Simulation tools for hadrontherapy: radiobiological modelling and simulations

XV Seminar on Software for Nuclear, Subnuclear and Applied Physics
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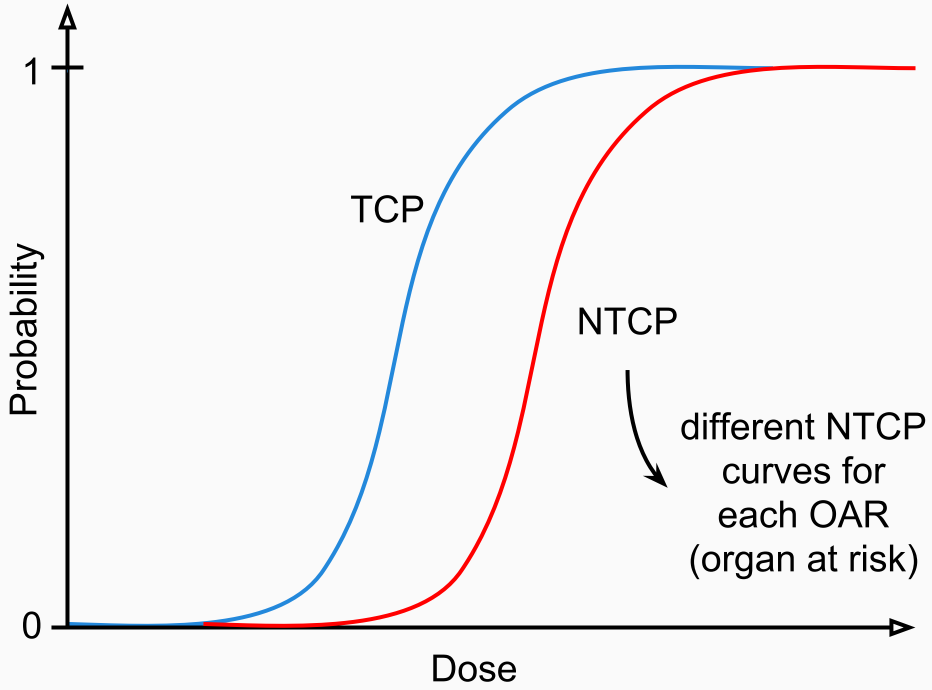
Istituto Nazionale di Fisica Nucleare

Therapeutic Index: TCP/NTCP



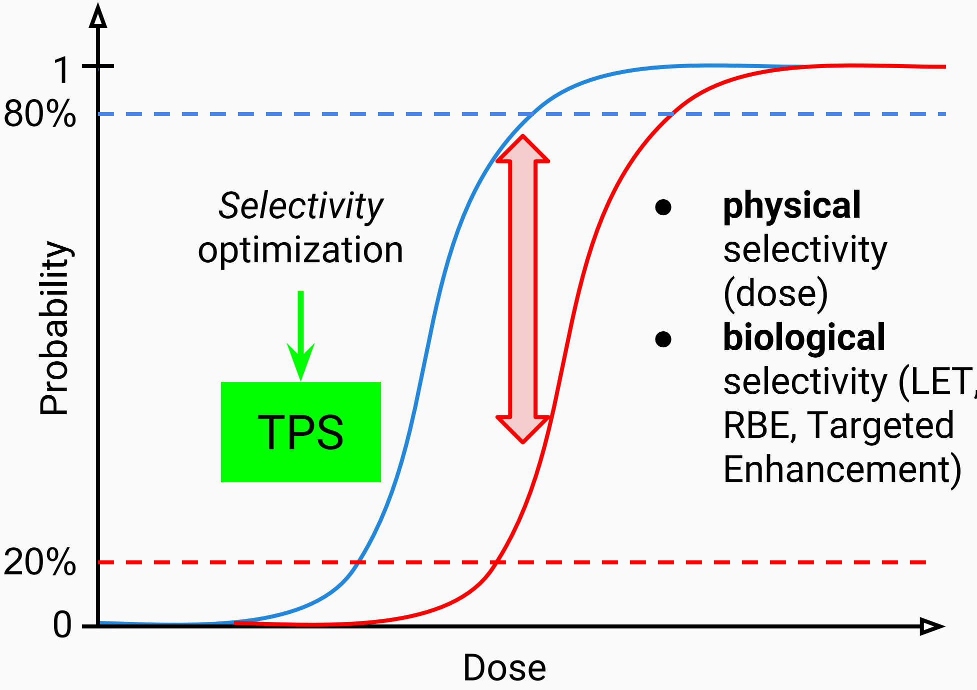
Tumor Control Probability (TCP)
Simple Poissonian Model:

$$\mathrm{TCP} = \exp(-N) = \exp(-\lambda \times S(D))$$

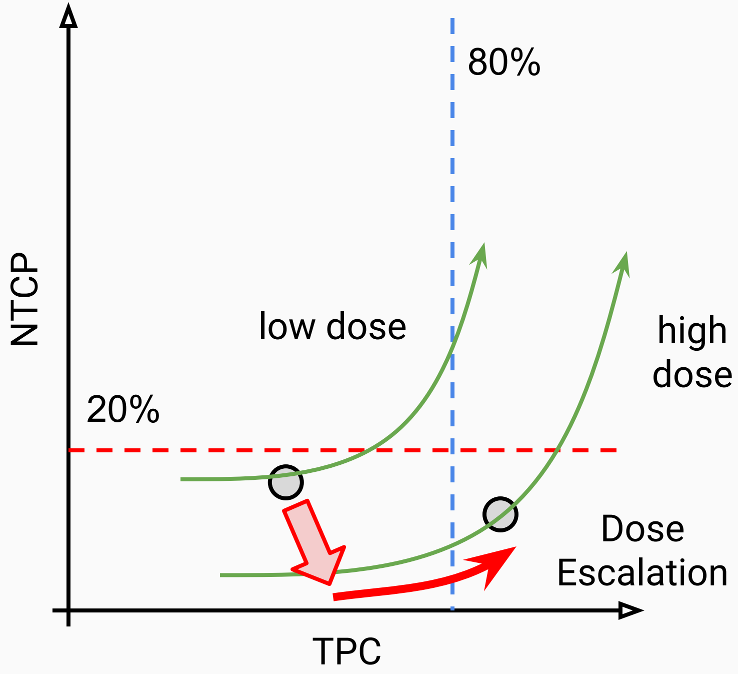
N := number of clonogenic cells
λ := n. of clonogenic cells prior irradiation
S := cell survival fraction

Normal Tissue Complication Probability (NTCP)
(more complex description to account the serial/parallel nature of the organ)

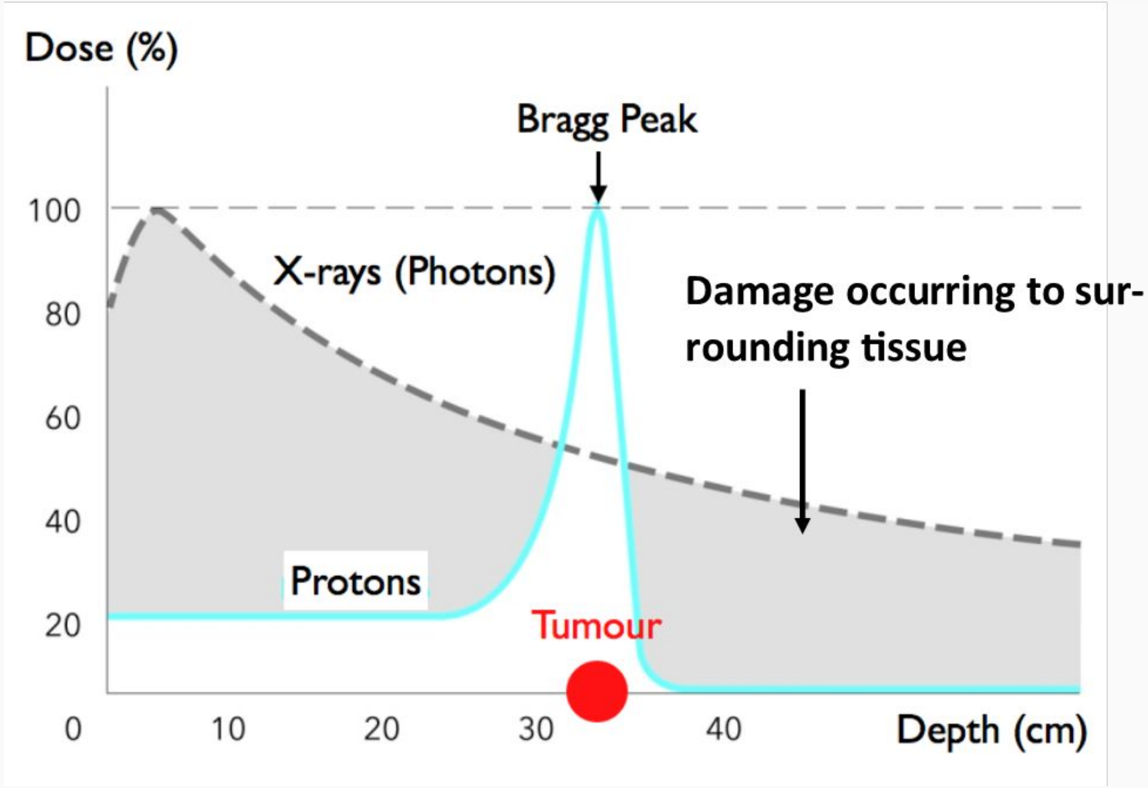
Treatment Plan Optimization → Treatment Planning System (TPS)



- **physical** selectivity (dose)
- **biological** selectivity (LET, RBE, Targeted Enhancement)



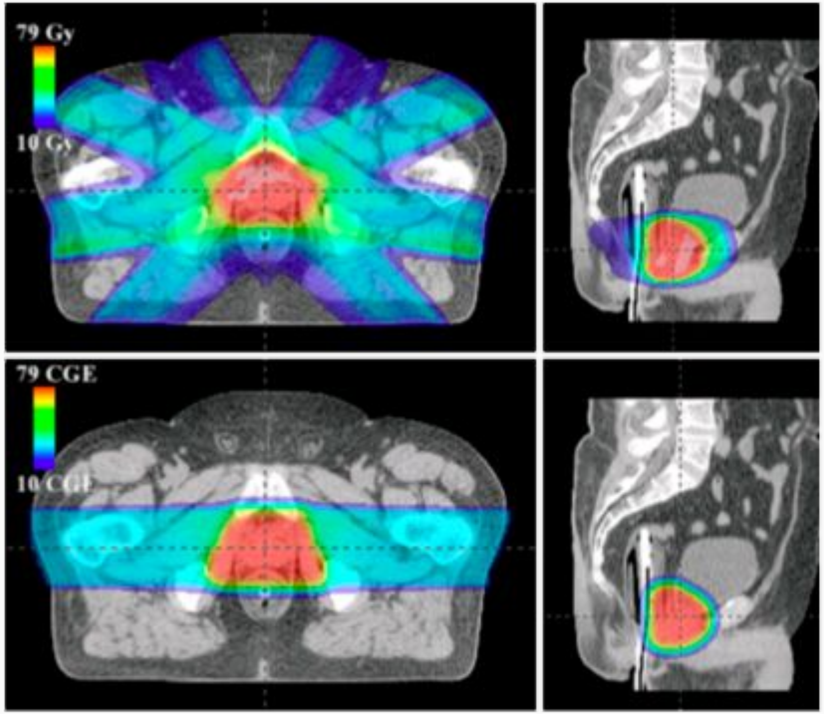
Physical selectivity - Choice of primary radiation



Physical selectivity - Comparison between IMRT and IMPT

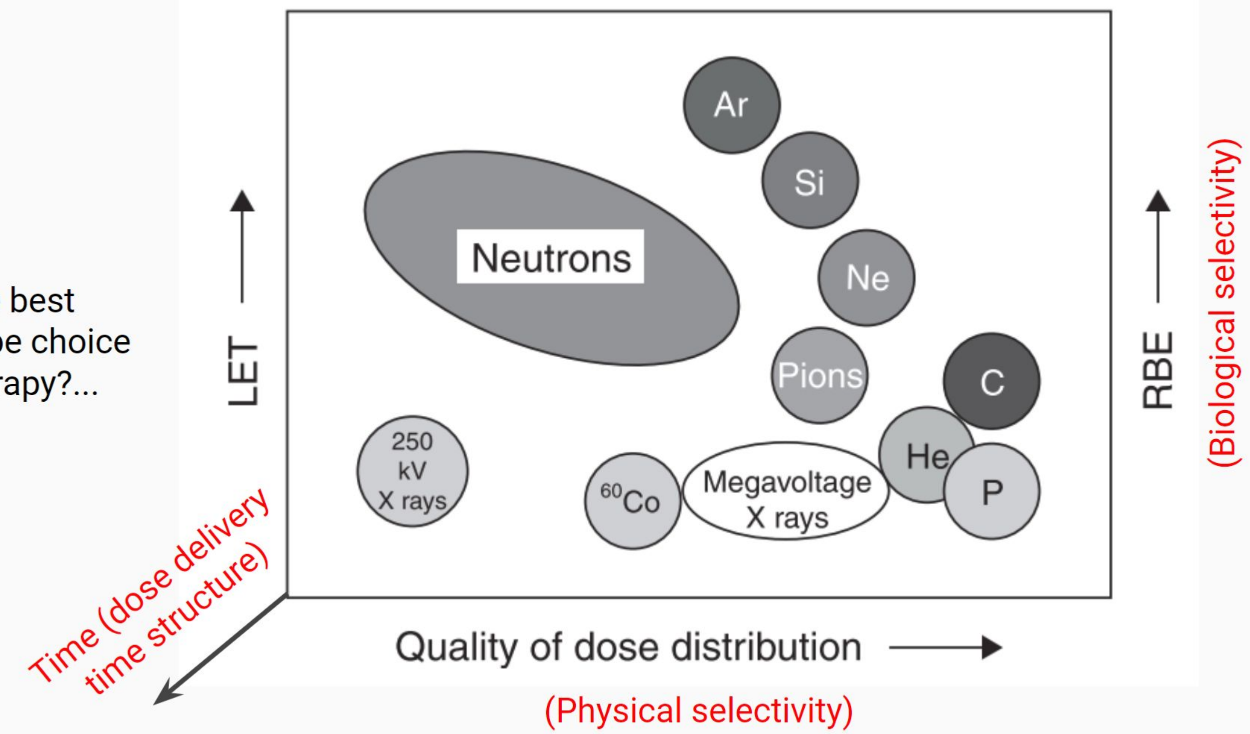
Intensity
Modulated
Radiotherapy
(**IMRT**)

Intensity
Modulated
Particle
Therapy (**IMPT**)

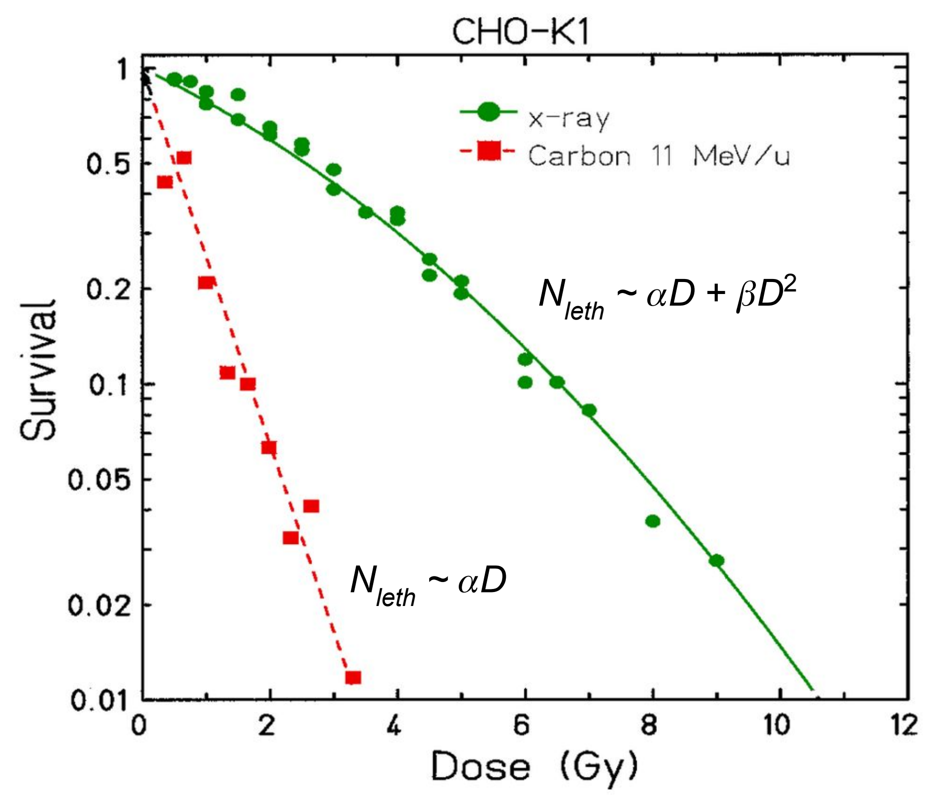


Choice of primary radiation - General aspects

Which is the best radiation type choice for radiotherapy?...



Dose Response - Survival Curves



Poisson process interpretation

The cell is inactivated if at least one "lethal event" happen when irradiated.

The survival fraction is hence the probability to observe zero lethal events after irradiation.

The number of lethal events, N_{leth}, is assumed to follow a Poisson statistics with an average that depend on the dose, $\bar{N}_{leth} = \bar{N}_{leth}(D)$:

$$N_{leth} = \text{Pois}(\bar{N}_{leth})$$

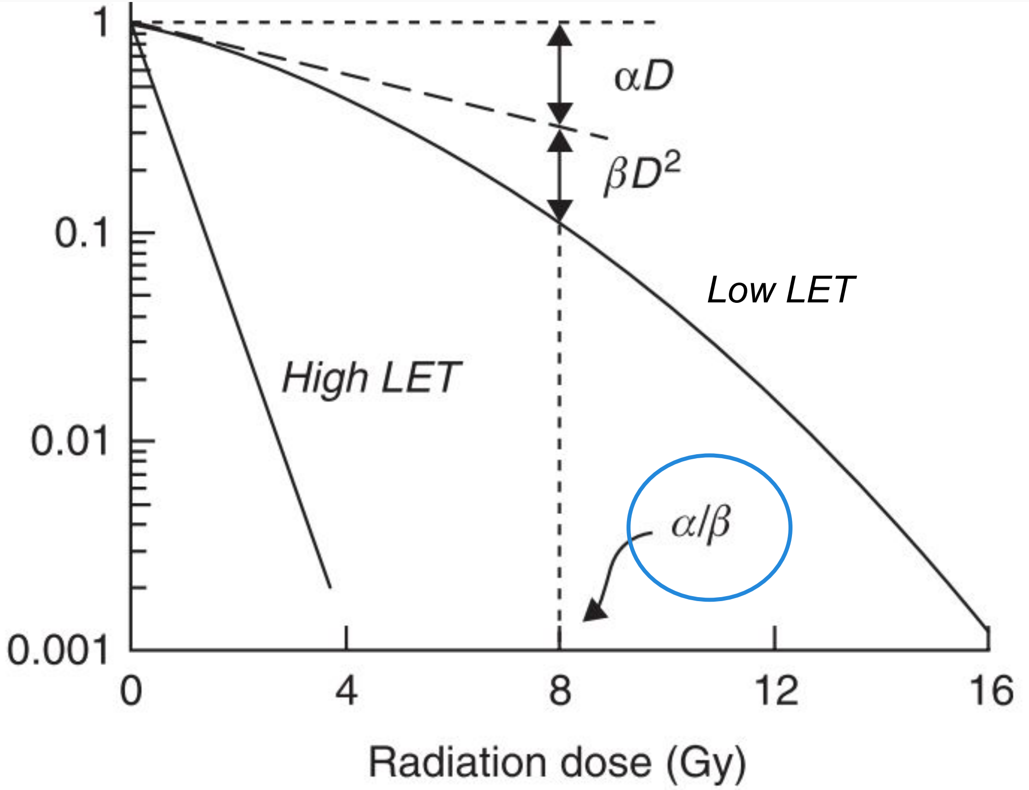
$$S = \exp(-\bar{N}_{leth})$$

Cell Survival - The Linear Quadratic (LQ) Model

$$-\ln(S) = \alpha D + \beta D^2$$

There are two components of cell killing: one is **proportional to dose** (αD), while the other is **proportional to the square of the dose** (βD^2).

Although we can regard this as based on pure mathematics (i.e. the simplest formula which describes a curve), it has also been possible to attach radiobiological mechanisms.



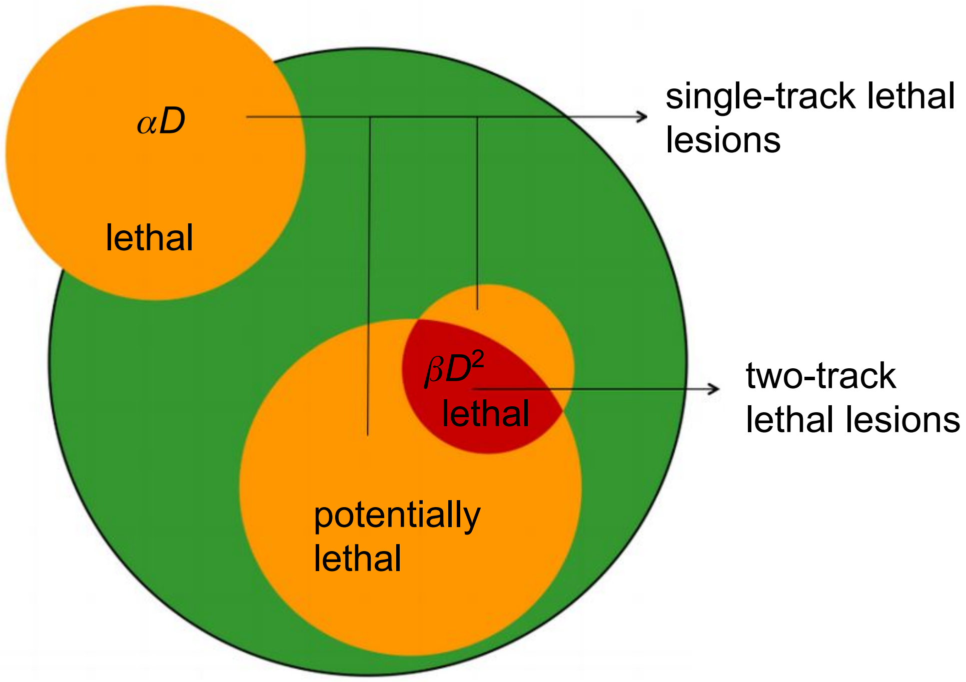
Cell Survival - The Linear Quadratic (LQ) Model

One simple idea is that the linear component (αD) might result from **single-track events** while the quadratic component (βD^2) might arise from **two-track** events.

Ionizing radiation is considered to produce two different types of lesion: **repairable** (i.e. potentially lethal) lesions and **non-repairable** (i.e. lethal) lesions.

The lethal lesions produce single-track lethal effects and therefore give rise to a linear component of cell killing (αD).

Repairable lesions from two different tracks could combine to produce a lethal lesion (βD^2) .



Dose delivery time structure effects - Fractionation

The dose is delivered in N_f fractions with big inter-fraction time >> τ and dose per fraction $D_f = D/N_f$:

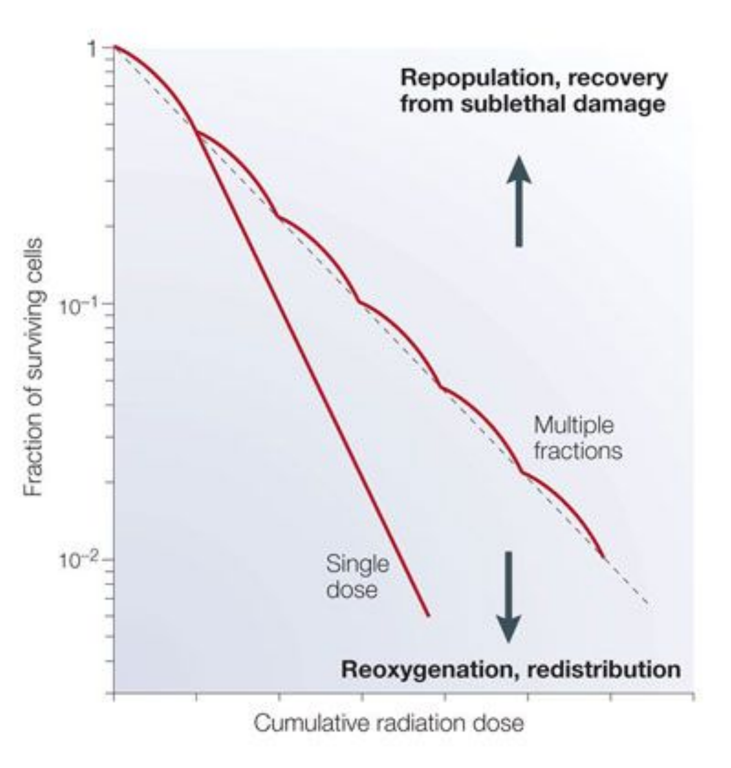
$$S(D) = \prod_{f=1}^{N_f} S(D_f)$$

→ Uncorrelated events

$$= \exp\left(-\alpha D - \beta \sum_{f=1}^{N_f} D_f^2\right)$$

$$= \exp\left(-\alpha D - \frac{1}{N_f}\beta D^2\right)$$

$$\Rightarrow G = \frac{1}{N_f}$$



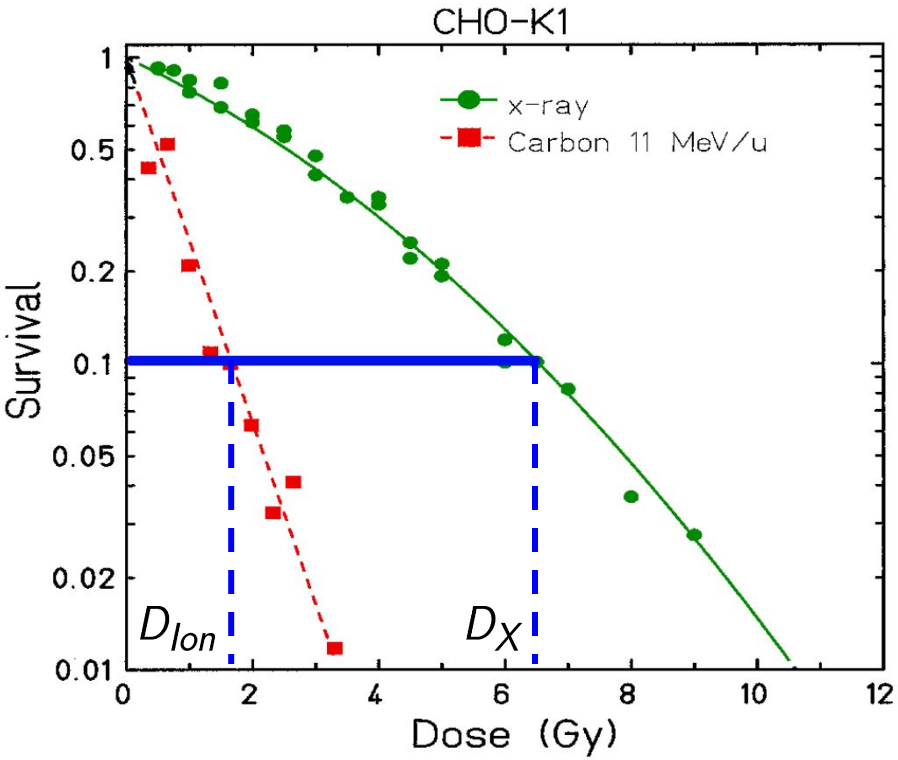
Relative Biological Effectiveness (RBE)

Relative Biological Effectiveness

RBE

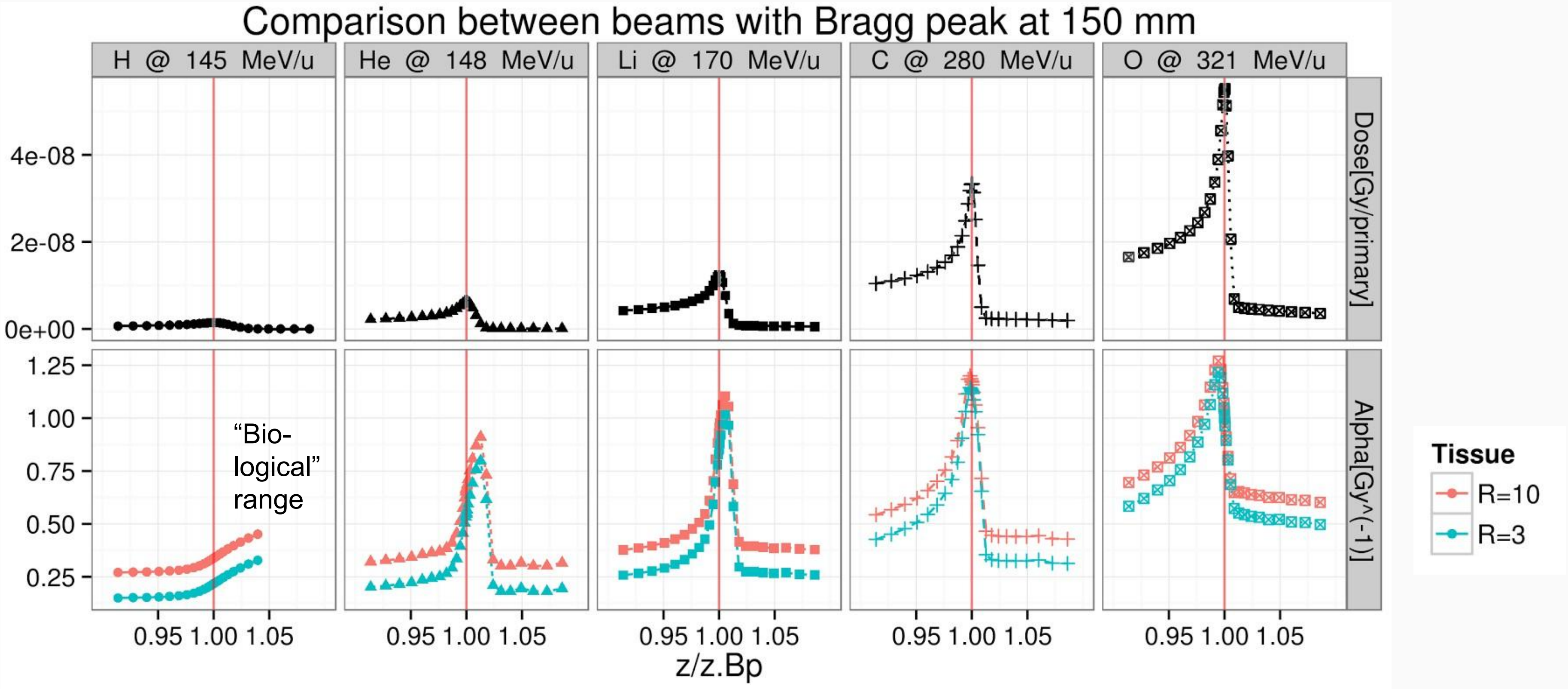
$$RBE_n = \frac{D_X}{D_{Ion}}\bigg|_{S_X=S_{Ion}=n}$$

RBE ~ 1.1 for protons
RBE > 1 for ions



WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

“Colocalization of High LET / RBE - High Dose” - Ion Optimality

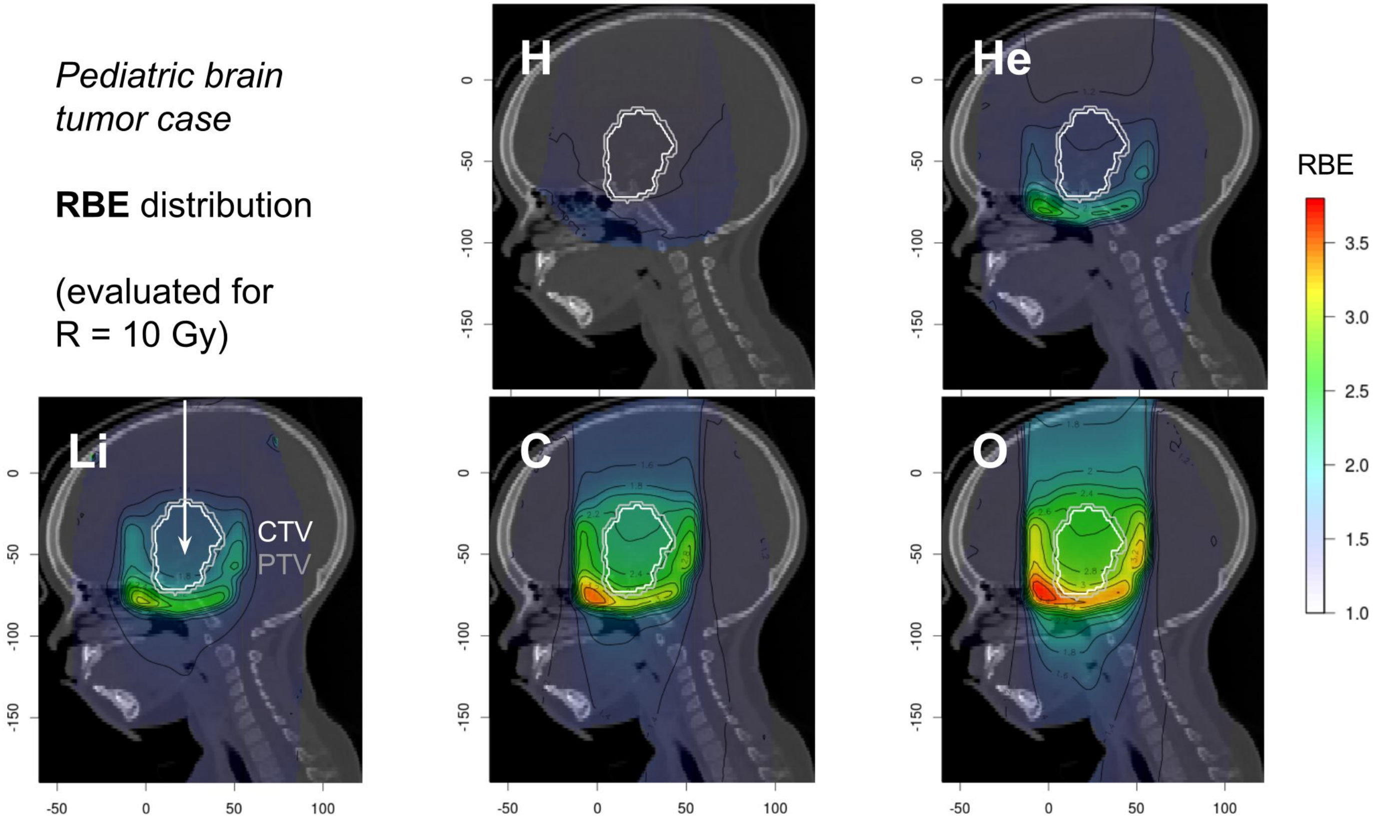


"Colocalization of High LET / RBE / Dose" - Ion Optimality

Pediatric brain tumor case

RBE distribution

(evaluated for R = 10 Gy)



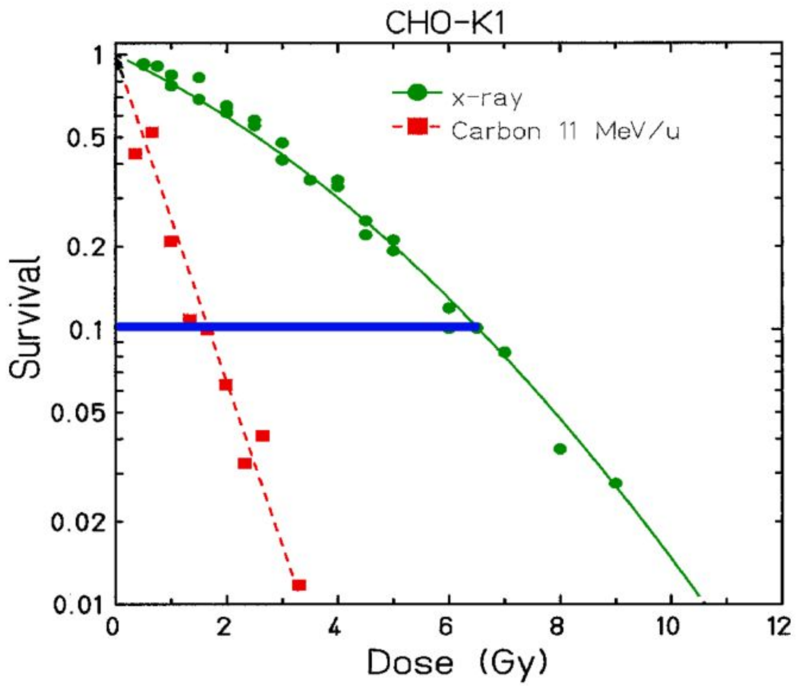
Relative Biological Effectiveness vs. Dose

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

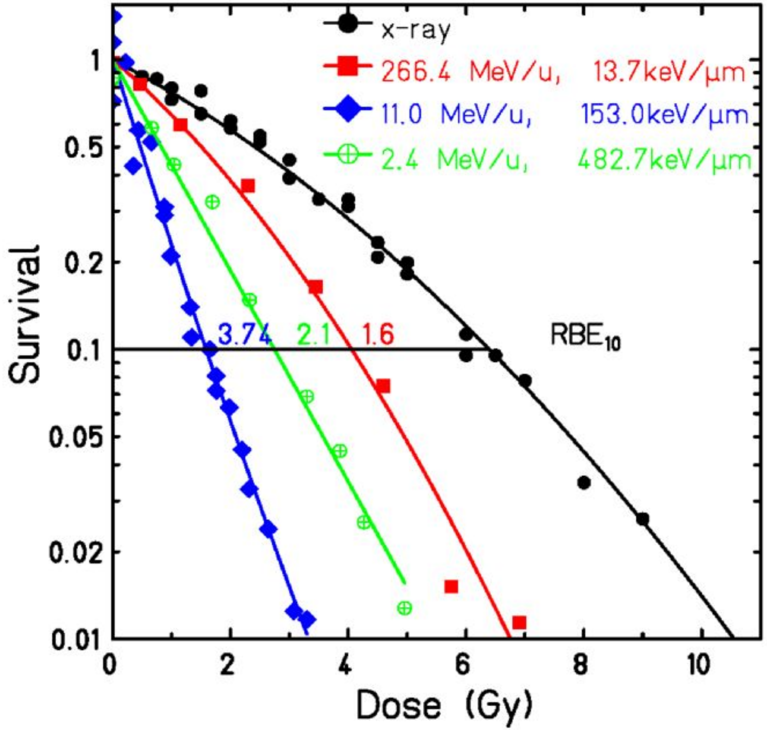
Relative Biological Effectiveness vs Kinetic Energy

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



WK Weyrather, J Debus - Clin. Onc. 23 (2003)

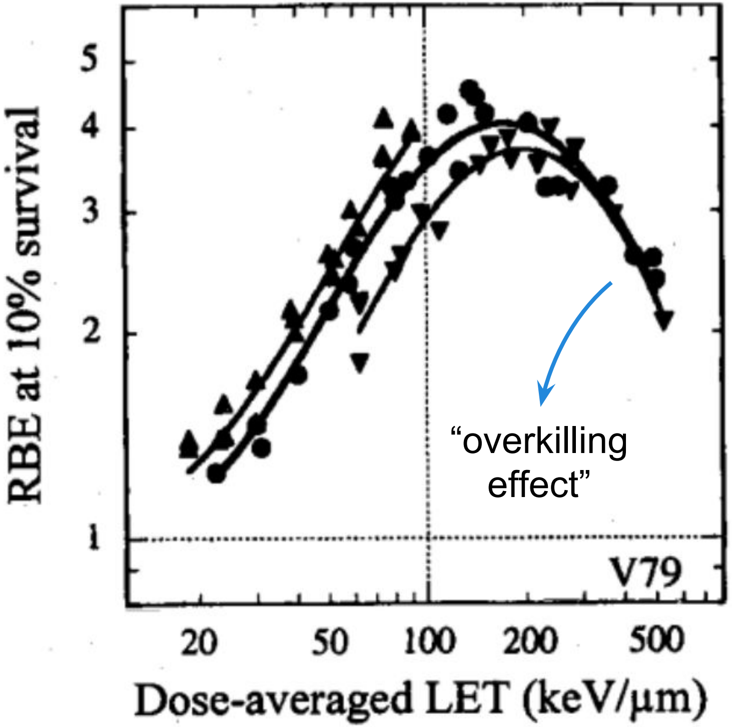
Relative Biological Effectiveness vs. Linear Energy Transfer (LET)

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



Y Furusawa *et. al.* - Rad. Res. 154 (2000)

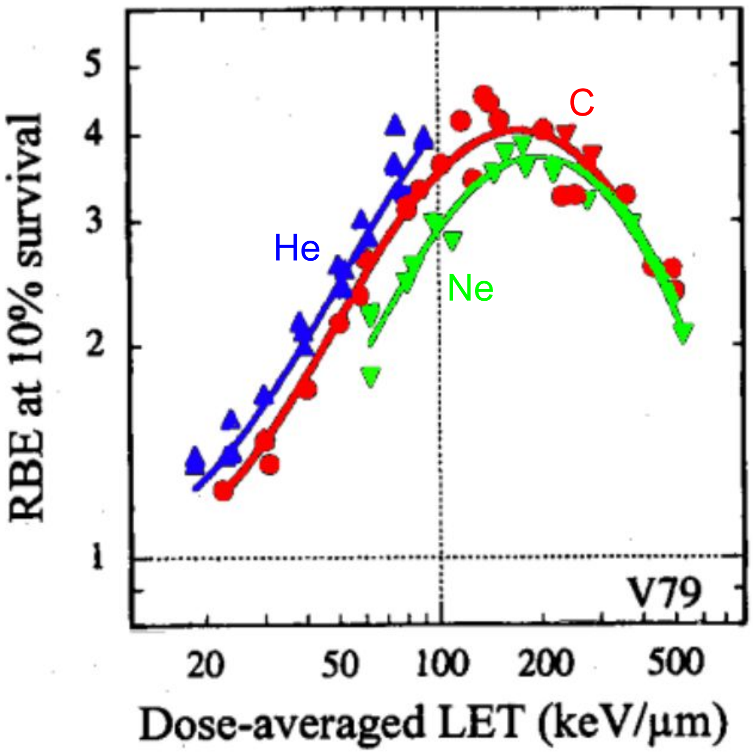
Relative Biological Effectiveness vs. particle type

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



Y Furusawa *et. al.* - Rad. Res. 154 (2000)

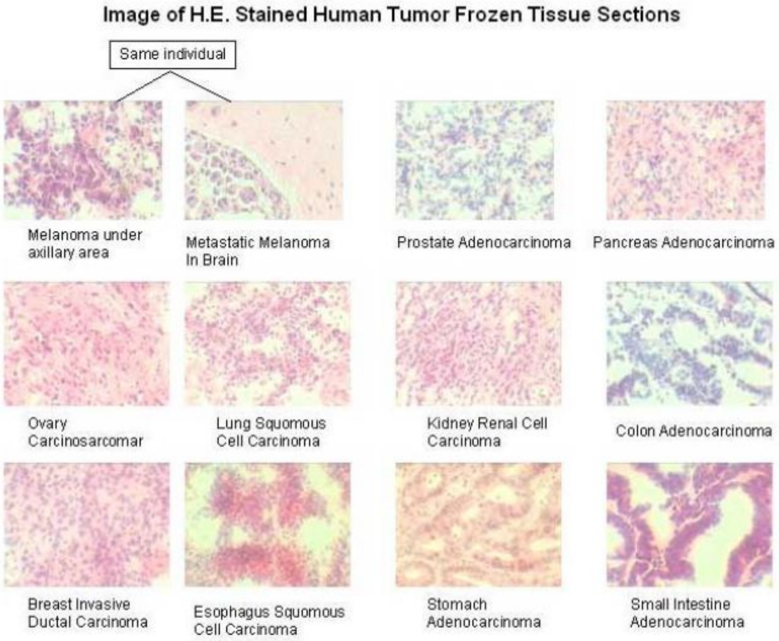
Relative Biological Effectiveness vs. tissue/cell type

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



BioChain Institute, Inc.

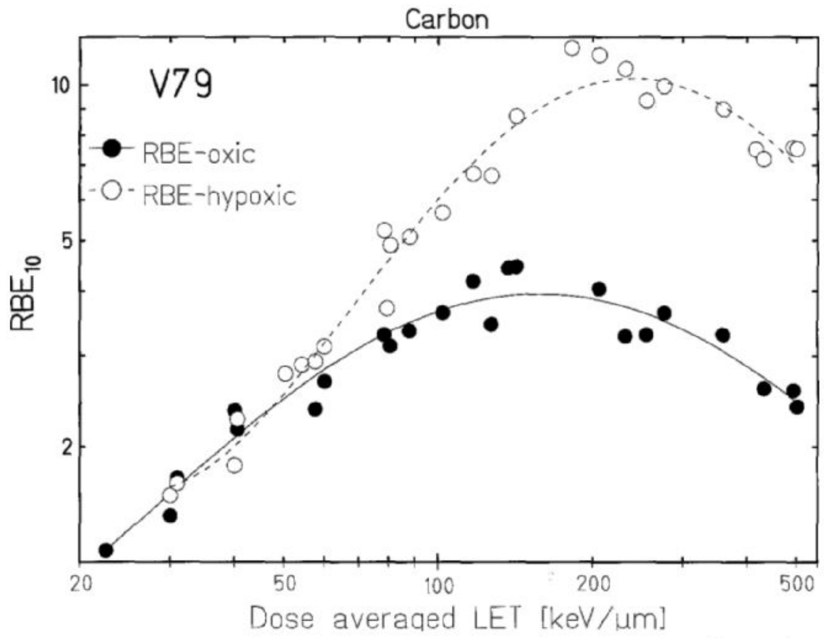
Relative Biological Effectiveness vs. oxygenation conditions

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint



WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

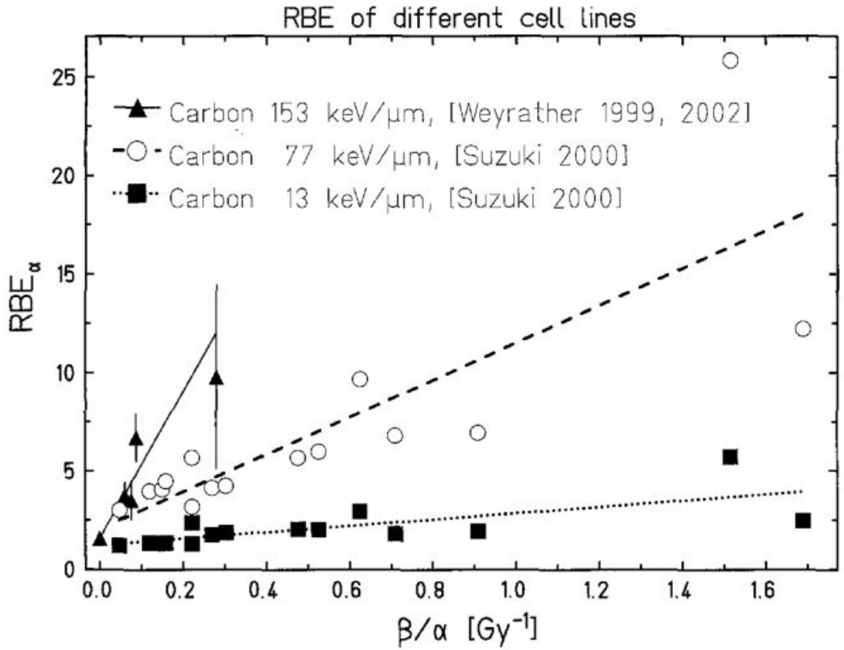
Relative Biological Effectiveness vs. α_X / β_X

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X / β_X)
- Biological endpoint



WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

Relative Biological Effectiveness modelling (clinically used models)

Physical Parameters

- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

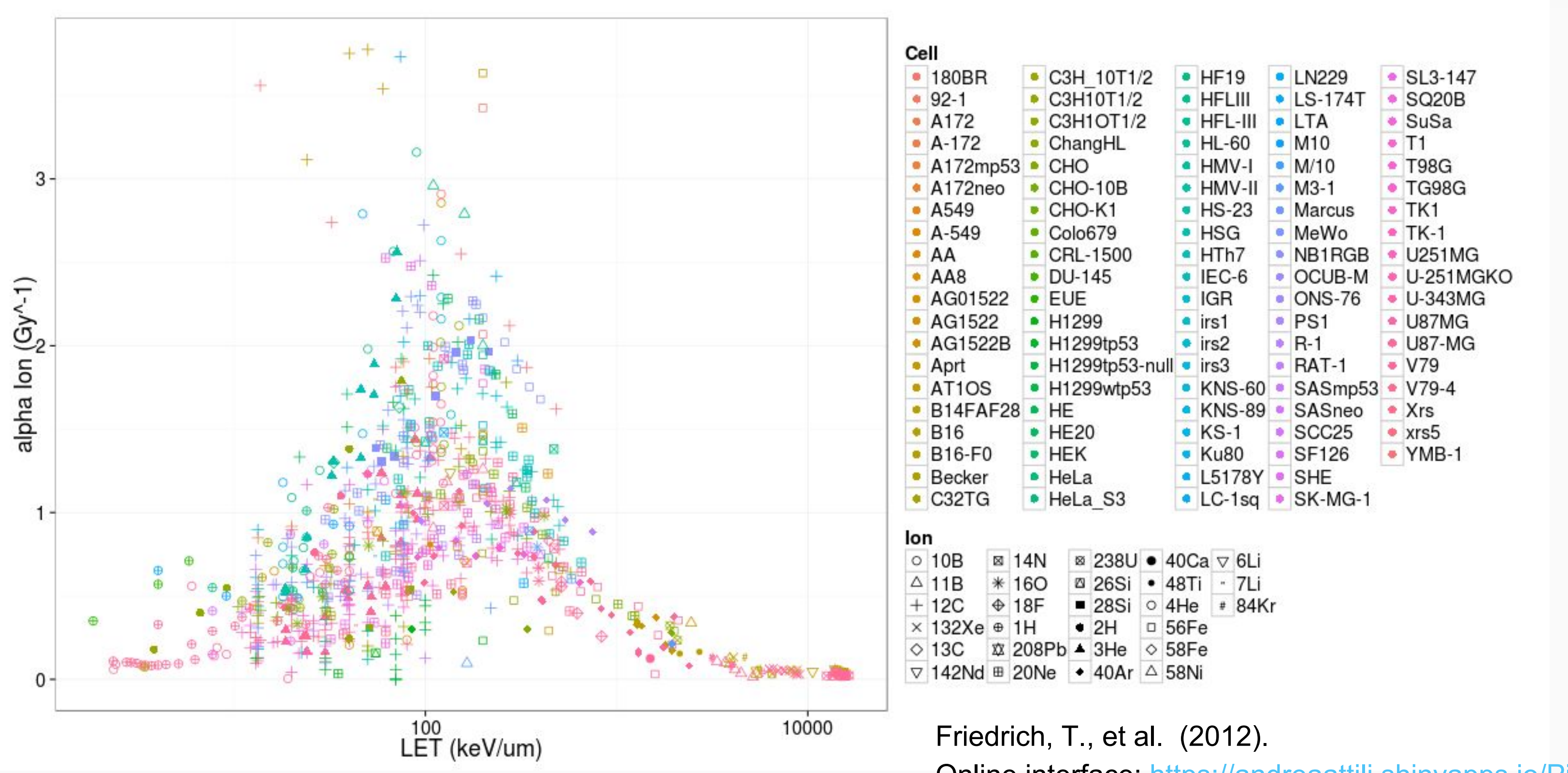
Biological Parameters

- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X/β_X)
- Biological endpoint

- Local Effect Model (**LEM**)
- Microdosimetric Kinetic Model (**MKM**)
- [...]

"Survival" simulation code

Particle Irradiation Data Ensemble (PIDE) project (https://www.gsi.de/bio-pide)

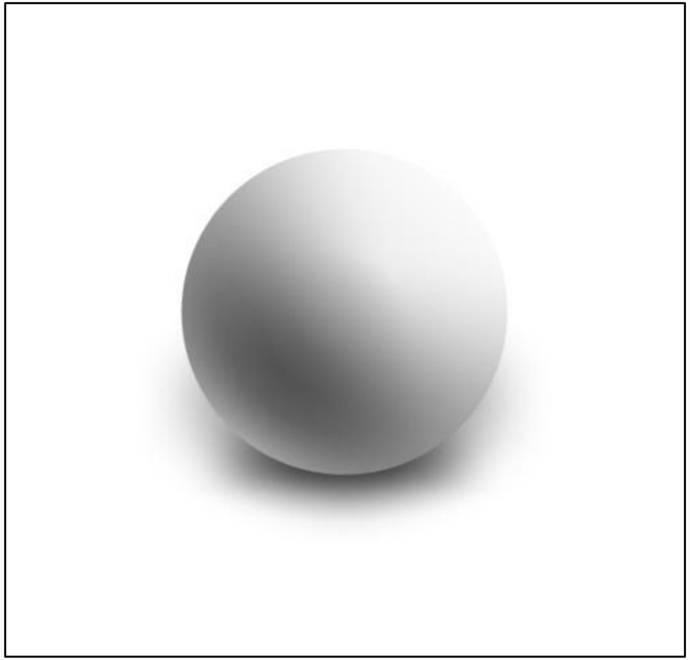


Friedrich, T., et al. (2012).

Online interface: https://andreaattili.shinyapps.io/PideApp/

Semi-phenomenological modelling approaches

“This is not a cow”
--- René Magritte



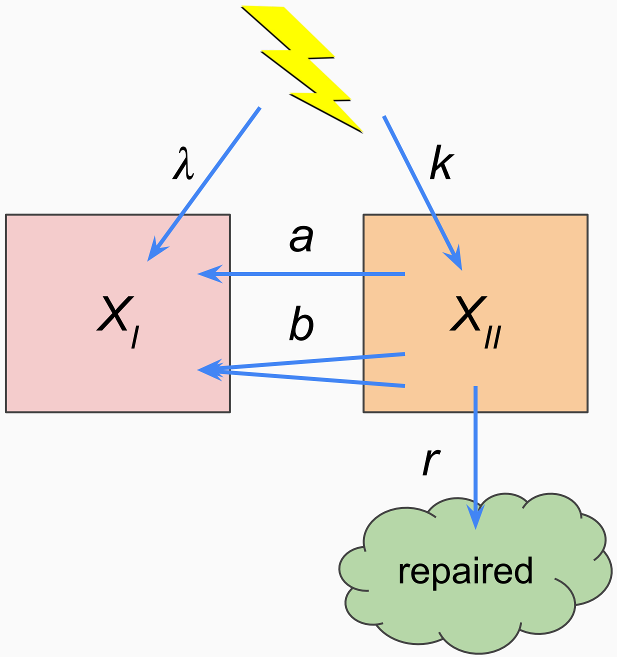
“This is a cow”
--- Anonymous physicist

Stochastic semi phenomenological modelling - The kinetic equations

Kinetic equations:

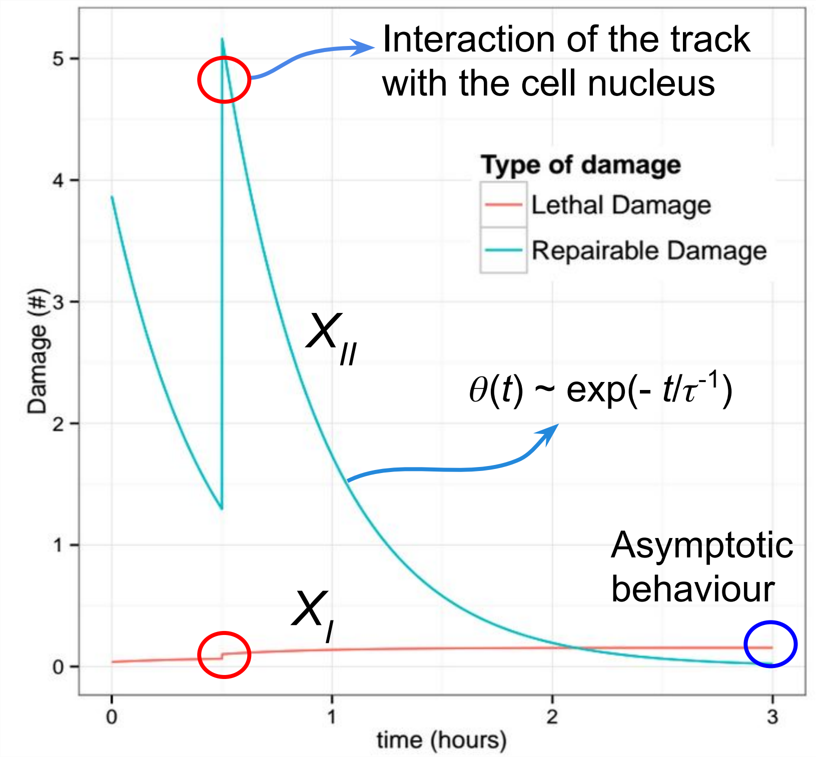
$$\begin{cases} \dot{x}_I^{(cd)} = \lambda \dot{z}^{(cd)} + a x_{II}^{(cd)} + b(x_{II}^{(cd)})^2 \\ \dot{x}_{II}^{(cd)} = k\dot{z}^{(cd)} - (a+r)x_{II}^{(cd)} - 2b(x_{II}^{(cd)})^2 \end{cases}$$

- z → microscopical absorbed dose
- x_I → type-I lesions: associated with clustered DNA damages which are **directly lethal** for the cell
- x_{II} → type-II lesions: non-directly lethal damages that may be **repaired**, spontaneously **converted to irreparable damages** or undergo **pairwise combination**.



Hawkins, R. B. (1996). *International Journal of Radiation Biology*

Analytical derivation of the LQ formalism from the kinetic equations



Hawkins, R. B. (1996). *International Journal of Radiation Biology*

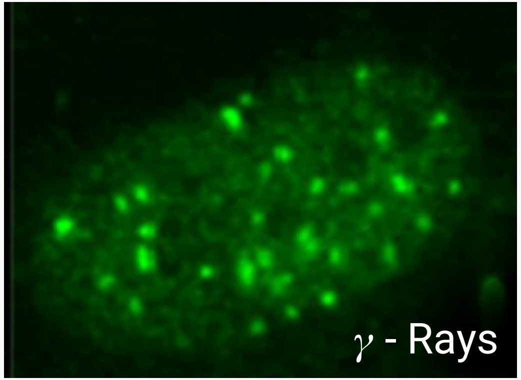
Cell survival is derived from the asymptotic solution of the kinetic equations:

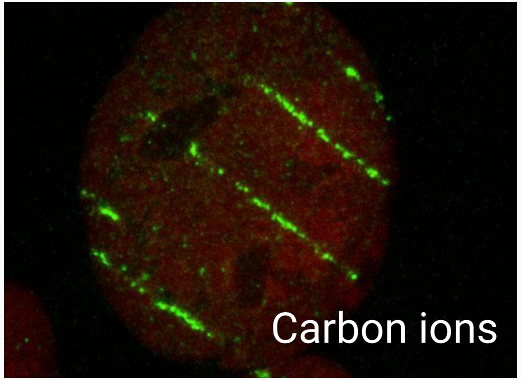
$$\langle N_{leth} \rangle = \langle x_I(t \to \infty) \rangle \simeq (\alpha_0 + \beta_0 \bar{z}_{1D}) D + \beta_0 D^2$$

Where z_{1D} is the dose-averaged microscopical absorbed dose and following the approximation, α_0 and β_0 are a function of rate parameters (λ, k, a, b, r). Since z_{1D} (x-rays) << z_{1D} (ions), $\alpha_0 \cong \alpha_X$ and $\beta_0 \cong \beta_X$

$$S \stackrel{?}{=} \exp(-\langle N_{leth} \rangle)$$

High LET radiation: Clustering of lesions





Clustering effect: Increased biological effectiveness due to the smaller distance of the lesions (*colocality*)

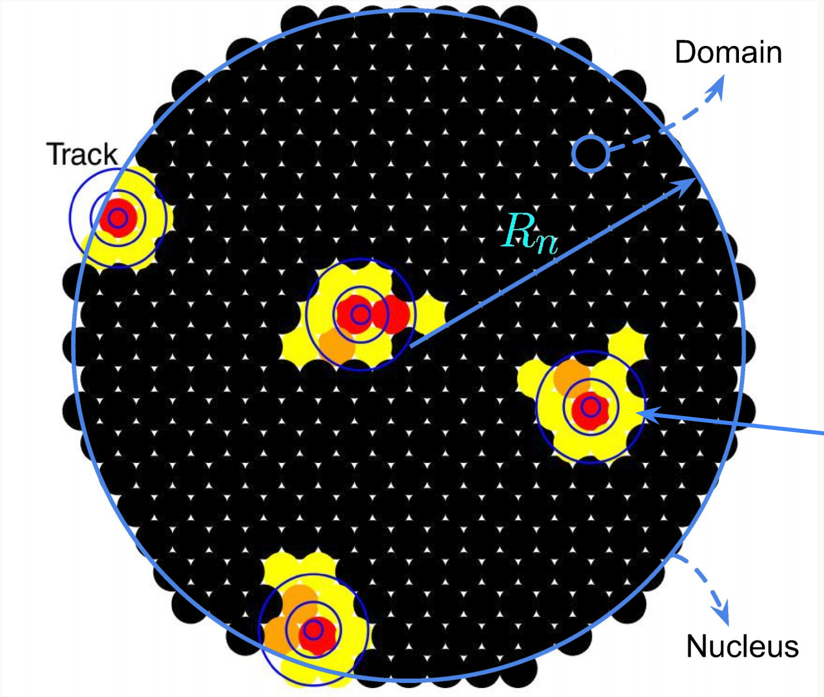
Introduction of "Sites" or "Domains":

Microdosimetric Kinetic Model (MKM)

Complete Locality approximation:

Local Effect Model (LEM)

Lesion colocation in cell nucleus and microdosimetric spectra (MKM)



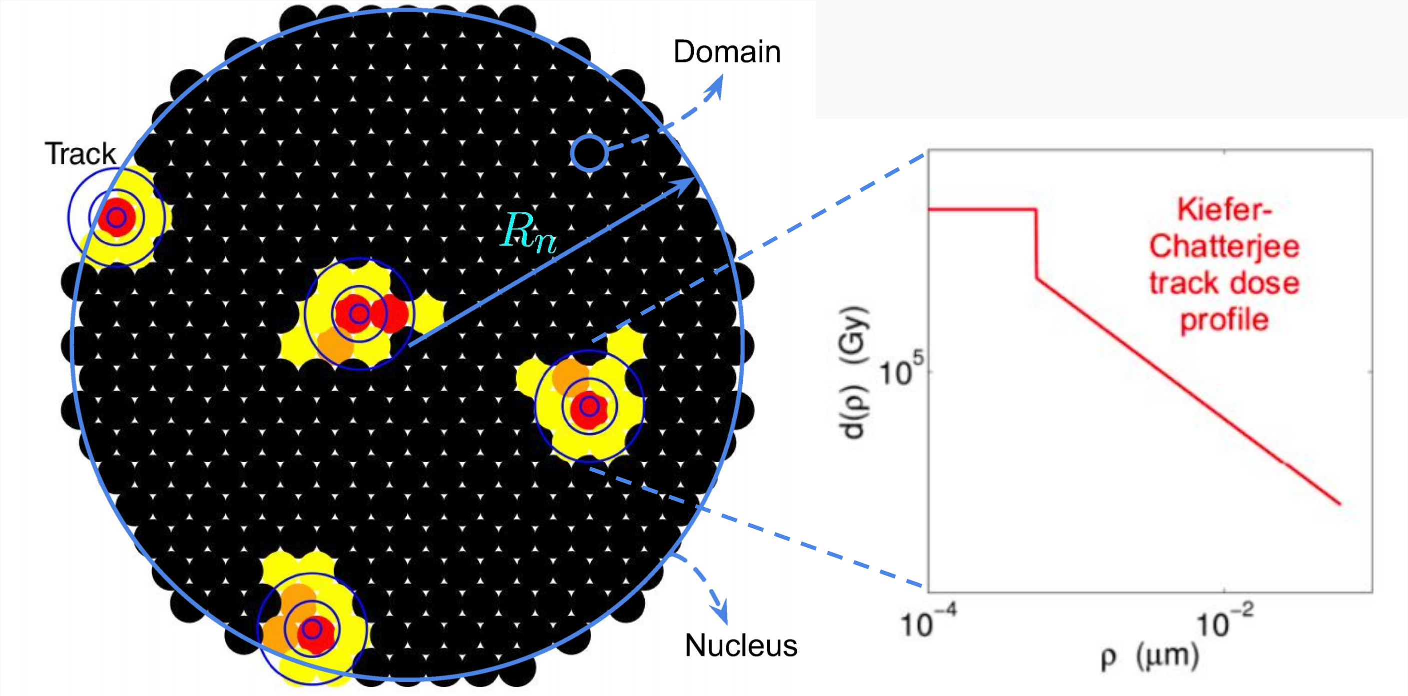
$$\bar{N}_{leth} = \sum_d \left\{ \underbrace{(\alpha_0 + \beta_0 \bar{z}_{1d})}_{\alpha_P} D_d + \underbrace{\beta_0}_{\beta_P} D_d^2 \right\}$$

Particle energy spectrum

In principle, z_{1d} can be obtained from **microdosimetric measurements** of energy spectra, e.g. via a tissue-equivalent proportional counter (TEPC)

Hawkins, R. B. (1996). *International Journal of Radiation Biology*,
Kase, y., et al. (2006). *Radiation Research*

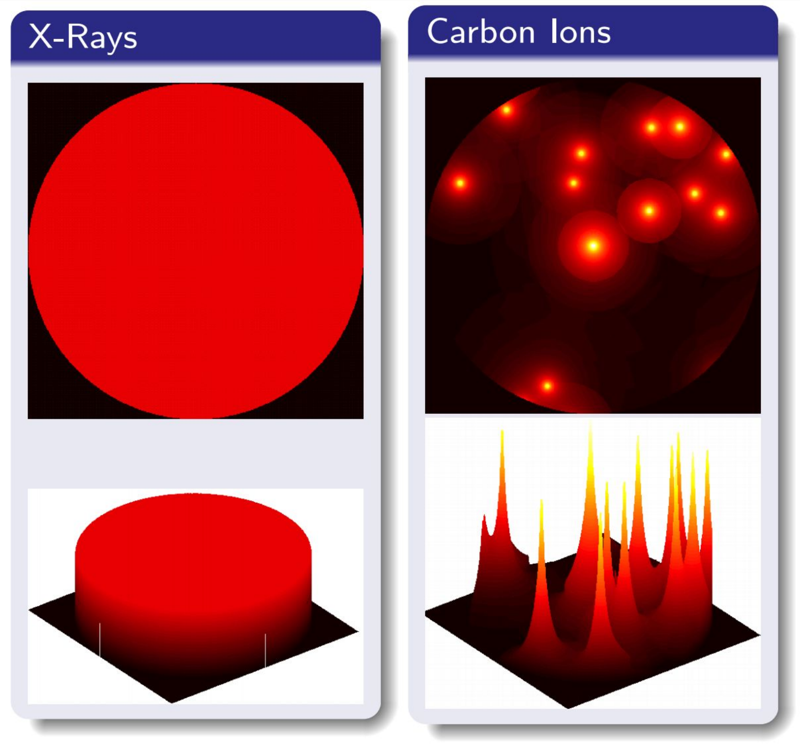
Lesion colocation in cell nucleus and microdosimetric spectra (MKM)



In practice, z_{1d} is obtained numerically using an **amorphous track model,** combination of the Kiefer model for the penumbra region (Kiefer et al. 1986) and the Chatterjee model for the core radius (Chatterjee et al. 1976)

Kase, Y., et al. (2008). *Physics in Medicine and Biology*,
Inaniwa, T., et al. (2010). *Physics in Medicine and Biology*

Local Effect Model (LEM I, II, III) approach



Scholz, M., et al. (1997) Radiation and Environmental Biophysics

- Concept of Local Effect → factorization of the macroscopic effect in infinitesimal subvolumes of the cell nucleus.

$$N_{leth} = \int_{V_N} n(d(\vec{x}))\, \mathrm{d}\vec{x}$$

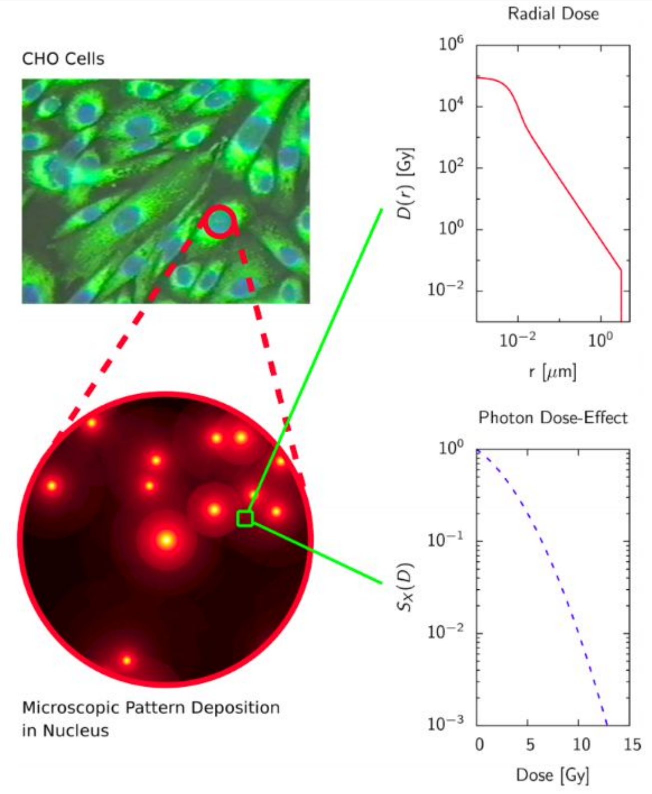
- The main assumption of the LEM is that equal local doses should lead to equal local effects, independent on the radiation quality.

$$n(D) = -\ln(S_X(D))/V_N$$

$$N_{leth} = \frac{1}{V_N} \int_{V_N} \{\alpha_X D(\vec{x}) + \beta_X D(\vec{x})\}\, \mathrm{d}\vec{x}$$

$$\Rightarrow \quad S \stackrel{?}{=} \exp(-\langle N_{leth} \rangle)$$

Local Effect Model IV approach



Direct link of the local dose deposition pattern to the photon dose response curve describing the observable endpoint under consideration.

$$S(D) = \begin{cases} e^{-(\alpha_X d + \beta_X d^2)}; & d < D_t \\ e^{-(\alpha_X D_t + \beta_X D_t^2 + s_{max}(d - D_t))}; & d \geqslant D_t \end{cases}$$

- In **LEM IV** an intermediate step has been introduced: final biological response of a cell to radiation is directly linked to the initial spatial DNA damage distribution induced by radiation rather than the local dose distribution.
- It is assumed that similar DSB patterns should lead to similar effects, independent of the radiation quality leading to these patterns.

Statistical considerations

Sparsely Ionizing Radiation

- Low LET $\rightarrow$ High Fluence.
- Every Cell is exposed to a similar ionization field.

$$N_{leth} = \text{Pois}(\bar{N}_{leth})$$

$$S = \exp(-\bar{N}_{leth})$$

Densely Ionizing Radiation

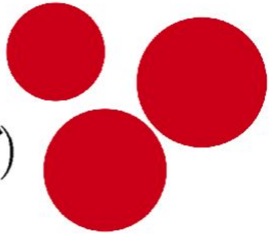
- High LET $\rightarrow$ Low Fluence.
- Every Cell is exposed to a different ionization field (c).

$$N^{(c)}_{leth} = \text{Pois}(\bar{N}^{(c)}_{leth})$$

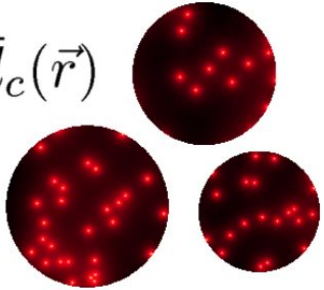
$$N_{leth} \neq \text{Pois}(\langle \bar{N}^{(c)}_{leth} \rangle_c)$$

$$S = \langle S_c \rangle_c = \langle \exp(-\bar{N}^{(c)}_{leth}) \rangle_c \neq \exp(-\langle \bar{N}^{(c)}_{leth} \rangle)$$

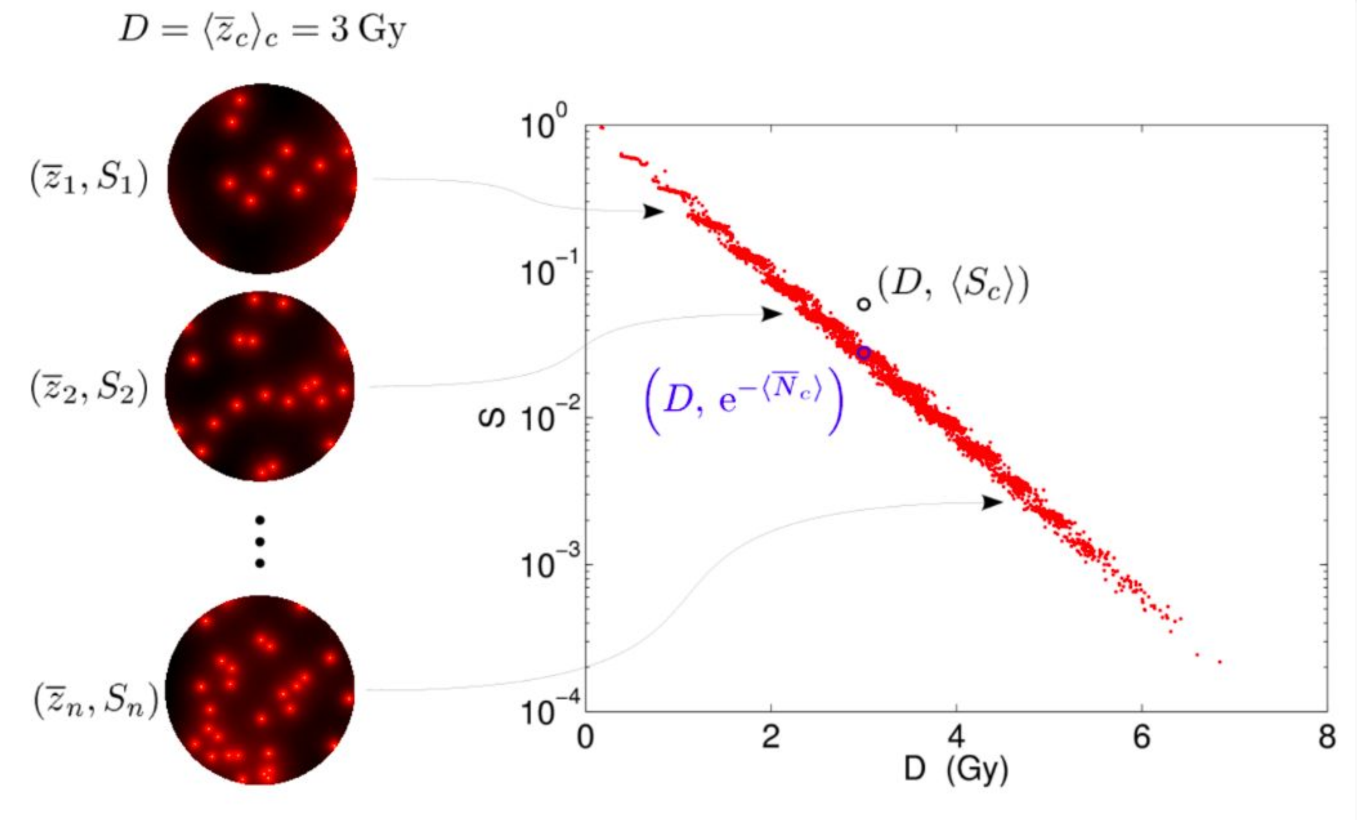
$\bar{d}(\vec{r})$



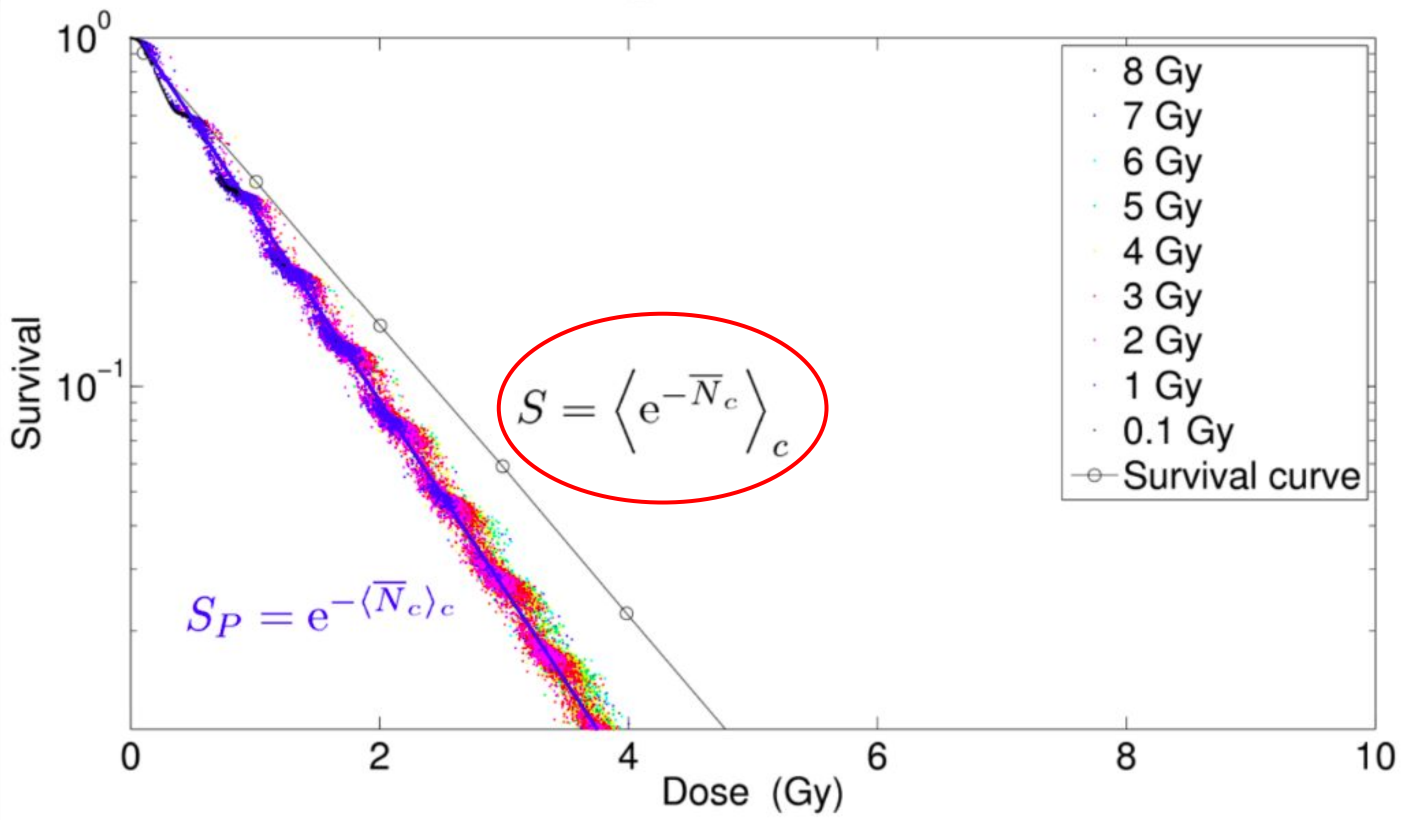
$\bar{d}_c(\vec{r})$



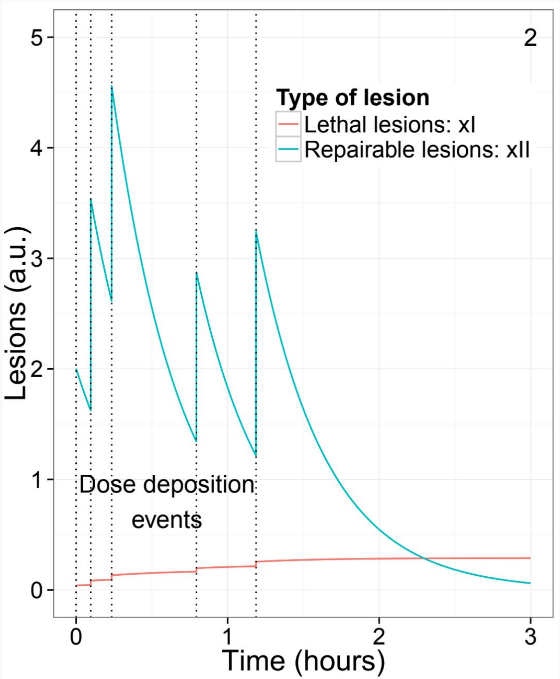
Monte Carlo approach: Cell population fluctuations



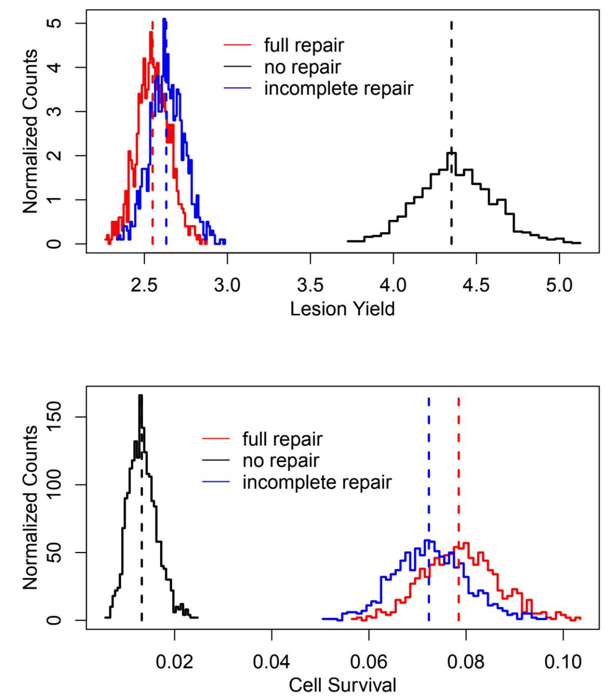
Monte Carlo approach: averaging the survivals over the cell population

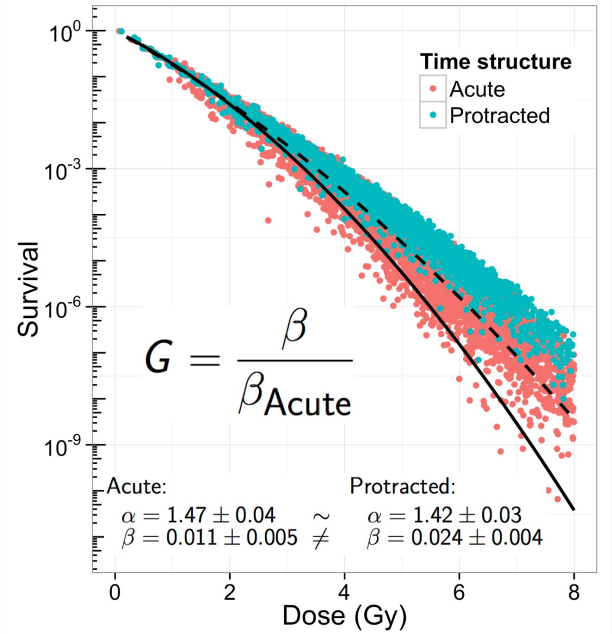


Repair kinetics: Monte Carlo time resolved approach (MCt)

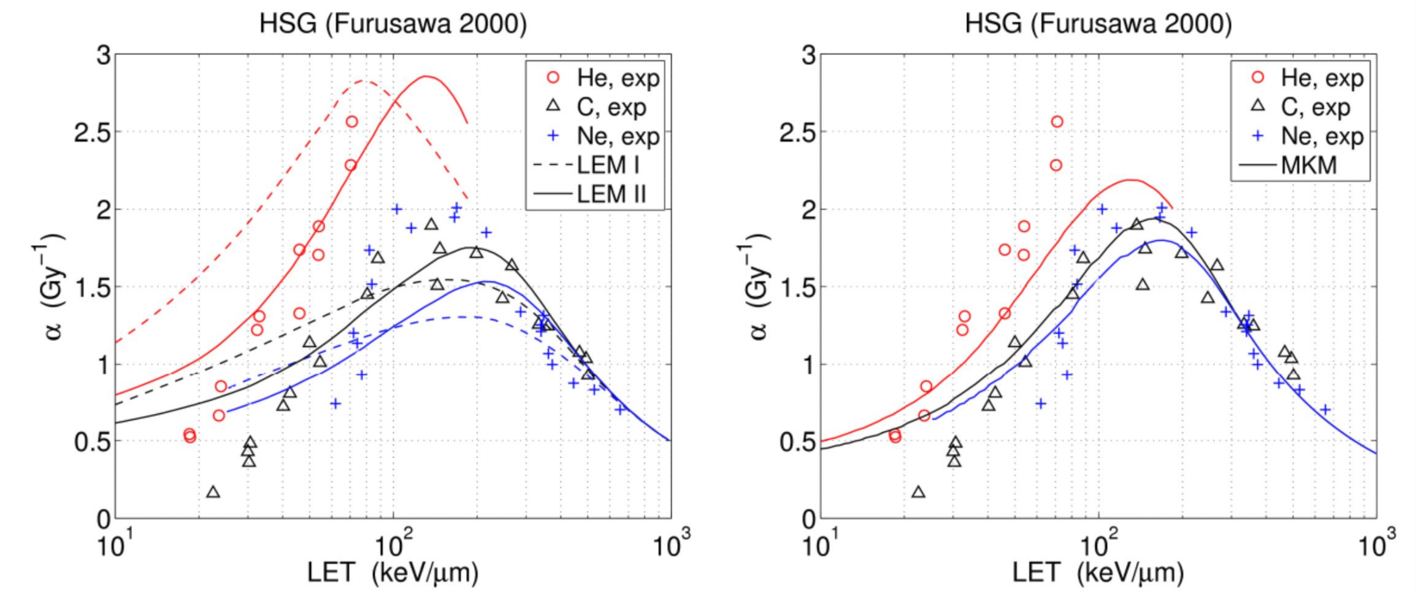


H particles at 10 MeV, V79 cells, $N = 10$ fractions, $D_f = 1$ Gy per fraction





Some evaluations and comparisons with experimental data



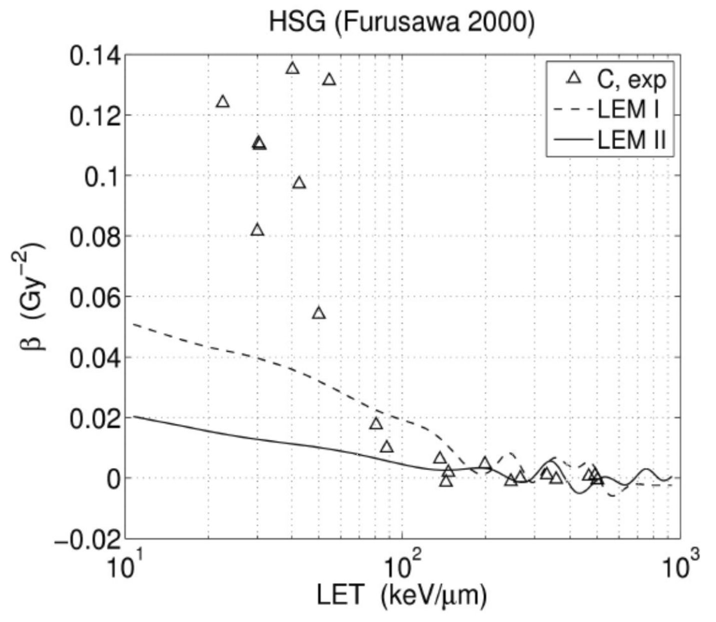
LEM

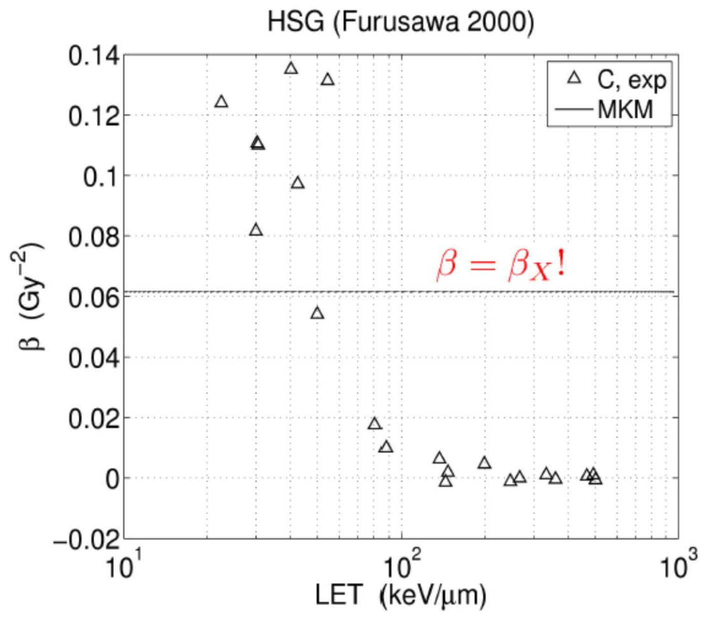
$$\begin{cases} \alpha_X = 0.313\ \mathrm{Gy}^{-1} \\ \beta_X = 0.0615\ \mathrm{Gy}^{-2} \\ D_t^{\mathrm{I}} = 30\ \mathrm{Gy} \\ D_t^{\mathrm{II}} = 6\ \mathrm{Gy} \\ R_{nucl} = 5\ \mu\mathrm{m} \end{cases}$$

MKM

$$\begin{cases} \alpha_X = 0.313\ \mathrm{Gy}^{-1} \\ \beta_X = 0.0615\ \mathrm{Gy}^{-2} \\ R_d = 0.34\ \mu\mathrm{m} \\ \sigma = \pi\ 4.6^2\ \mu\mathrm{m}^2 \end{cases}$$

Some evaluations and comparisons with experimental data





LEM

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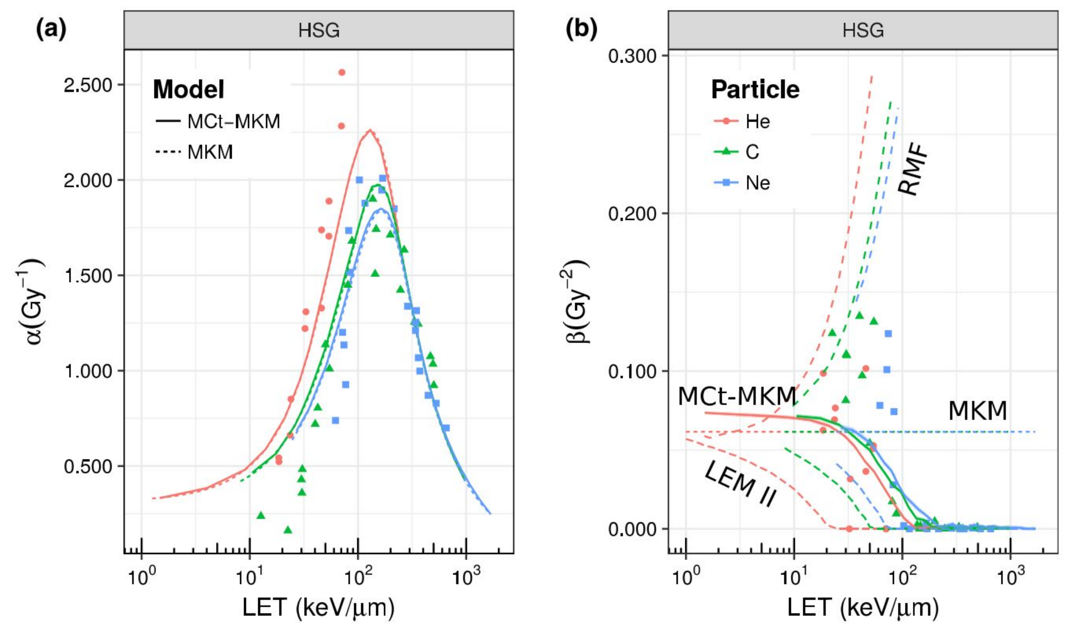
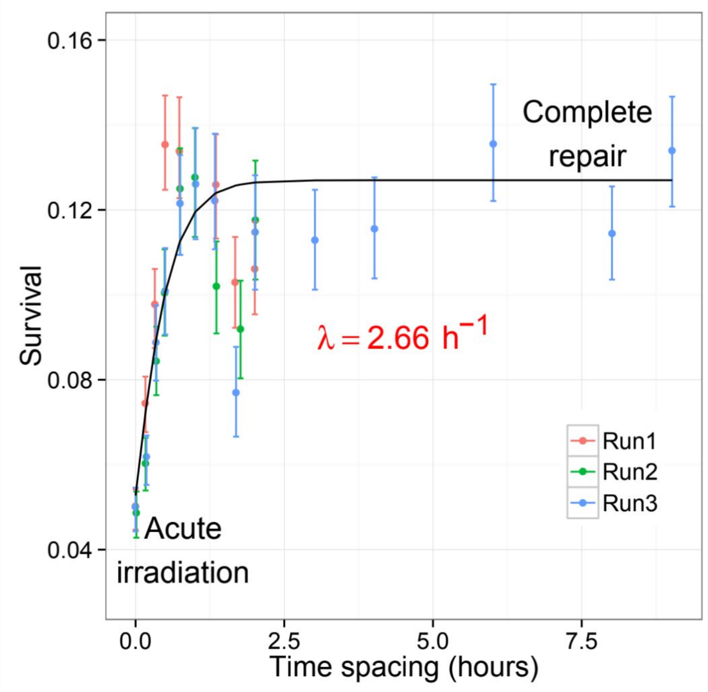
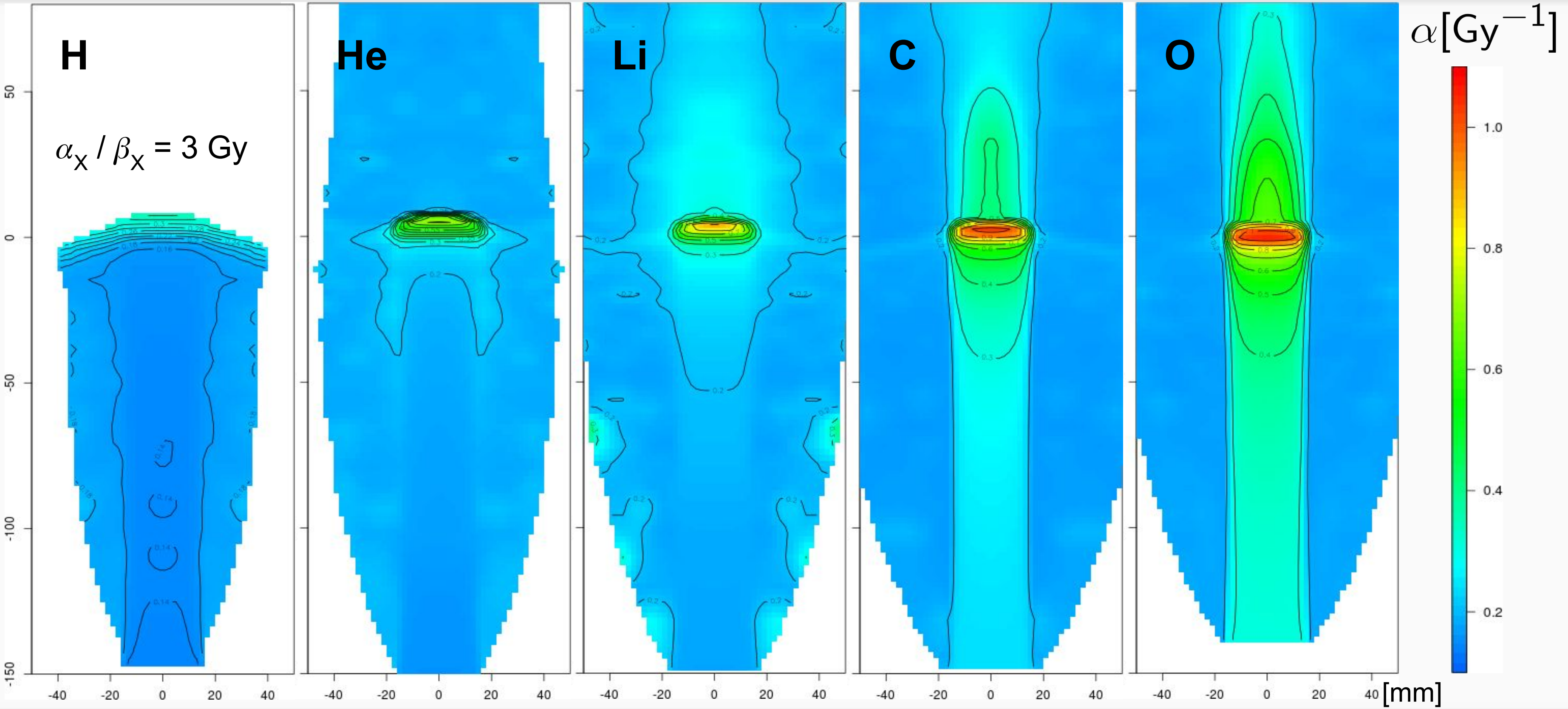
Some evaluations and comparisons with experimental data





α distribution for different ion beam (evaluated with MKM for α_X / β_X = 3 Gy)



The “Survival” code

The “Survival” code

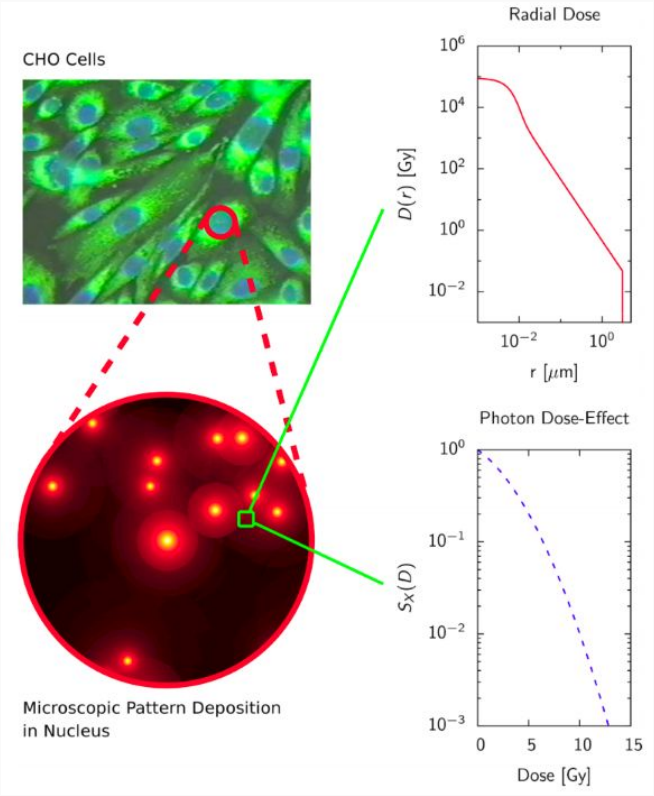
This software was developed by the INFN (Istituto Nazionale di Fisica Nucleare) in collaboration with the University of Torino (UniTO, Physics Department) and provides different implementations of some radiobiological models to predict the cell survival after irradiation. The implemented models are (for the moment): **LEMI**, **LEMII**, **LEMIII**, **MKM** and **MCt-MKM**.

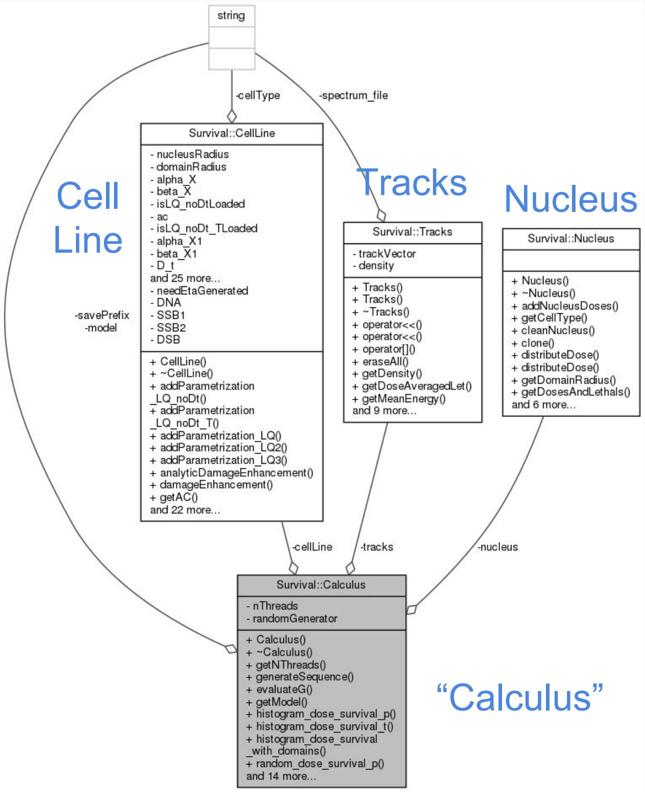
The code is written in **C++** and makes use of the **GSL** (GNU Scientific Libraries) and **OpenMP** (Open Multi-Processing) external libraries.

Reference:

- Manganaro, L., Russo, G., Bourhaleb, F., Fausti, F., Giordanengo, S., Monaco, V., … Attili, A. (2018). “Survival”: a simulation toolkit introducing a modular approach for radiobiological evaluations in ion beam therapy. *Physics in Medicine and Biology*, 1–15. https://doi.org/10.1088/1361-6560/aab697

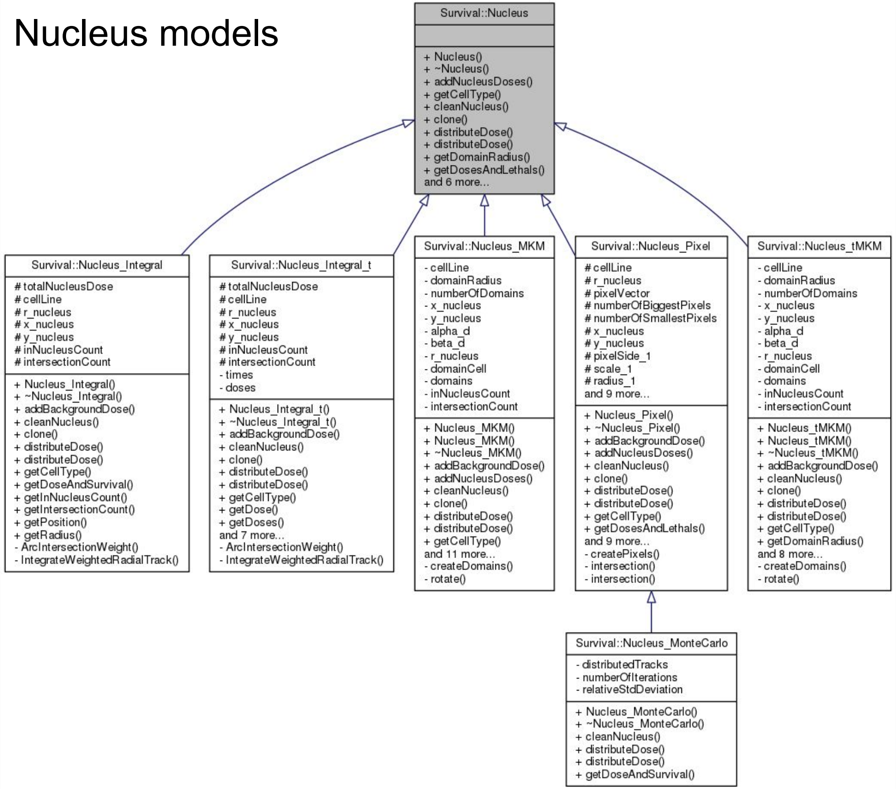
Object oriented approach to modelling



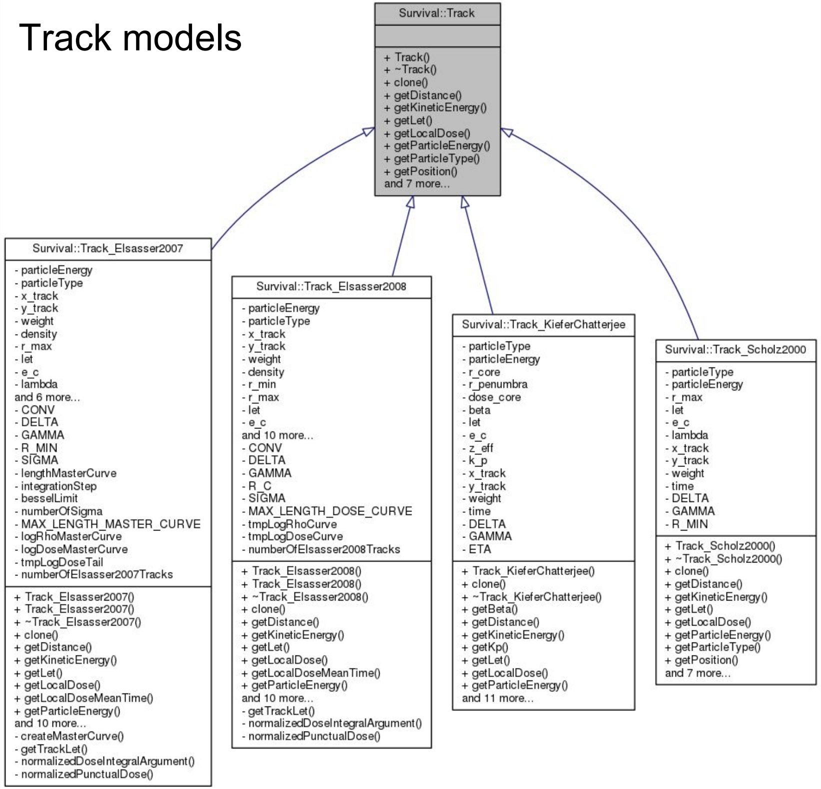


Object oriented approach to modelling - Abstraction

Nucleus models



Track models



Implemented models

- **LEM I**: M. Scholz and G. Kraft, "Track structure and the calculation of biological effects of heavy charged particles", Advances in Space Research 18, 5-14 (1996).
- **LEM II**: T. Elsässer and M. Scholz, "Cluster effects within the local effect model", Radiation Research 167, 319-329 (2007).
- **LEM III**: T. Elsässer, M. Krämer and M. Scholz, "Accuracy of the local effect model for the prediction of biologic effects of carbon ion beams in vitro and in vivo", International Journal of Radiation Oncology-Biology-Physics 71, 866-872 (2008).
- **LEM I,II,III rapid calculation GSI**: M. Krämer and M. Scholz, "Rapid calculation of biological effects in ion radiotherapy", Physics in medicine and biology 51, 1959-1970 (2006).
- **LEM I,II,III rapid calculation INFN**: G. Russo (2011), PhD Thesis.
- **MKM + amorphous track structure** introduction: Y. Kase, T. Kanai, N. Matsufuji, Y. Furusawa, T. Elsasser, and M. Scholz, "Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation", Physics in Medicine and Biology 53, 37-59 (2008).
- **MCt-MKM**: Manganaro, L., Russo, G., Cirio, R., Dalmasso, F., Giordanengo, S., Monaco, V., … Attili, A. (2017). A Monte Carlo approach to the microdosimetric kinetic model to account for dose rate time structure effects in ion beam therapy with application in treatment planning simulations. Medical Physics, 44(4), 1577–1589.

Thank You!

Thank You!

- Next: “Survival” mini-tutorial
  http://rpubs.com/batuff/392381