

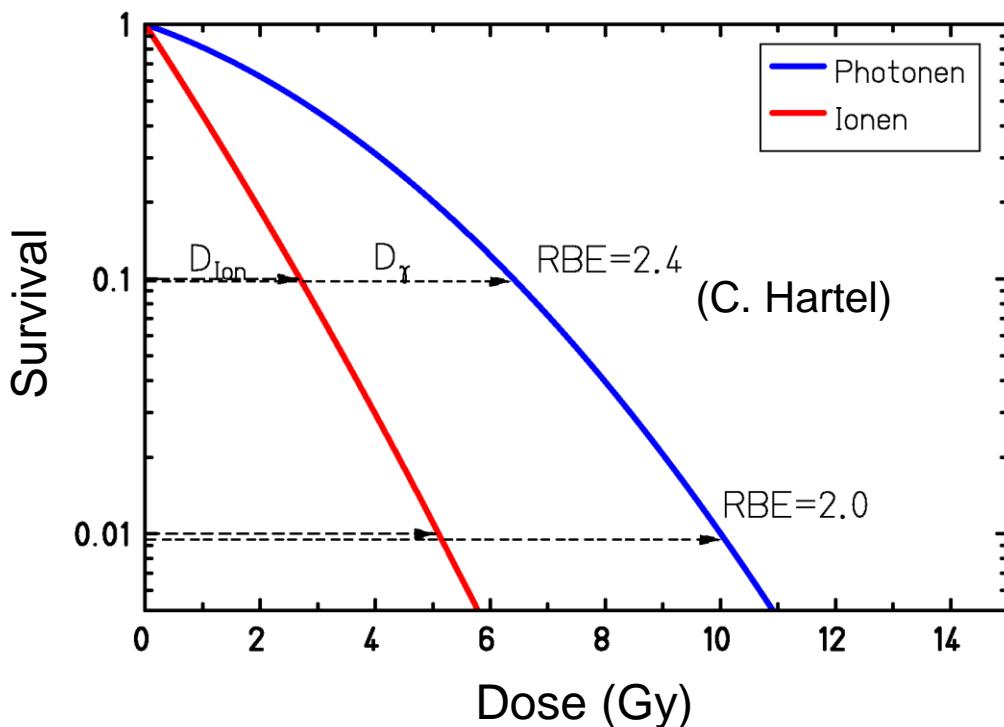
RBE comparison and impact analysis

Thomas Friedrich

GSI, Darmstadt, Germany

- Why and what: RBE?
- RBE characteristics: Radiobiology experiments
- Modelling
 - Japanese approach (dose scaling + MKM)
 - European approach (LEM I)
 - Advanced models (LEM IV)
- Strategies for model benchmarking
- Link to treatment planning
- RBE for protons
- Proton hypofractionation
- Criticism and challenges

Definition of RBE



$$RBE = \left. \frac{D_\gamma}{D_{Ion}} \right|_{\text{Isoeffect}}$$

“Relative biological effectiveness”

- RBE depends on:
 - LET
 - Dose
 - Particle type
 - Radiosensitivity
- complex quantity!

- Challenges
 - RBE systematics
 - RBE in complex radiation fields

RBE for different endpoints

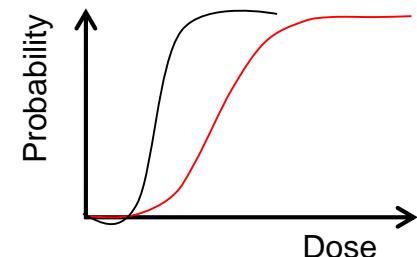
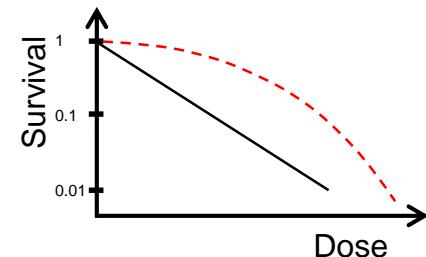
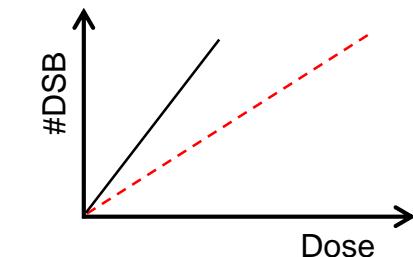
- DNA-DSB induction (linear)

$$N(t) = c_1 D$$

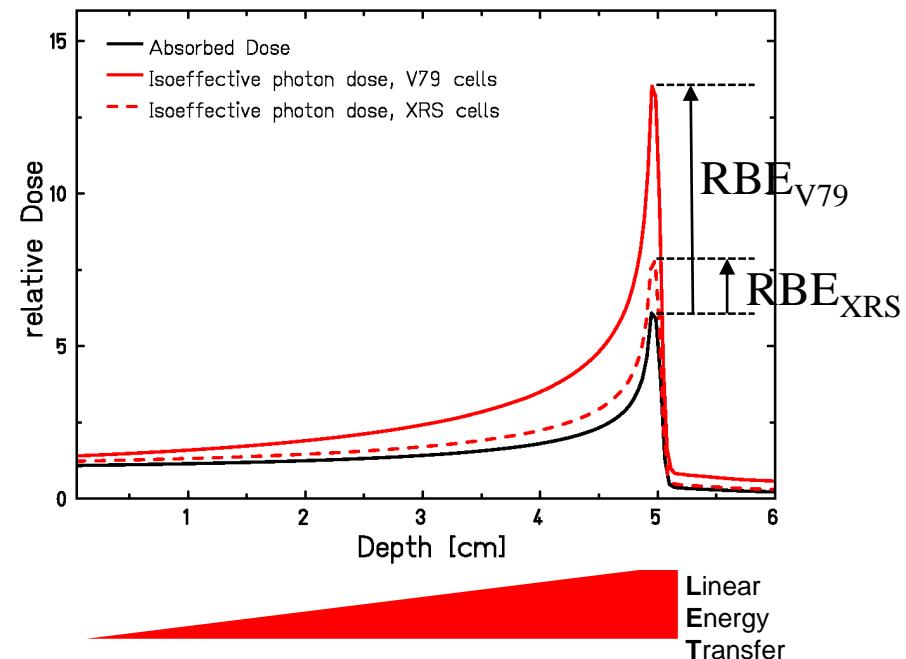
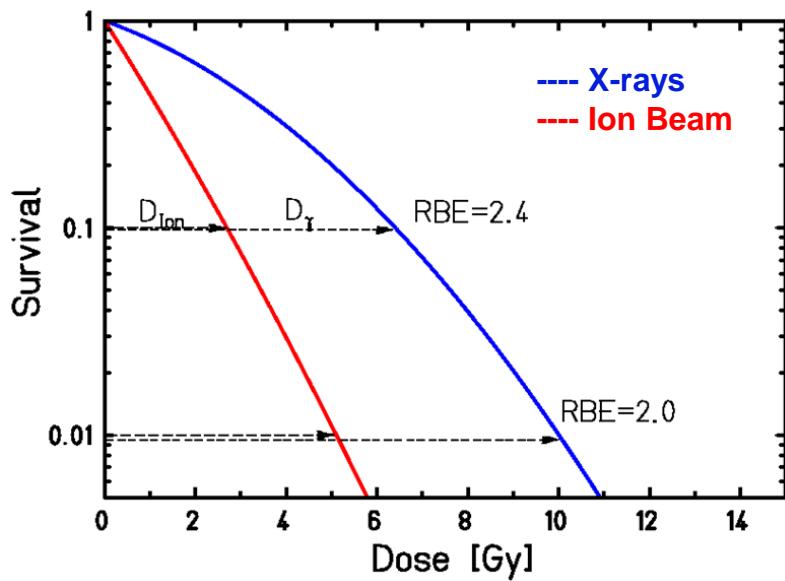
- Survival curves (linear-quadratic)

$$S = e^{-(\alpha D + \beta D^2)}$$

- Tumor control / Normal tissue damage (sigmoid)



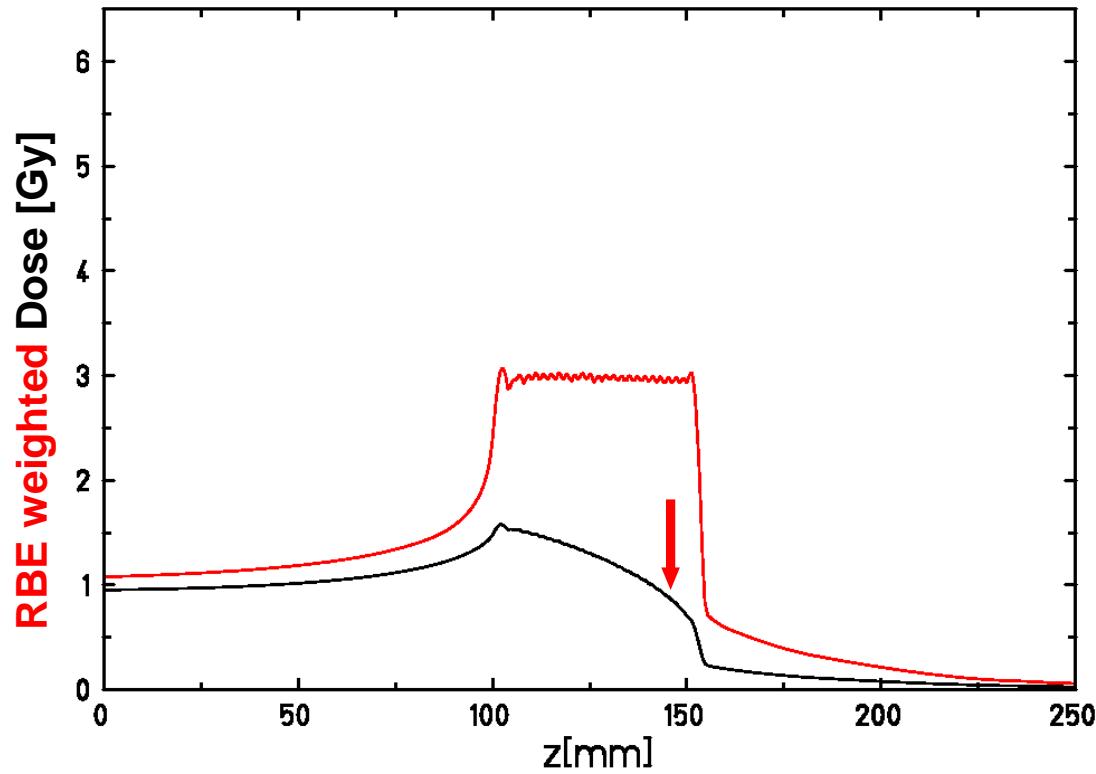
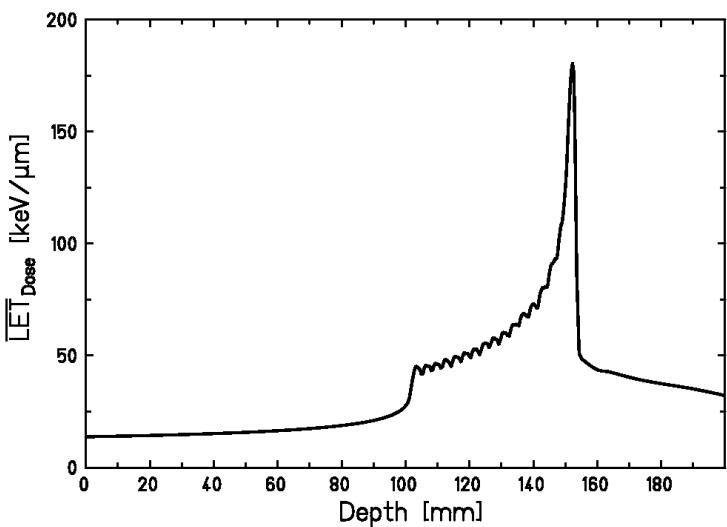
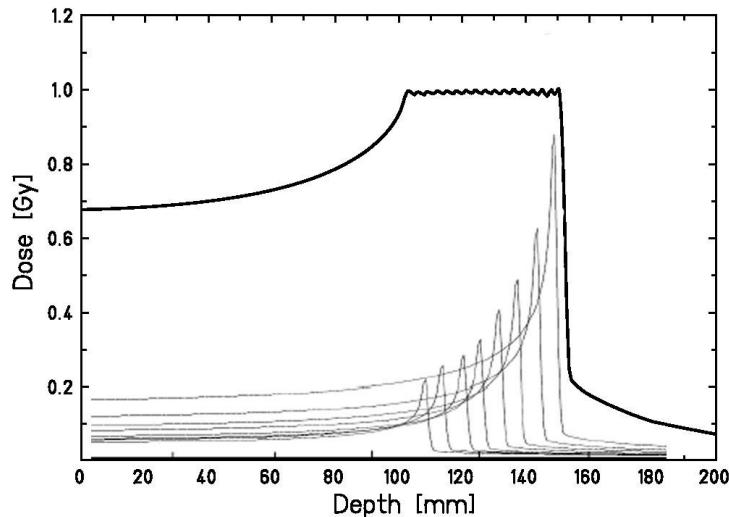
Why and what: RBE



$$RBE = \frac{D_{Photon}}{D_{Ion}} \Bigg|_{Isoeffect}$$

Depth/LET dependence → Physics
 Cell line dependence → Biology

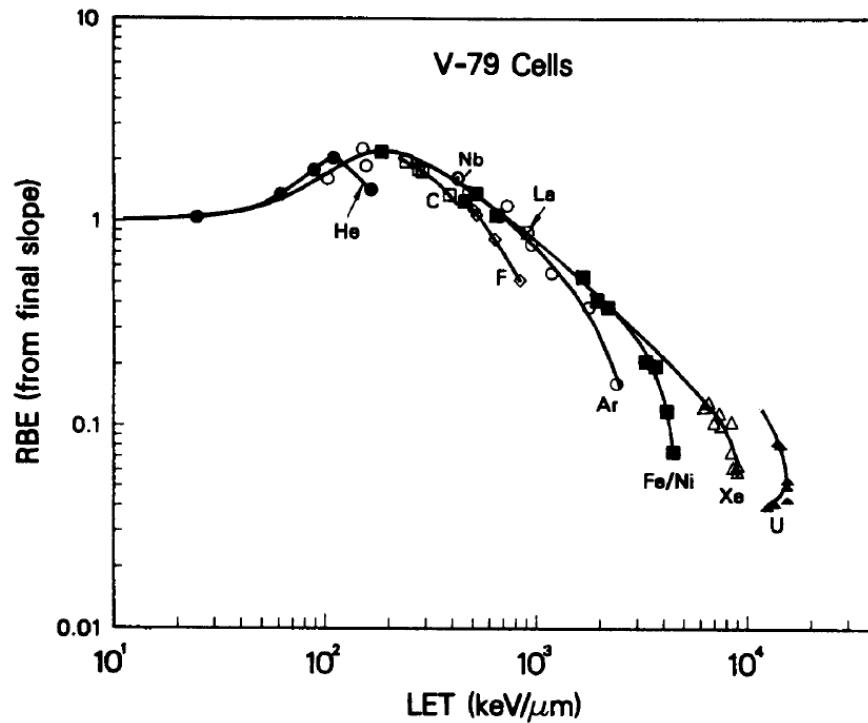
Why and what: RBE



Reduction of dose towards distal peak
to account for increase of RBE

RBE characteristics: Radiobiology experiments

RBE depends on LET

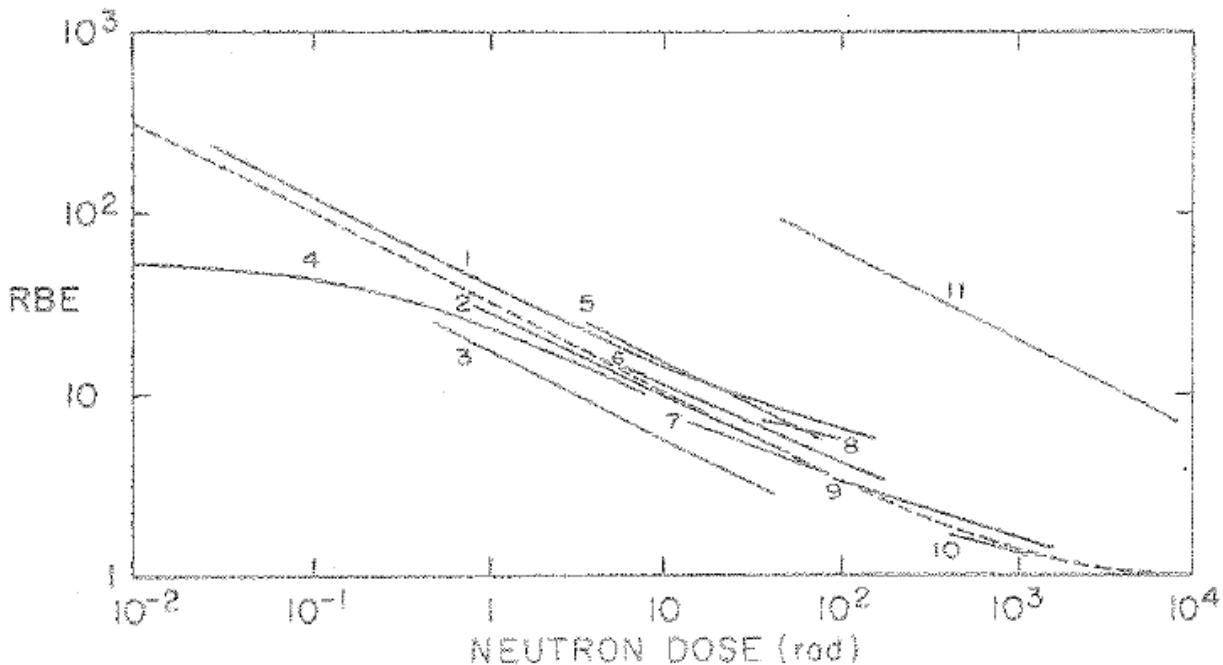


LET↑ → RBE↑ (RBE↓)
D↑ → RBE↓
Z↑ → RBE↓
α/β↑ → RBE↓

Kraft & Scholz, Adv.Space Res. 1994

RBE characteristics: Radiobiology experiments

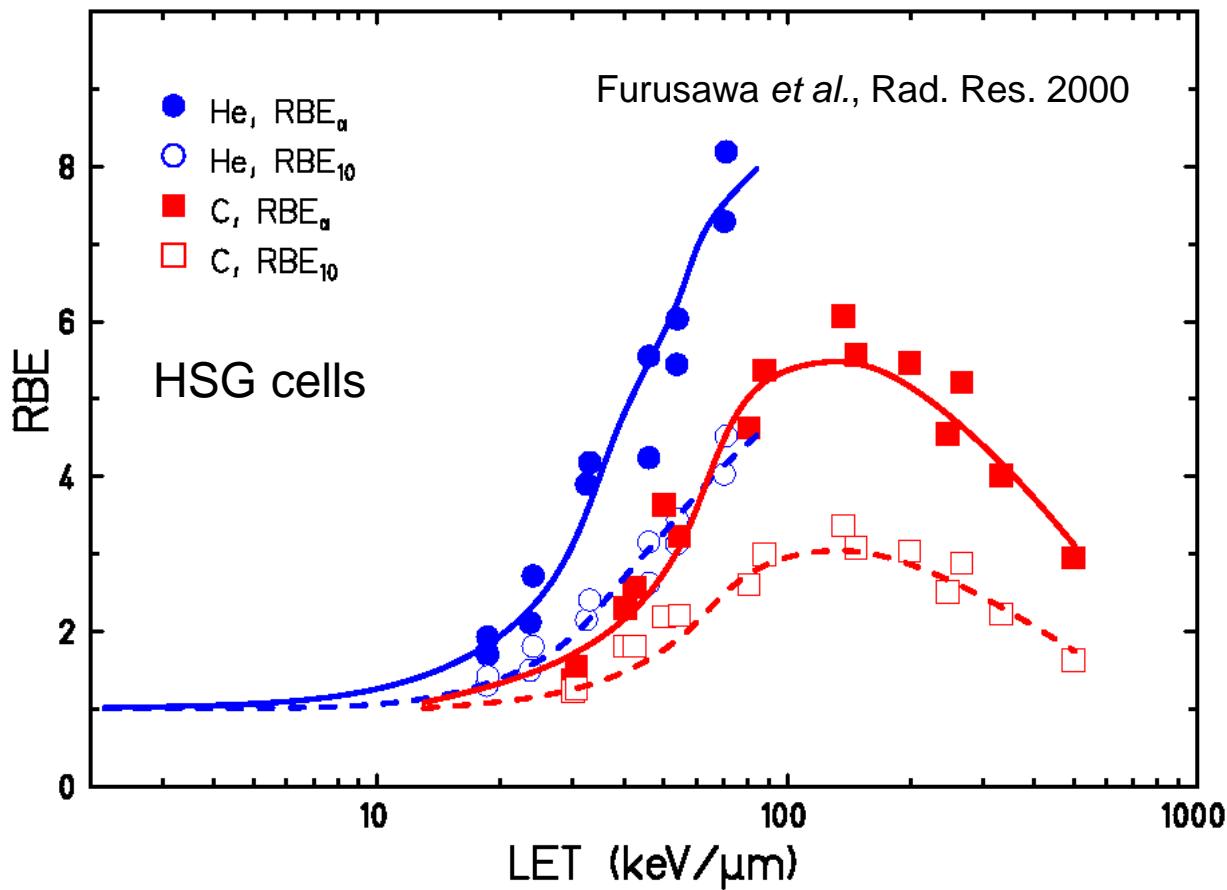
RBE depends on dose



Kellerer, Curr. Top. Radiat. Res. Quarterly 1972

LET↑ → RBE↑ (RBE↓)
D↑ → RBE↓
Z↑ → RBE↓
α/β↑ → RBE↓

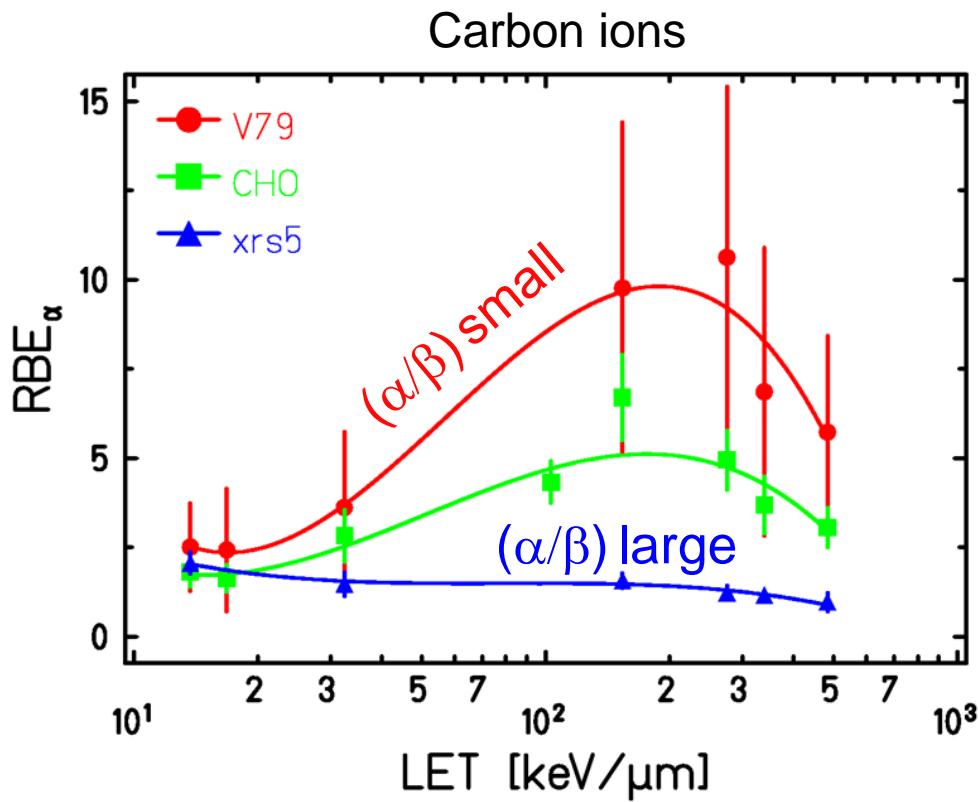
RBE depends on particle species



LET↑ →	RBE↑ (RBE↓)
D ↑ →	RBE↓
Z↑ →	RBE↓
$\alpha/\beta \uparrow \rightarrow$	RBE↓

RBE characteristics: Radiobiology experiments

RBE depends on radiosensitivity



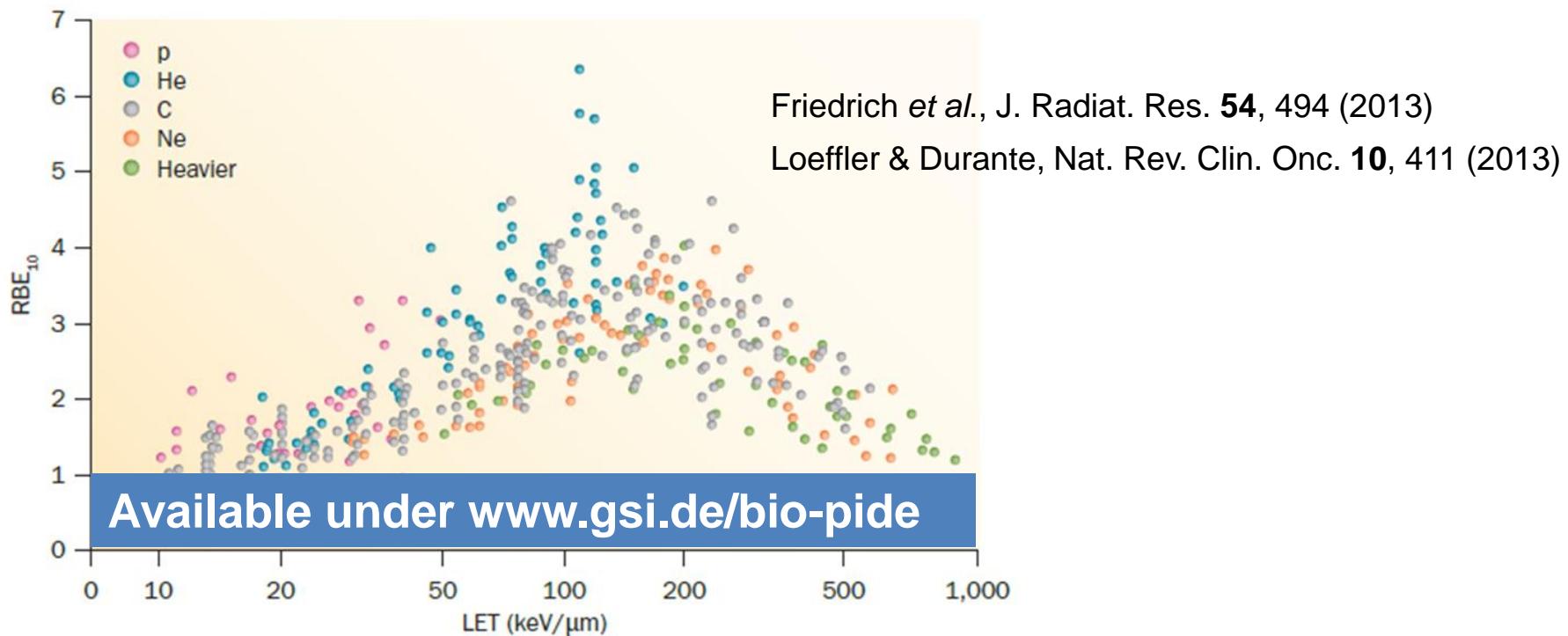
LET↑ → RBE↑ (RBE↓)
D↑ → RBE↓
Z↑ → RBE↓
α/β↑ → RBE↓

Weyrather et al. IJRB 75, 1357 (1999)

Particle irradiation data ensemble (PIDE)

Collection of experimental data

- > 70 publications
- > 800 photon and ion dose response curves (tabled α and β values)
- Various ion species, LET, energies, irradiation conditions, cell lines, ...



Available under www.gsi.de/bio-pide

ÜBER UNS

FORSCHUNG/BESCHLEUNIGER

JOBS/KARRIERE

PRESSE

@WORK

GSI > @Work > Forschung > Biophysik > Forschungsfelder > Biological Modelling > PIDE Project

Forschung

APPA/PNI

Biophysik

Forschungsfelder

DNA-Repair

Chromosome Aberrations

Tissue Effects

Clinical Radiobiology

Biological Modelling

PIDE Project

Physikalische Modellierung

Medical Physics

Radiation Physics

Weltraumforschung

ESA-IBER

NIRS IOL

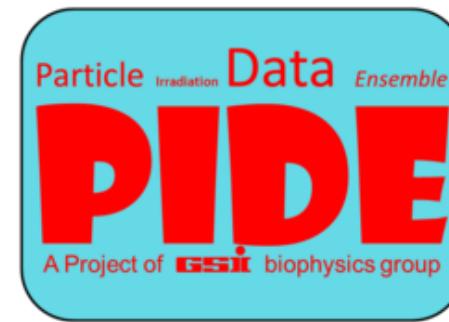
KVSF

PIDE Project

Access to the Particle Irradiation Data Ensemble

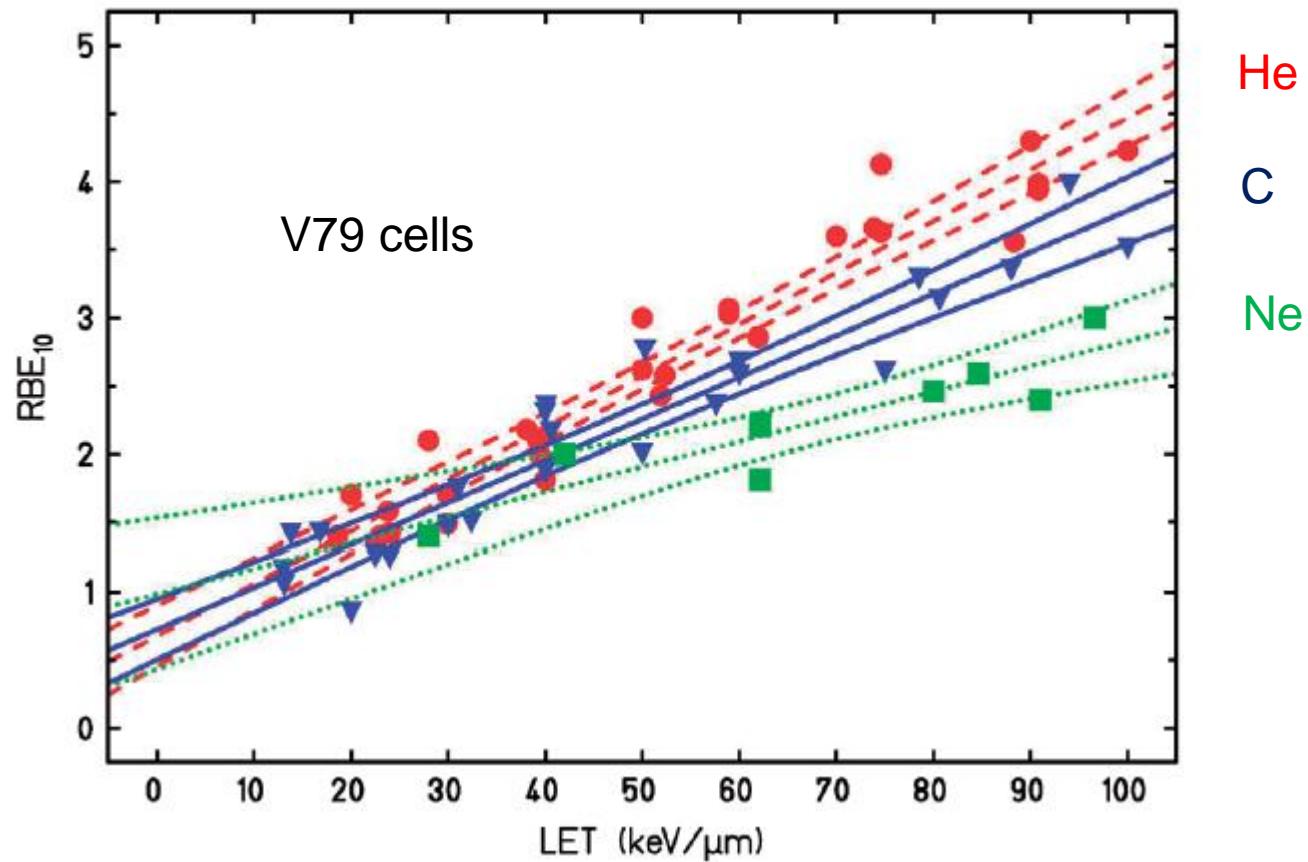
PIDE is:

- A radiobiological data base compiling more than 800 pairs of in-vitro cell survival experiments after photon and ion irradiation
- A compilation of results drawn from about 75 publications
- Convenient to study the relative biological effectiveness (RBE) for clonogenic cell survival as endpoint, or to benchmark RBE predicting models against experimental data
- Using the linear quadratic model to parameterize the radiosensitivity of the cell lines
- Discriminating between biological target, radiation quality and delivery techniques; all of these are relevant for RBE
- Presented as tables stored in an Excel file
- Freely available to the research community after registration on this home page



RBE characteristics: Radiobiology experiments

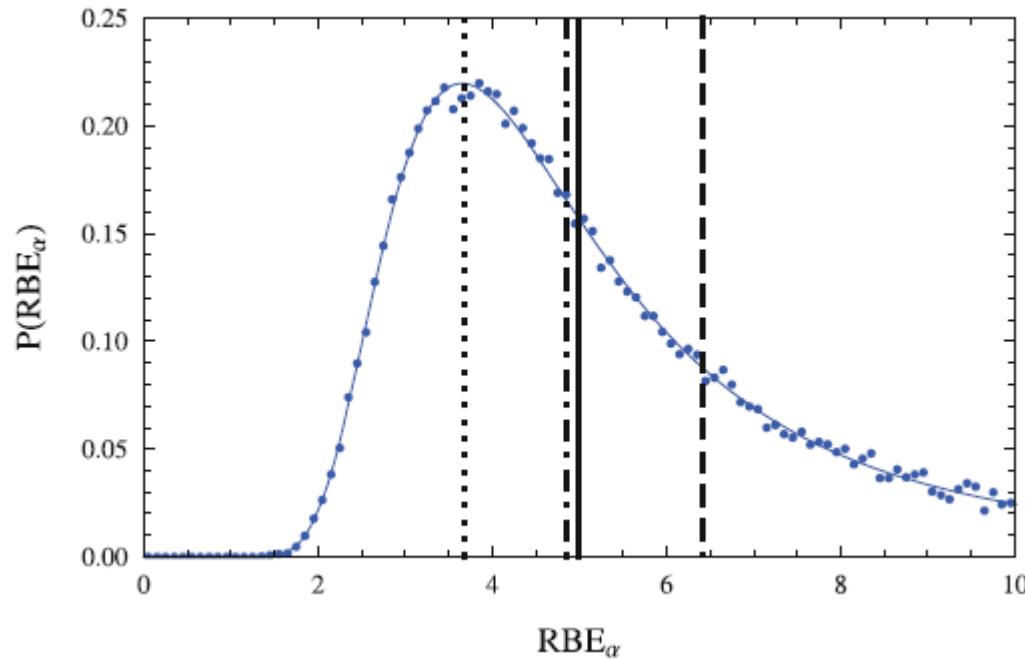
RBE depends not only on LET



Friedrich et al. Acta Oncol 2013

RBE uncertainty

- Ratio of two Gaussian random variable = random variable with long tailed distribution function



[Same issue for deriving α/β ratios]

Friedrich, Radiat Environ Biophys 2010

RBE characteristics: Radiobiology experiments

Preclinical endpoints:
RBE depends on fractionation

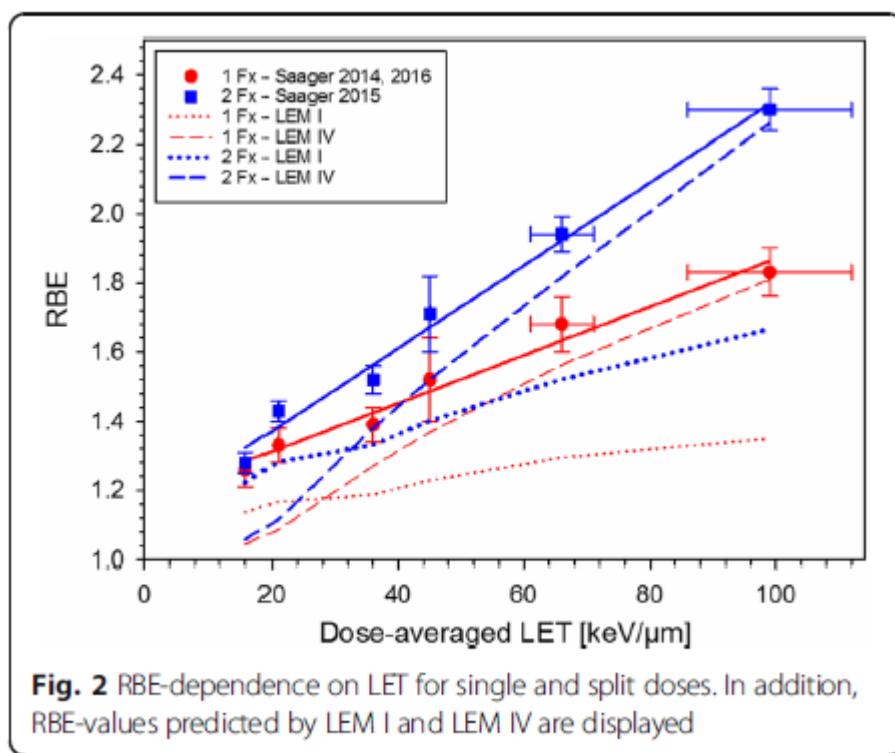


Fig. 2 RBE-dependence on LET for single and split doses. In addition, RBE-values predicted by LEM I and LEM IV are displayed

Saager et al. Radiat Oncol 2018

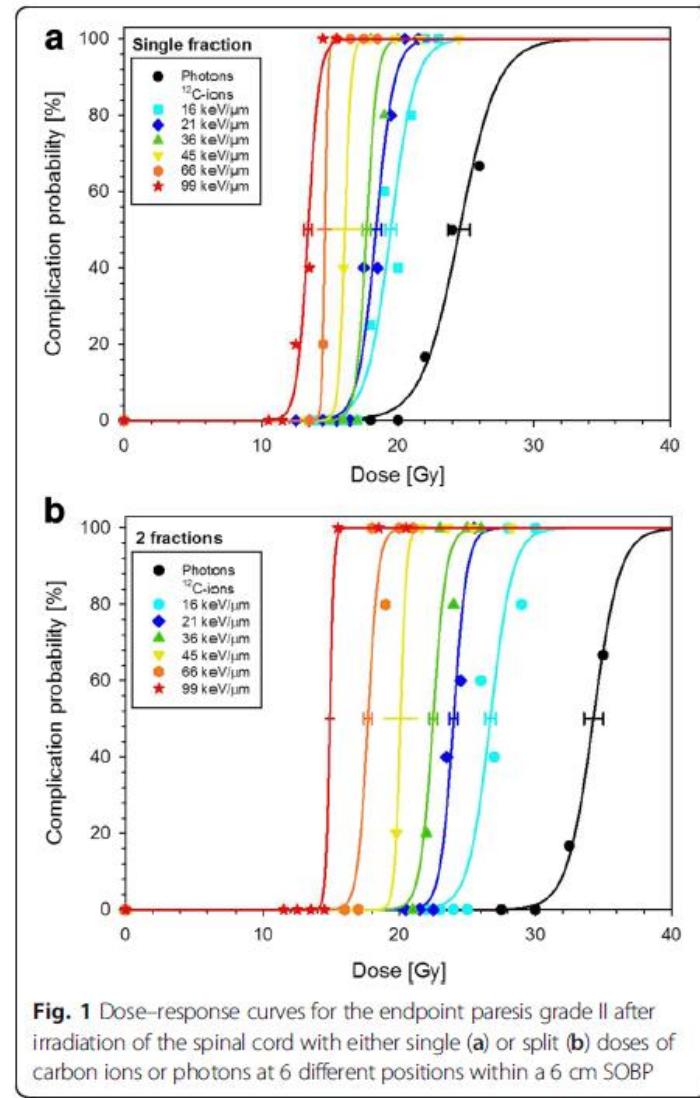
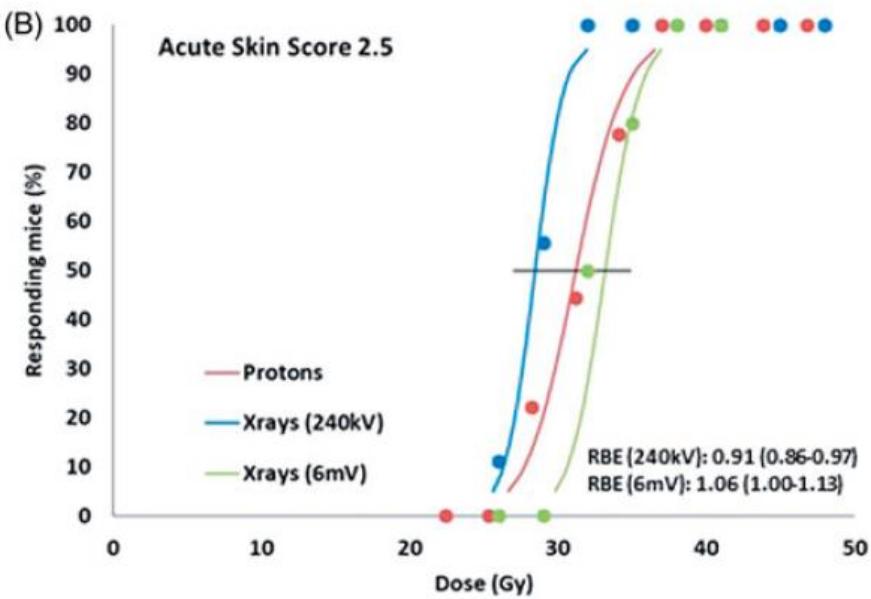
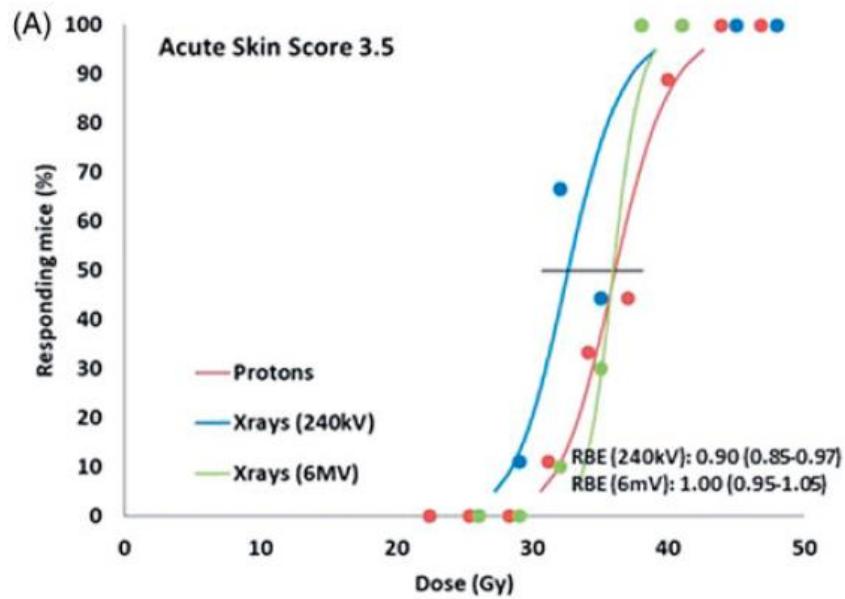


Fig. 1 Dose-response curves for the endpoint paresis grade II after irradiation of the spinal cord with either single (a) or split (b) doses of carbon ions or photons at 6 different positions within a 6 cm SOBP

Preclinical endpoints:
RBE depends on reference radiation



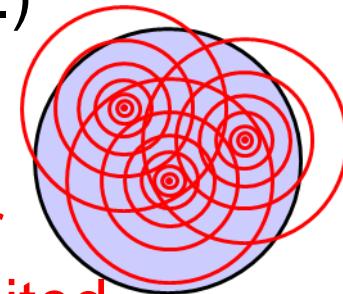
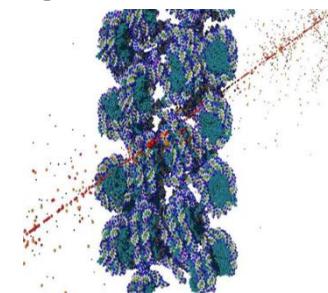
Sørensen et al. Acta Oncol 2017

“Essentially, all models are wrong,
but some are useful!”



George E.P. Box, statistician

- Two basic strategies of high LET effect modelling
 - „**Ab initio**“ models: detailed and complex
 - Physics: Monte-Carlo Transport calculations
 - Biology: Assumptions
 - Good tools to investigate mechanistic relationships, but limited predictive power
- **Pragmatic models:** Empirically based, simple
 - Physics: Representative quantities (LET...) or amorphous track structure
 - Biology: From reference situation
- Low number of free parameters, simple for applications, good predictive quality, but limited mechanistic basis.



Physics aspects of ion beams

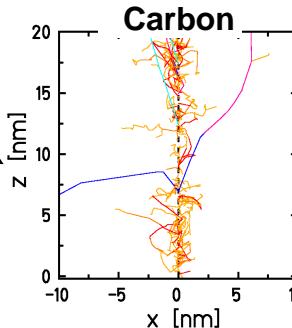
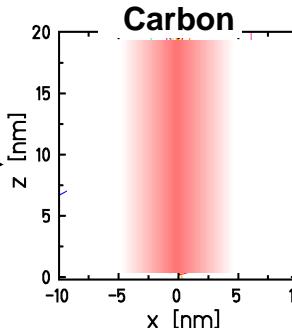
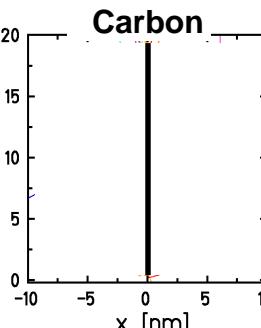
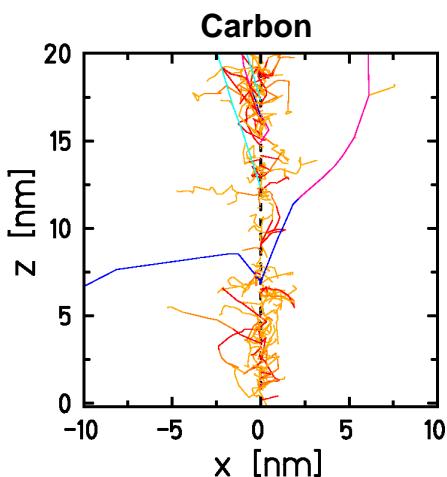
Model representation:

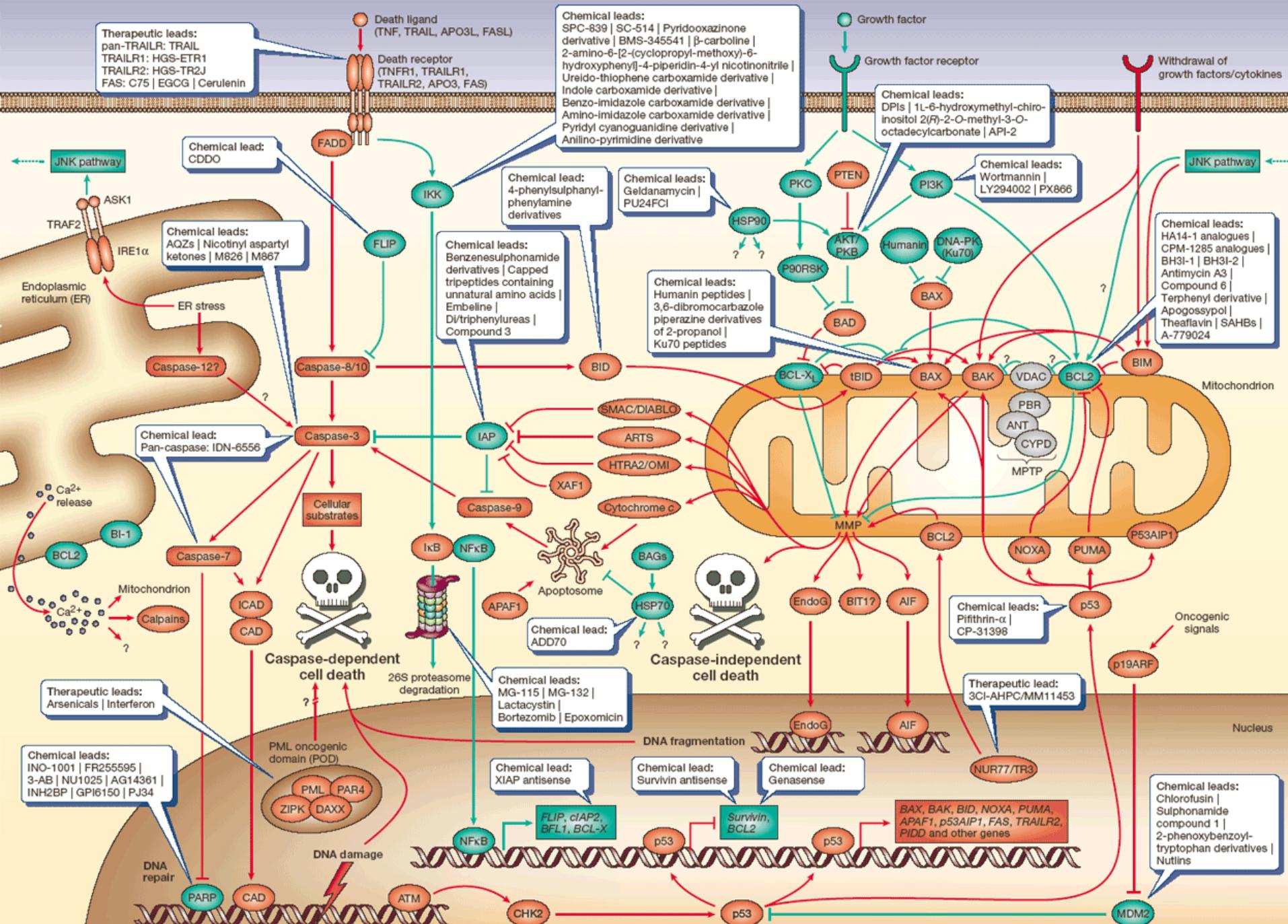
1-dimensional
„LET-approximation“

2-dimensional
„amorphous track“

3-dimensional
Full reconstruction

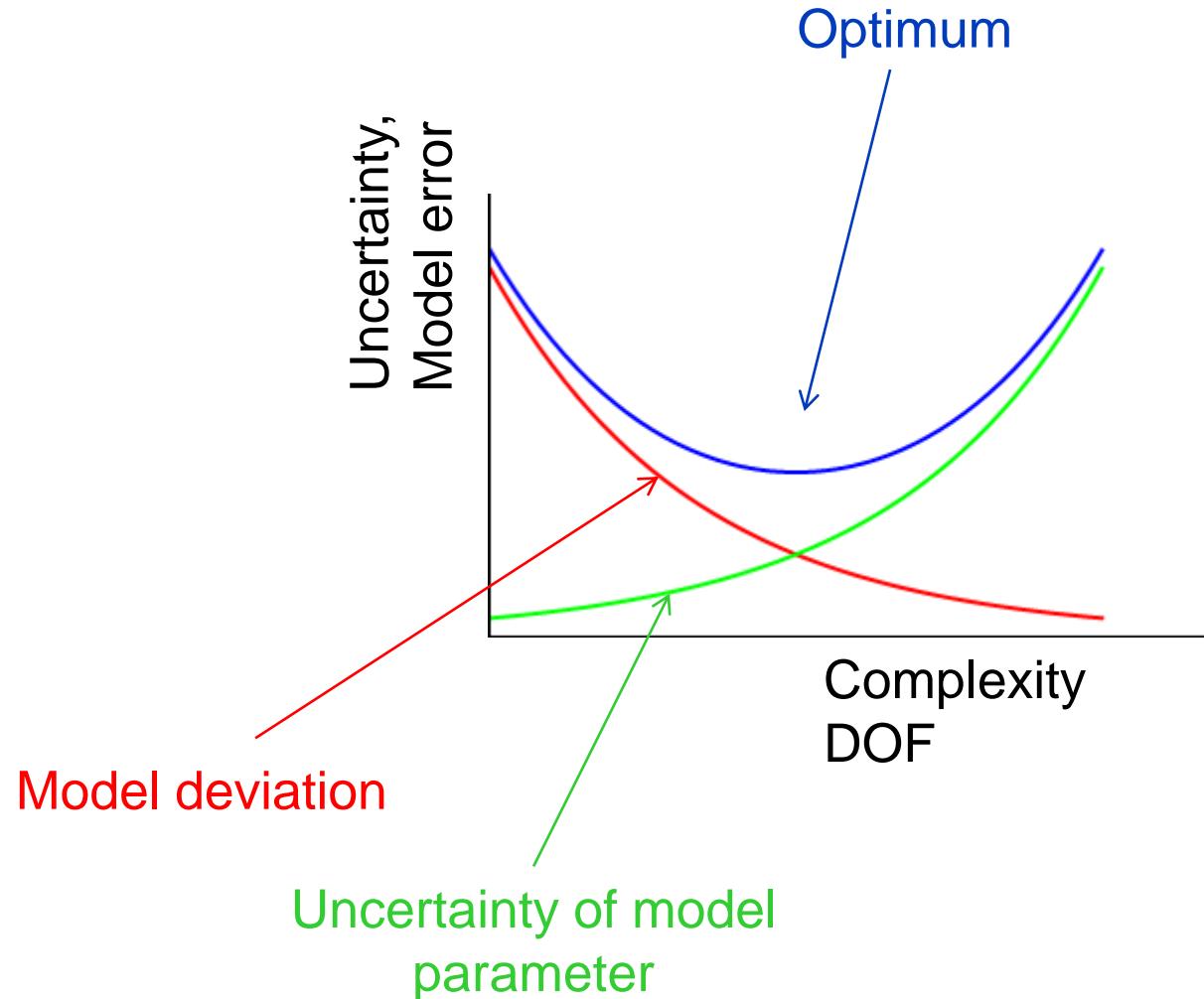
Track structure

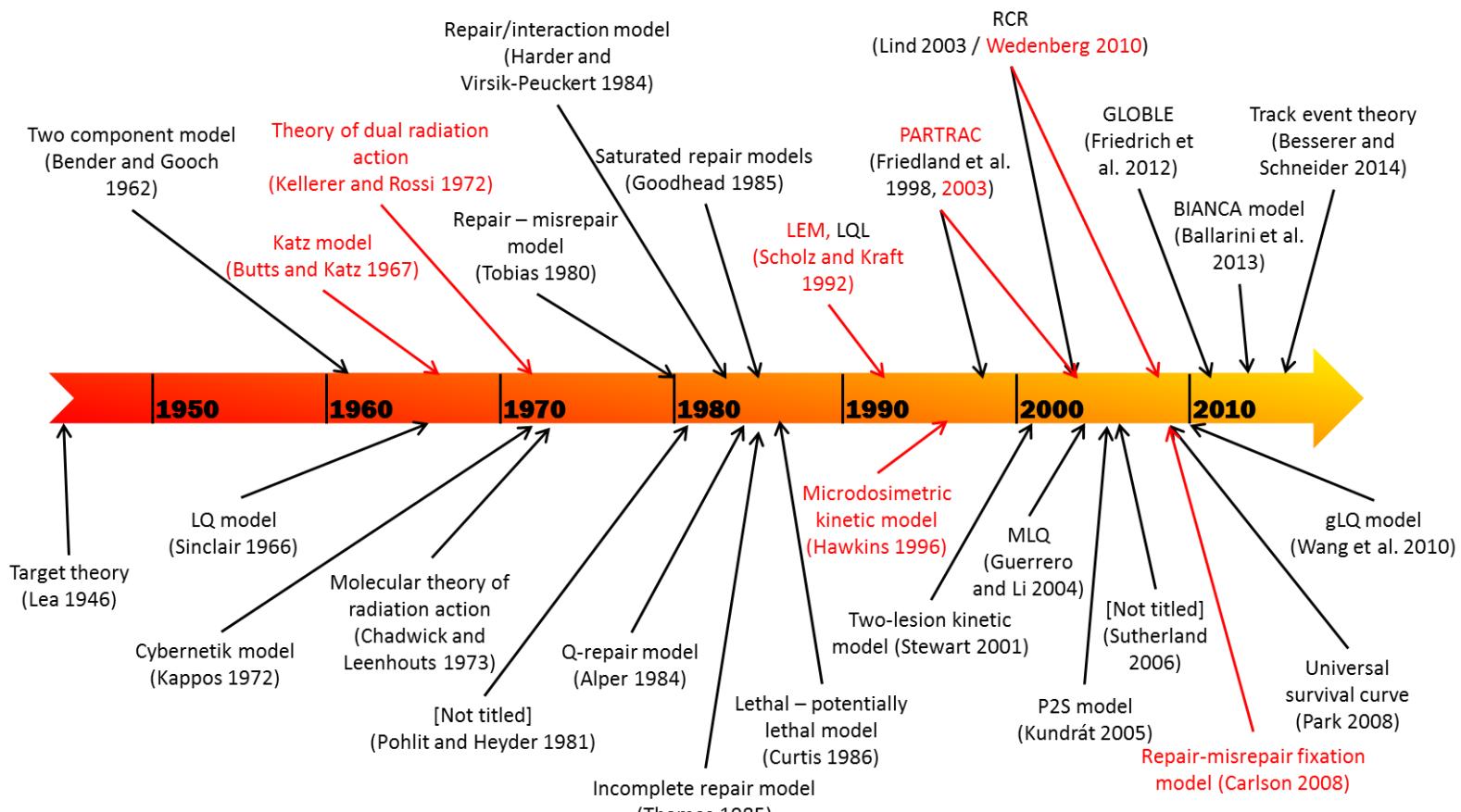




Task in modelling:

- Simple phenomenon
- Complex relationship
 - Physics
 - Biology

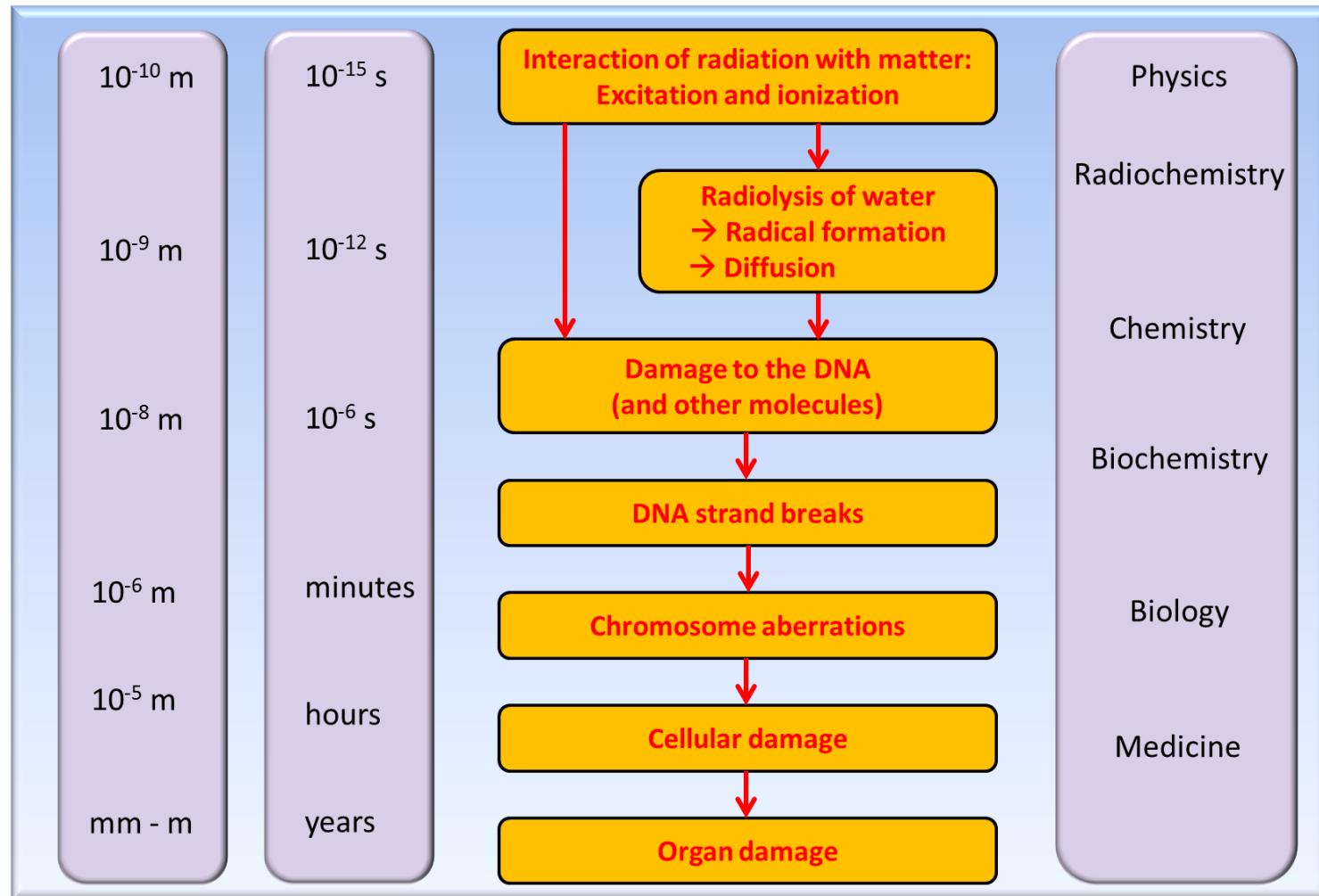




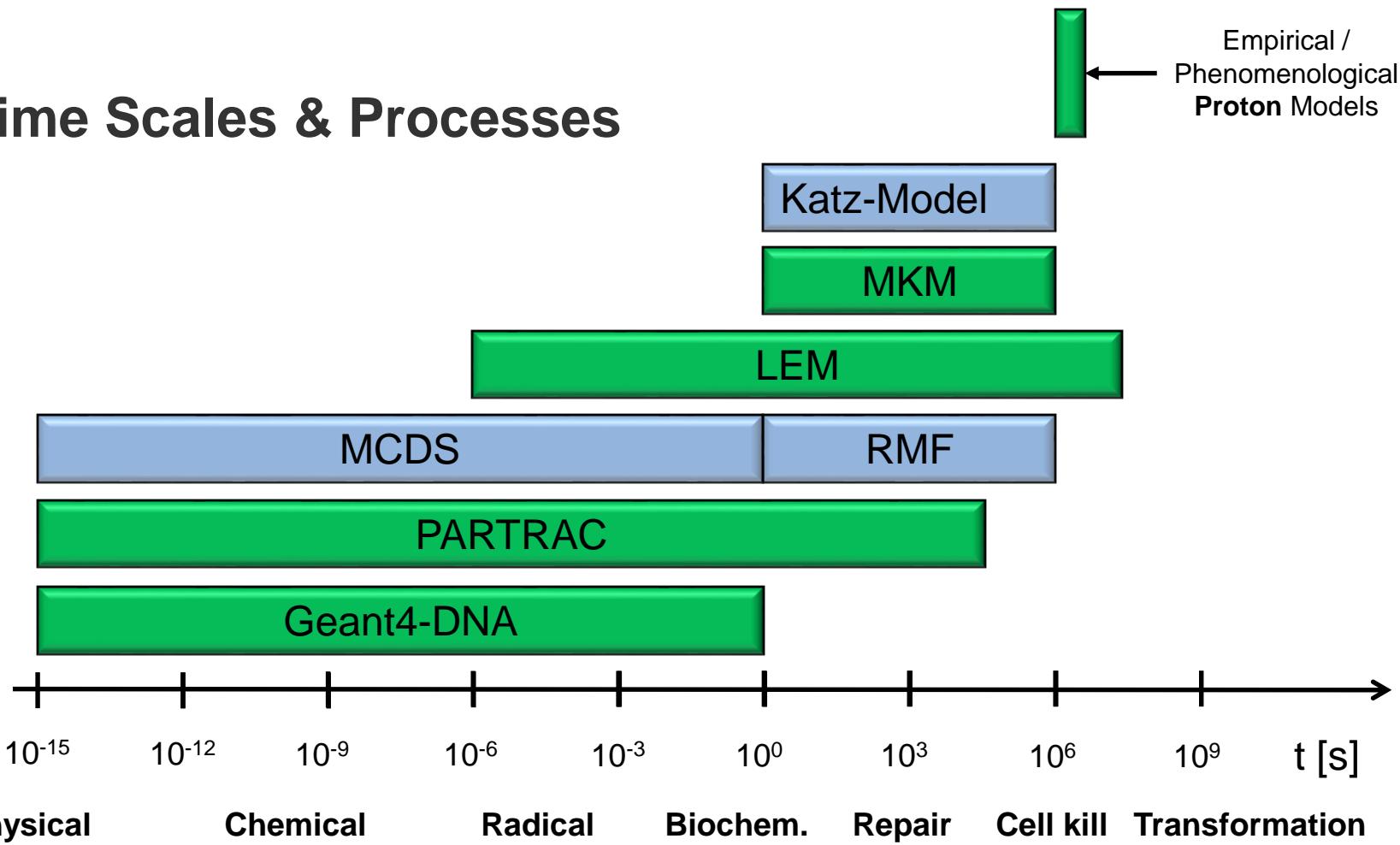
Black:
Red:

General purpose modelling
Modelling of high-LET / ion beam effects

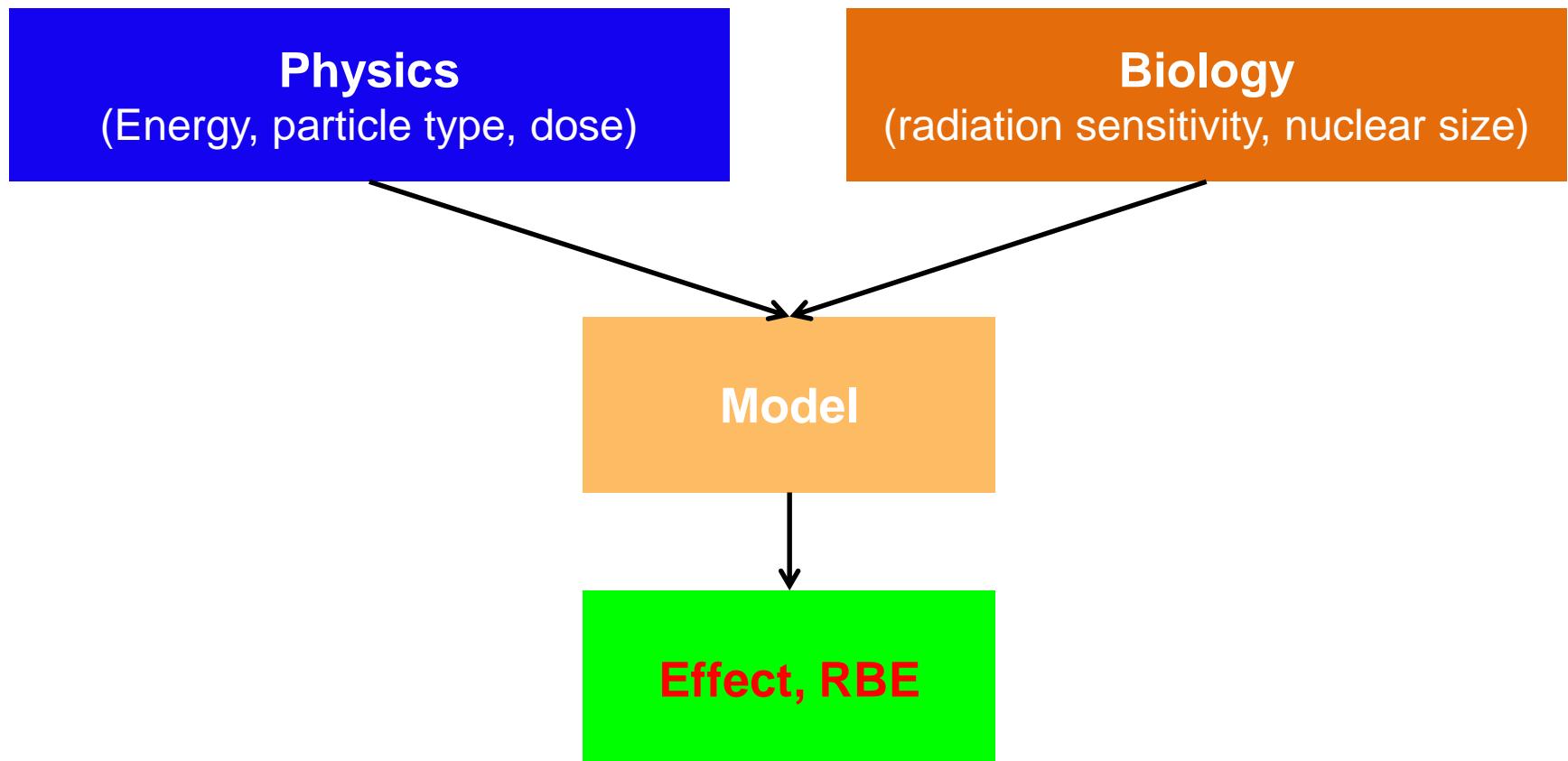
Space and Time in Radiation Response



Time Scales & Processes



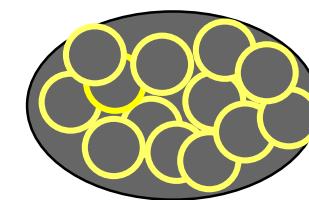
Course of RBE modeling



Microdosimetric Kinetic Model

- Extension of the Dual Radiation Action Model
- Cell nucleus divided into microscopic sites called *domains* ($\sim \mu\text{m}$)
- Survival fraction s_d of a domain after a spec. energy z is absorbed

$$-\ln s_d = Az + Bz^2$$

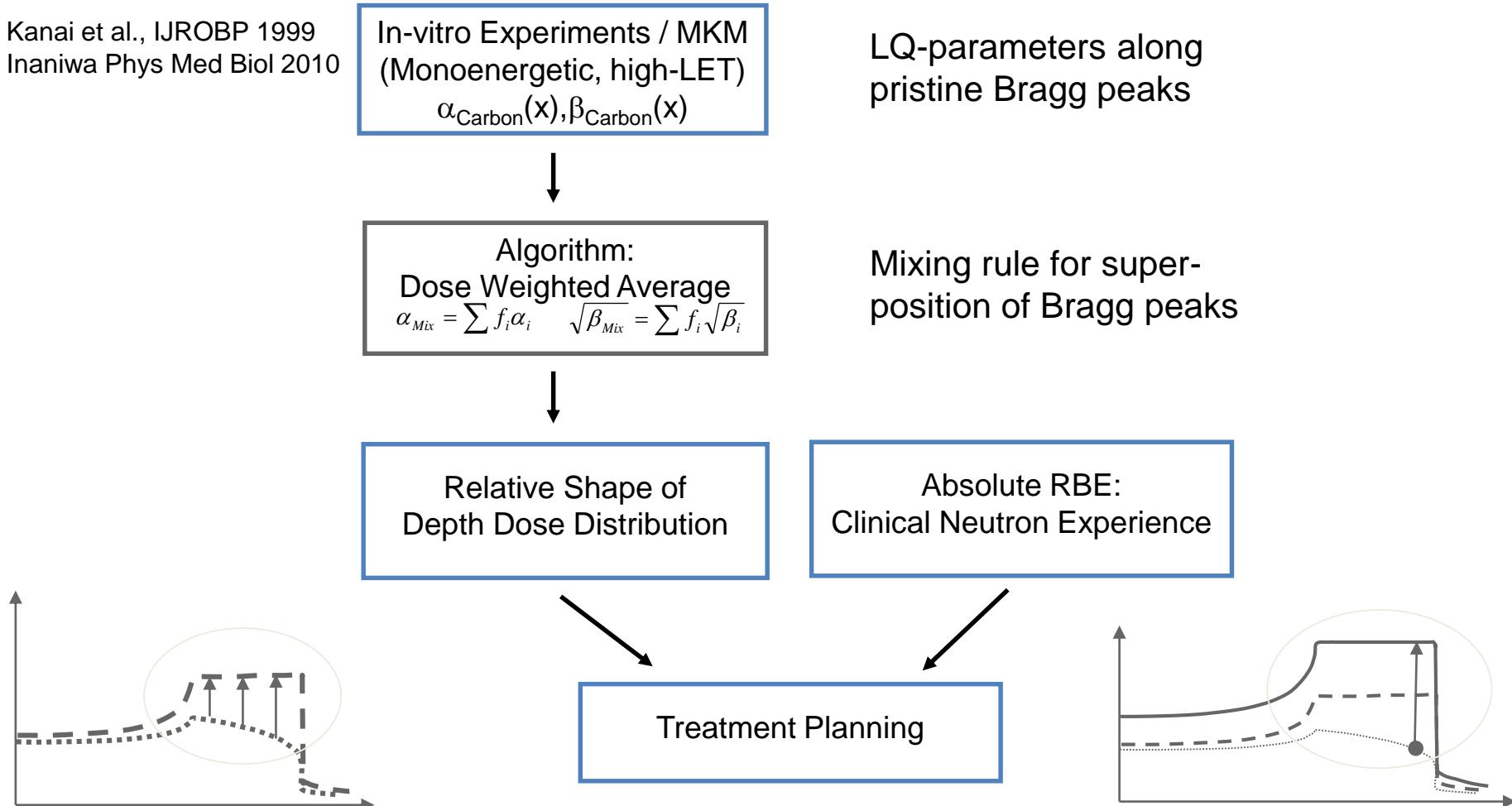


- Assumed to be independent of the radiation quality
- Number of hits to a domain: Poisson distribution
- Survival fraction of a cell: S
- The cell survives if all domain survive

$$-\ln S = (\alpha_0 + \beta z_{1,D})D + \beta D^2$$

Hawkins, Rad. Res. 160, 61-69 (2003)

Kanai et al., IJROBP 1999
 Inaniwa Phys Med Biol 2010



LQ-parameters along
pristine Bragg peaks

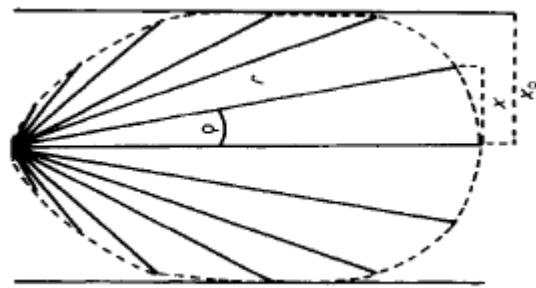
Mixing rule for super-
position of Bragg peaks

Absolute RBE:
Clinical Neutron Experience

Treatment Planning

Amorphous track structure models

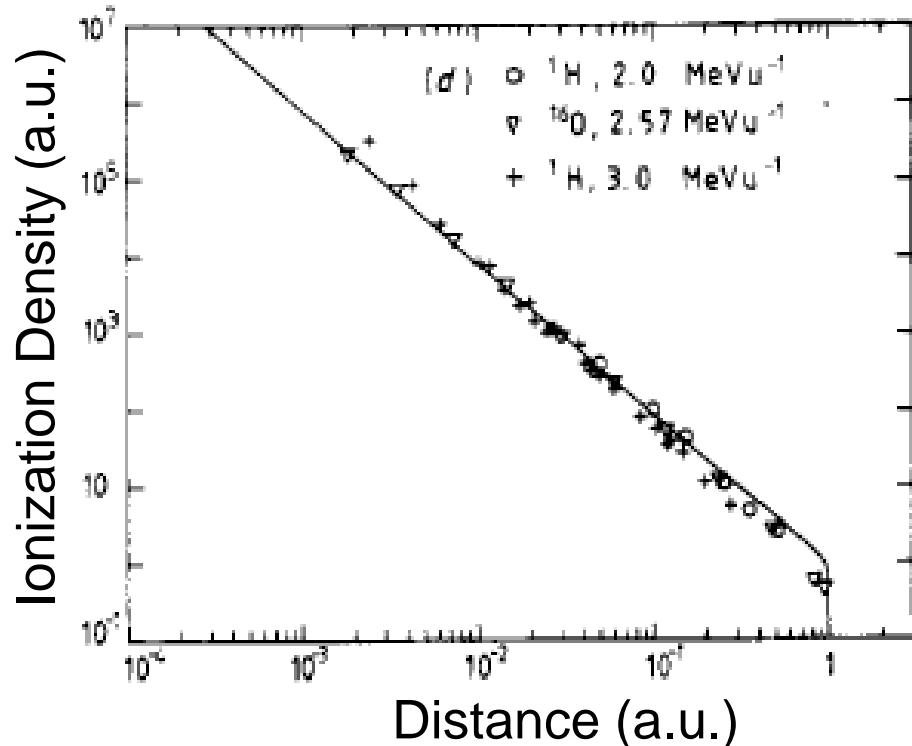
Relativistic ballistics:
Electron spectrum



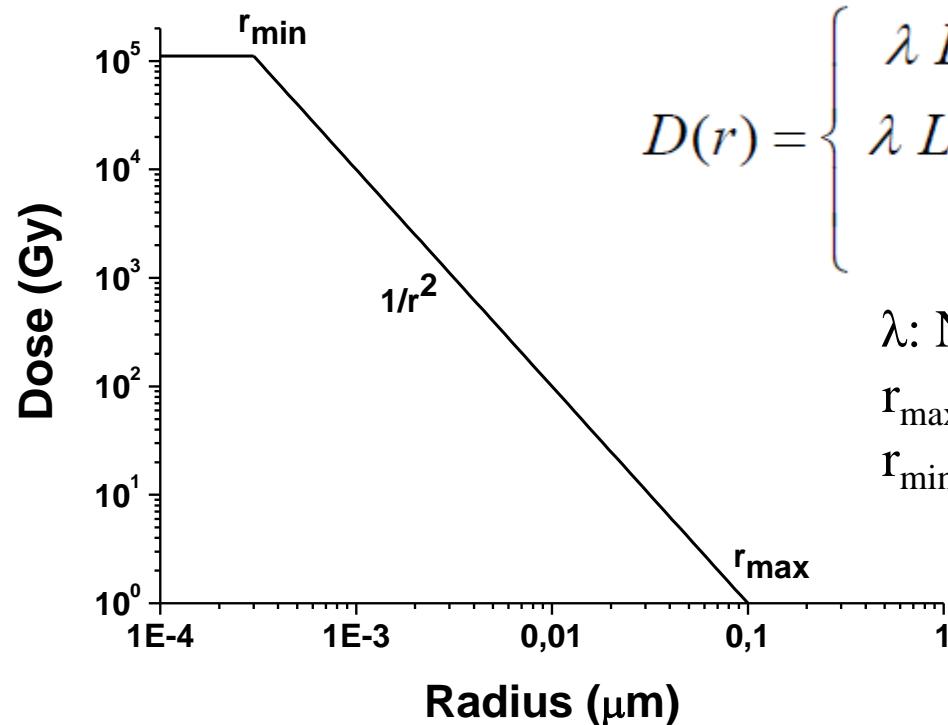
$$\rightarrow \rho_e(x) = 1.25 \times 10^{-4} \frac{Z^{*2}}{\beta^2} x^{-2}$$

(Kiefer, Phys. Med. Biol. 1986)

Microdosimetric measurements



Amorphous track structure



$$D(r) = \begin{cases} \lambda \text{LET} / r_{\min}^2 & : r < r_{\min} \\ \lambda \text{LET} / r^2 & : r_{\min} \leq r \leq r_{\max} \\ 0 & : r > r_{\max} \end{cases}$$

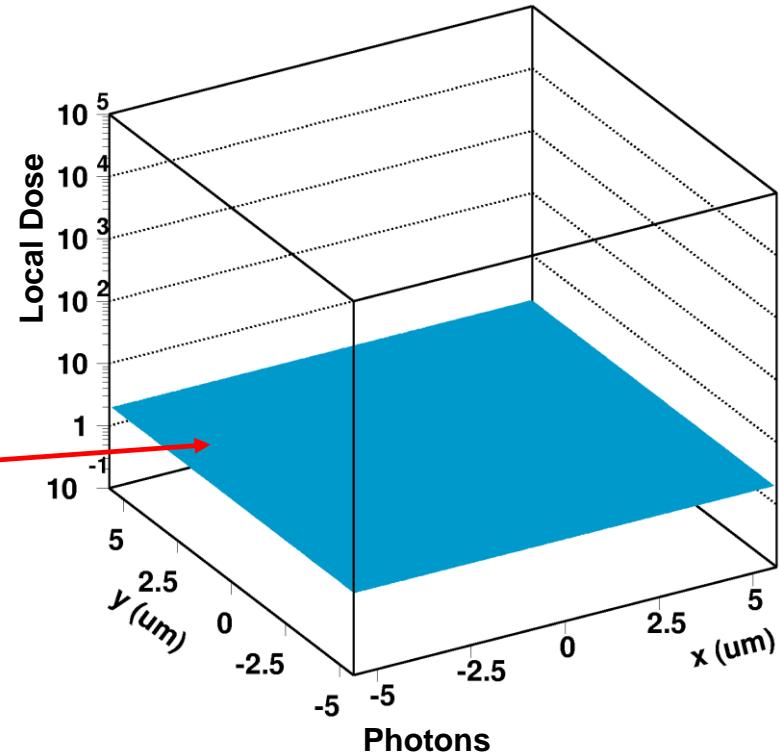
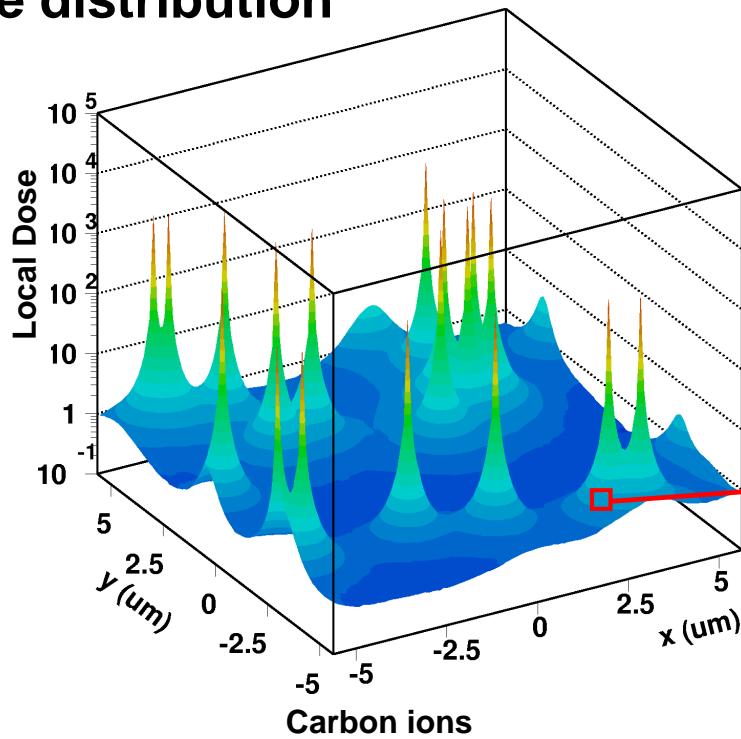
λ : Normalization

$r_{\max} = 0.062 E^{1.7}$ (E in MeV/u, r_{\max} in μm)

$r_{\min} = \beta r_c$ ($r_c = 6.5 \text{ nm}$)

- Probability distribution for ionization events („local dose“)
- Probability distribution for biologic lesions

Dose distribution

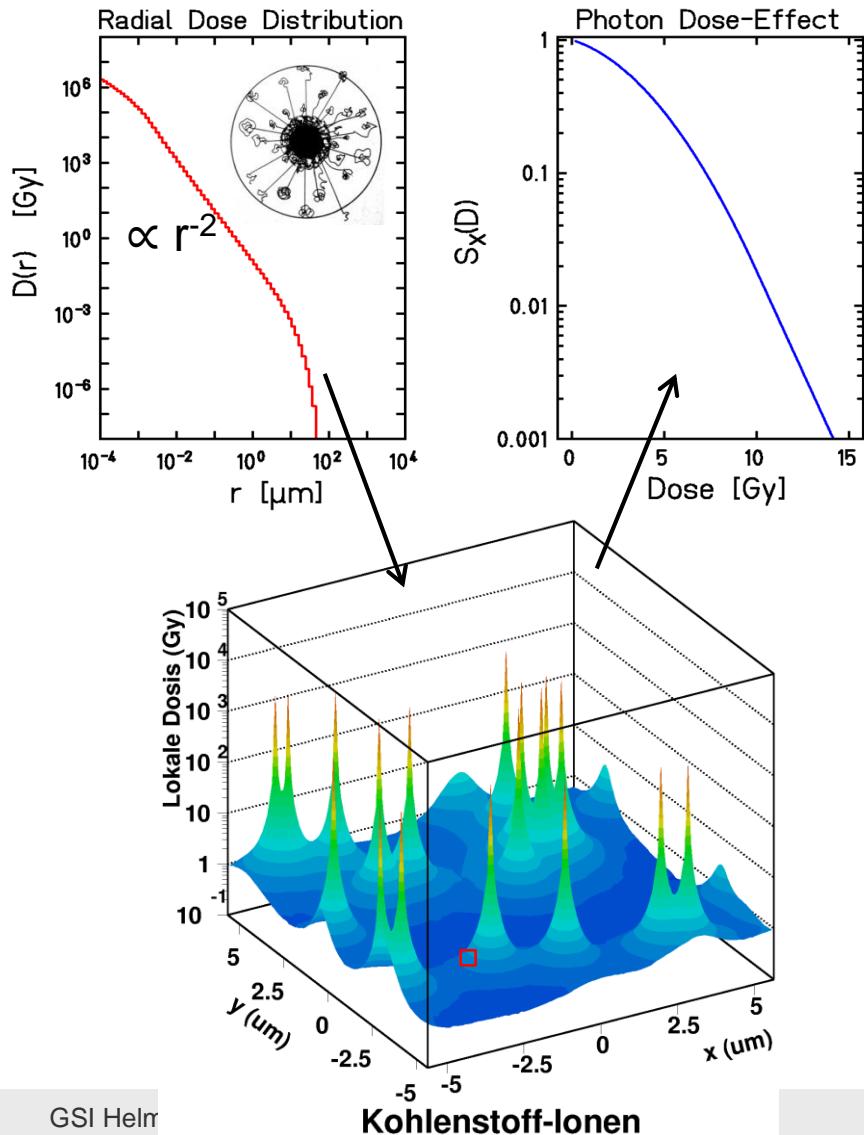


Microscopically the damage does not depend on radiation quality

Basic idea of LEM:

Extrapolate effect of photons to effect of ions

Integration over local effects



LEM I

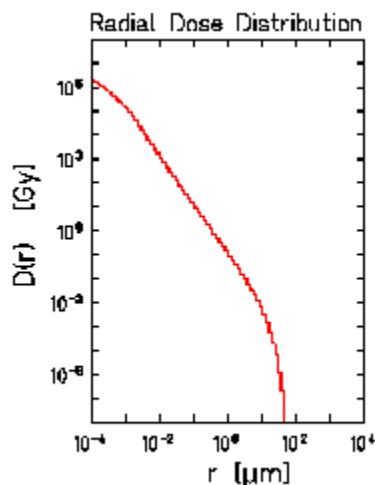
Summation over local effect increments

$$S = V_n^{-1} \exp \left\{ - \int \ln S_X(D(\vec{r})) d^3r \right\}$$

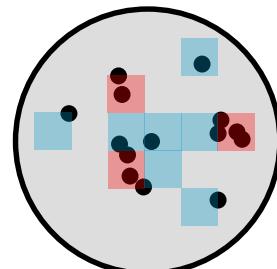
LEM I

- Adjusted for carbon ions
- Accurate predictions in target region
- Used in therapy ($\alpha/\beta = 2$ Gy)

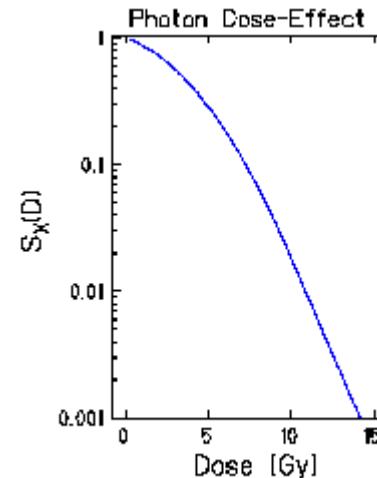
Scholz et al., Radiat. Environ. Biophys. 1997



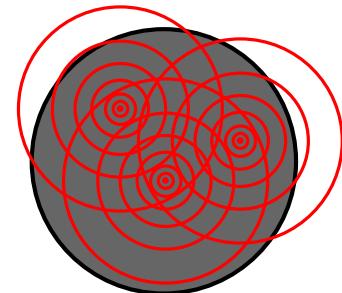
Amorphous
track structure



LEM IV



Equivalent
photon dose



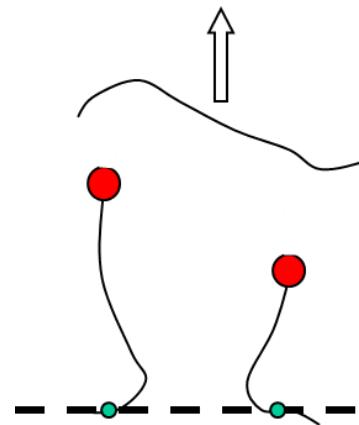
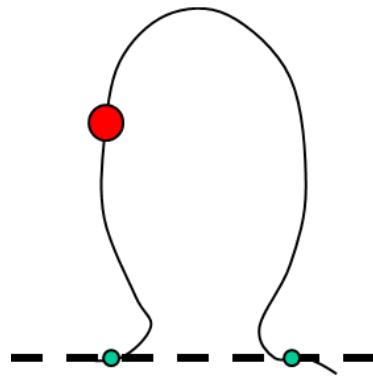
Local dose
distribution

Lesion
statistics

■:	7
■:	3

RBE

Lesions to chromatin loops



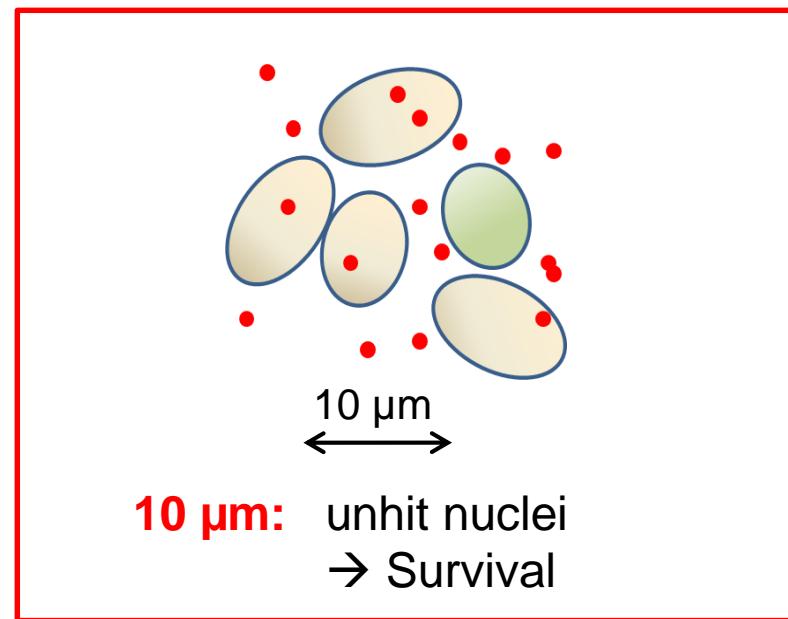
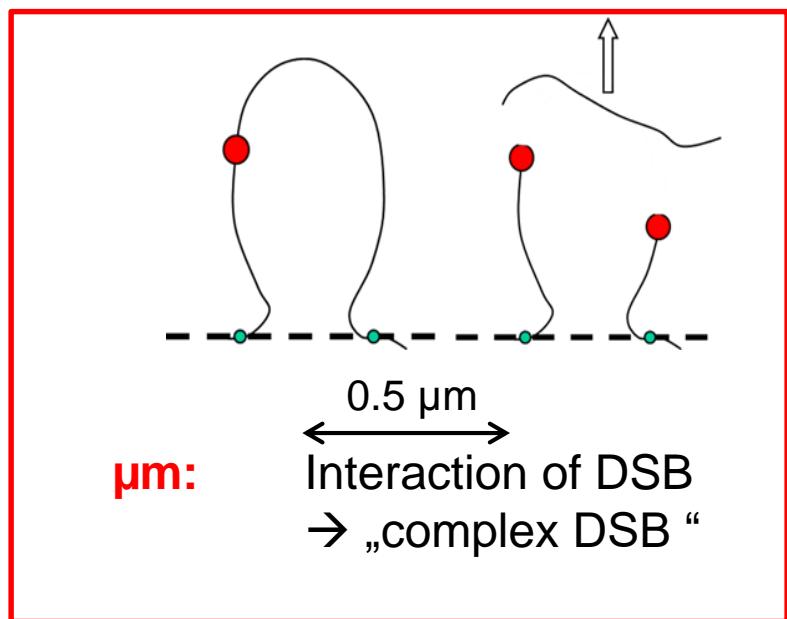
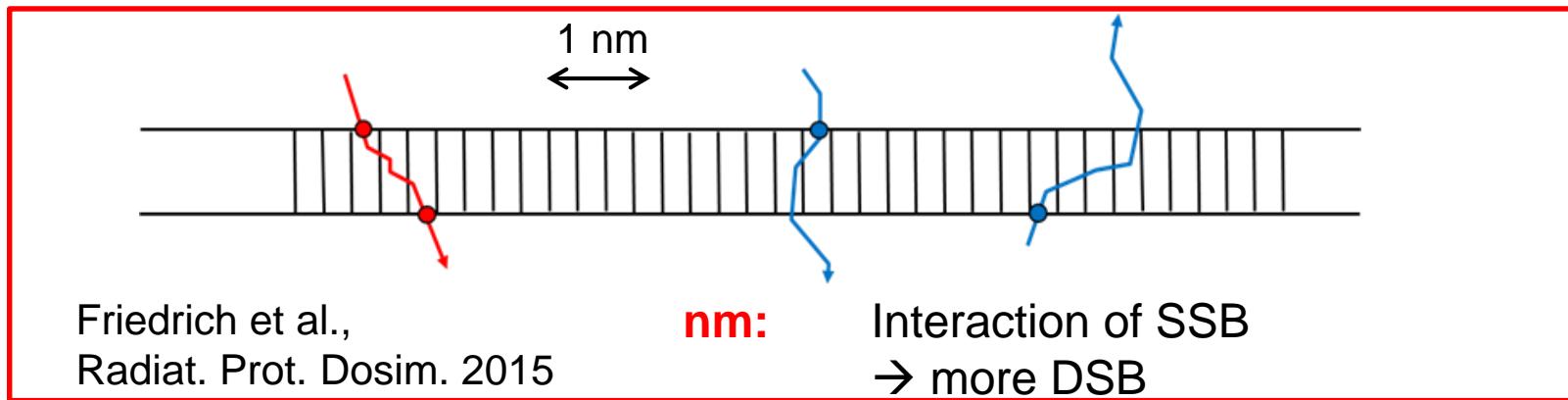
Isolated DSB (iDSB)

- One DSB within a loop
- Simple to repair
- Low lethality

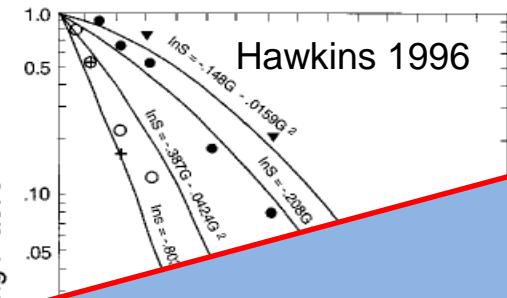
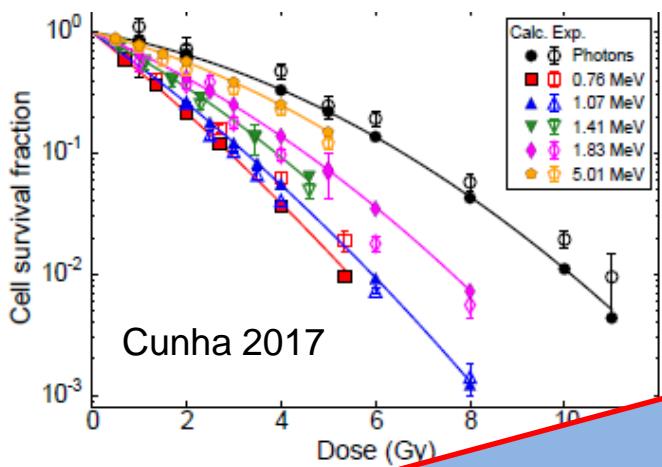
Clustered DSB (cDSB)

- Two or more DSB within a loop
- Harder, slower repair
- High lethality

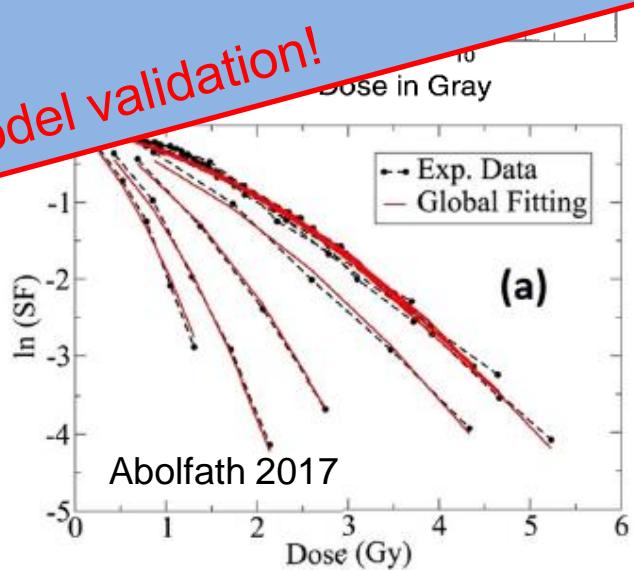
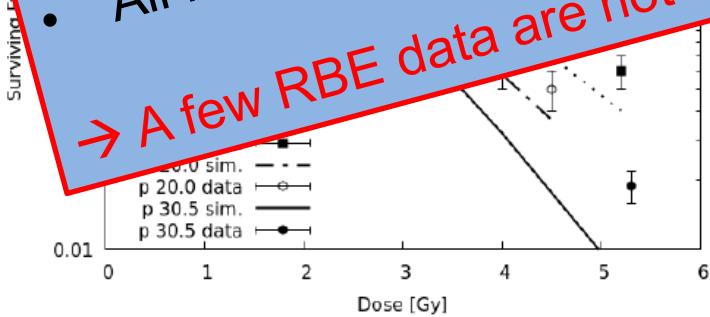
- Length scale ~ 0.5 μm ~ 2 Mbp
- Non-local interaction
- Independent lesion processing in different domains



Model benchmarking



- Contradiction:
- Models have different assumptions and make different predictions
 - All models describe RBE data well
- A few RBE data are not sufficient for model validation!

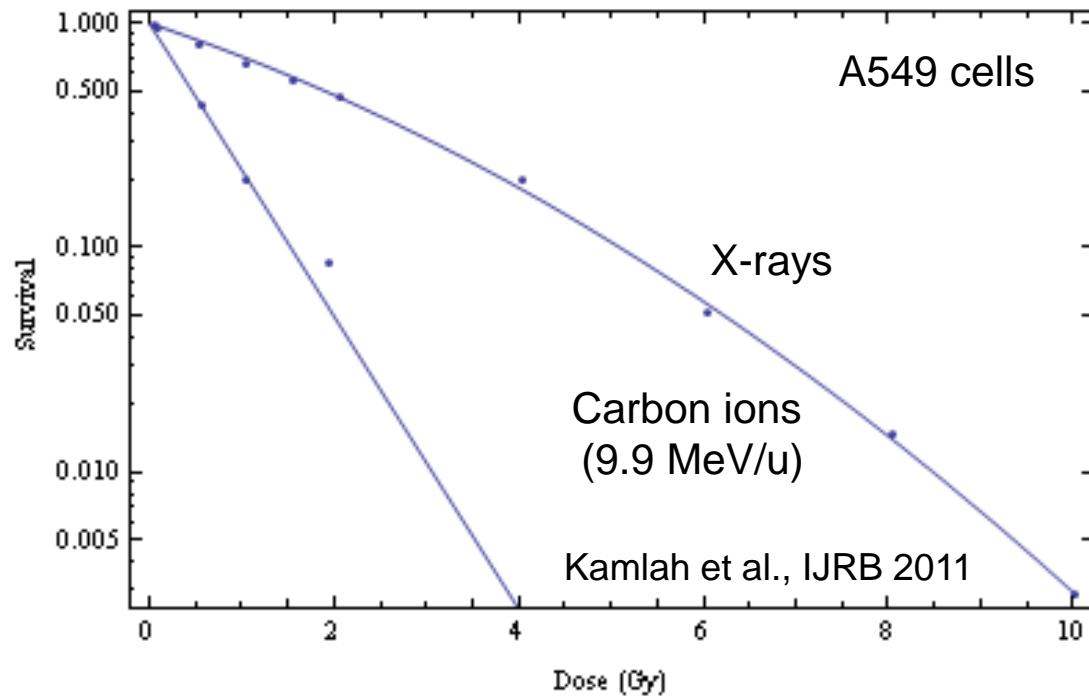


A proposed list of strategies to challenge model assumptions

1. Reflect rich **systematics of RBE(D, LET, Z, α/β)**
 2. Use large **data collections** to reach significance
 3. Test model performance for other **radiation qualities**
 4. Apply model to **different exposure scenarios**
 5. Extend model foundations to **different endpoints**
 6. Perform **dedicated experiments** addressing model assumptions
 7. Check for **model robustness**
-
- Such strategies allow to explore the performance and limitations of model ingredients
 - Consistency test by jointly describing different aspects

Here: Application examples for LEM IV

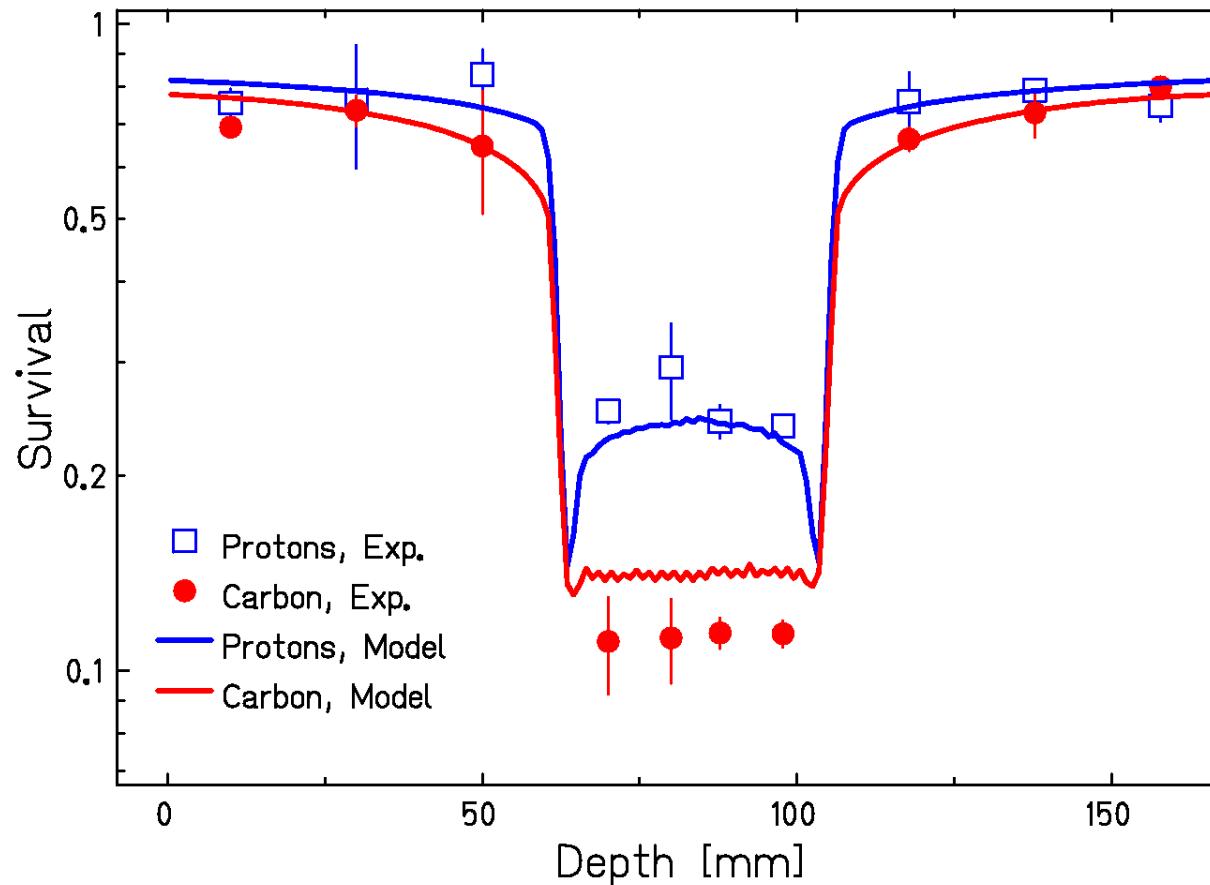
Model benchmarking



Local effect model “LEM IV”: Prediction of high LET action, no fit!

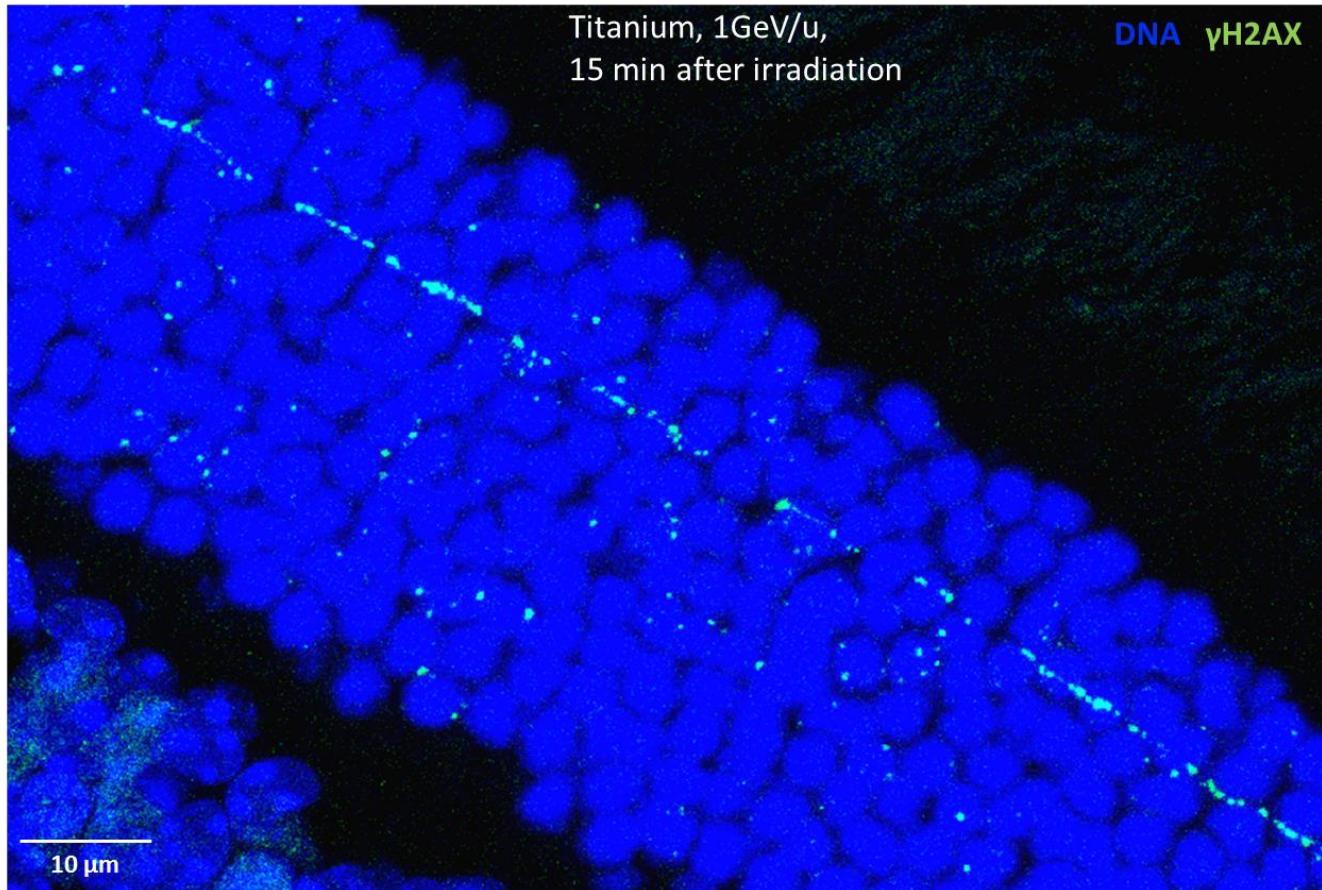
Elsässer *et al.*, IJROBP **78**, 1177 (2010)
Friedrich *et al.*, IJRB **88**, 103 (2012)

Extended Bragg peaks for therapy



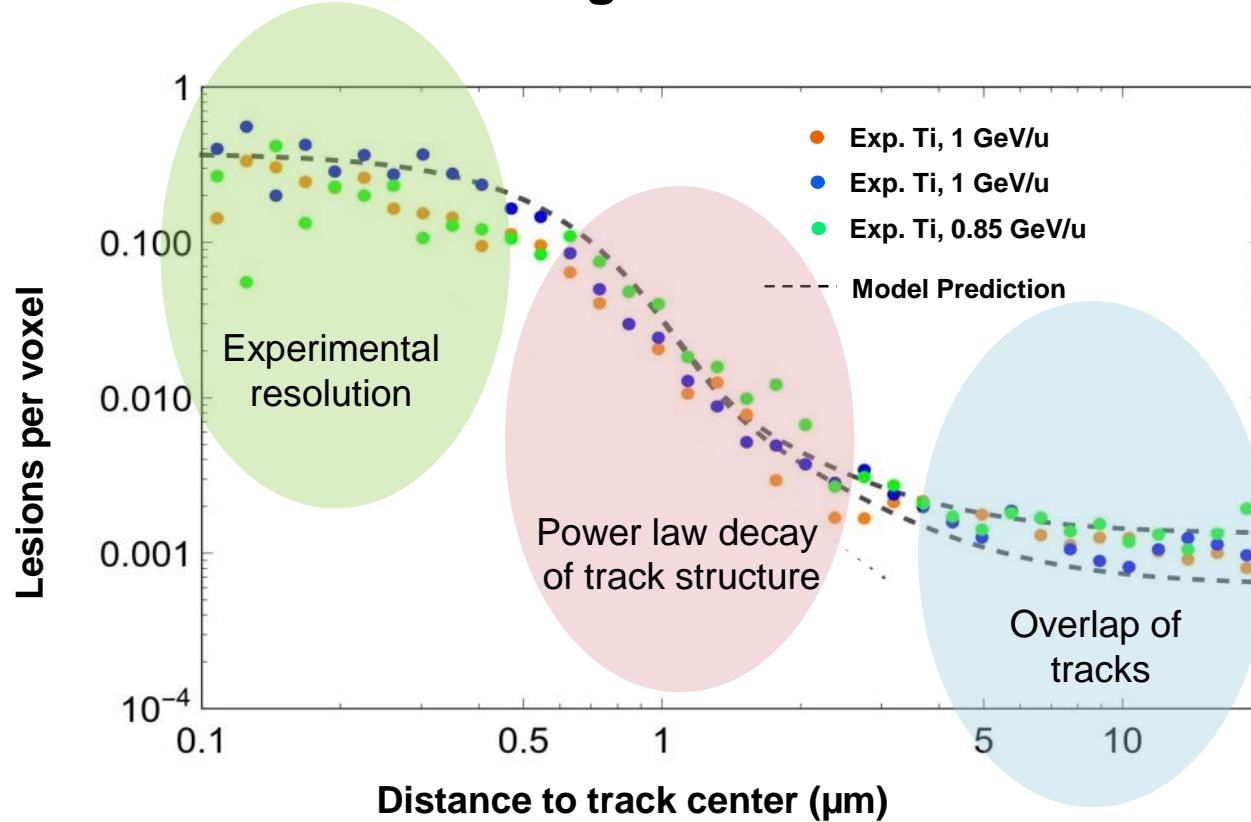
LEMIV (Elsässer et al., IJROBP 2010)

How does dose translate into biologic lesions in tissue?



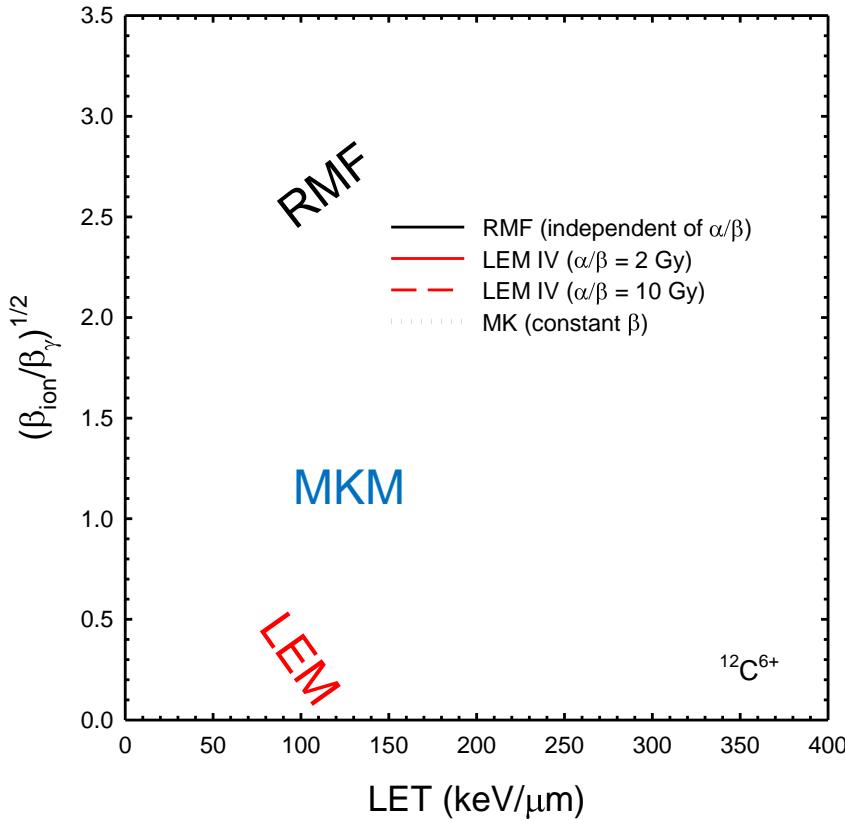
Mirsch et al., PNAS 2015

How does dose translate into biologic lesions in tissue?



Result: We understand the spatial lesion distribution caused by high energetic ions

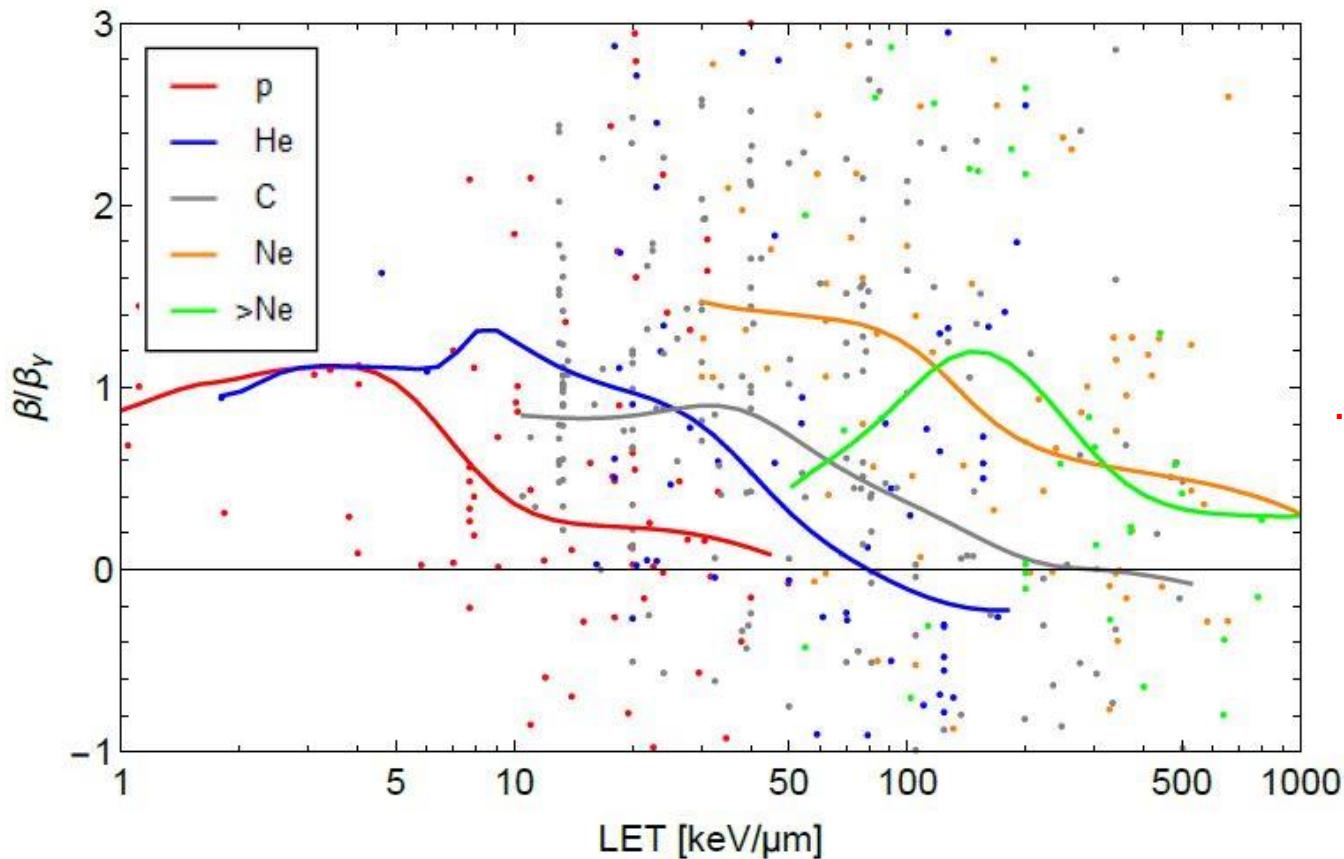
The debate about the β -term: Does it rise or fall with LET?



Different models make
different predictions...

Stewart et al., Med Phys 2018

Model benchmarking

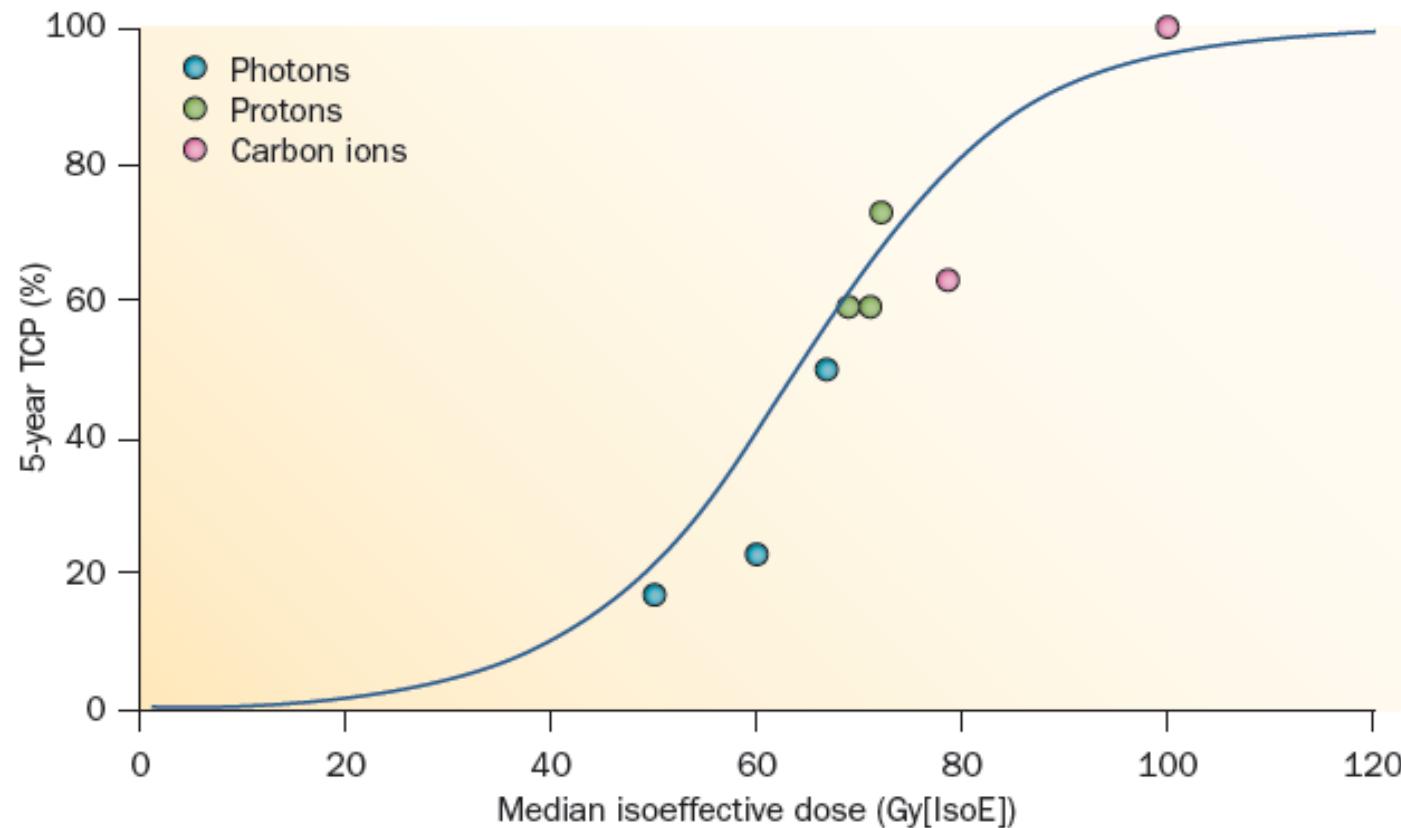


... and the data base helps
to reveal the
experimental trend

Friedrich et al., J. Radiat. Res. **54**, 494 (2013)

→ Find model capabilities and limitations

- Tumor control of chordoma patients (GSI pilot study)

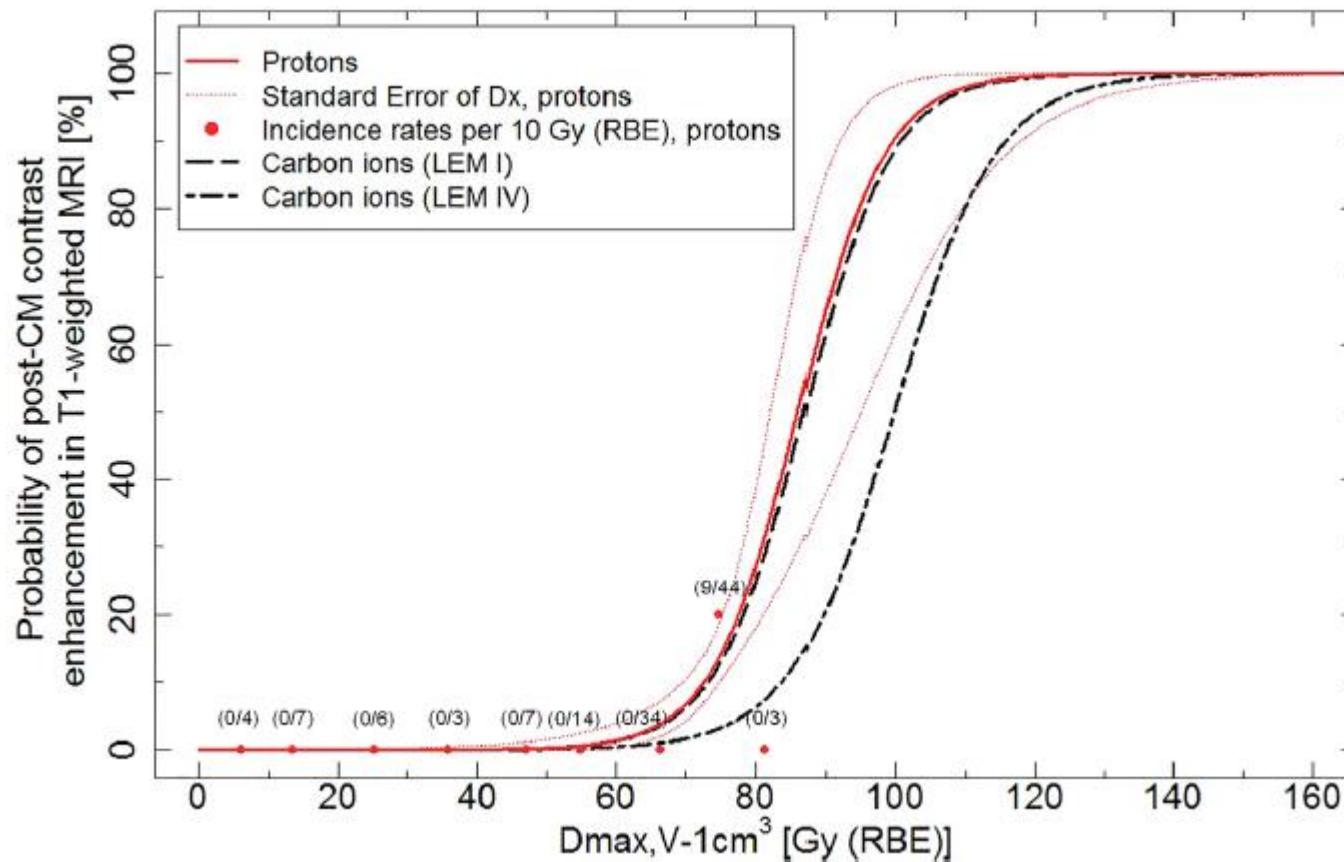


Grün *et al.*, PMB **57**, 7261 (2012)

Loeffler and Durante, Nat. Rev. Clin. Oncol. **10**, 411 (2013)

Model benchmarking

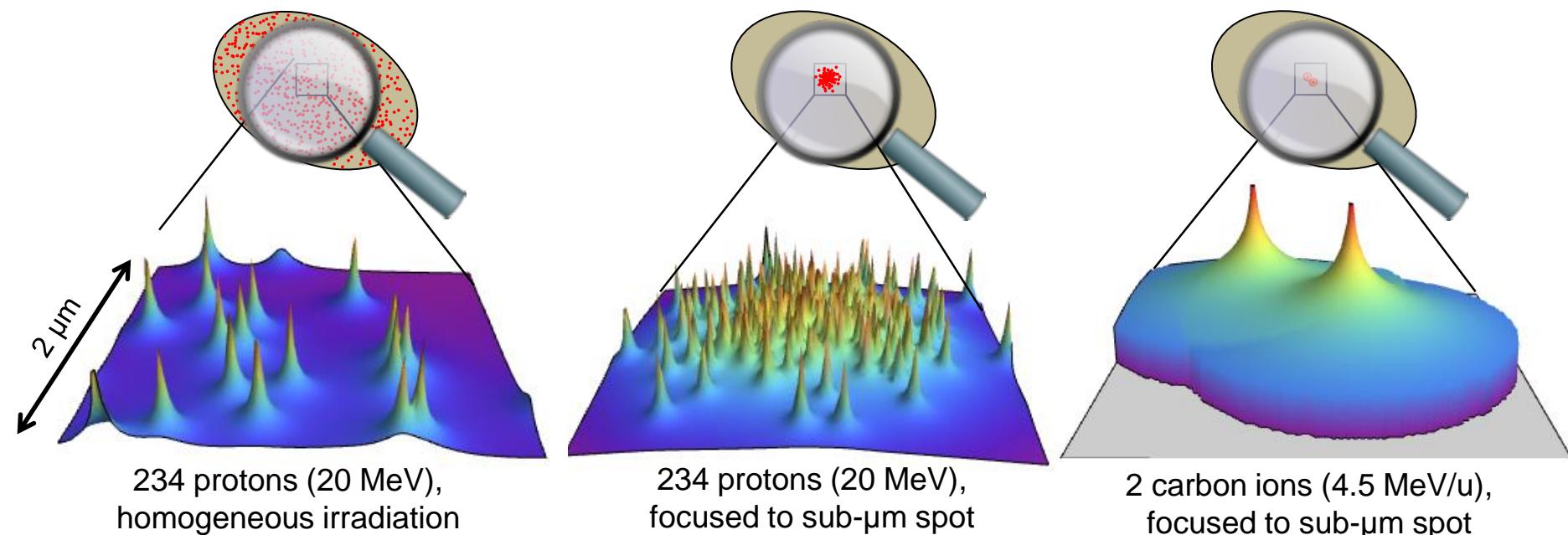
- LEM I vs LEM IV: temporal lobe reactions



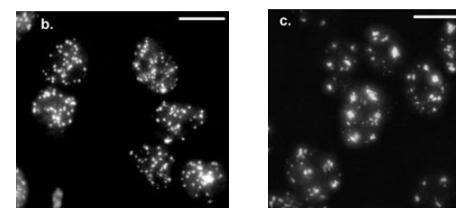
Schlamp et al., IJROBP 2010; Gillmann et al. Radiother Oncol 2018

Why are ions so effective?

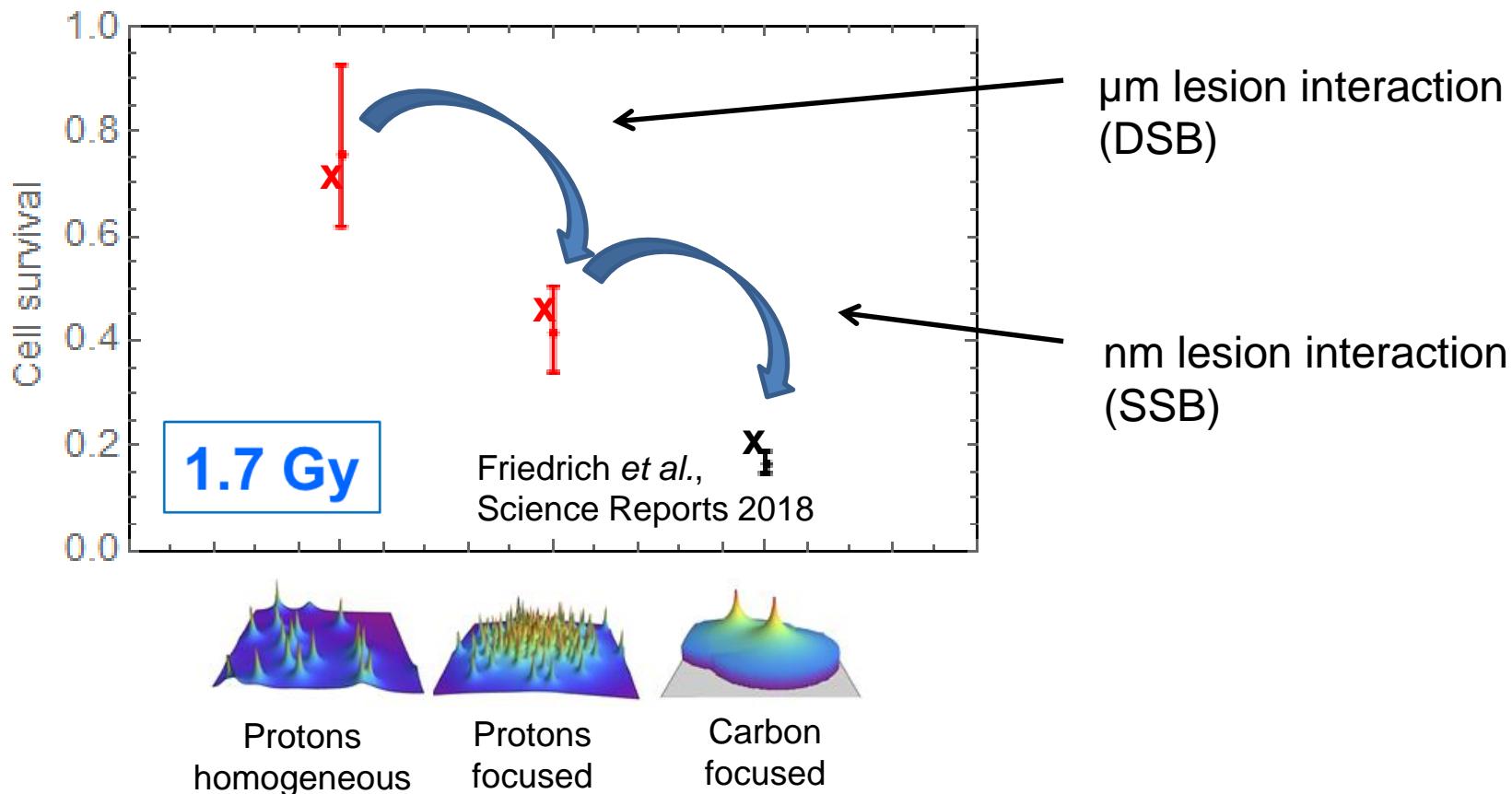
A dose of 1.7 Gy could mean...



→ Test biologic response with microbeam



Model benchmarking



→ Coexistence of lesion interaction mechanisms

Coexistence of different radiation qualities

- A SOBP is composed of several pristine Bragg peaks
→ multiple beams
- Remaining particle energy and LET vary for each beam with depth
→ Biologic effect different for each beam and depth
- What is the effect of the superposition?
 - Several model approaches
 - TDRA: Beam synergy (Zaider and Rossi)

$$\bar{\alpha} = \frac{\sum_i D_i \alpha_i}{\sum_i D_i} \quad \text{and} \quad \sqrt{\bar{\beta}} = \frac{\sum_i D_i \sqrt{\beta_i}}{\sum_i D_i}$$

- General procedure: $RBE = 1.1$ (ICRU78) in radiation field, including entrance channel
 - Possible reasons: High LET target fragments, more weight for low energetic electrons as compared to photons
 - Motivation: Old in-vivo data (Tepper, Urano: skin reactions, jejunal crypts, ...)
- RBE is commonly regarded as a burden rather than as chance in protons: Try to avoid high LET regions
- First deviations from this ‘dogma’: Use LET_D as surrogate for RBE
 - This deserves a RBE that depends linear on LET
 - Try to homogenize LET distribution, avoid high LET in risk organs

Empirical RBE models for protons: RBE is linear in LET

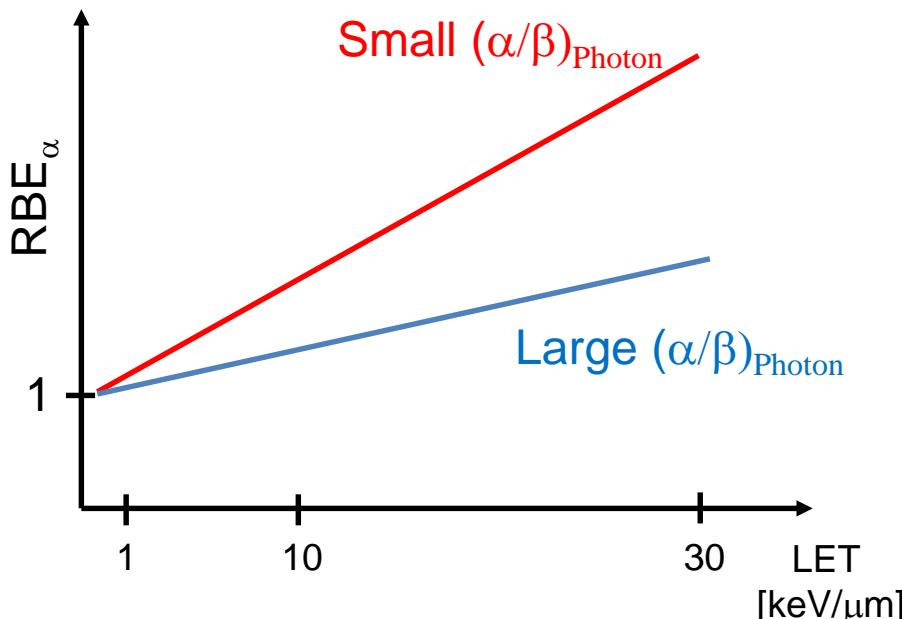
$$RBE_{max}(LET) = \frac{\alpha}{\alpha_{phot}} = 1 + \frac{qL}{(\alpha/\beta)_{phot}} \quad (\text{Including cell type dependence through } \alpha/\beta)$$

β_{Ion}

Similar equation or constant

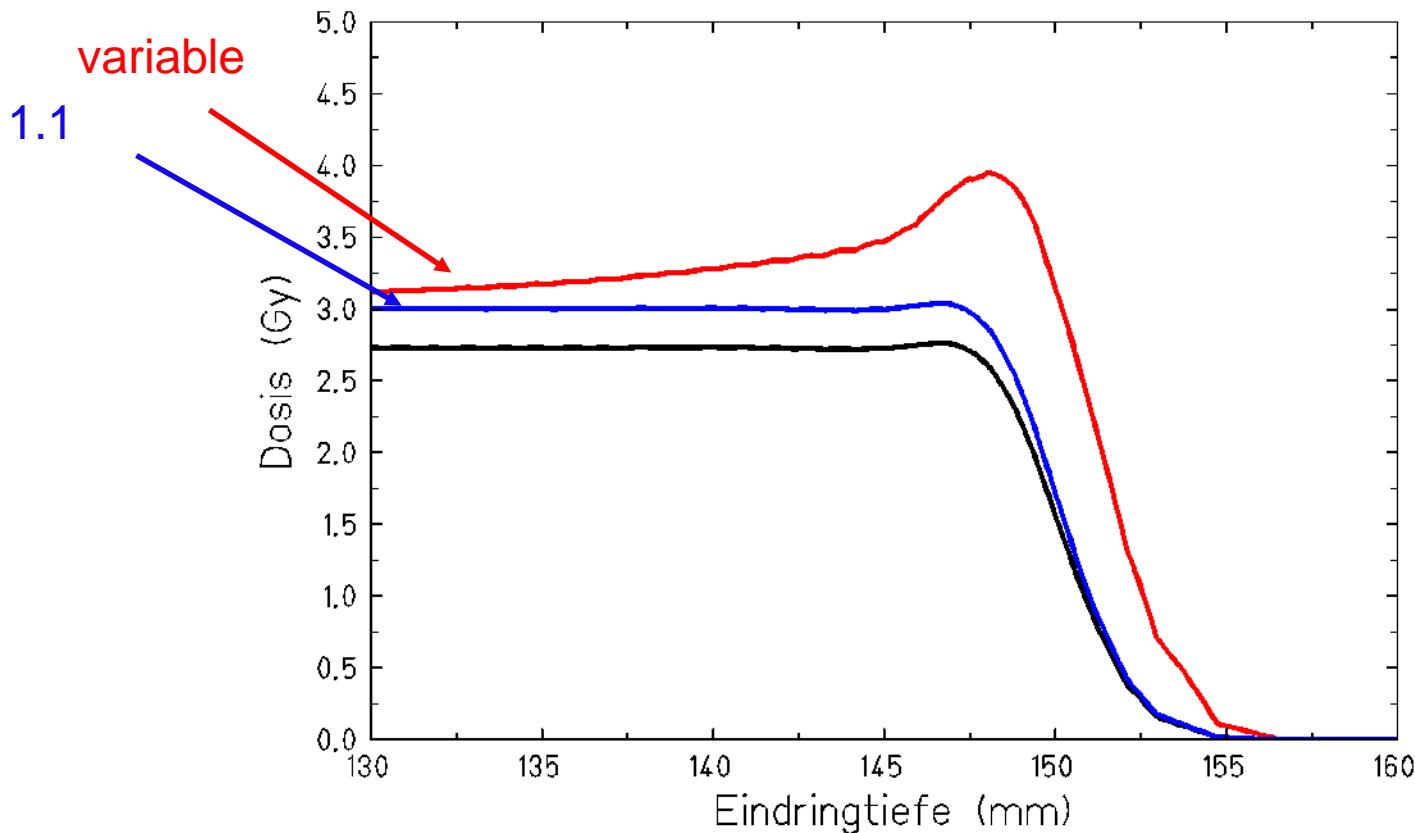
Wedenberg et al.
Acta Oncol. 2013

$$RBE \left(RBE_{max}, RBE_{max}, \left(\frac{\alpha}{\beta} \right)_x, D \right) = \frac{1}{2D} \left(\sqrt{\left(\frac{\alpha}{\beta} \right)_x^2 + 4D \left(\frac{\alpha}{\beta} \right)_x RBE_{max} + 4D^2 RBE_{min}^2} - \left(\frac{\alpha}{\beta} \right)_x \right)$$



- Restriction to protons
- Dose dependence questionable
- No mechanistic rationale
- But: simple !

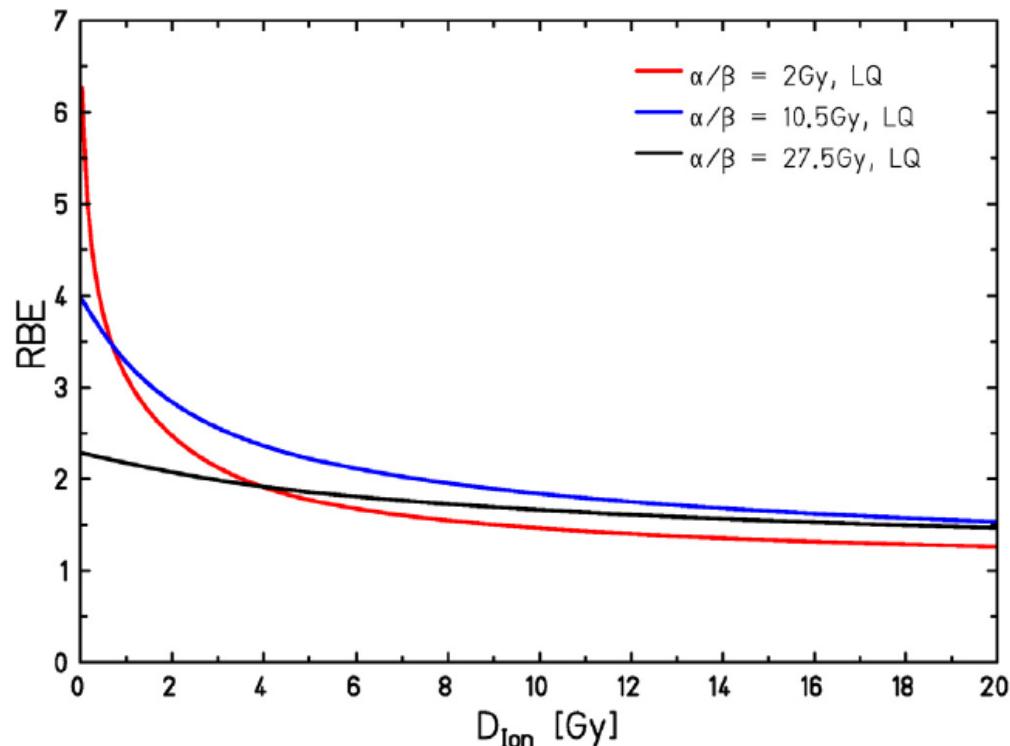
Extended range: RBE enhances irradiated target size



Grün et al. Med Phys 2013

Hypofractionation

- Sparing effect of normal tissue allows hypofractionation
- However, only few studies with protons (all use RBE = 1.1)
- Probably no RBE effects visible on sound statistical basis
- But: if RBE goes down to zero, the 1.1 dogma implies underdosage!



Friedrich et al. Phys. Med. 2014

- Lack of knowledge in volume effects does not allow interpretation of RBE in a voxelized plan
- Is the LQ model for fractionation conversion appropriate?
 - Really same proportion of killed tumor mass fraction?
 - What is RBE for large doses?
- What are lethal lesions? What is complex damage?
- Reporting RBE: Comparison of RBE values obtained with different methods is tedious and source of misconceptions
- A conservative use of RBE does not exploit potential of particle therapy → RBE escalation?