MICROBE-IT:

MICROdosimetry-based Biological Effectiveness assessment in Ion Therapy

WP2 - linking N/MD to RB

February, 3 2021

A Attili et al.

WP2: Outlook

- The Microdosimetric Kinetic Model (MKM) approach(es)
- Open issues and improvements
  ⇒ The GSM^2 (*Generalized Stochastic MD Model*)
  - "Inter-" and "intra-cell" stochasticity
  - Repair kinetics
  - Track structure information
  - Mixed Fields open issues
- Exp. validation
- 1° year objectives and milestones

WP2 Personnel		
Name	**Title, Institution**	**FTE (%)**
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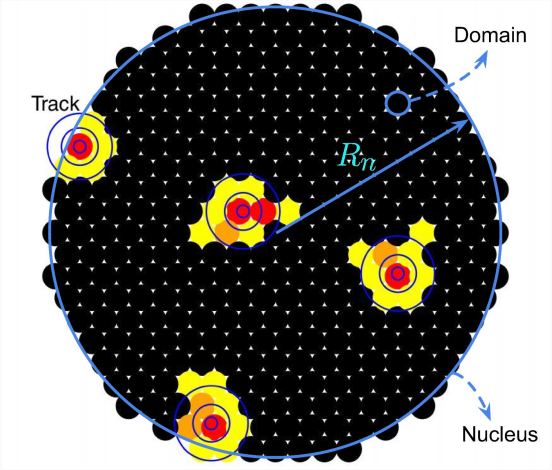
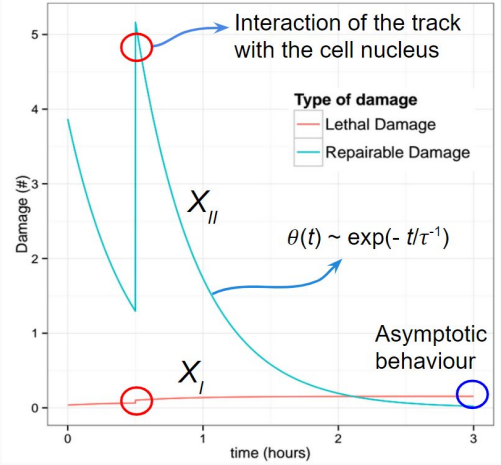
Francesco Cordoni	Assegnista, UNIVR, INFN-TIFPA	50
Giusi Irma Forte	Ricercatrice, IBFM-CNR, INFN-LNS	100
Luigi Minafra	Ricercatore, IBFM-CNR, INFN-LNS	50
Giorgio Russo	Ricercatore, IBFM-CNR, INFN-LNS	30
Emanuele Scifoni	Primo Ricercatore, INFN-TIFPA	35
Marco Schwarz	Direttore staff fisica medica, APSS, INFN-TIFPA	10
Francesco Tommasino	Ricercatore (RTDB), UNITN, INFN-TIFPA	15

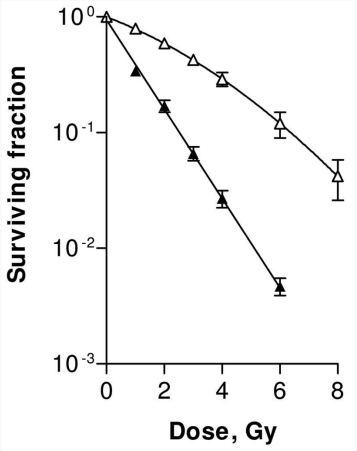
Linking Microdosimetry to Radiobiology: the MKM approach



Multi-track energy deposition pattern in cell nucleus



DNA Repair kinetics



(VE Bellinzona, FG Francesco, M Missiaggia, F Tommasino, E Scifoni, C La Tessa and A Attili (2021) Linking microdosimetric measurements to biological effectiveness in ion beam therapy: a review of theoretical aspects of MKM and other models, Frontiers in Physics, doi: 10.3389/fphy.2020.578492)

Linking Microdosimetry to Radiobiology: the MKM approach

Microdosimetry

Structural Microdosimetry/ Nanodosimetry

Track Models/MC

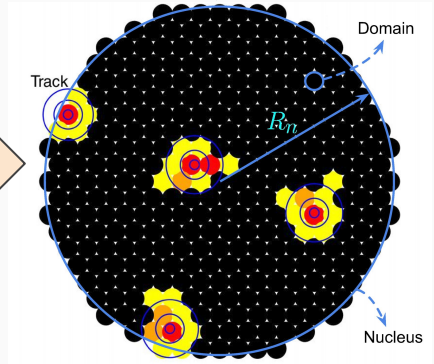
MCL

$\{z_d, z_n\}$

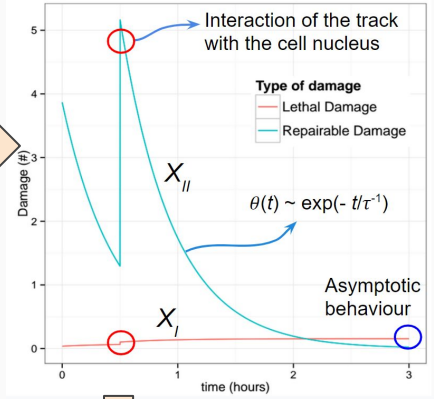
Energy deposition spectrum

$\langle z_d \rangle^*, \langle z_d^2 \rangle^*$

"corrected" first and second moment

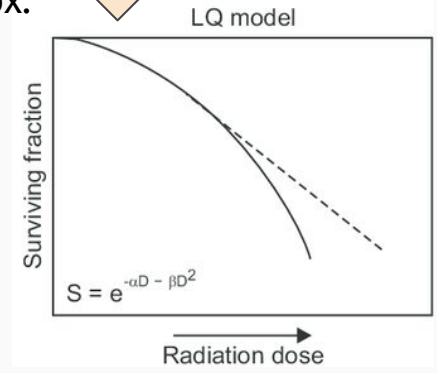


Multi-track energy deposition pattern



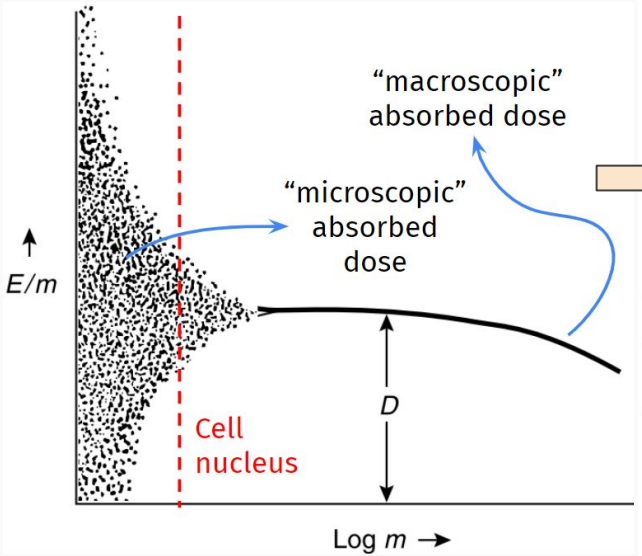
DNA Repair kinetics (deterministic approx.)

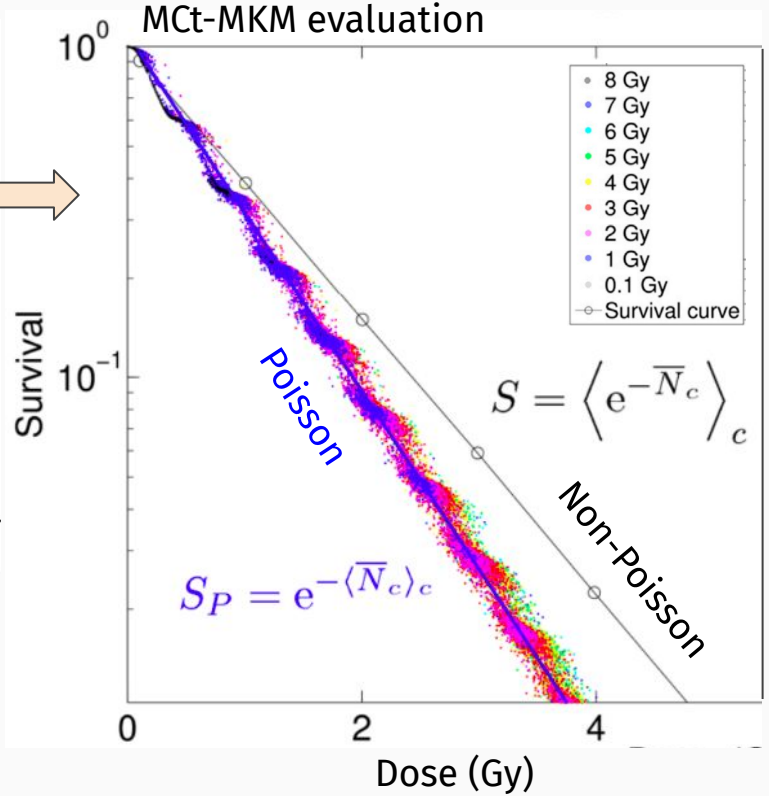
Poisson approx.



Cell Survival

“Inter-cell” stochastic processes - Energy deposition (d,n)



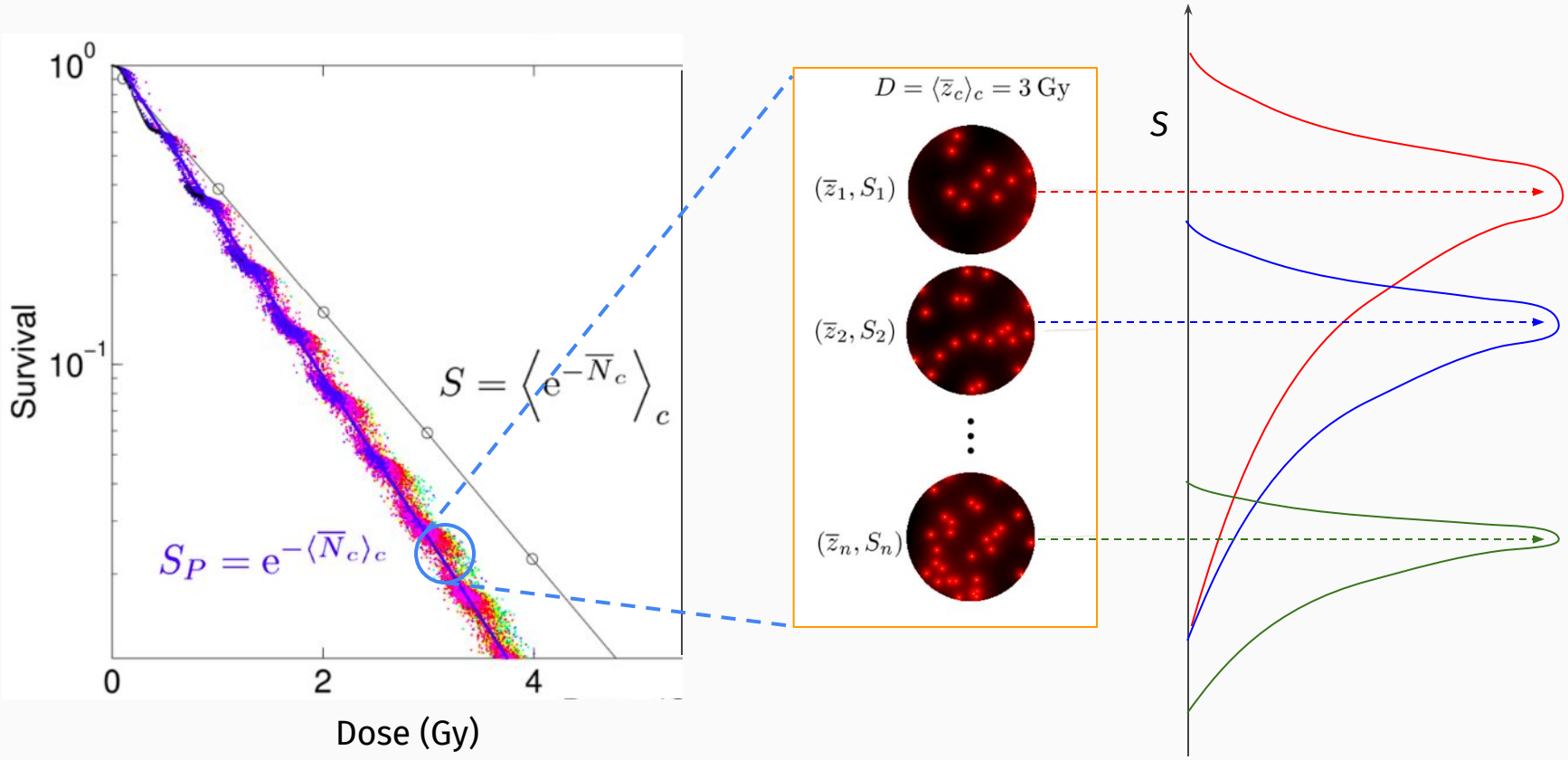


- Fluctuations play a major role at the level of cellular masses / volumes.

MKM approaches:

- Non-Poisson correction
- “Saturation” correction (used clinically)
- SMKM e DSMKM
- MCt-MKM (time-resolved MC approach)
- **GSM²** (generalized stochastic microdosimetric model).

“Intra-cell” stochastic processes - Cell response (GSM²)



Repair Kinetics investigations

- First order repair:

$$dY/dt = -CY$$
$$\Rightarrow \theta(t) = \exp(-\lambda t)$$
$$\lambda = \ln 2 / T_{1/2}$$

- Multi time constant repair:

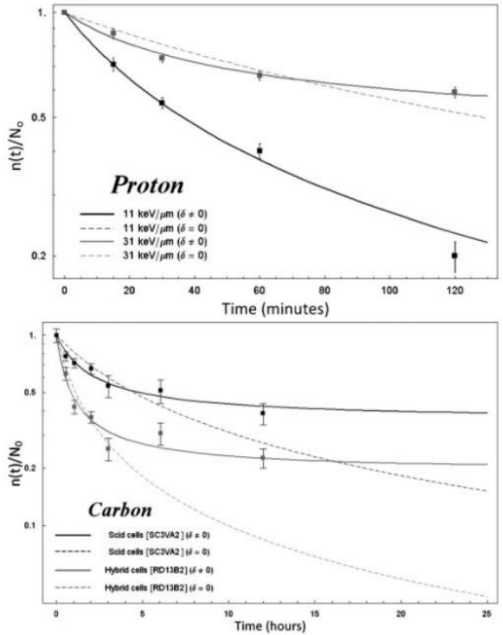
$$\Rightarrow \theta(t) = \sum_i A_i \exp(-\lambda_i t)$$

- Second order repair:

$$dY/dt = -CY^2$$
$$\Rightarrow \theta(t) = 1/(zt+1)$$
$$z^{-1} = T_{1/2}$$

- Second order repair with fraction of irreparable damage (δ):

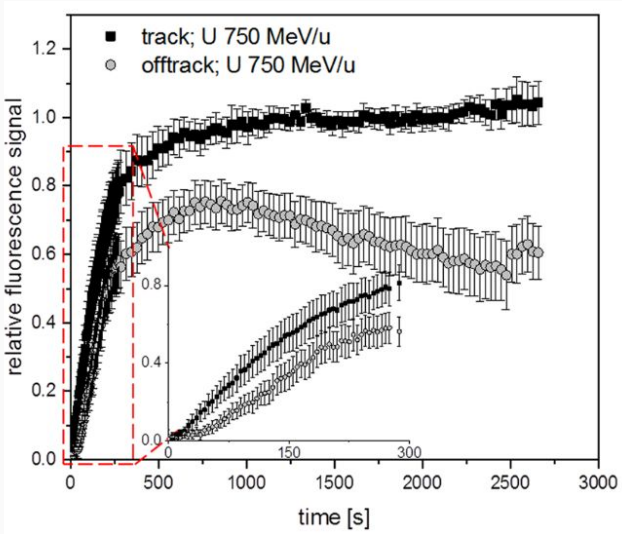
$$d(Y-\delta)/dt = -C(Y-\delta)^2$$
$$\Rightarrow \theta(t) = (1+(\delta/Y(0))zt)/(zt+1)$$



DSB Repair kinetics in V79 exposed with protons and Scid (SC3VA) exposed woth Carbon ions.[a]

[a] A. Carabe-Fernandez *et al.*, *Br. J. Radiol.* **84** (2011)

Differential Repair kinetics (?)



Jakob, B., et al. (2020), *Scientific Reports*, 10(1), 1443.

Track structure information from MD spectra (?)

MC Simulations / TPS evaluations

PHSP interacting with the cell/MD {A, Z, E_{kin}}

Micro/nano-TEPCL

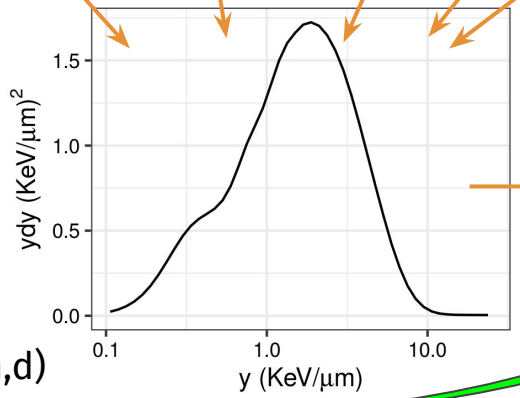
Si Tele-scope

Micro Plus

SiC

HDM

detector specifics



MKM/G SM^2

RB Experiments

Cell Structure (n,d)

Track models, Geant4-DNA, Trax-CHEM, ...

Non-MD models (LEM, etc.)

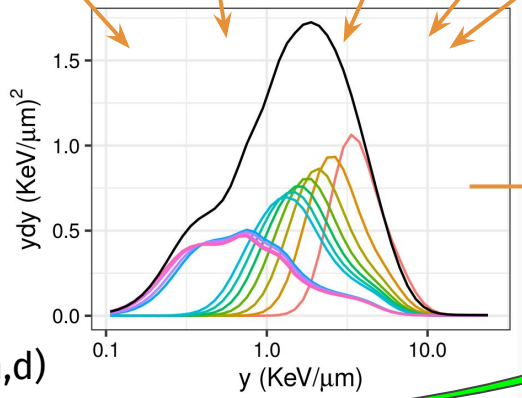
Track structure information from MD spectra (?)

MC Simulations / TPS evaluations

PHSP interacting with the cell/MD {A, Z, E_{kin}}

Micro/nano-TEPCL ⇔ Si Tele-scope ⇔ Micro Plus ⇔ SiC ⇔ HDM

detector specifics



⇔
Transfer functions between micro/nano-dosimeters and Cell systems (beyond the mean cord length appr.)

MKM/GSM²

RB Experiments

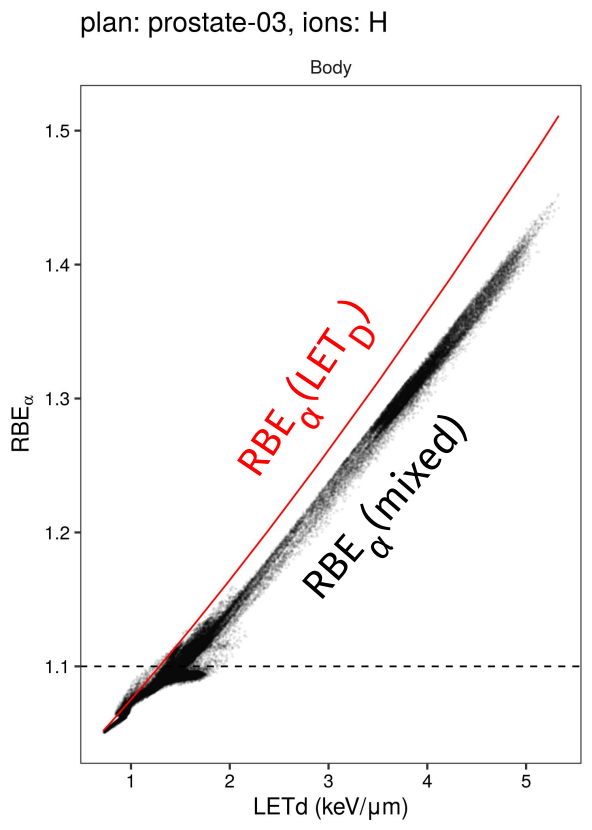
Cell Structure (n,d)

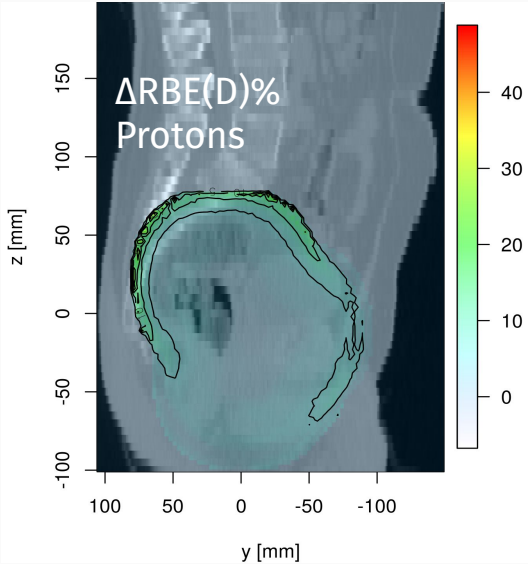
Track models, Geant4-DNA, Trax-CHEM, ...

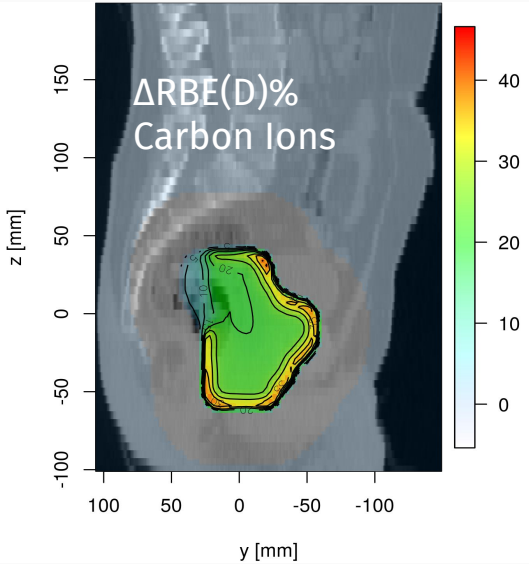
Mixture Models + Track models

Non-MD models (LEM, etc.)

The Mixed field problem in treatment simulations: LET_D vs. full spectra







ΔRBE(D)% = [RBE(D, LETD) - RBE(D, mixed)]/RBE(D, mixed) x 100

The Mixed field problem in treatment simulations: pre- vs. post-mixing

"Pre-mixing"

Spectrum components

Total spectrum

Rad.Bio. Model

Full mixed effect **(α , β)**

E.g. MKM (although only first and second component of the spectrum are used are commonly used)

"Post-mixing"

Spectrum components

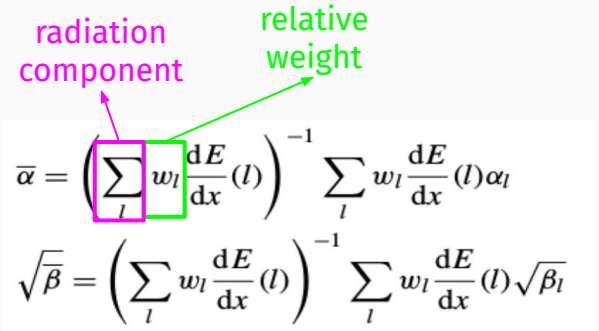
$l = 1 \dots N$

Rad.Bio. Model

$(\alpha_1, \beta_1) \dots (\alpha_N , \beta_N)$

Full mixed effect **(α , β)**

E.g. mixed-field formalism:

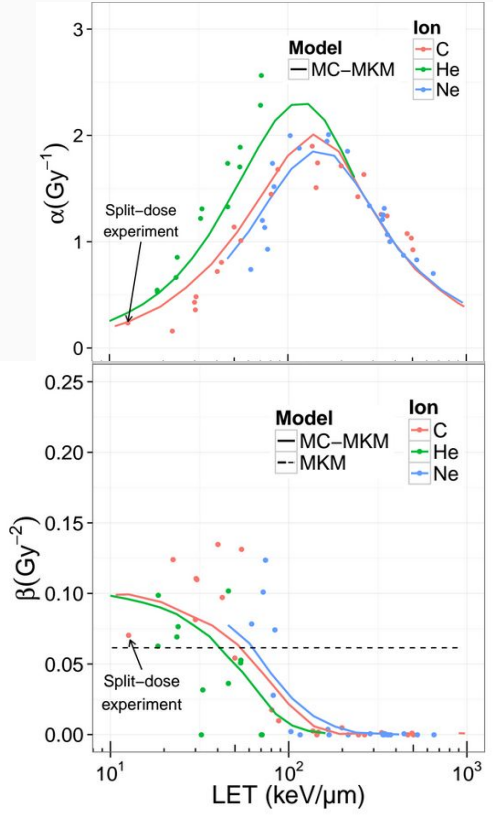


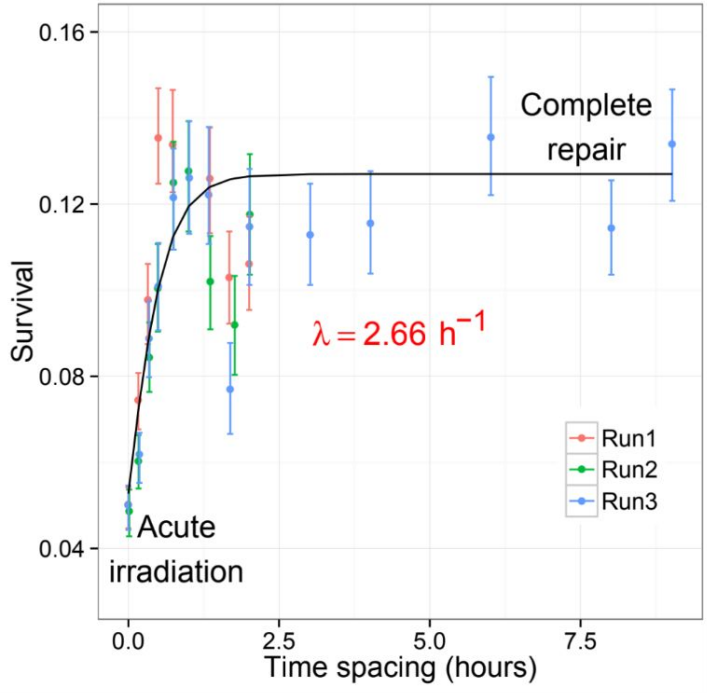
Model verification: clonogenic assay & DNA Repair Kinetics

1. Analysis from literature (PIDE).

2. Evaluation of the influence of split-dose irradiation on survival fractions by means of **clonogenic** assay (*in vitro*).

3. Investigation of the influence of split dose-irradiation on key markers expression of DNA damage response (DDR) by **western blotting** analysis (*in vitro*).





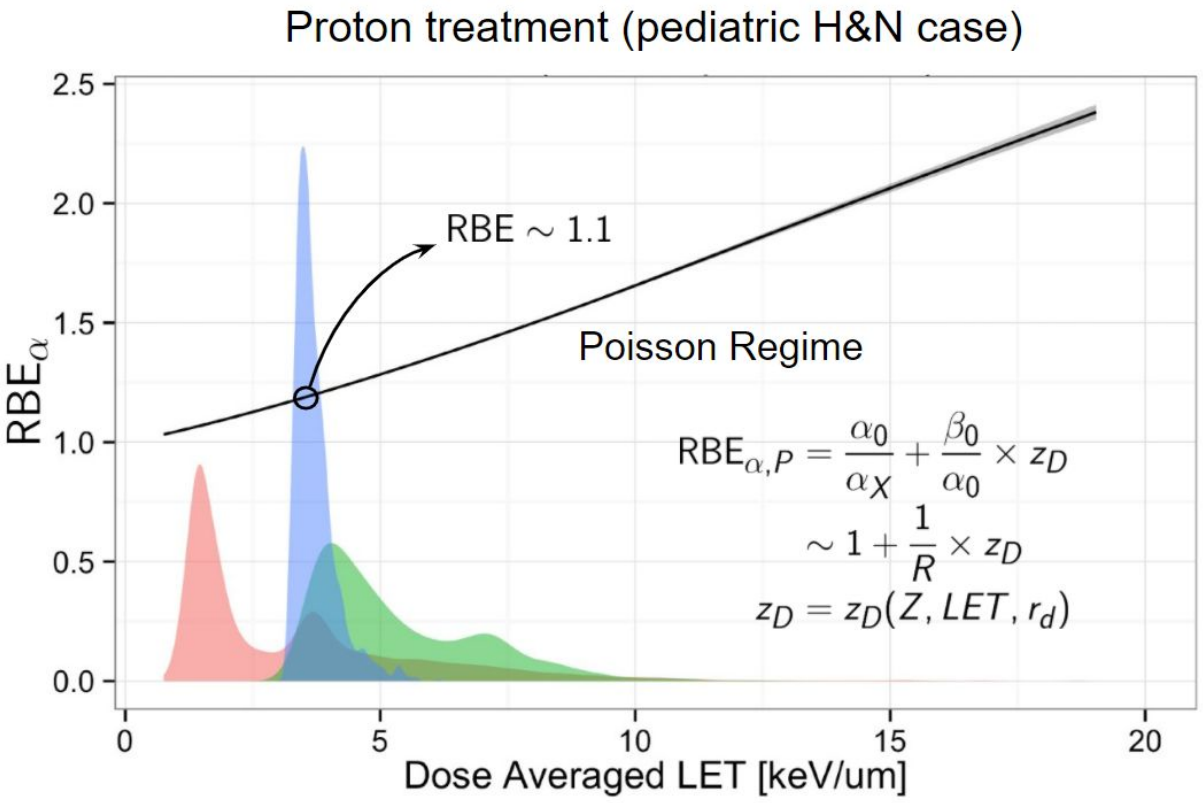
Inaniwa T, et al. (2013), *Rad. Res.*
Manganaro L, et al. (2017), *Med. Phys.*

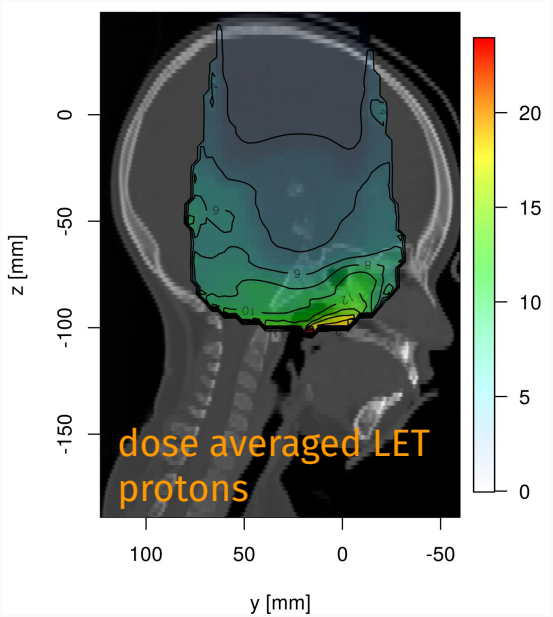
Objectives and Milestones

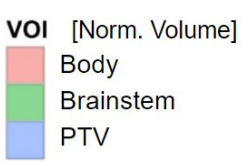
	2021												2022											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
M2.1 Evaluation of the effect that a dose-average LET-based description of radiation quality has on treatment planning																								
M2.2 Preliminary development of GSM2 model																								
M2.3 Radiobiological measurements (protons - TPTC)																								
M2.4 Radiobiological measurements (carbon ions - CNAO)																								
M2.5 GSM2 model optimization for including inter and intra for including inter and intra cells stochastic fluctuations																								
M2.6 RBE measurements in combination with WP1 (protons - TPTC)																								
M2.7 RBE measurements in combination with WP1 (carbon ions - CNAO)																								
M2.8 GSM2 model validation and benchmark																								

Spares

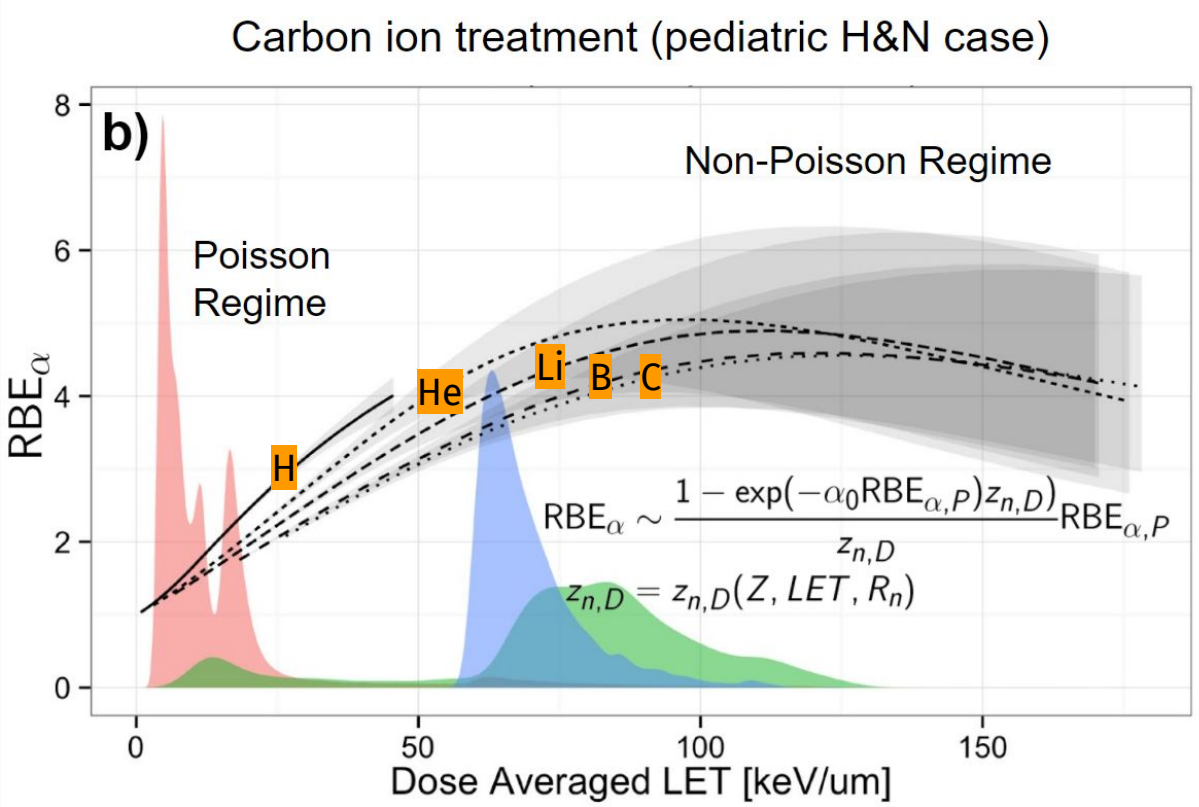
Poisson regimes in treatments

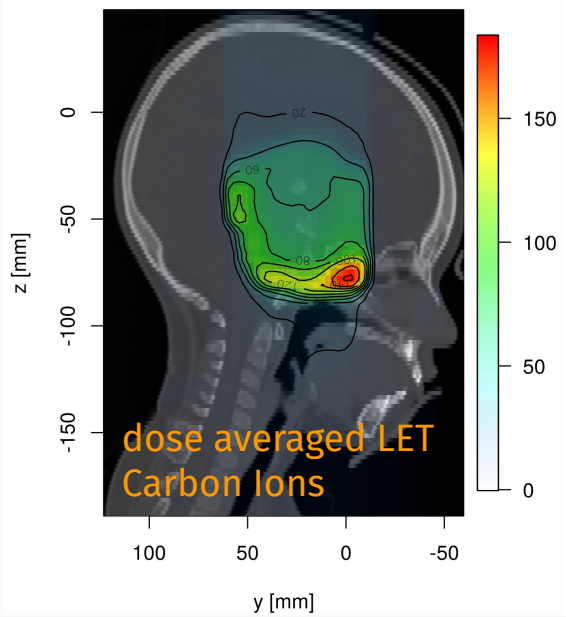


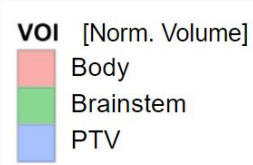




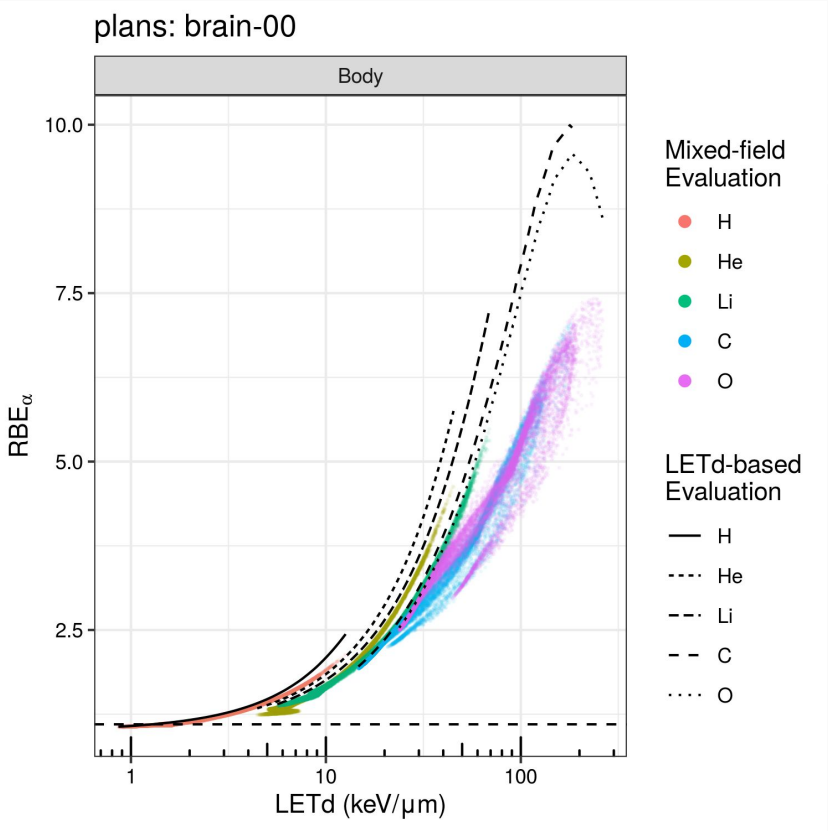
Non-Poisson regimes in treatments

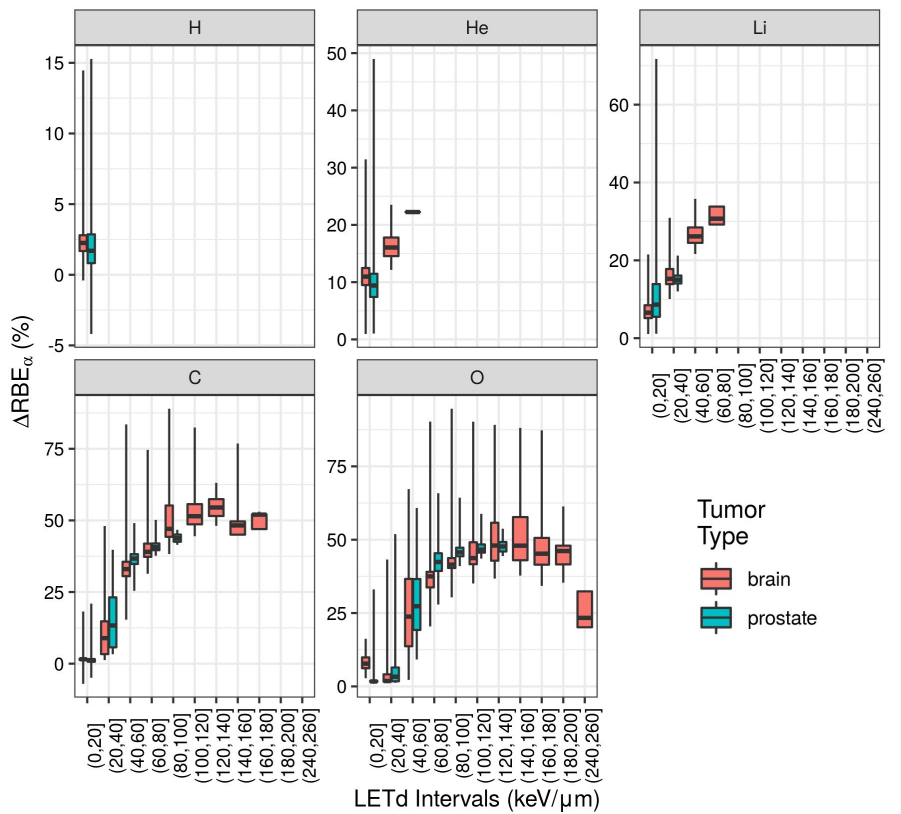




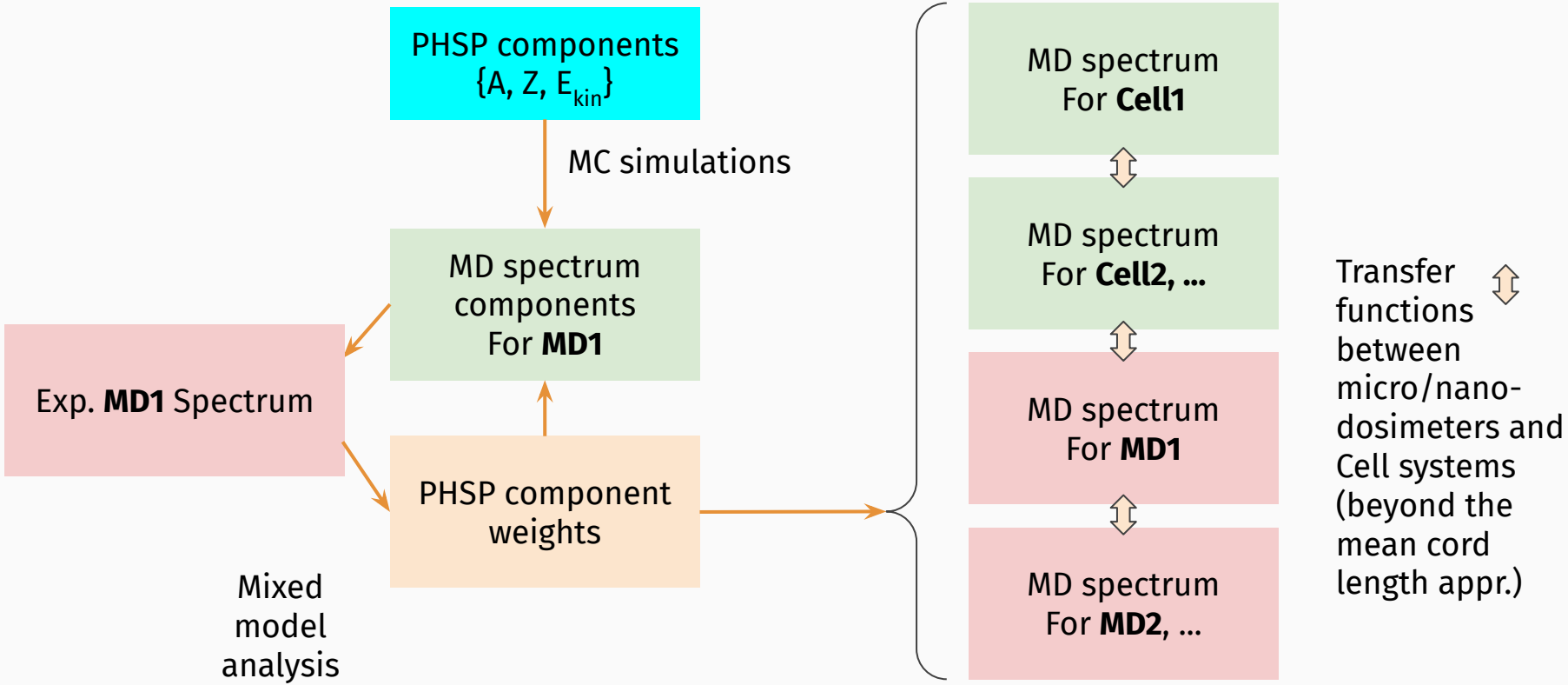


The Mixed field problem in treatment simulations: LET_D vs. full spectra

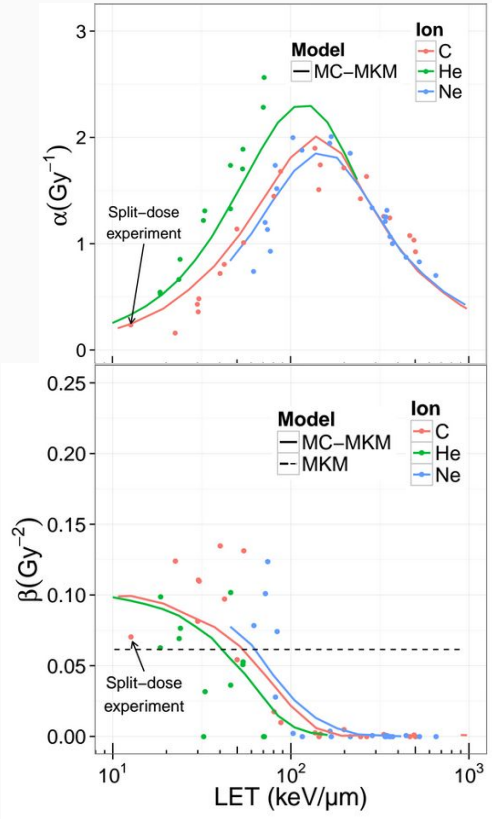


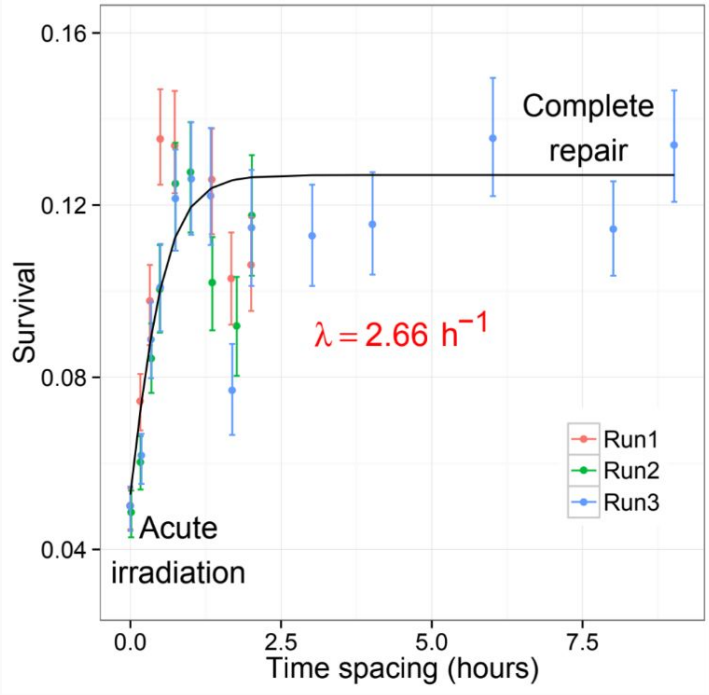


Mixture model analysis to reconstruct the phase space



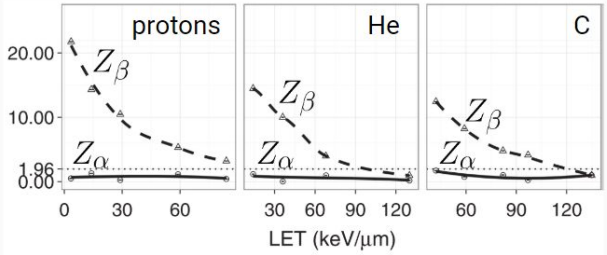
Model verification: In vitro “split dose” experiments





$$Z_x = \frac{|x_{Acute} - x_{Nonacute}|}{\sqrt{\sigma^2_{x_{Acute}} + \sigma^2_{x_{Nonacute}}}} \qquad x = (\alpha, \beta)$$

V79 cells



$$G = \frac{-\ln\langle S_c\rangle_c - \alpha D}{\beta D^2}$$

Inaniwa, T., et al. (2013). *Radiation Research*; Manganaro, L., et al. (2017). *Medical Physics*.