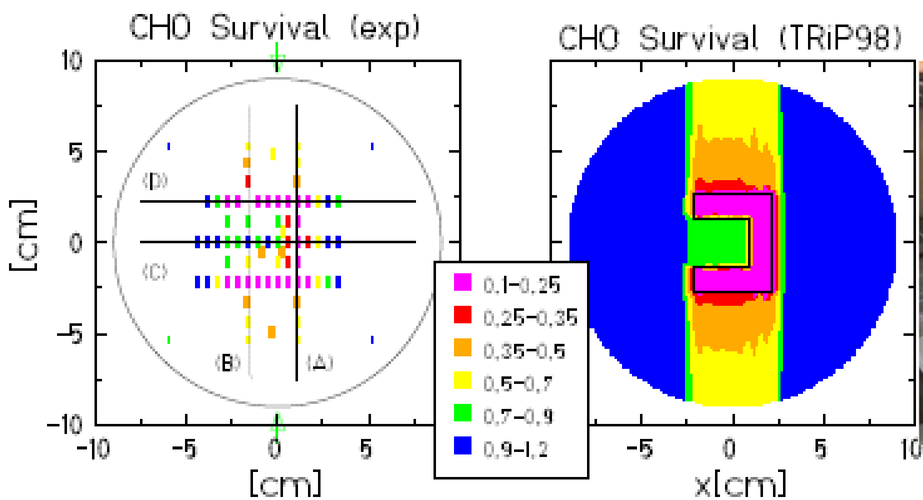


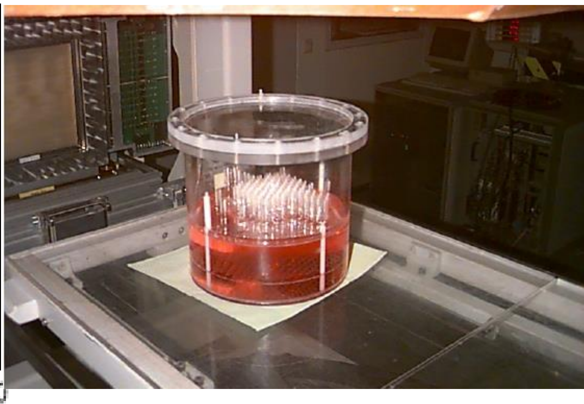
Wenzl&Wilkens 2011

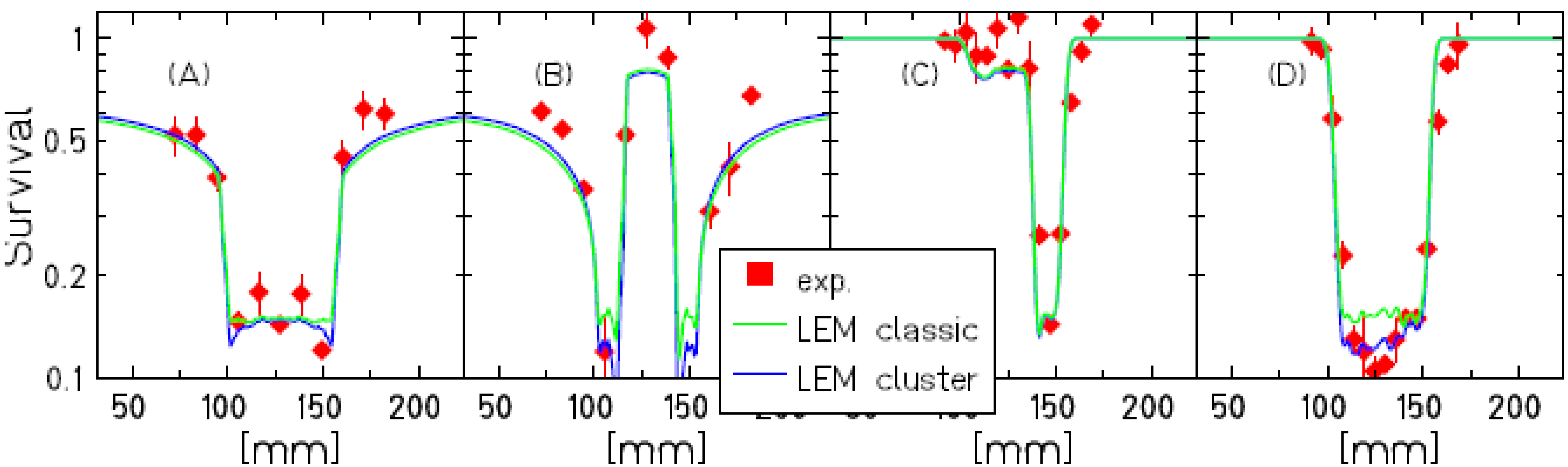
The GSI approach to ion beam radiation research



Biological dose verification

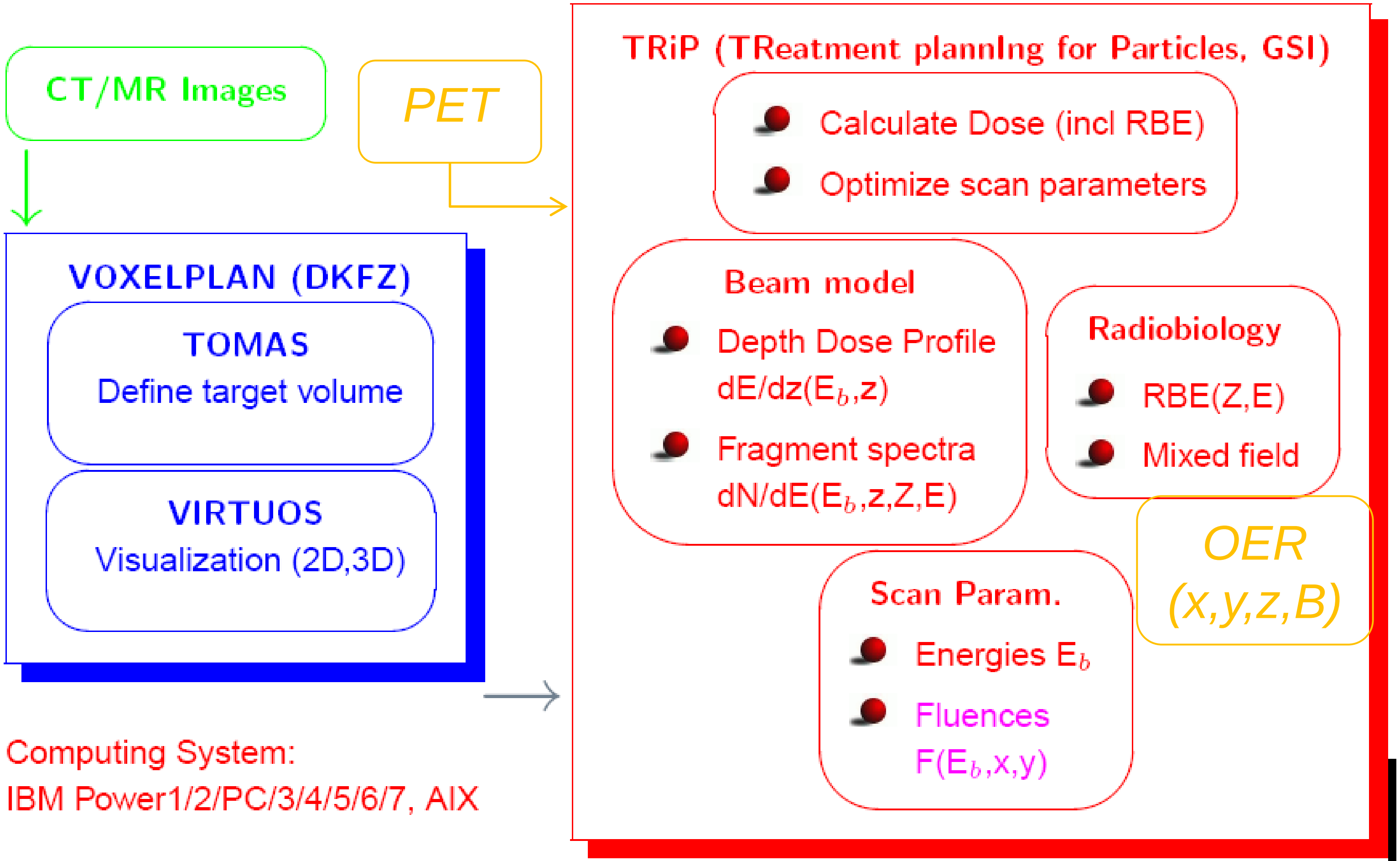






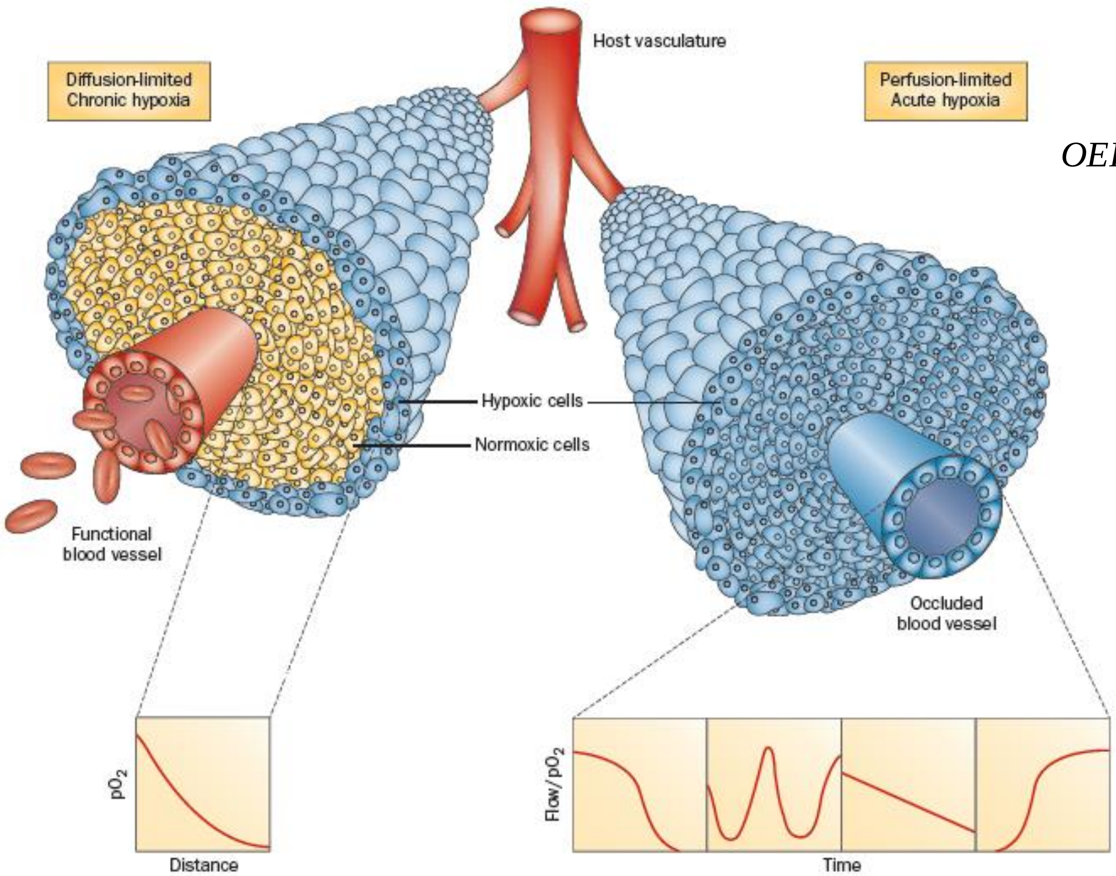
•*Kraft-Weyrather et al.*

TRiP98



M. Krämer et al, Phys. Med. Biol., 45/11 (2000) 3299.
…Eur. Phys. J. D, 60 (2010) 195.

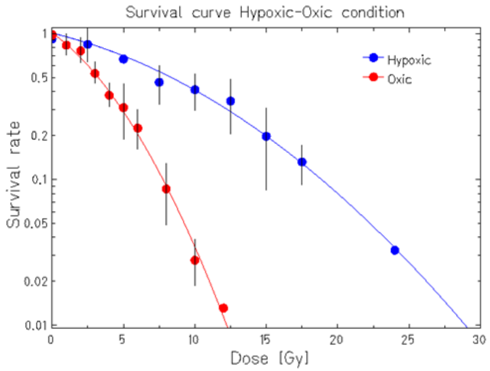
Contrasting Hypoxia

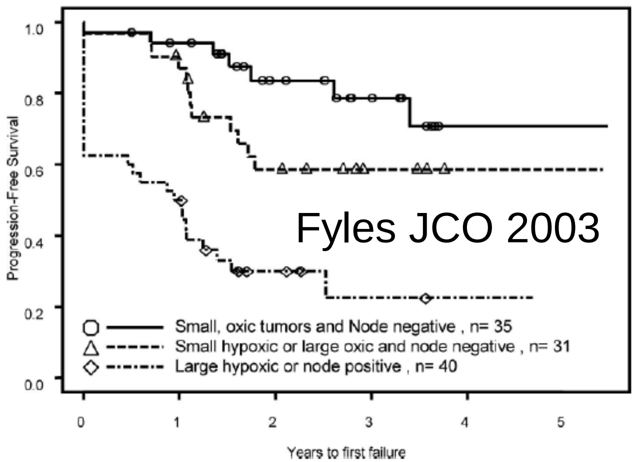


Horsman et al *Nat. Rev. Clin. Oncol.* (2012)

Oxygen Enhancement Ratio

$$OER = \left.\frac{D_{hypoxic}}{D_{normoxic}}\right|_{same\,effect} \quad ; \quad OER(p) = \left.\frac{D(p)}{D_{normoxic}}\right|_{same\,effect}$$





High LET quenching of radicals

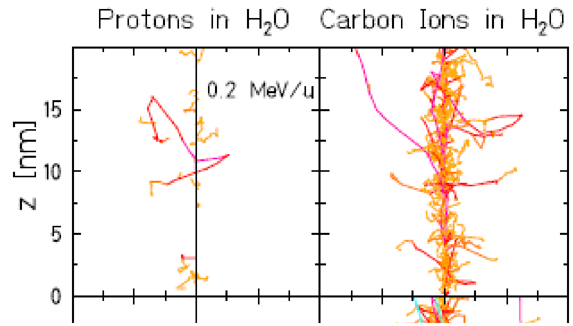
- Track density effect

$$H^\bullet + H^\bullet \longrightarrow H_2$$

$$e_{aq}^- + e_{aq}^- \xrightarrow{H_2O} H_2 + 2\,OH^-$$

$$^\bullet OH + {}^\bullet OH \longrightarrow H_2O_2$$

Recombination of radicals
Enhancing of molecular products yields



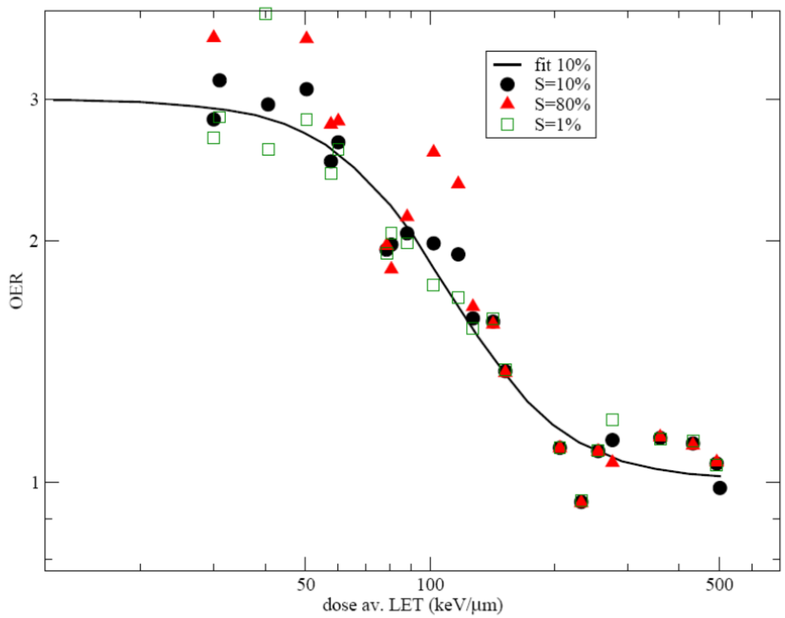
Kraemer et al.

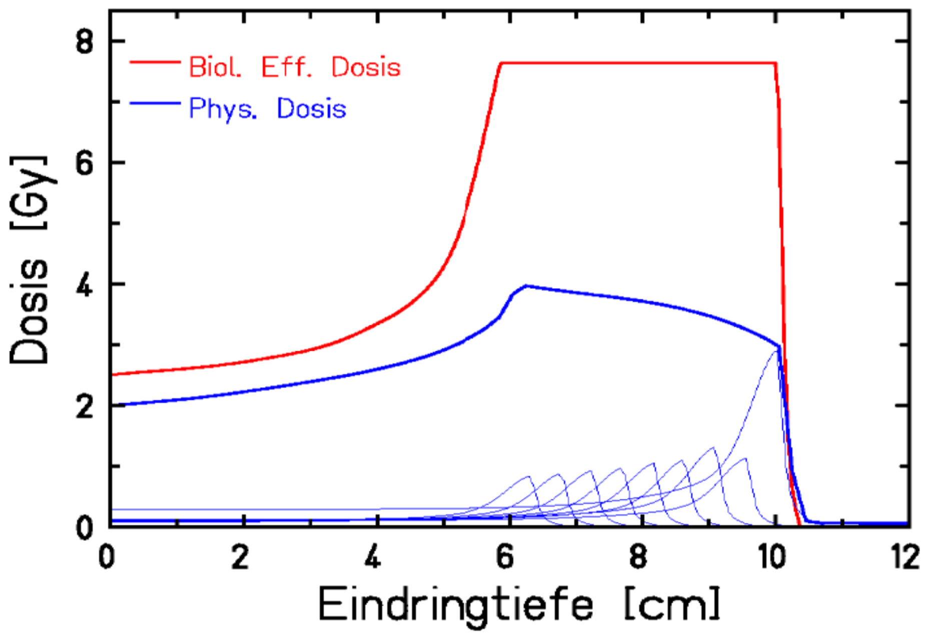
LET (keV µm^{-1})	e^-_{aq}	OH	H	H_2	H_2O_2	HO_2
0.2	0.26	0.27	0.055	0.045	0.068	0
61	0.072	0.091	0.042	0.096	1.00	0.005

Yields(µmol/J)

LaVerne et al.

Is this problem solved for high LET radiation?



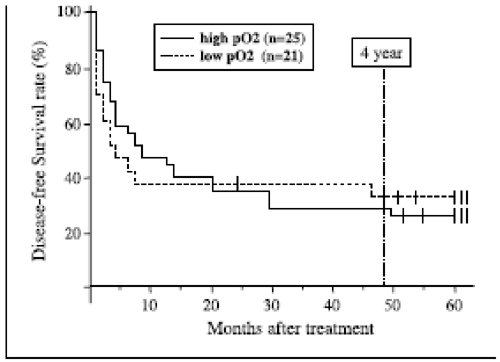


Furusawa et al., Radiat. Res. 2000

Carbon Beam Therapy Overcomes the Radiation Resistance of Uterine Cervical Cancer Originating from Hypoxia

Takashi Nakano, Yoshiyuki Suzuki, Tatsuya Ohno, et al.

Clin Cancer Res 2006;12:2185-2190. Published online April 11, 2006.



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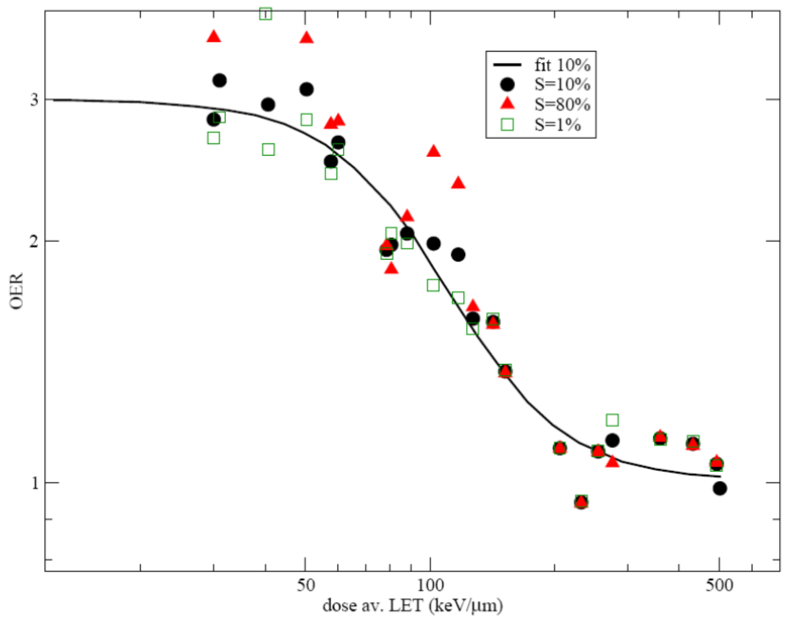

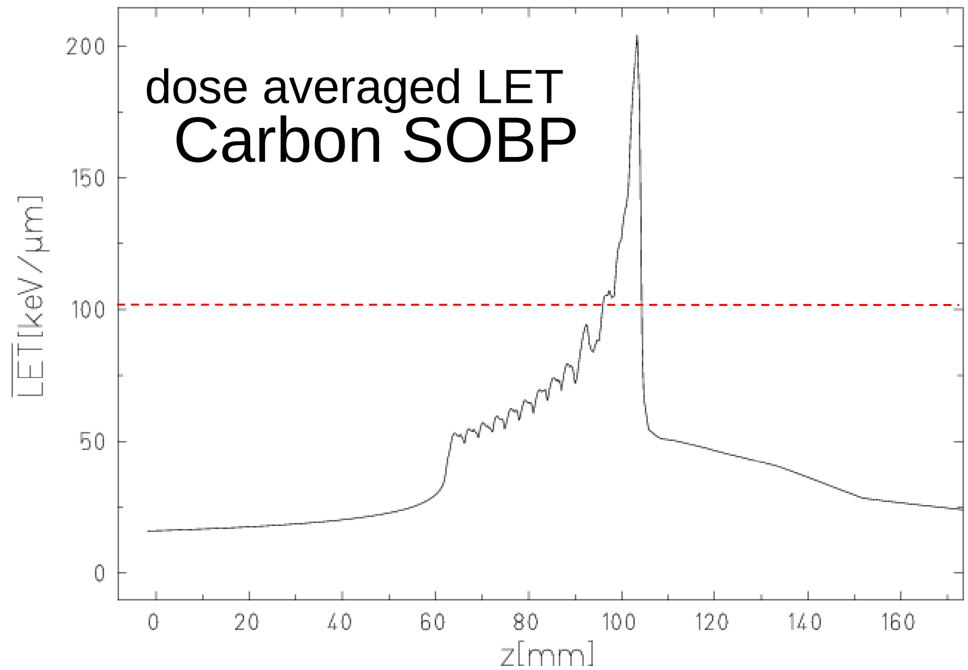

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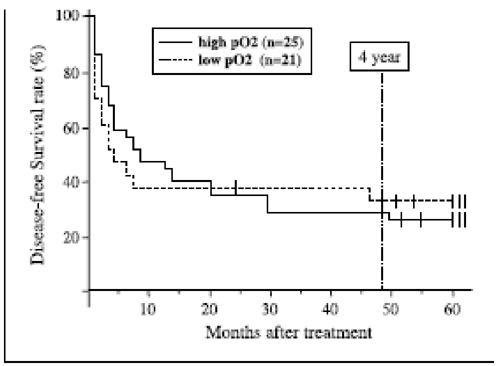
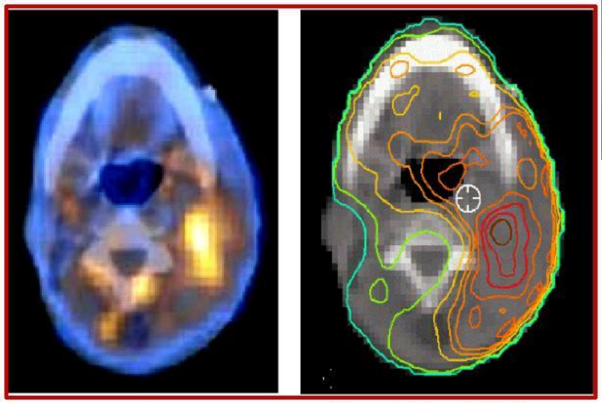
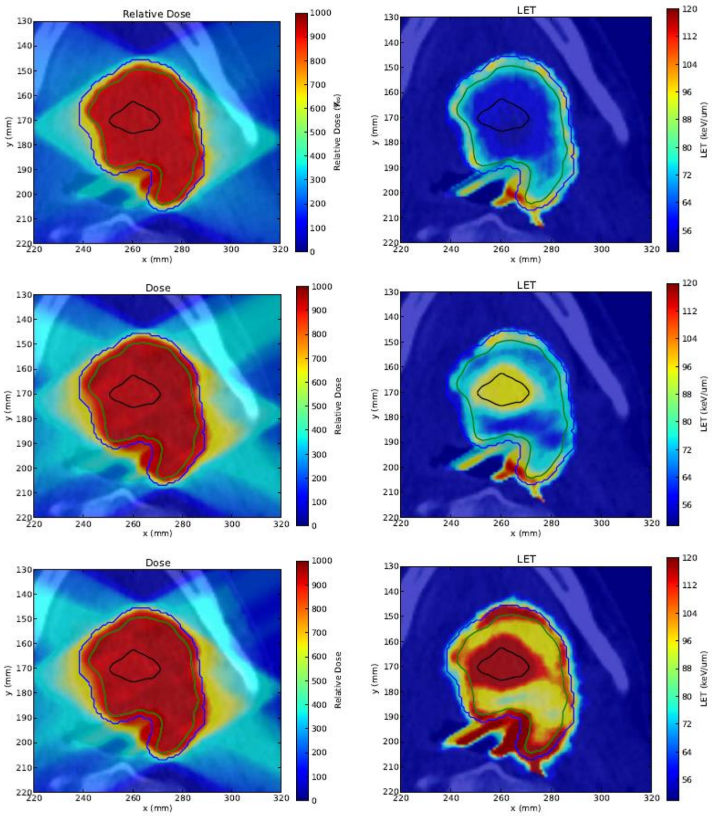


Painting Strategies



Thorwarth et al.2010

- Dose painting by contours
  - Boost dose in defined iso-uptake contours
- Dose painting by numbers
  - voxel-based prescription function
- LET painting
  - Redistribution of LET, to be maximized in the target volume, also using dose ramps



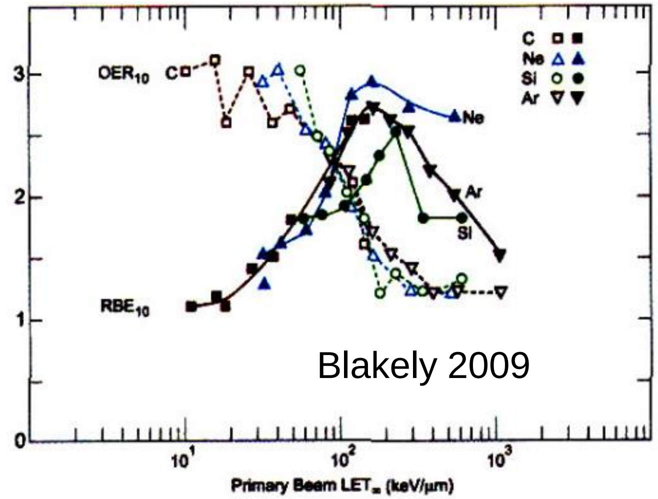
Bassler, et al. Acta Oncol 2013

“Killing” painting

- Restoring a prescribed survival level in the target volume, independently on the oxygenation level of different regions

- Taking fully into account the potential of ion beam active scanning dose delivery

- Close connection of RBE and OER
  - Maximum slope in the same LET range



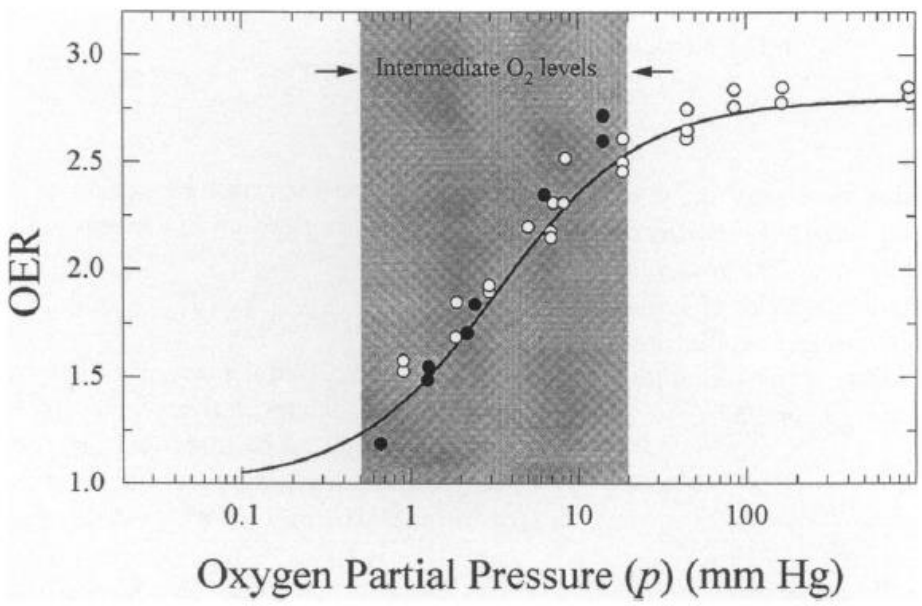
Blakely 2009

- LET and pO_2 dependence at the same time

Oxygenation level (X-rays only)

Cells at Intermediate Oxygen Levels Can Be More Important Than the “Hypoxic Fraction” in Determining Tumor Response to Fractionated Radiotherapy

Bradly G. Wouters and J. Martin Brown



Radiat. Res. 1997

Alper formula

$$\frac{S_{10\%}(pO_2)}{S_{10\%}^{N_2}} = \frac{m \cdot pO_2 + K}{pO_2 + K}$$

Alper and Howard-Flanders, *Nature* 1956

m=maximum relative sensitivity

K=ratio of the rate constants for chemical repair and oxygen fixation

OER(pO_2, LET) model
for adaptive particle treatment planning

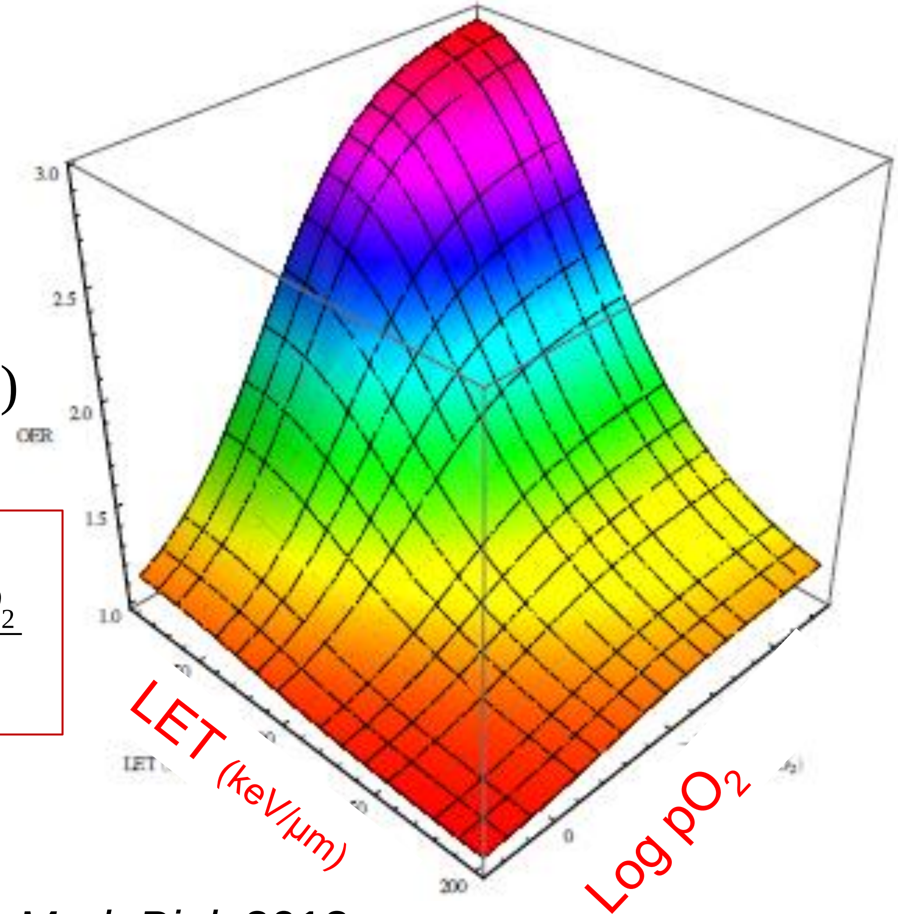
$$D^{i}_{bio}(\vec{N}) = \sqrt{\frac{\alpha_i \cdot \vec{c}_i^{\,T} \cdot \vec{N} + \beta_i \cdot (\vec{c}_i^{\,T} \cdot \vec{N})^2}{\beta_x} + \left(\frac{\alpha_x}{2\beta_x}\right)^2} - \frac{\alpha_x}{2\beta_x} \quad ;$$

from Krämer & Scholz, *Phys. Med. Biol. 2006*

$$\alpha'_i\,(\overline{LET}_i, pO_{2,i}) = \alpha_i \,/\, OER(\overline{LET}_i, pO_{2,i})$$

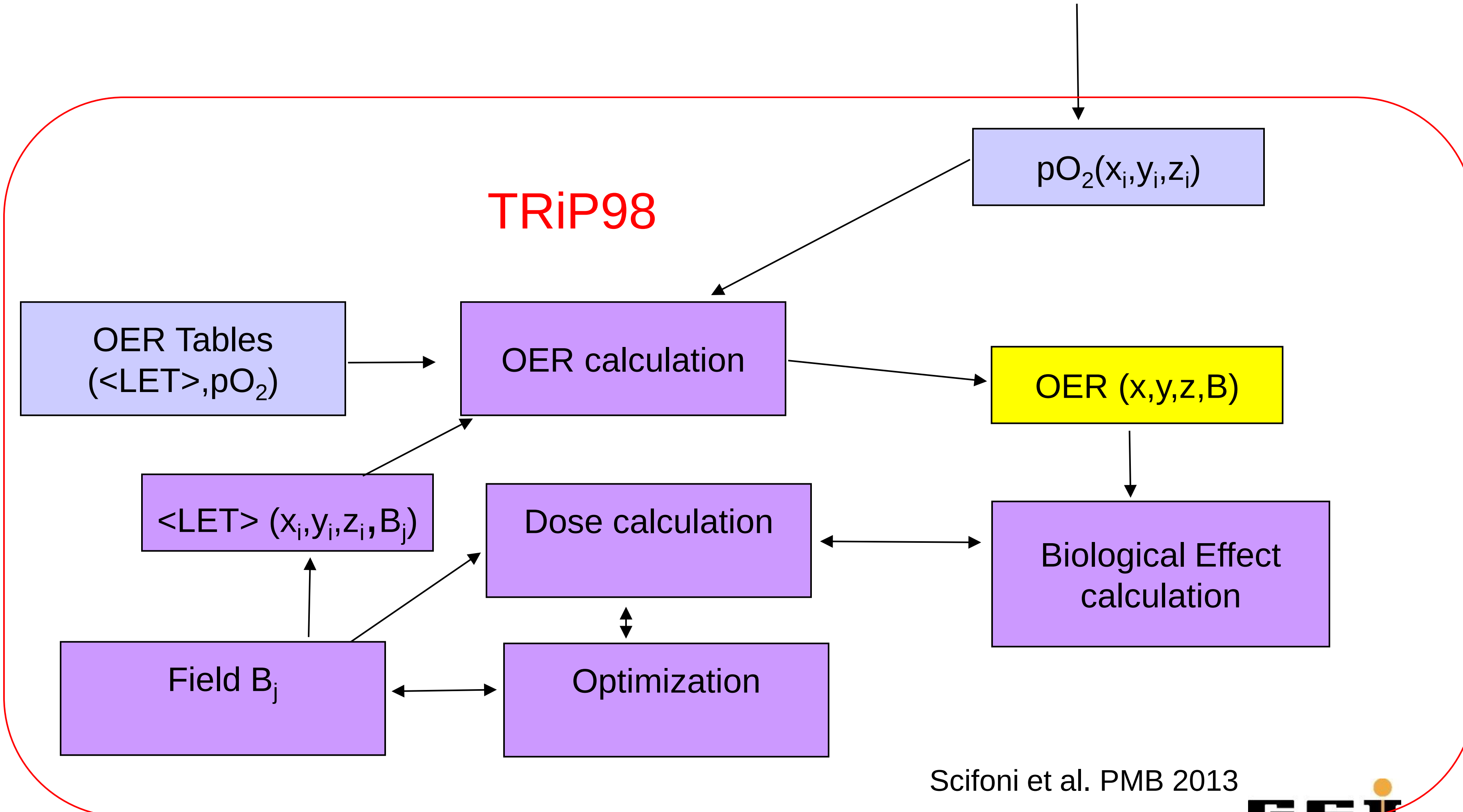
$$\sqrt{\beta'}_i\,(\overline{LET}_i, pO_{2,i}) = \sqrt{\beta_i} \,/\, OER(\overline{LET}_i, pO_{2,i})$$

$$OER(\overline{LET}, pO_2) = \frac{b(Ma + \overline{LET}^{\alpha})/(a + \overline{LET}^{\alpha}) + pO_2}{b + pO_2}$$



Scifoni *et al.*, *Phys. Med. Biol*. 2013

TRiP98-OER

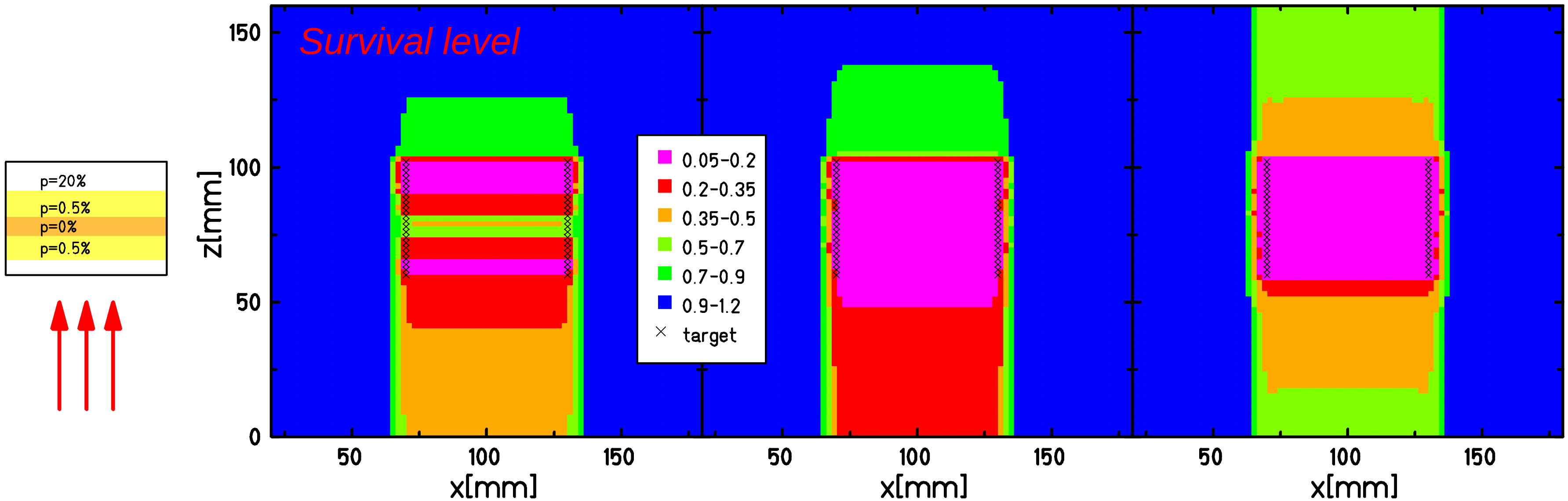

TRiP98
pO2(xi,yi,zi)
OER Tables
(<LET>,pO2)
OER calculation
OER (x,y,z,B)
<LET> (xi,yi,zi,Bj)
Dose calculation
Biological Effect
calculation
Field Bj
Optimization
Scifoni et al. PMB 2013

Optimized plans with dose compensation

•*normoxic plan*

•*OER-optimized, 1Field*

•*OER-optimized, 2 fields*
Multiple Field Optimization

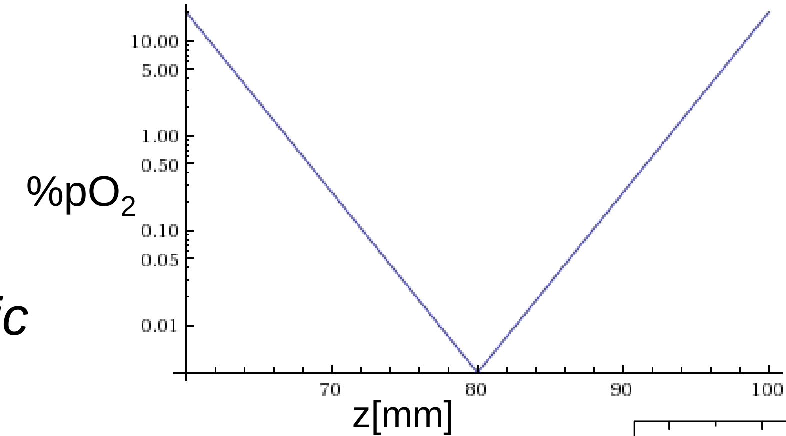


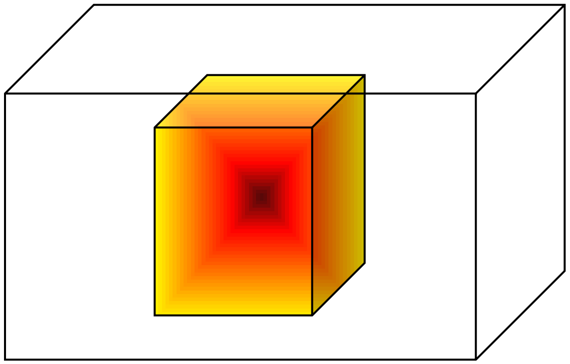
Optimization “decides” contribution of different fields according to hypoxia distribution

Scifoni et al. PMB 2013

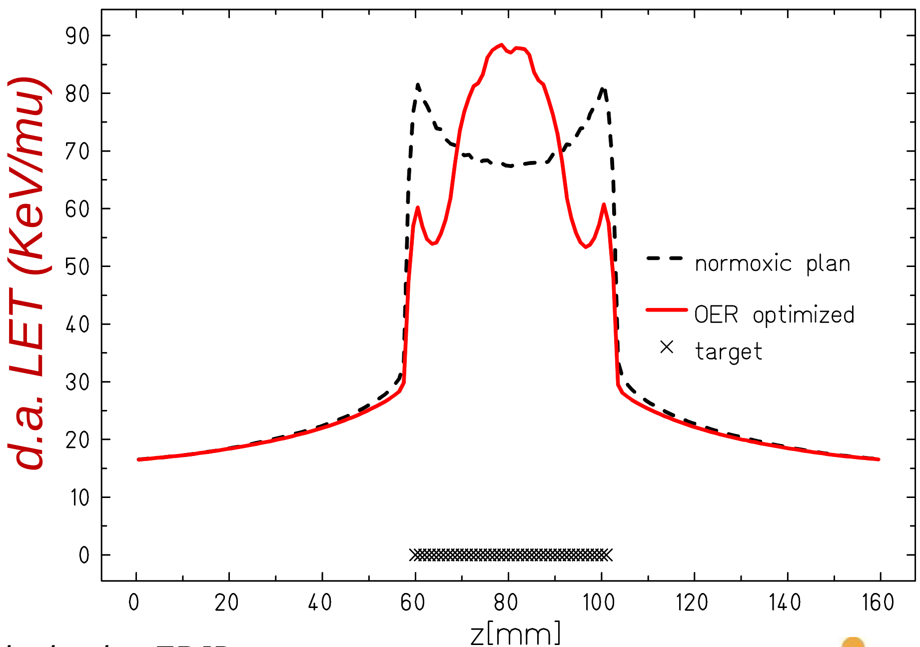
Realistic pO_2 distributions

Smooth pO_2 *gradient from a central anoxic core*





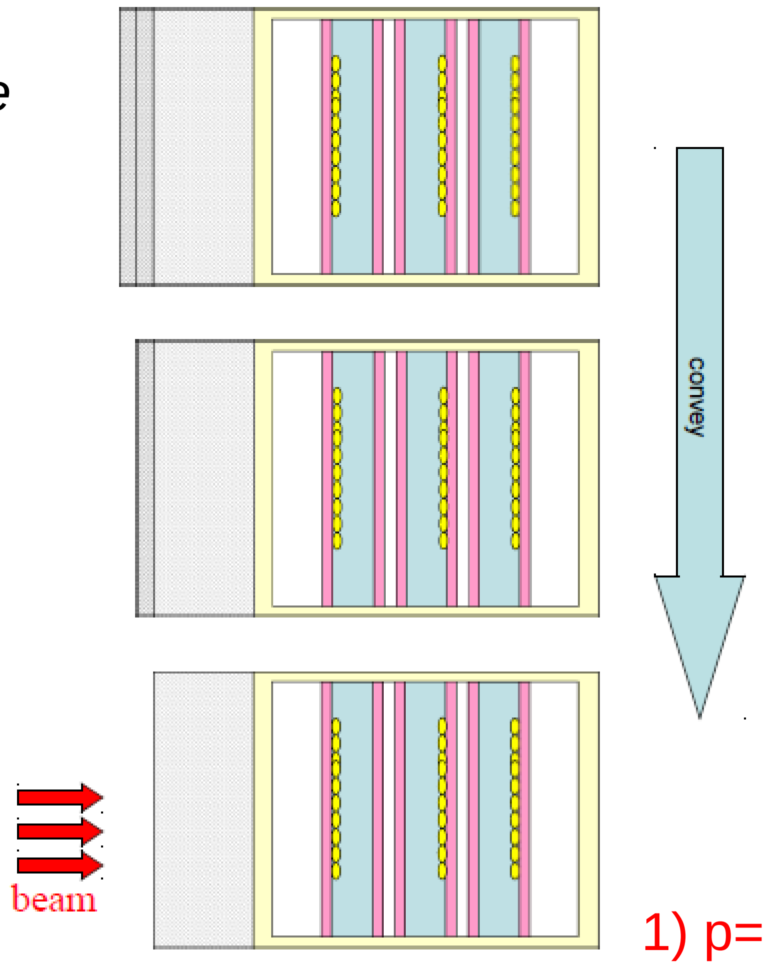
LET distribution automatically adjusted from the optimization through the "hypoxic gradients" to the oxygen distribution

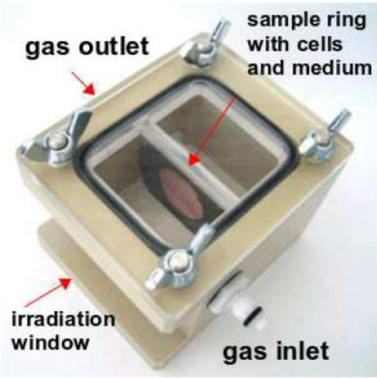


Krämer, Scifoni, Schmitz, Sokol, Durante, *submitted to EPJD*

Experimental verification

- *Densely sampling the last cm, zooming on the region of maximum LET effect*

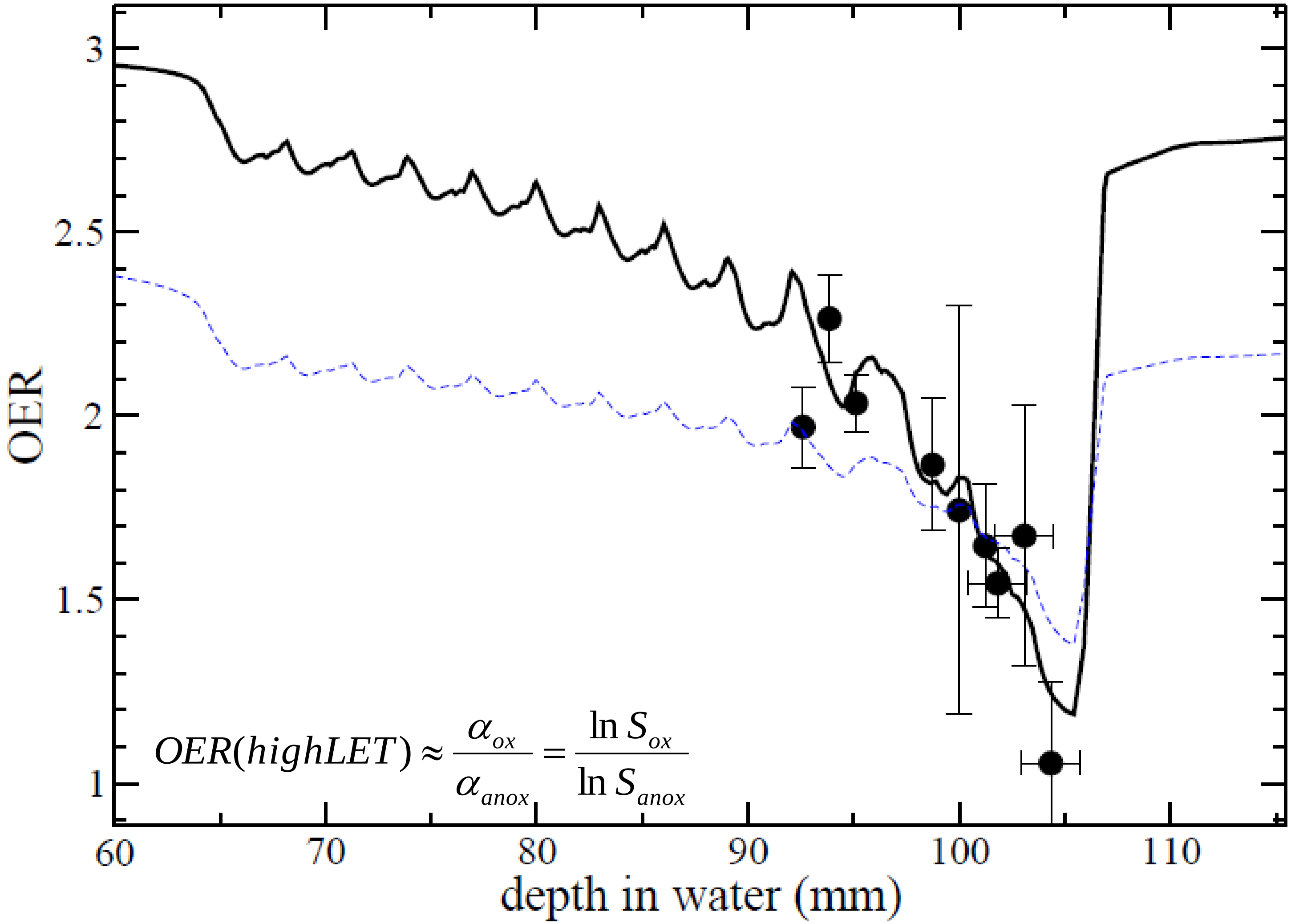




1) p=0

2) Normoxic

OER(z), experimental

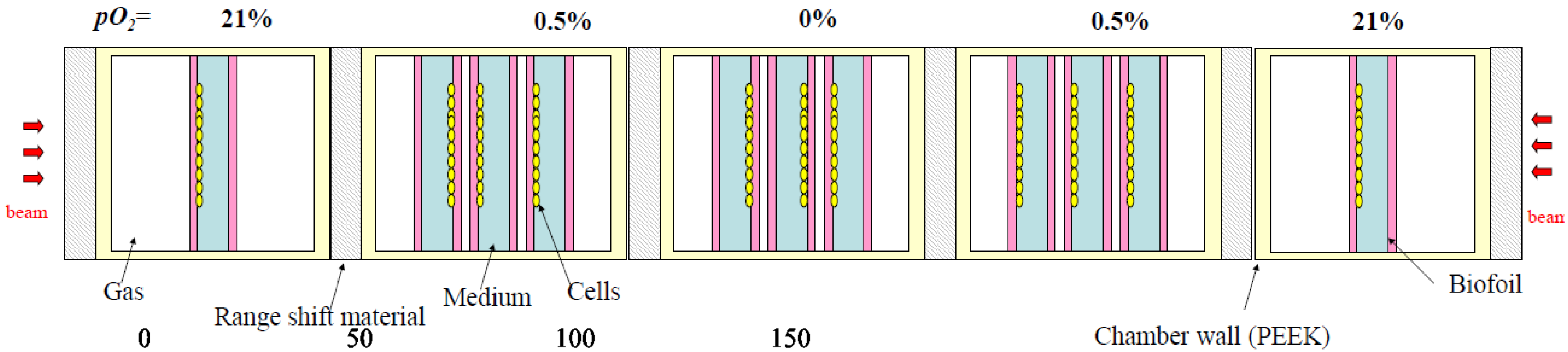


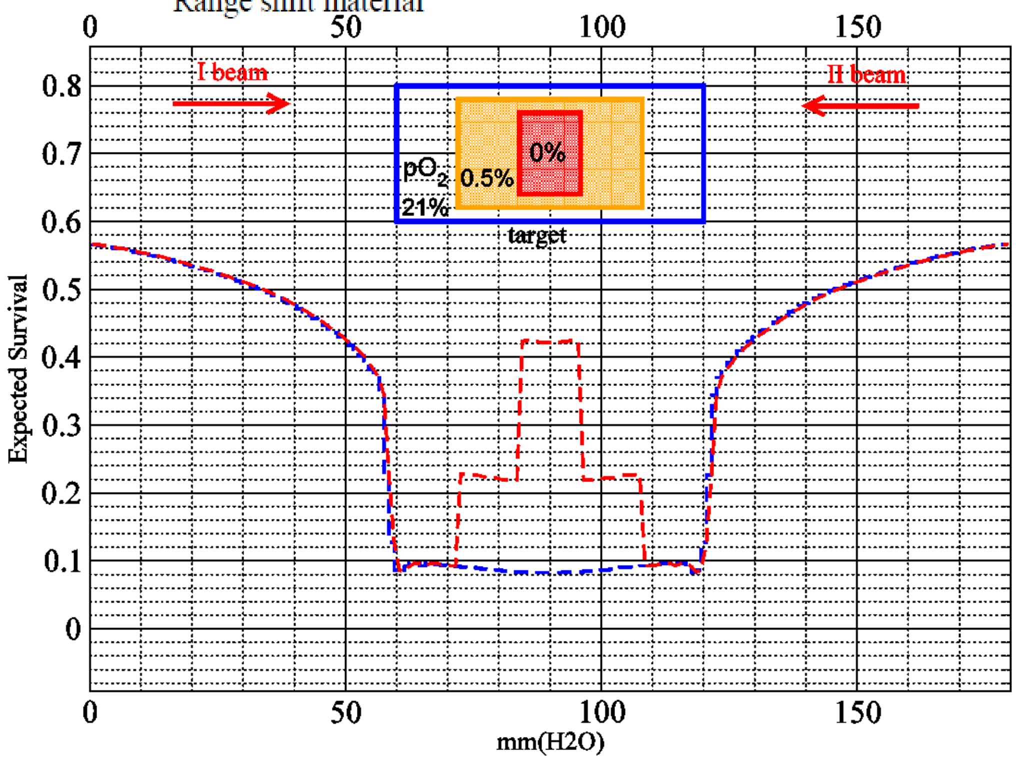
- TRiP-OER+ present model tables
- TRiP-OER+ model tables from Wenzl&Wilkens 2011

Scifoni, Tinganelli, Weyrather, Durante, Krämer, Phys. Med. Biol. 58 (2013) 3871–3895

Extended target irradiation

- validation of TRiP-OER, 2 Fields, 3 different O_2

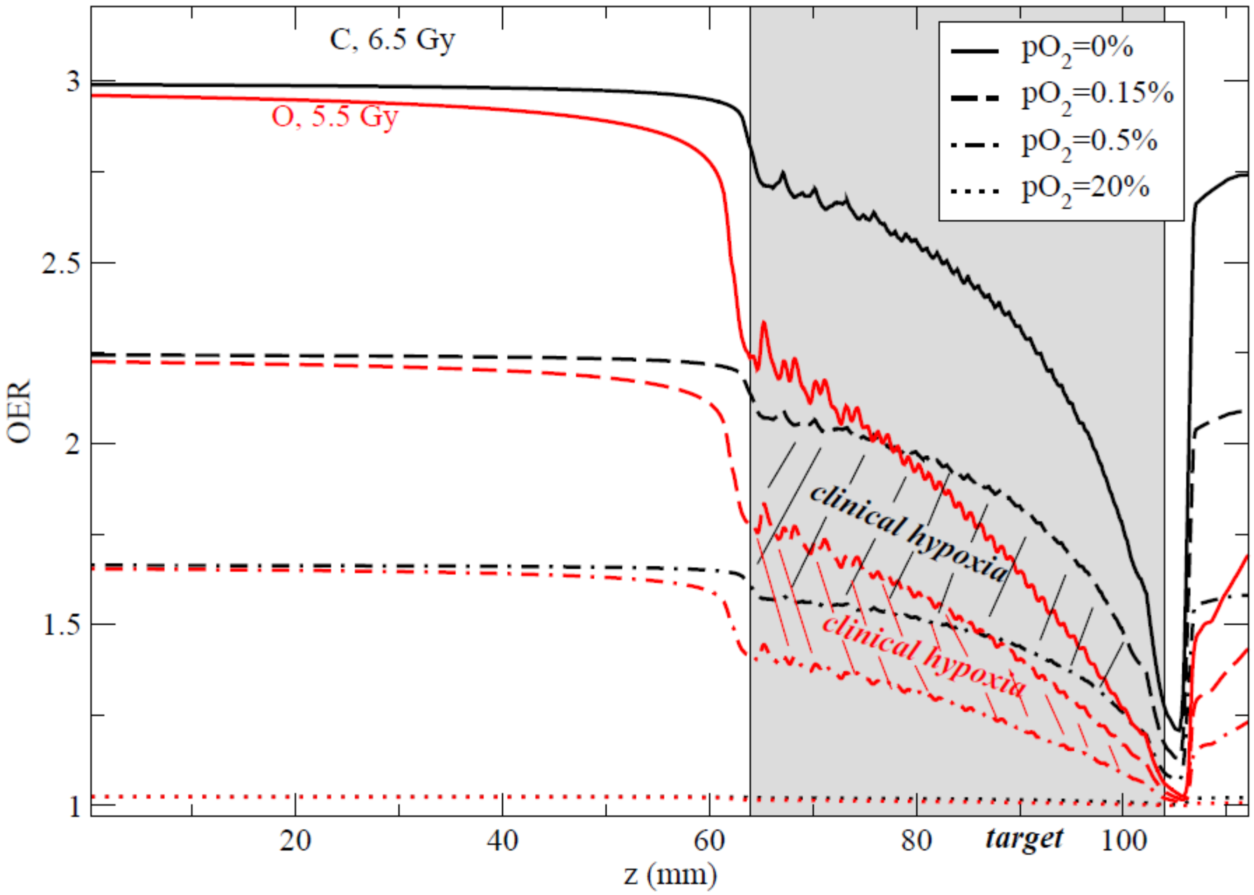




- *November BT @HIMAC preliminary test with 2 passive fields Cfr with expected survival predicted by TRiP-OER*

- *March BT @GSI including OER-optimization (restoring uniform survival)*

Using different ions: Oxygen vs Carbon beam



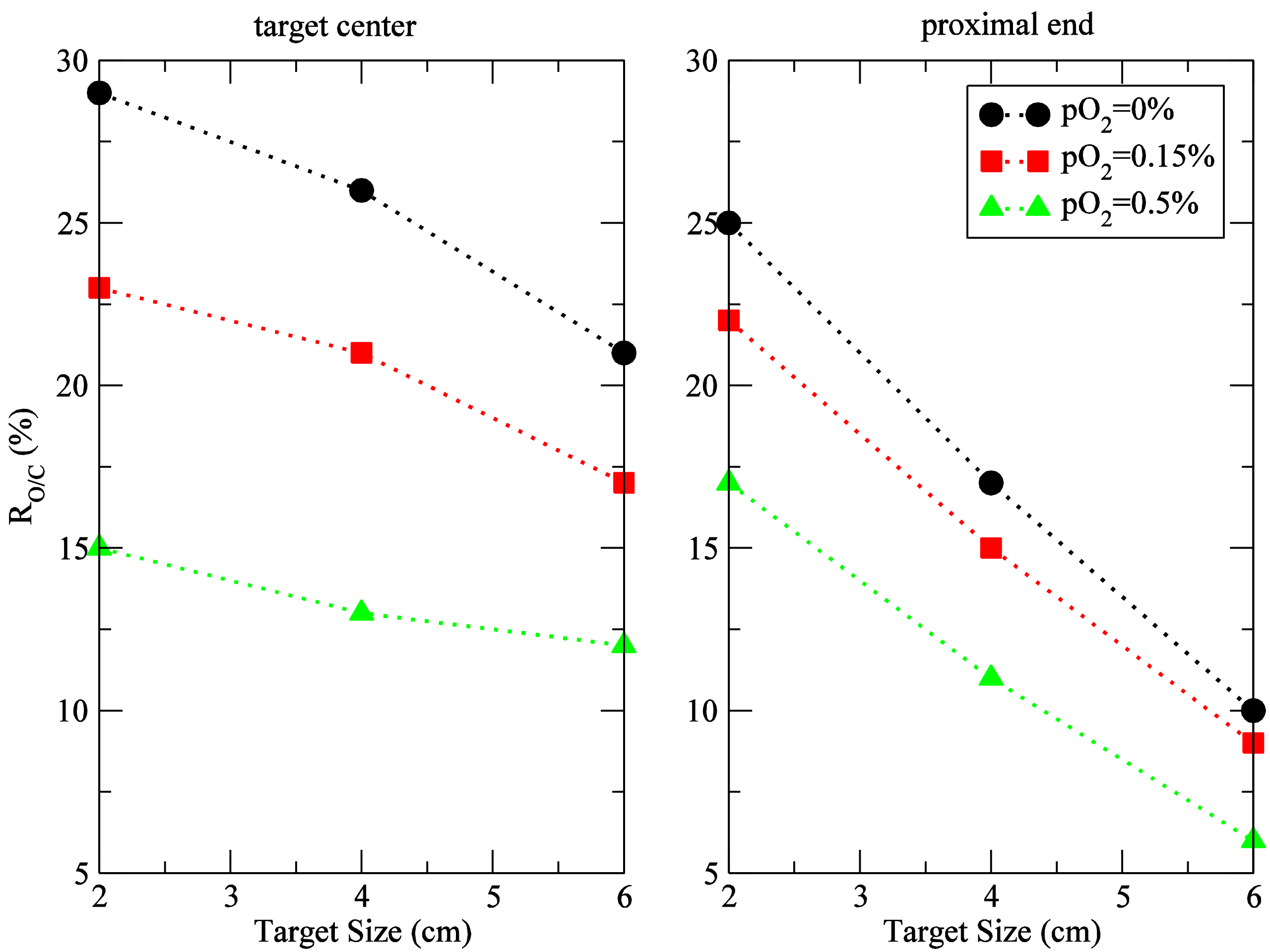
- C, O, p and soon He available @HIT
- Joining OER driven and Multiion modality in next TRiP release

Krämer, Scifoni, Waelzlein, Durante JPCS 2012

Scifoni et al PMB 2013

O vs C for different tumor sizes

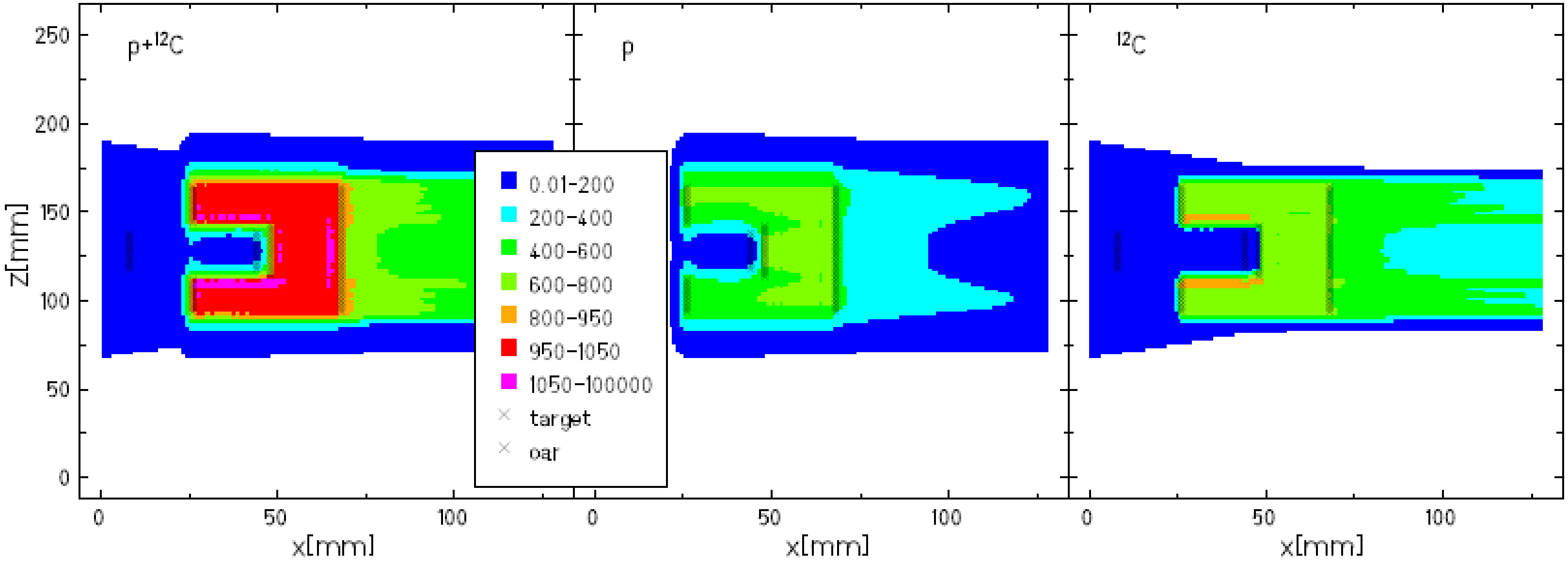
Relative OER reduction $R_{O/C} = (\mathrm{OER}_C - \mathrm{OER}_O)/\mathrm{OER}_C$



Multi-ion treatment planning

- TRiP version for a biologically optimised multi-ion treatment plan
- TPS enhanced to handle more than one ion beam modality at once (e.g. $^{12}C+^{16}O$, $p+^{12}C$)

OAR dose constraint prefers ^{12}C over ^{1}H at the edges



Krämer, Scifoni, ,Schmitz, Sokol, Durante, *submitted to EPJD*

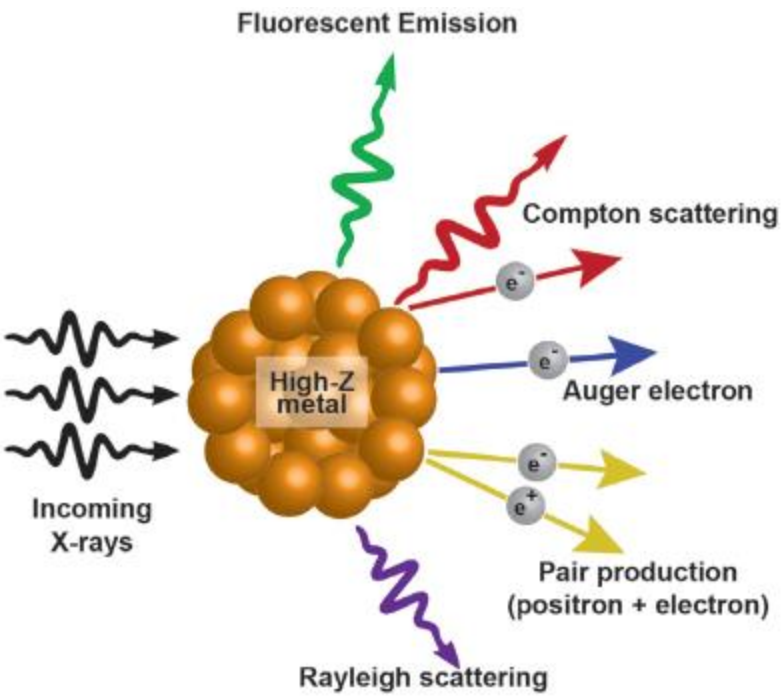
Summary Oxygen effect

- Intratumor Heterogeneity (hypoxia) can be tackled from particle therapy
- First TPS for particles implemented to account for OER and to optimize on iso-survival differently oxygenated areas: *Killing optimization* with intrinsic LET redistribution and dose compensation by the multiple field optimization
- Carbon Ion beams can be optimized for hypoxic tumors – moderate effect
- Use of larger LET ions (^{16}O) quantitatively assessed and encouraged for boosts or multimodal plans
- Experimental biological dosimetry on extended target irradiation match

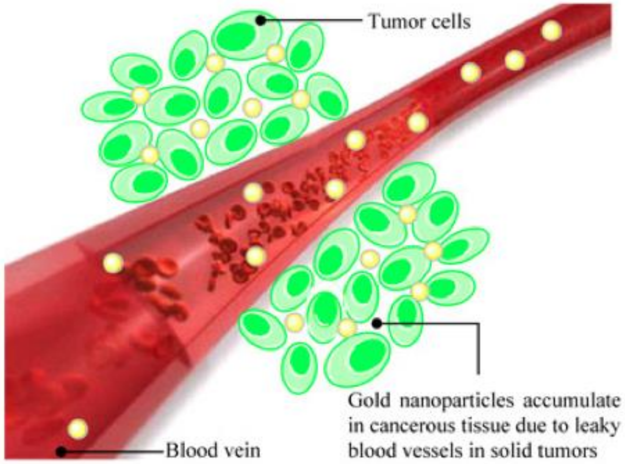
Challenges for Micro/Nanodosimetry:

-OER on the nanoscale: impact of LET particle type on radicals´ formation&recombination (ARGENT project)

Nanoparticle sensitization



Kwatra et al. Transl. Cancer Res. 2013



http://www.nanomedicine.dtu.dk

NP: high cellular uptake in tumours

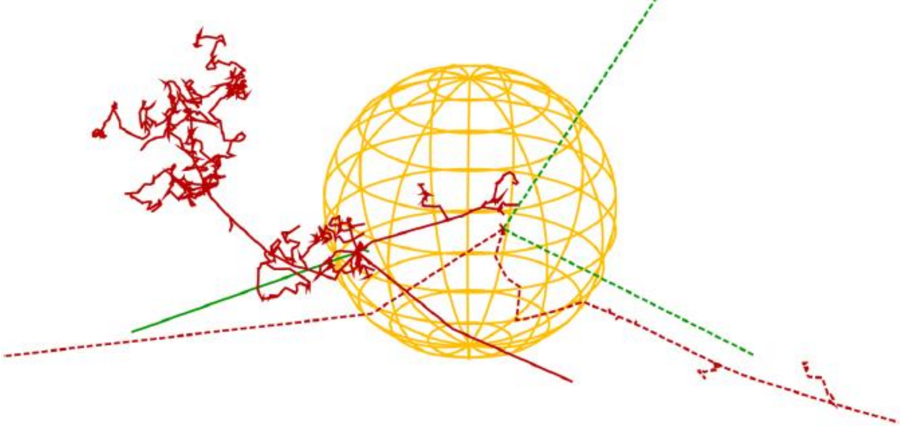
well known adavantage for photons;
high Z ➔ high e^- emission vs. high absorption

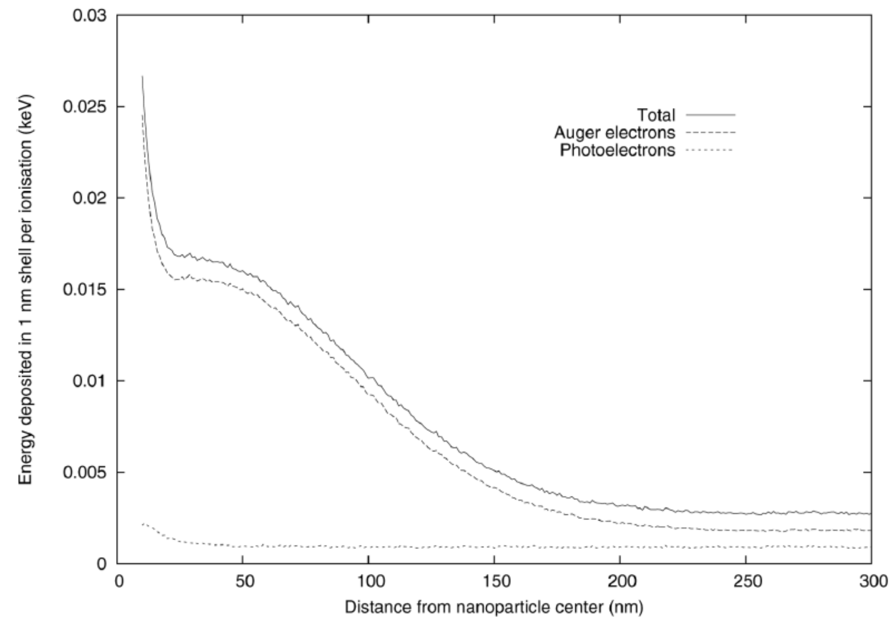
advantage with ion irradiation?

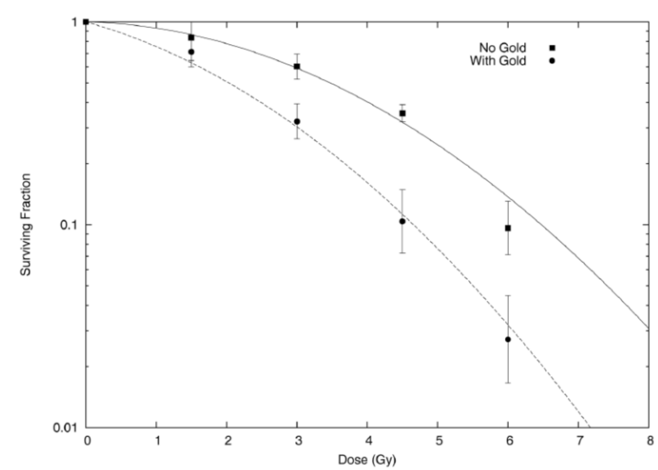
Au NP with photons

- Auger electrons play a crucial role for photons
- local dose enhancement analysis based on a LEM application @QUB

a)



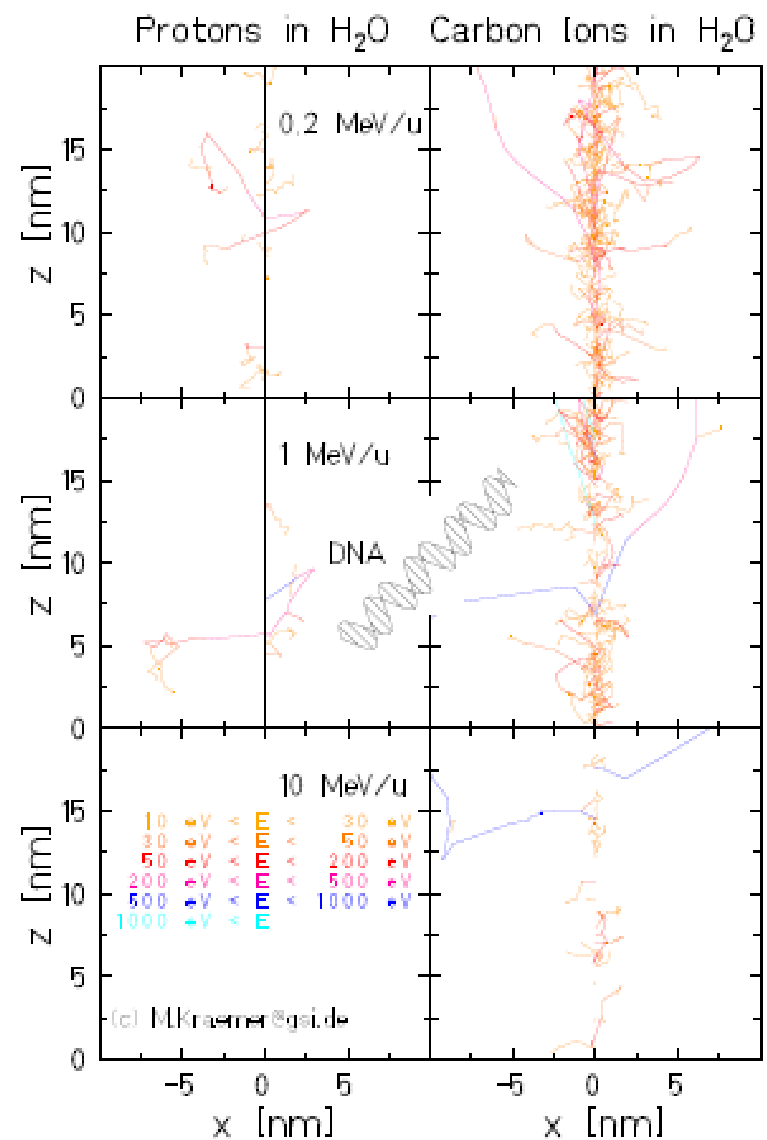


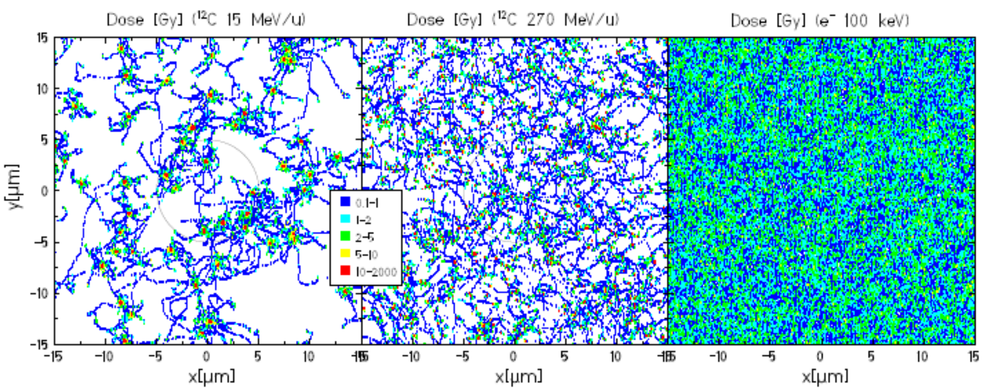


Mc Mahon et al. Sci. Rep. 2011

Ion Track Structure -TRAX

- Monte Carlo code developed at GSI
- micro/nanometer scale
- ions, electrons, through different target materials
- elementary interactions
  - elastic scattering,
  - ionization,
  - excitation





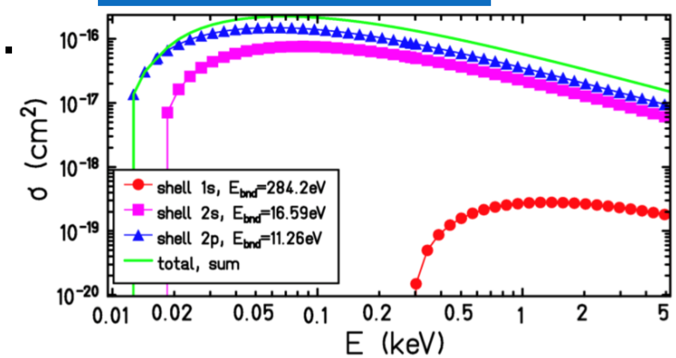
•*Kraemer et al.1996- 2014*

Cross section extensions

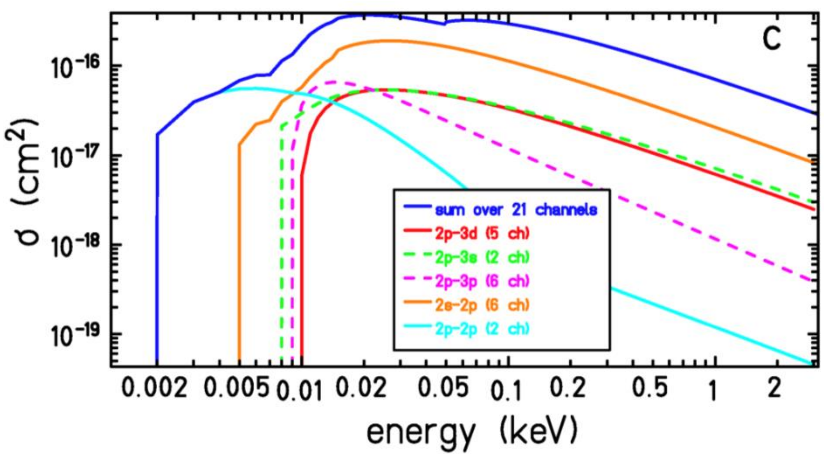
- database compiled, assessed and implemented (read-in, dσ/dΩ ➔σ)

- **C, Ni, Ag, Au** + Al, Fe, Gd, Pt, H_2O, …

ionization E_{bnd}

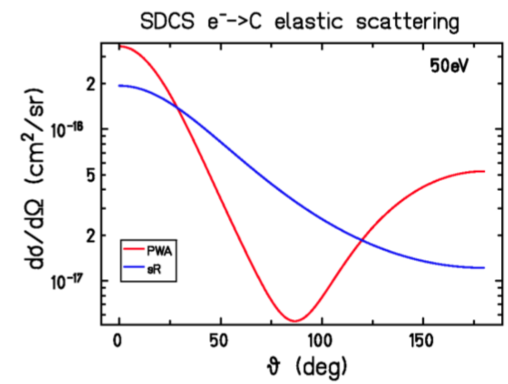


excitation ***various low E channels***

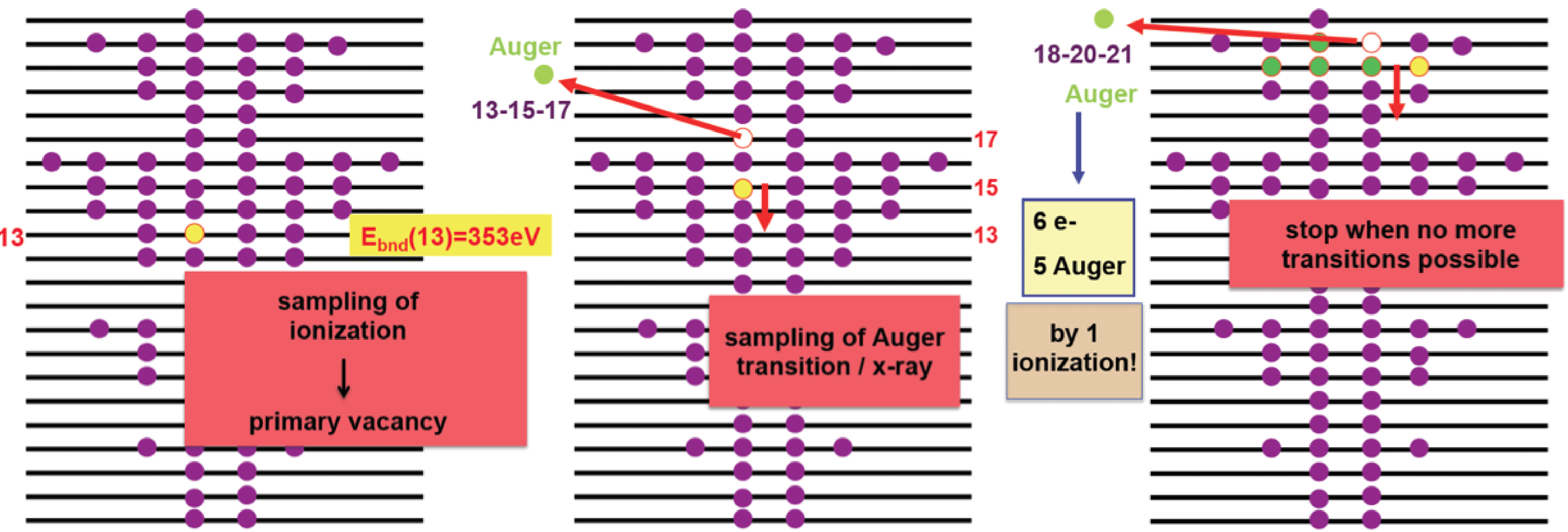


elastic

sR-PWA
dσ/dΩ



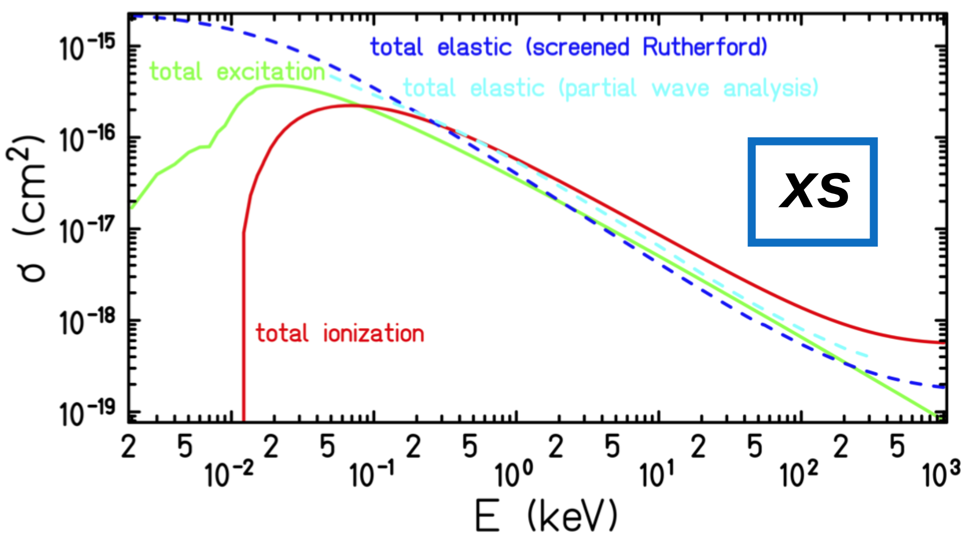
Auger electrons including cascades (high Z targets)



External target files :
- read in at start-up
- transition probabilities
- flourescence yields

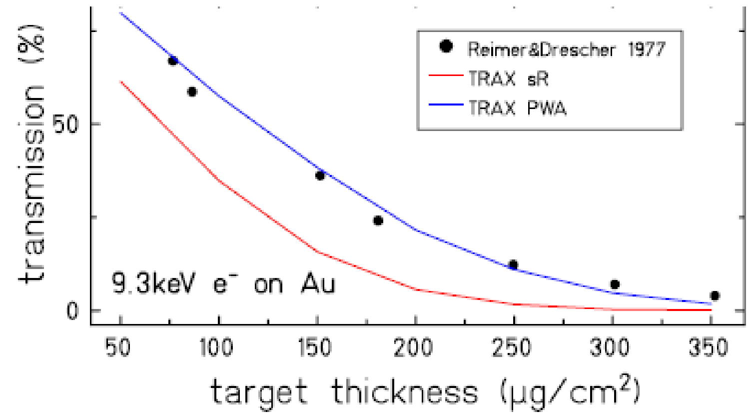
low E
➔ short ranges (nm)

Validation of radiation transport



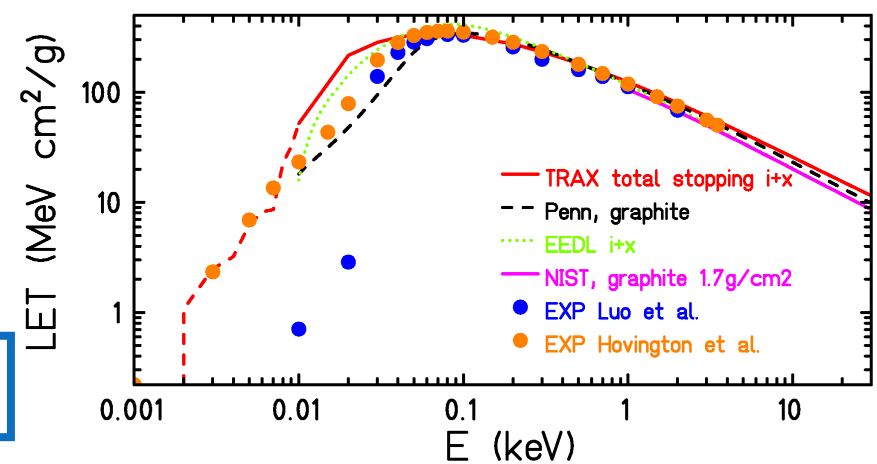
+ *backscattering* ➔ *elastic*

+ *transmission*

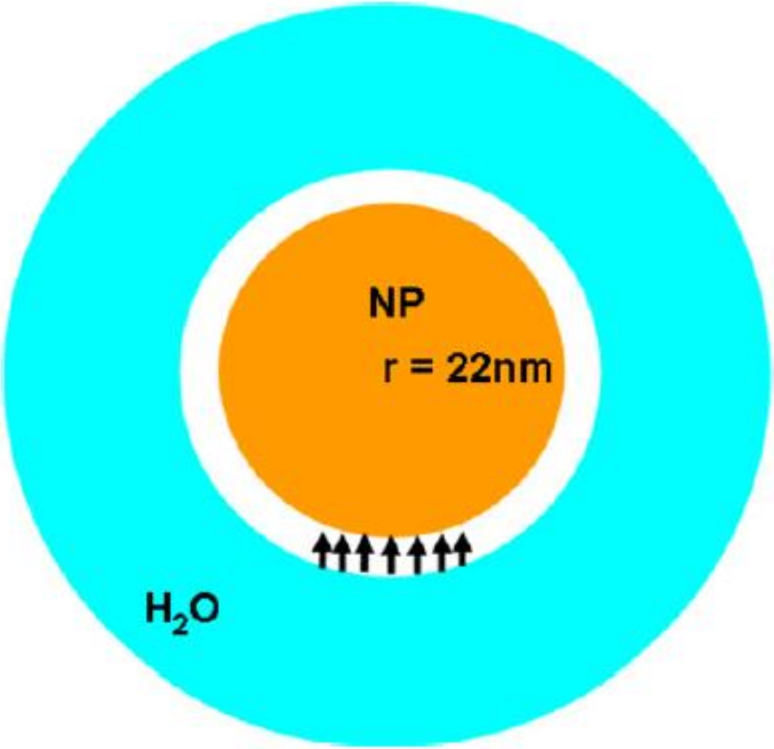


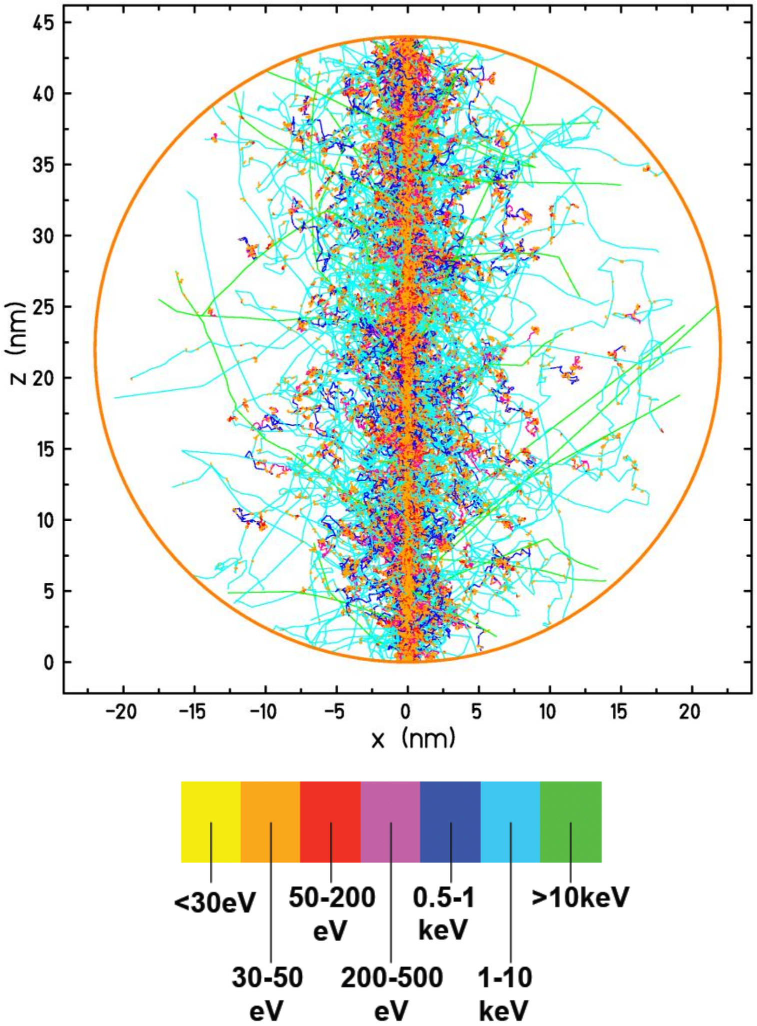
$$S(E)=\sum_i \Delta E_i \cdot \sigma_i(E)+\sum_j \int (T+I_j)\cdot \frac{d\sigma_j(E,T)}{dT}\, dT$$

stopping power

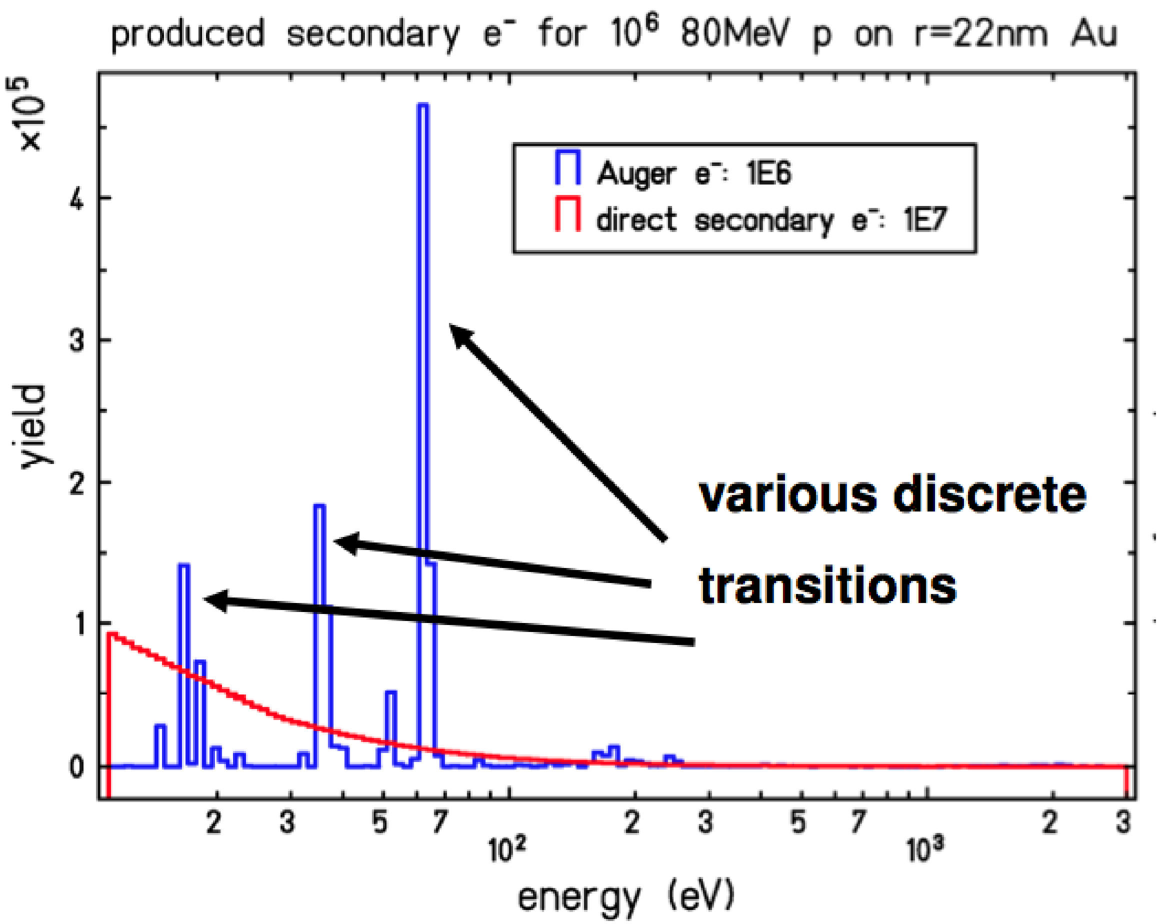


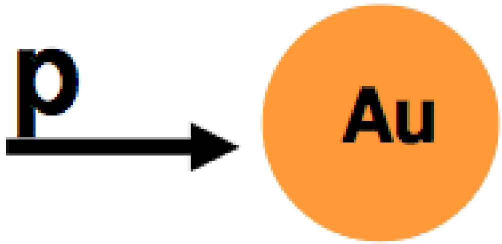
Simulation geometry





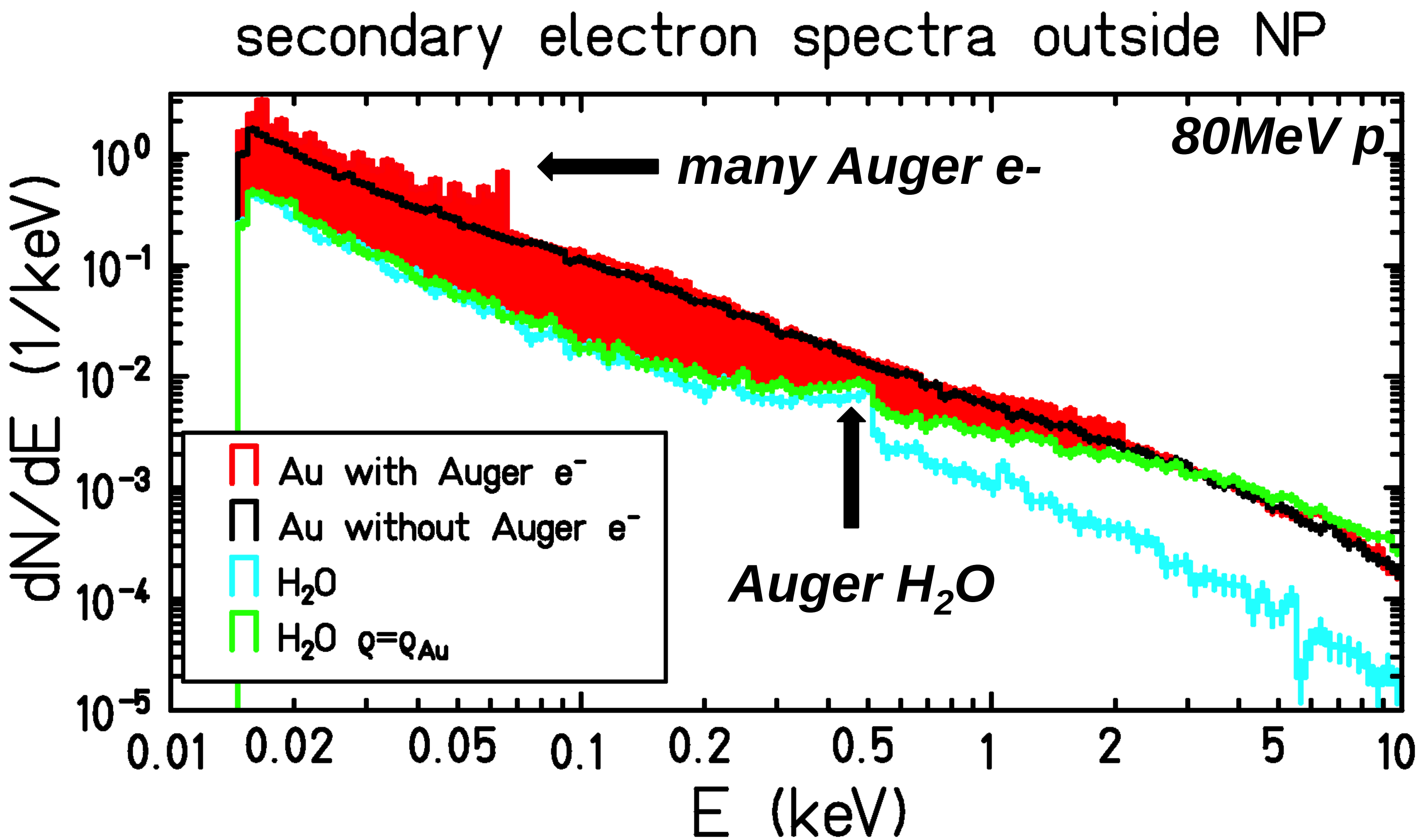
Produced e^- inside nanoparticle

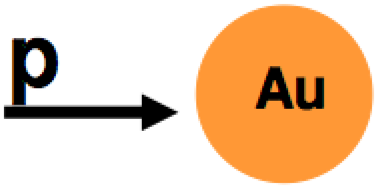




Auger e^- important @ low E

Escaping e$^-$ from NP





e- yield for Au-NP+p enhanced

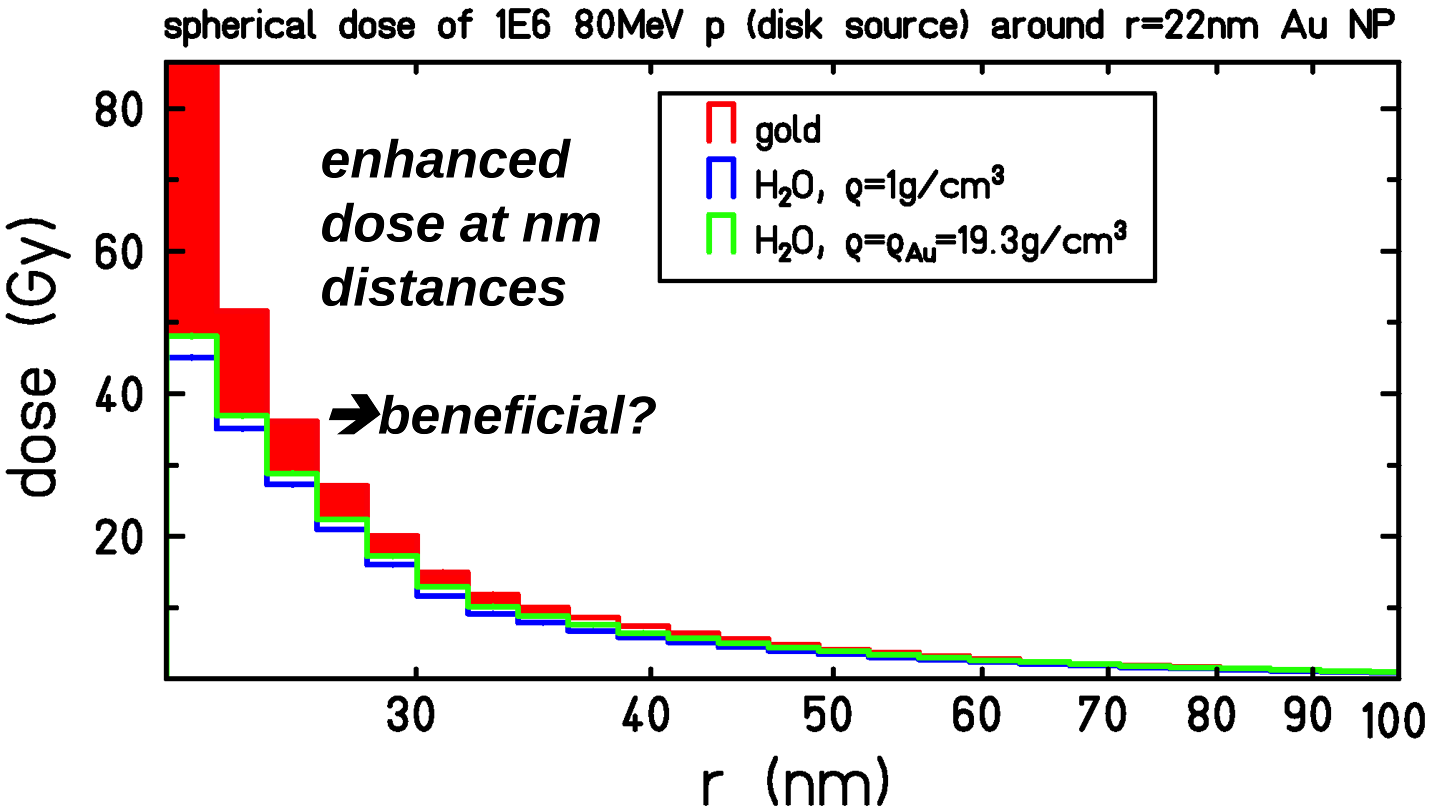
indication for advantages

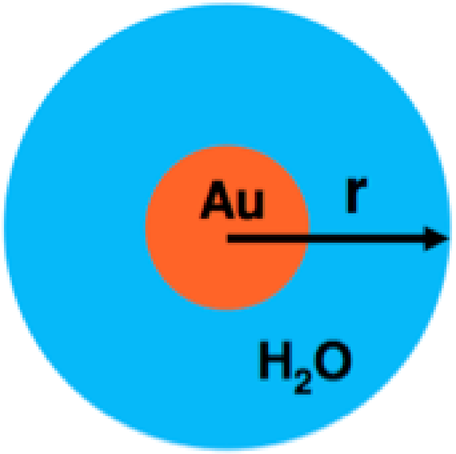
↓

local damage

Wälzlein, Scifoni, Krämer, Durante, Phys. Med. Biol. 59,1441 (2014)

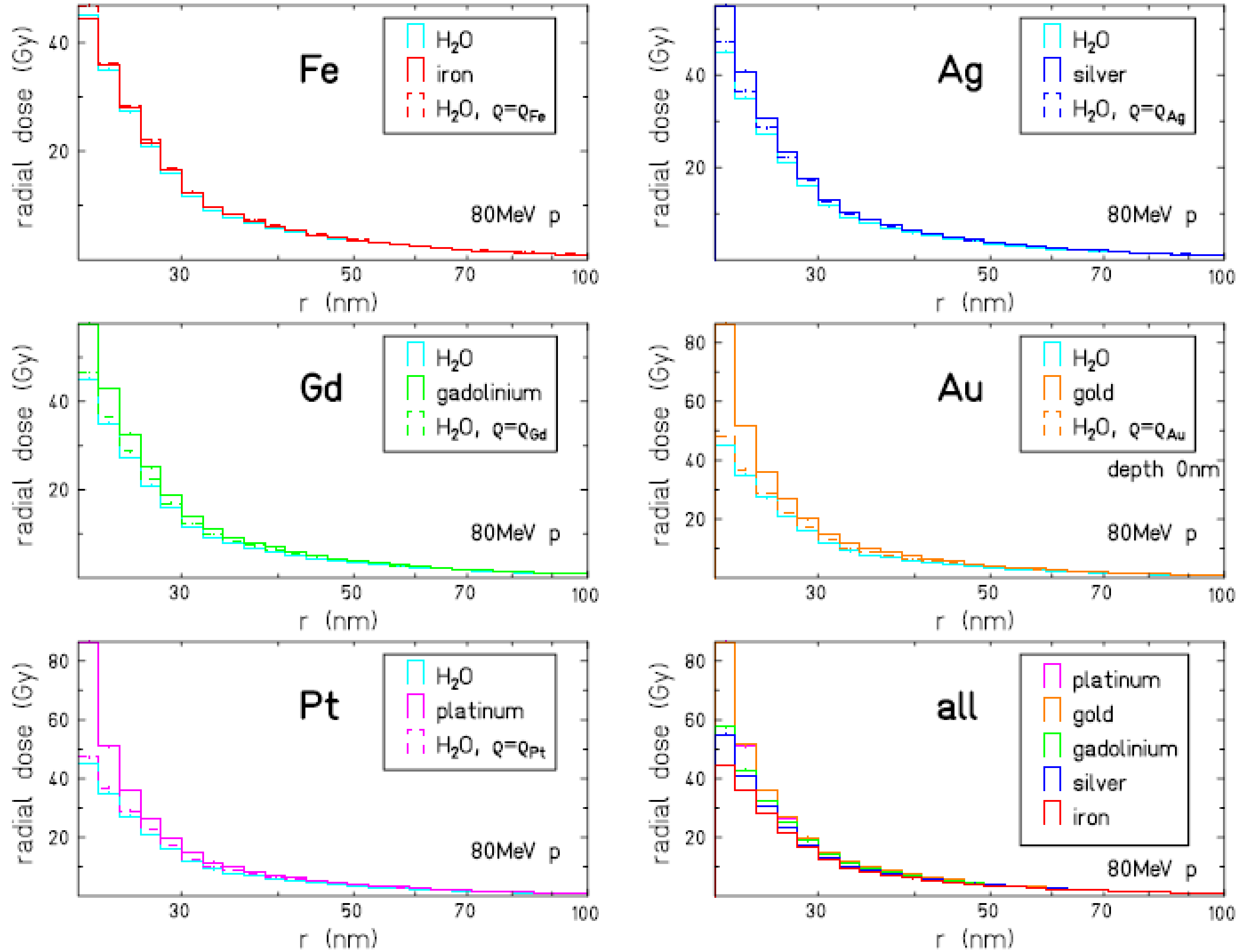
Local dose outside the nanoparticle





Wälzlein et al., Phys. Med. Biol. 59,1441 (2014)

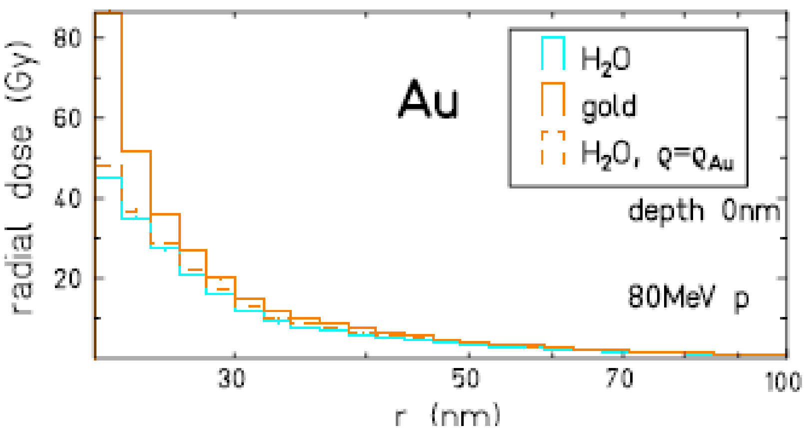
different Z



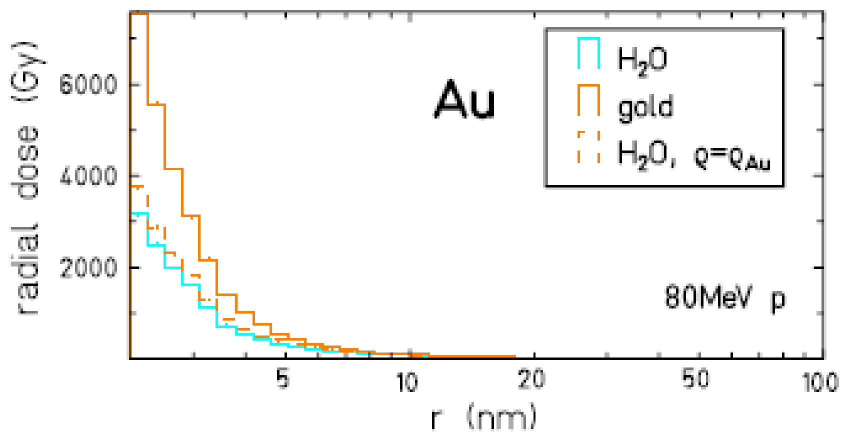
Wälzlein et al., Phys. Med. Biol., 2014

different size

22 nm



2 nm



Wälzlein et al., Phys. Med. Biol., 2014

Small effect: mainly surface electrons matters

Summary Nanoparticle sensitization

- proton irradiation of high Z NP studied for first time on track structure level
- under the assumption of ion traversal, a significant dose enhancement is observed
- the most promising NP are Pt and Au
- Auger electrons have a crucial role, while cascades contribute only marginally

Challenges for Micro/Nanodosimetry:

-nanoscopic dose measurements in presence of NP
-realistic simulations including buildup from outside NP
-Radiation quality changes, impact on radicals

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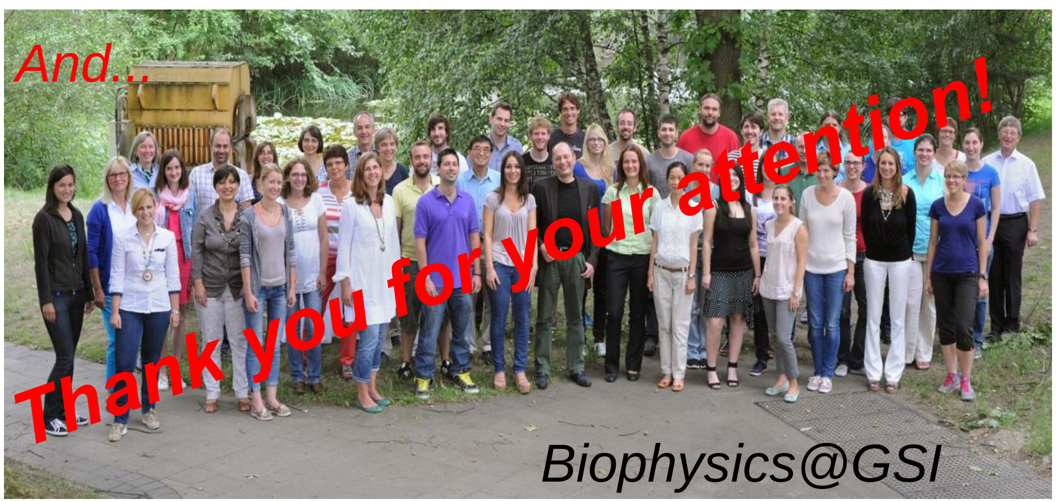
- N. Bassler (Aarhus)



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Nano-IBCT

GSI