The BIANCA biophysical model/MC code: calculations of radiation-induced cell damage in view of hadrontherapy treatments

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Pavia's bridge

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The BIANCA model/code

*(**BI**ophysical **AN**alysis of **C**ell death and chromosome **A**berrations, reviewed in Ballarini & Carante 2016, Radiat Phys Chem 128)*

- 2 parameters *with biophysical meaning*
- cell death *and chromosome aberrations*
- mechanism-based

Cell death

(lethal) chromosome aberrations

Energy deposition

DNA (cluster) damage

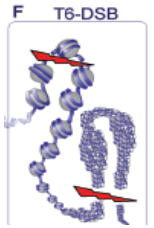
The model - assumptions *(version BIANCA II, Carante & Ballarini 2016, Front Oncol 6:76)*

irradiation

- radiation induces **DNA "Cluster Lesions" (CLs)**, so that each CL breaks the chromosome in 2 independent fragments

  *the **mean number of CLs per Gy and per cell** is the **1st adjustable parameter,***

  mainly dependent on radiation quality but also modulated by the target cell



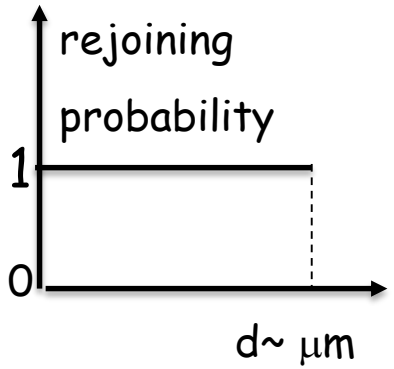
clusters of Double-Strand Breaks (Iliakis & coll 2016)

DNA damage

- chromosome fragments lead to chromosome aberrations following either **un-rejoining (with probability *f*),** or **distance-dependent incorrect rejoining**

  *the **fragment unrejoining probability f** is the **2nd parameter,***

  dependent on the target cell



chromosome damage

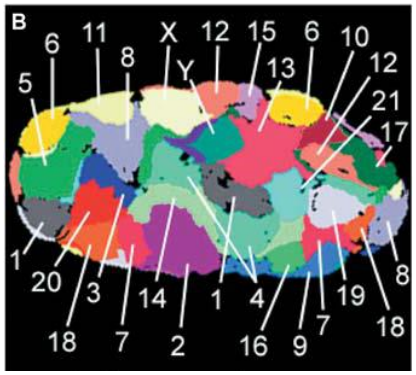
DICentric Ring DELetion

- some chromosome aberrations (**dicentrics, rings and deletions** visible in Giemsa) lead to **clonogenic cell death**

cell death

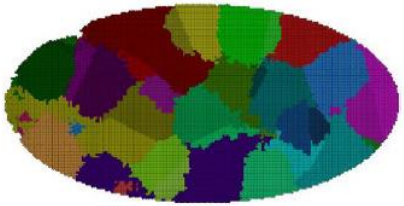
The model – simulation of target and projectile

Reality…



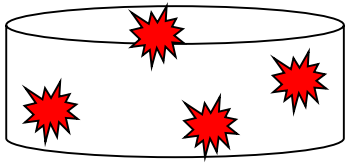
nucleus of human fibroblast with «chromosome territories» *(Bolzer et al. 2005)*

…and simulation:

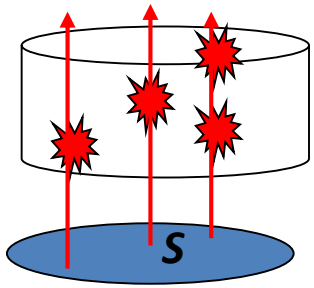


simulated nucleus of human fibroblast with chromosome territories and arm domains *(Tello et al. 2017, DNA Repair)*

- *chromosome territory = union of cubic voxels (side: 0.1 μm; no. of voxels proportional to the DNA content)*
- *different nucleus shapes and dimensions*
- *different genomes (human, hamster, rat)*



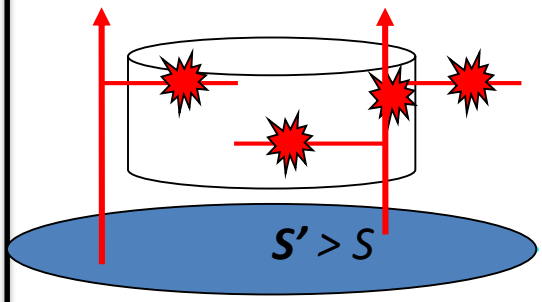
X- and γ-rays: CLs uniformly distributed in the cell nucleus



(low-energy) light ions like p and He: CLs distributed along segments

- *particles/cell:* $\langle n \rangle = D \cdot S/(0.16 \cdot LET)$

$\Rightarrow$ *CLs/particle =* $CL \cdot Gy^{-1} \cdot cell^{-1} \cdot 0.16 \cdot LET \cdot S^{-1}$



heavier ions like C: CLs distributed also radially

Model testing - X-rays

V79 cells, 'gold standard' in radiobiology
(exp. data: Carrano 1973)

- **Aberration yields** (3 Gy)

	Dicentrics+Rings/cell	Deletions/cell
exp.	0.410±0.018	0.556 ±0.026
sim.	0.410	0.568

(simulation error: ≤1%)

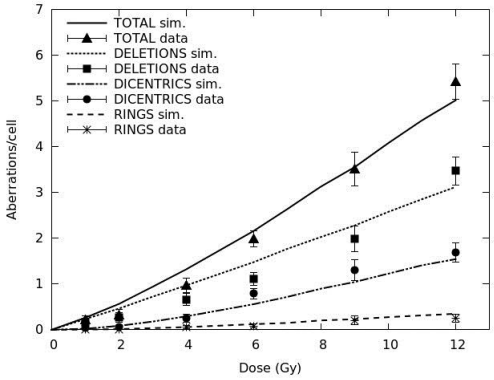
- **Cell survival** (3 Gy)

exp. S = 0.38 ±0.01
sim. S = 0.39

(model parameters: 1.7 CL·Gy^{-1}·cell^{-1}, f=0.08)

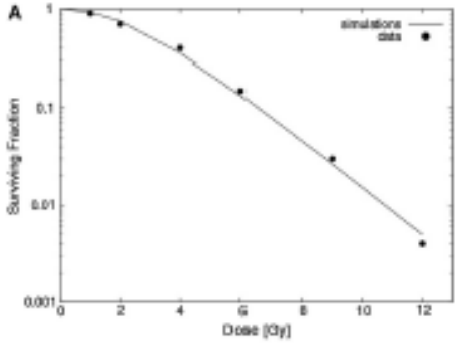
AG1522 cells, normal human fibroblasts
(exp. data: Cornforth & Bedford 1987)

- **Aberration yields**



(Ballarini & Carante 2016, Radiat Phys Chem 128)

- **Cell survival**

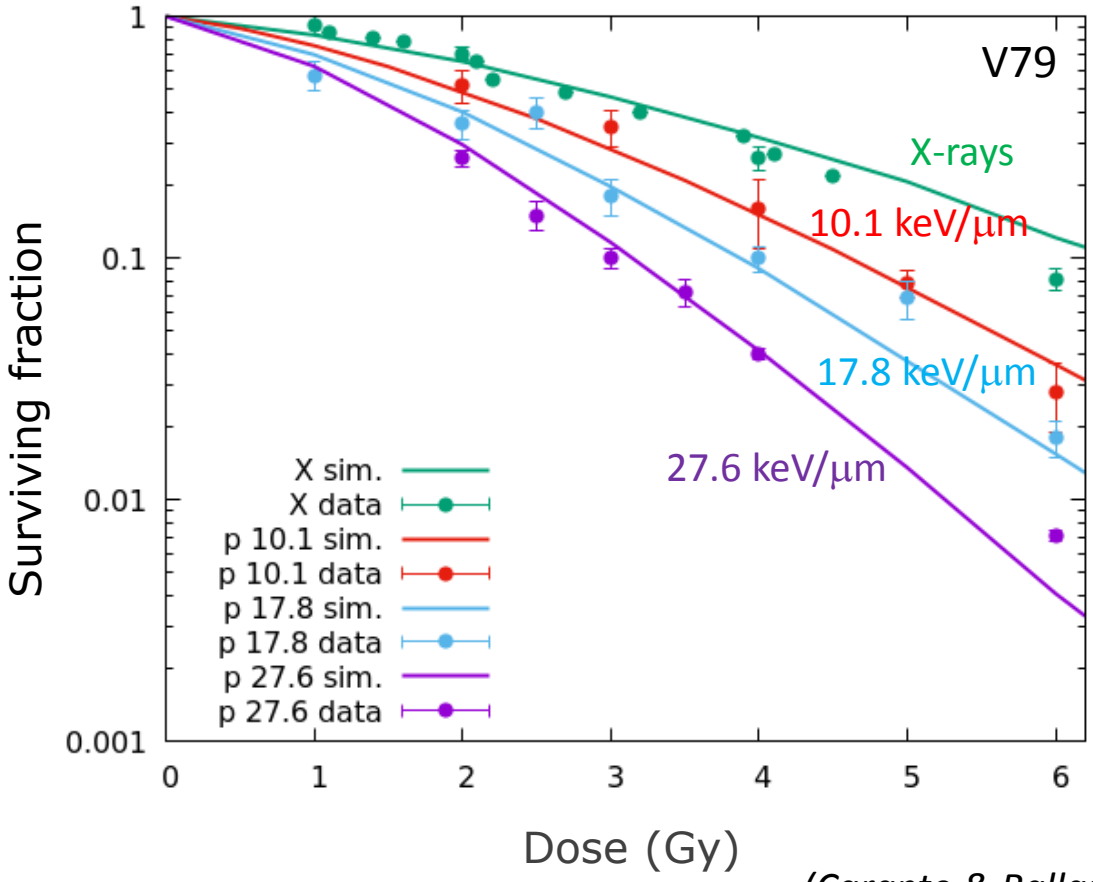


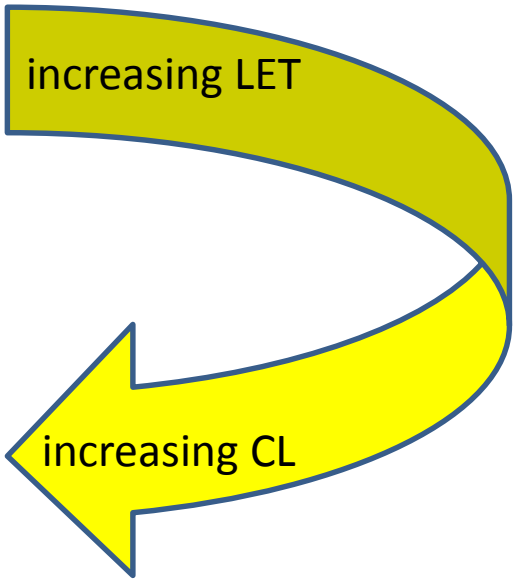
(model parameters: 1.3 CL·Gy^{-1}·cell^{-1}, f=0.18)

⇒ the model can reproduce cell survival and different aberration types by X-rays

Model testing - protons

parameters: ***f*** *(fragment un-rejoining probability)* ***unchanged*** *with respect to X-rays*
CL yields adjusted *separately for each LET (energy)*

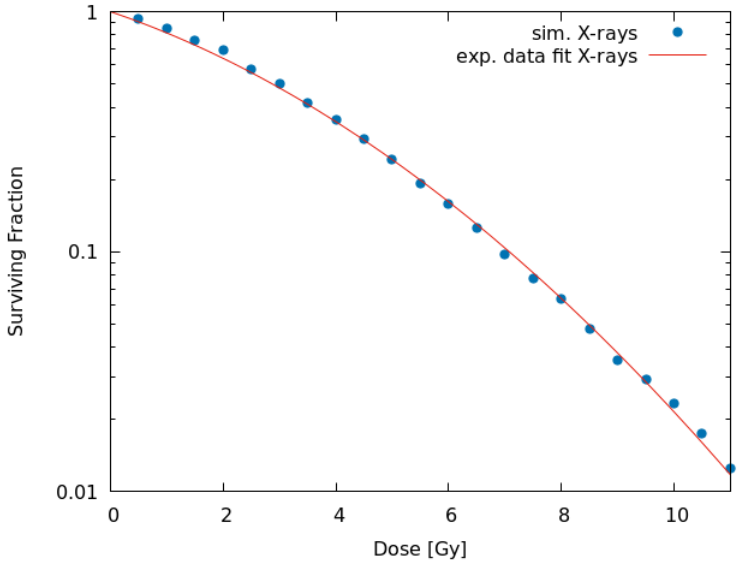




(Carante & Ballarini 2016, Front Oncol 6:76;
exp. data: Folkard et al. 1996, Belli et al. 1998)

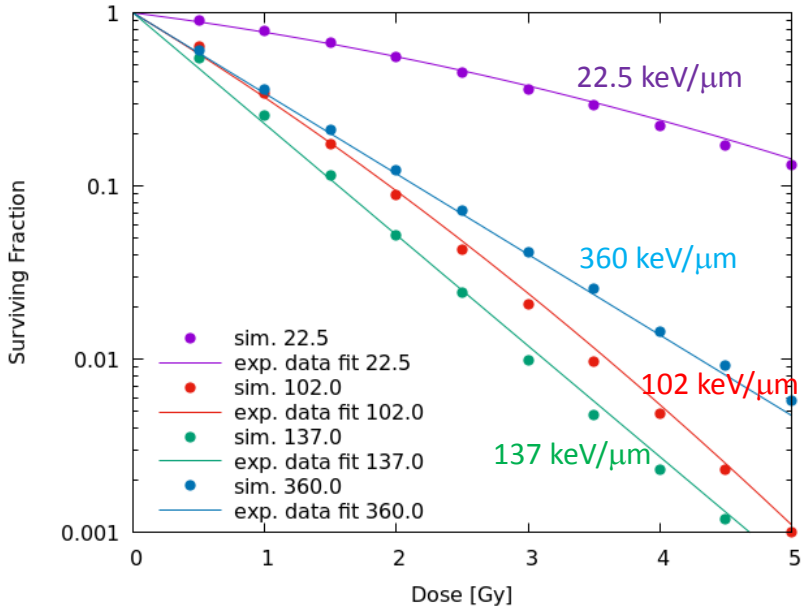
- *dicentrics, rings and deletions lead to cell death not only for X-rays, but also for protons*

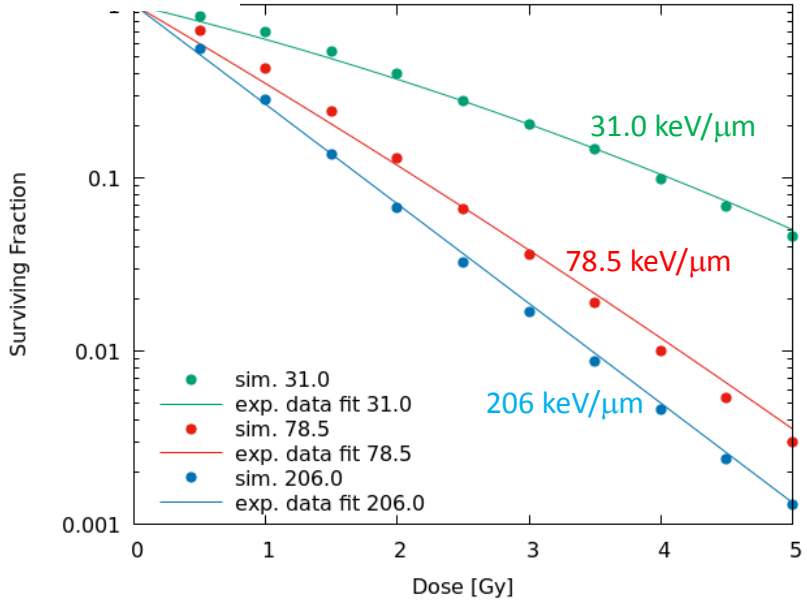
Model testing – Carbon ions



V79

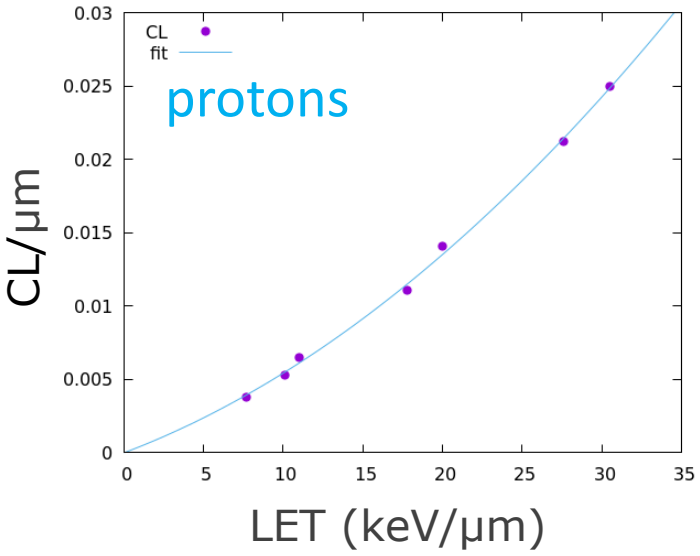
(C. Aimè 2017, Thesis, University of Pavia; exp. data from Furusawa et al. 2000)

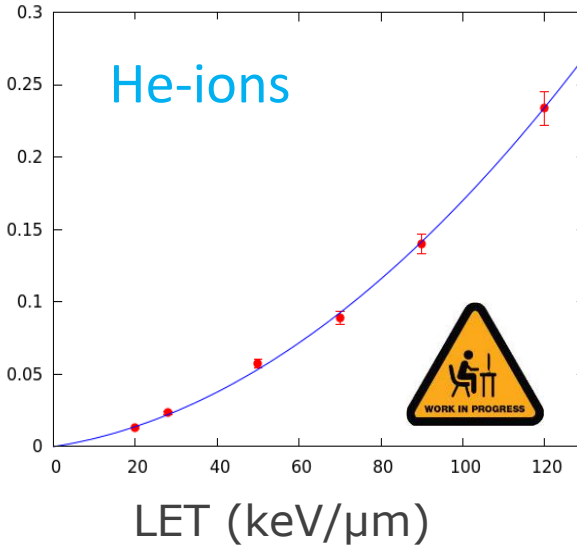


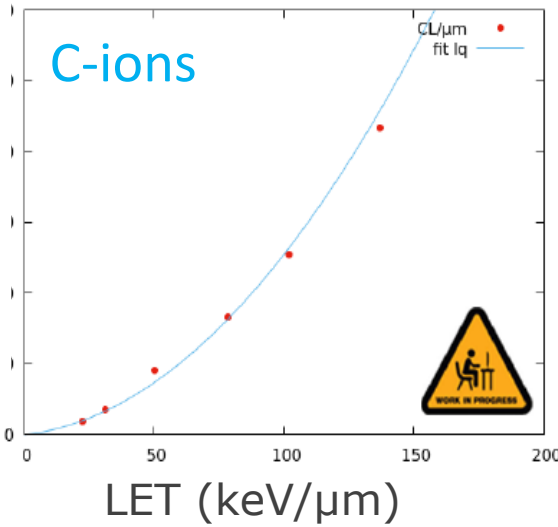


- *the approach also works for Carbon ions*

Dependence of Cluster Lesions on radiation quality







fit

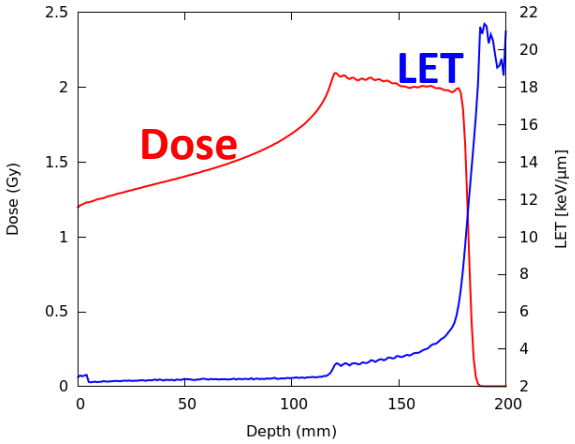
CL for “any” LET value

full predictions of cell death and chromosome aberrations

(“virtual experiments”!)

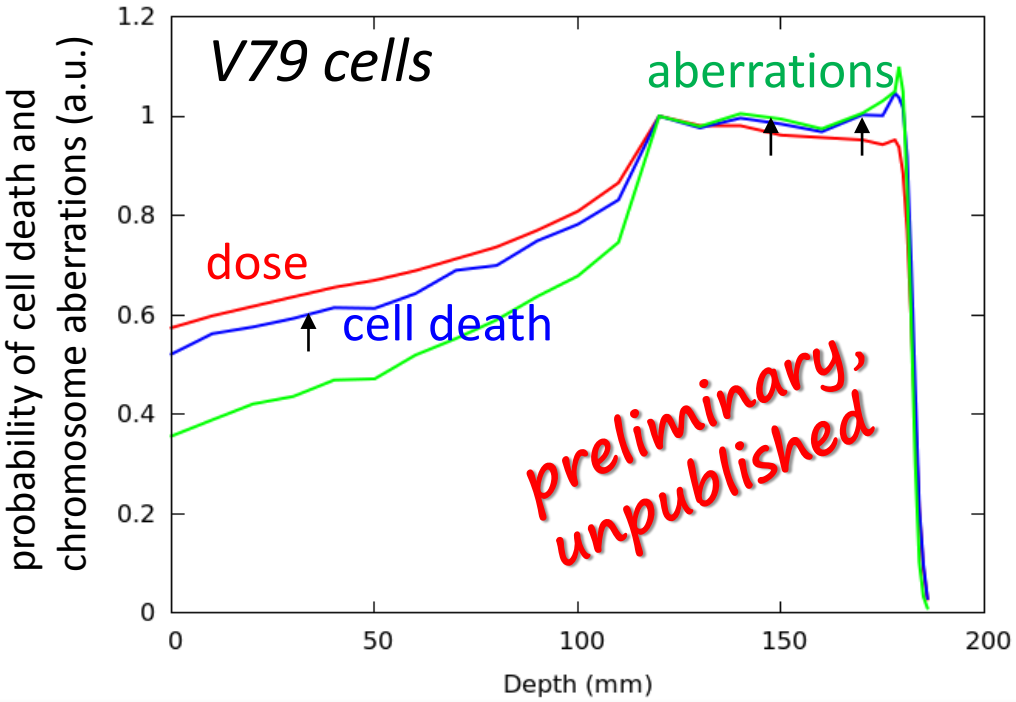
Applications for hadrontherapy:

prediction of cell death & chromosome damage for a proton SOBP @CNAO



(courtesy A. Mairani, CNAO)

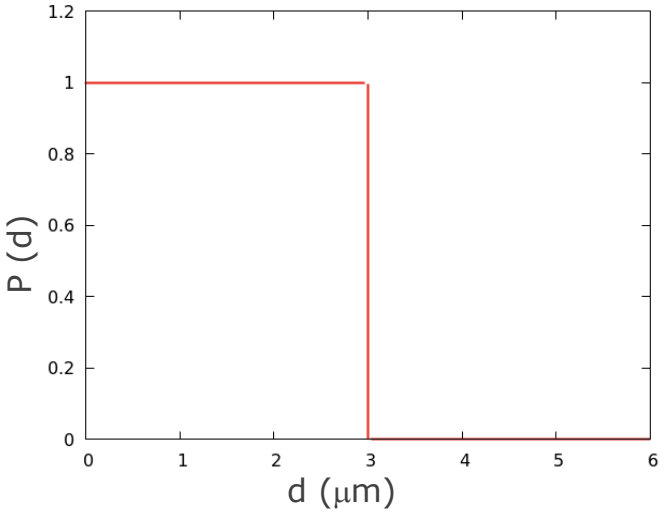
interface between BIANCA and the FLUKA radiation transport code

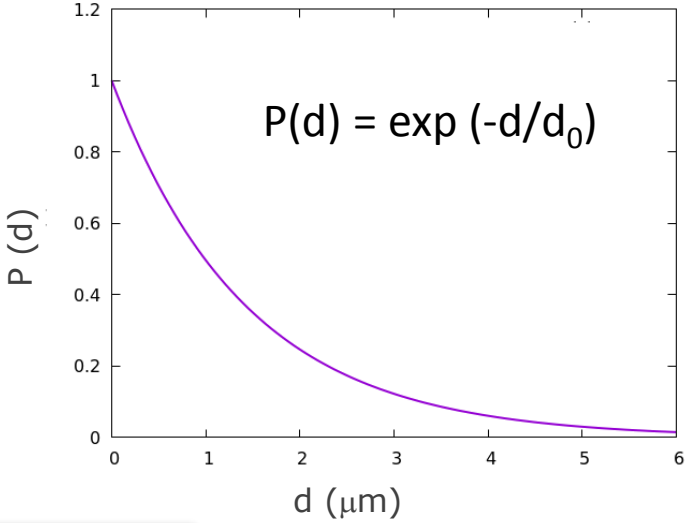


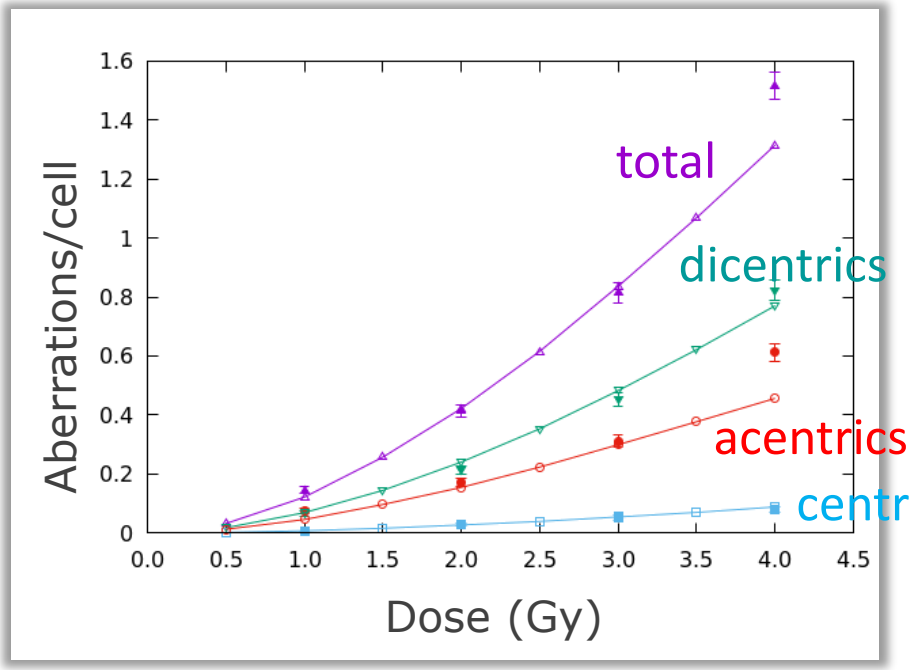
- simulations with 1-mm step
- increase of biological effectiveness in the distal region ⇒ RBE = 1.1 may be sub-optimal?

Model refinement *(in coll. with University of Campinas, Brazil):*

Probability of chromosome-fragment rejoining as a function of fragment distance







(Tello et al. 2017, DNA Repair)

Concluding remarks...

BIANCA, **mechanism-based** model with ***2 parameters***, *dealing with both* ***cell death (→effectiveness on tumor)*** *and* ***chromosome aberrations (→damage to healthy tissue)***

- *severe DNA damage and μm-level 'proximity effects' play an important role in chromosome-aberration induction*
- *dicentrics, rings and deletions lead to clonogenic cell death not only for X-rays but also for ions*
- *database of CLs → full predictions at 'any' depth of hadrontherapy beams*
- *using RBE=1.1 may be sub-optimal*

INFN projects 'ETHICS' and 'MC-INFN'

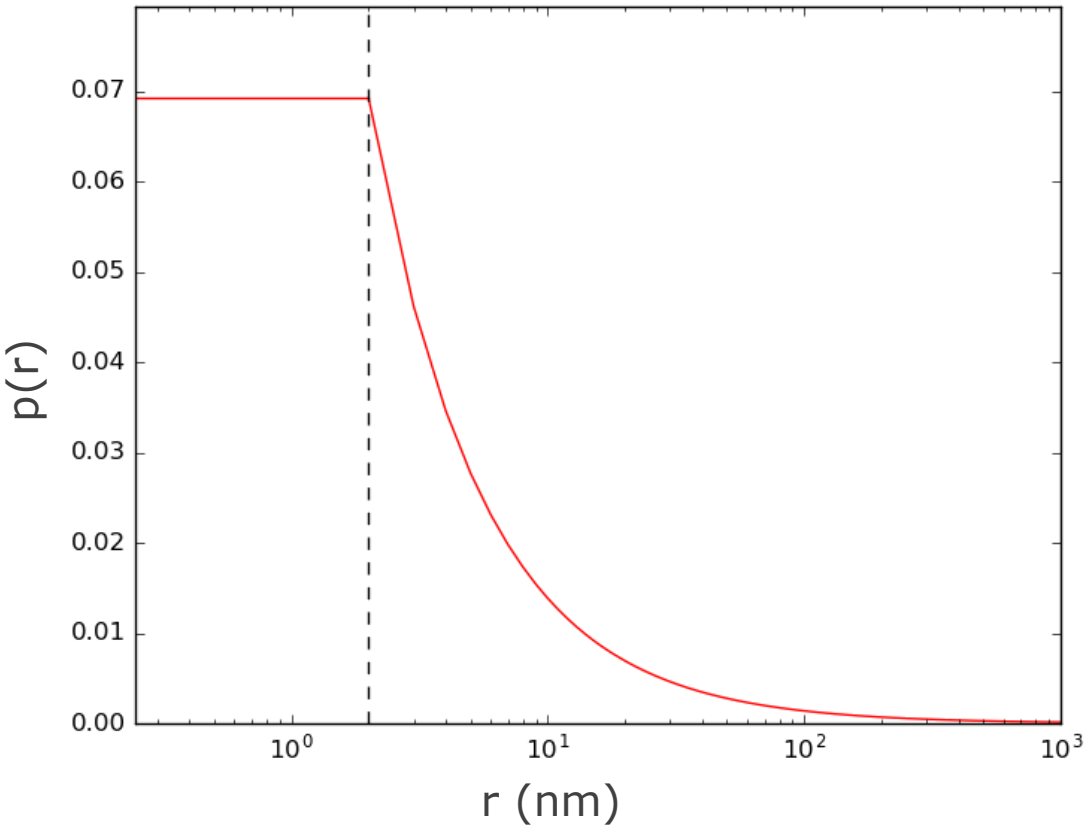
...and future developments:

- focusing on the interface with FLUKA
- extending the CL data-base to other cell lines
- testing the exponential distance-dependence for higher LET

…… ---------- ----------

Backup slides

Radial shift

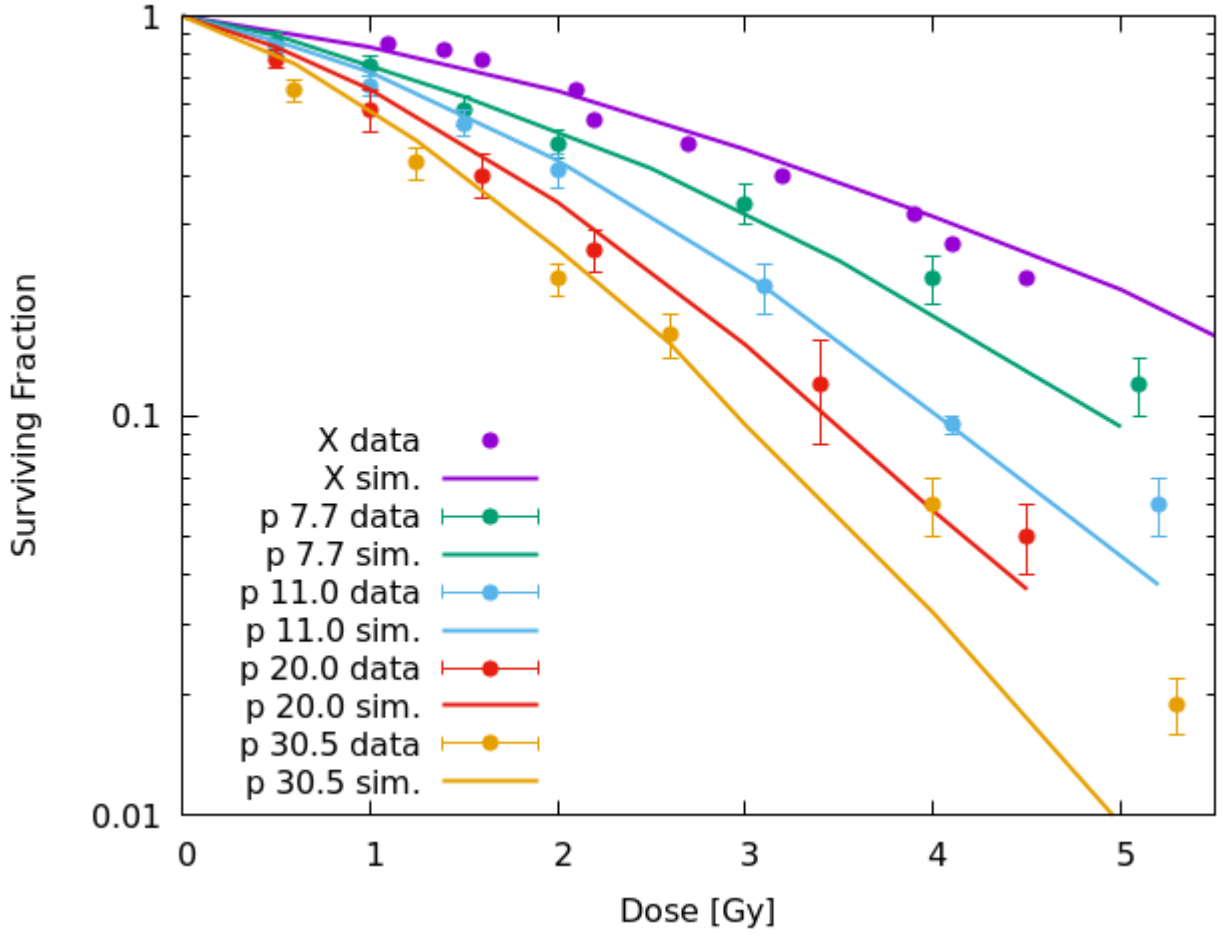


r_{min} = 2 nm

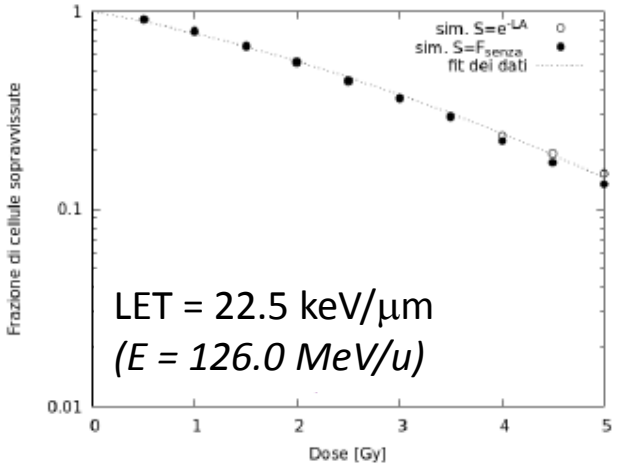
r_{max} [µm]=0.05·E[MeV/u]$^{1.7}$

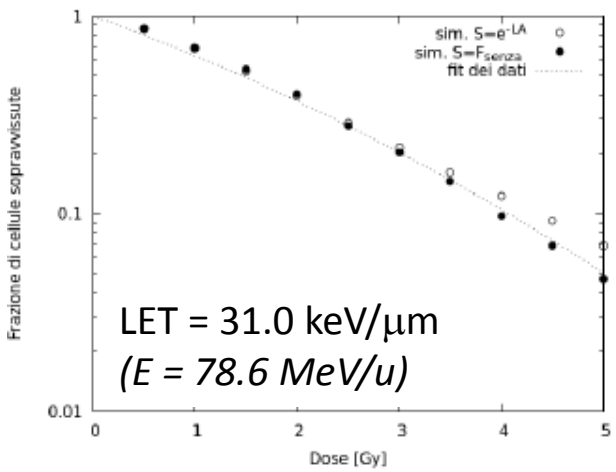
(Scholz and Kraft, 1992; Kiefer and Straatch, 1986)

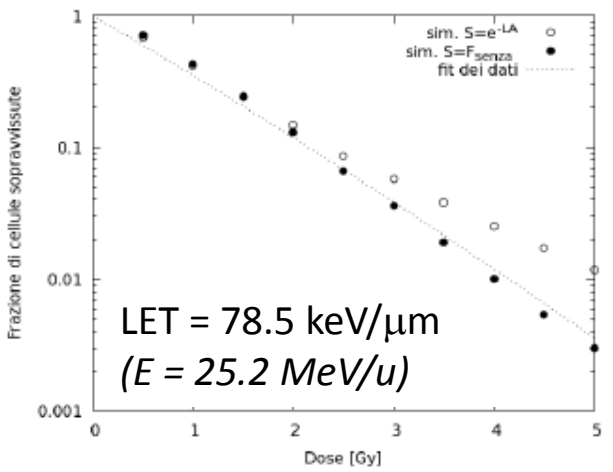
V79 protons Belli et al. 1998

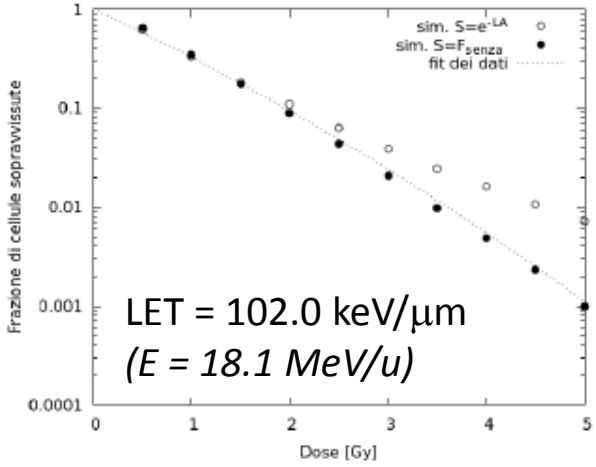


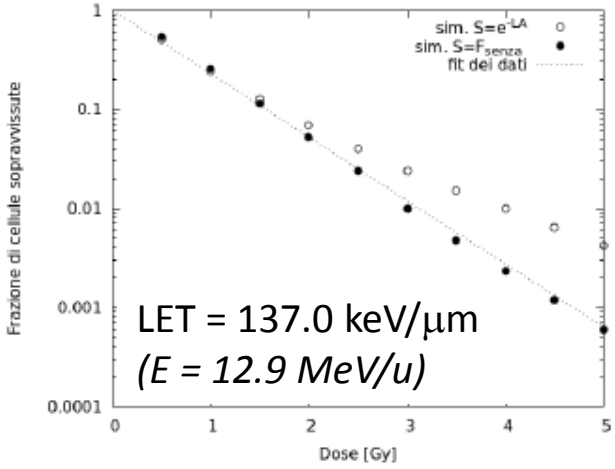
Model testing – Carbon ions

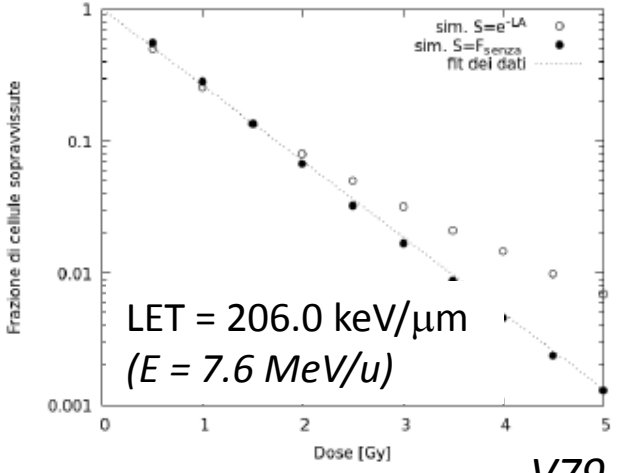












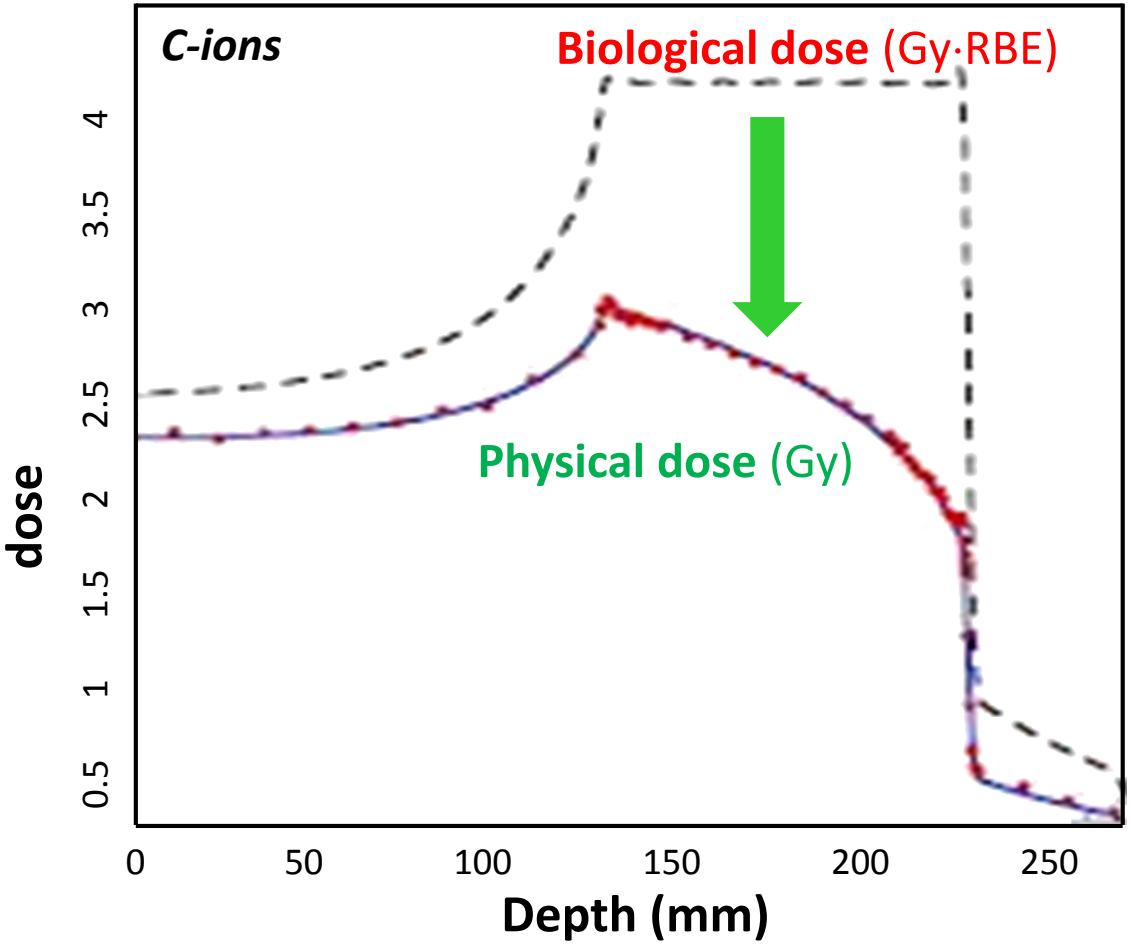
V79

(C. Aimè 2017, Thesis; exp. data from Furusawa et al. 2000)

- *the approach works also for Carbon ions (S = fraction of cells without lethal aberrations)*

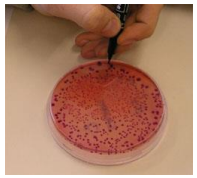
Applications for hadrontherapy

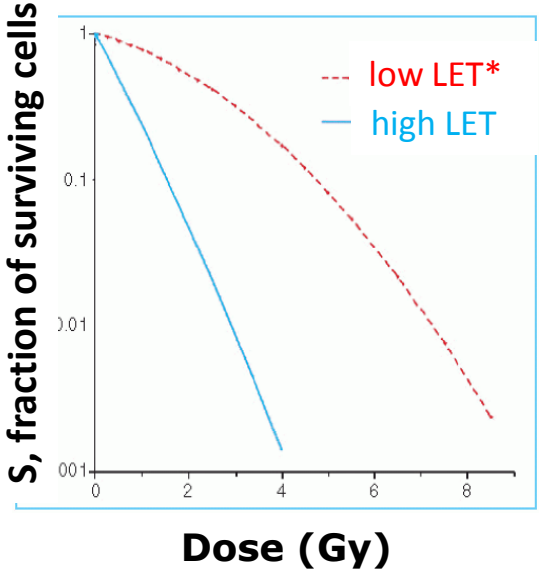
From biological dose to physical dose



Need of cell-survival curves at many different depths, that is different LET values

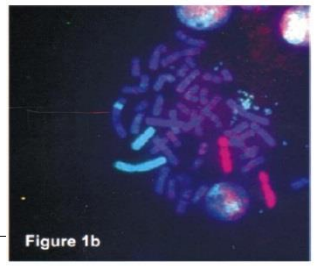
cell survival

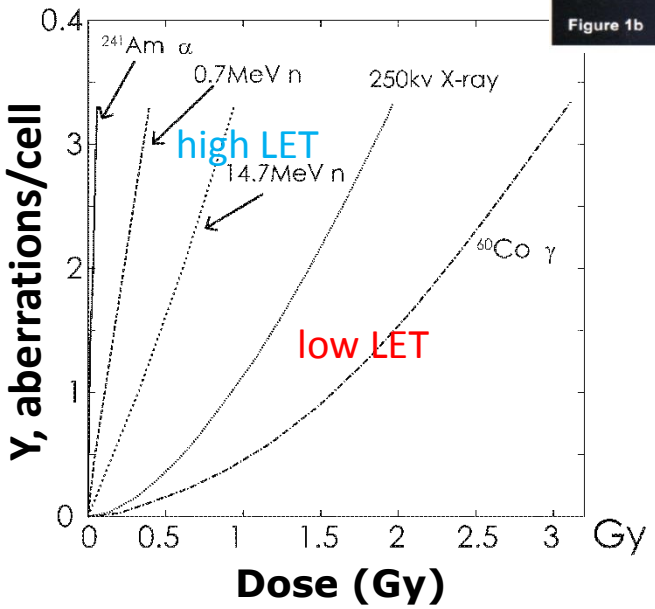




$S(D) = \exp[-(\alpha D + \beta D^2)]$

chromosome aberrations





$y(D) = \alpha D + \beta D^2$

high LET → quadratic term negligible

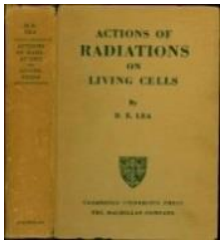
⇒ *aberrations are good candidates as cell «lethal lesions»*

**LET = Linear Energy Transfer → Stopping power (keV/μm)*

How modelling? *(examples)*

Chromosome aberrations

- **Breakage & Reunion theory** *(Lea, 1946):* irradiation → chromosome breaks → un-rejoining or (pairwise) incorrect rejoining of breaks *close in space and time*

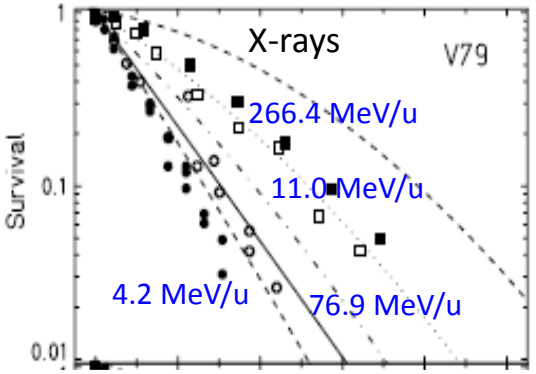


Cell death

- ***photons: Linear-Quadratic model***, $S(D) = \exp(-\alpha D - \beta D^2)$

- ***ions: Local Effect Model*** *(e.g. Scholz & Kraft 1994):* the damage in a small subvolume *(~nm)* of the cell nucleus is determined by the energy deposition in that subvolume, *independent of particle type & energy:* $N_{ion}/V \equiv \nu_{ion} = \nu_X \equiv N_X/V$

⇒ lethal lesions/cell for ions are calculated from the survival to X-rays:
$N_{ion} = \int \nu_{ion}(d(x,y,z))\, dV = \int -\ln S_X(d)/V\, dV$ *d(x,y,z) ≡ local dose*



(Scholz & Elsässer 2007)

Main open questions

- *features of 'critical' DNA damage leading to important effects including cell death and chromosome aberrations (Double-Strand Break clusters are good candidates but...what clustering level?)*
- *role of spatial distribution of such critical damage in the cell nucleus*
- *link between chromosome aberrations and cell death*
- *application of this information for cancer hadrontherapy*

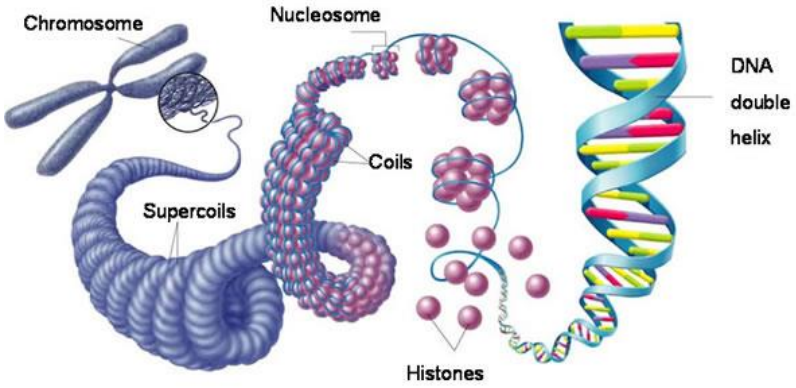
Why modelling?

- to interpret existing experimental data
- to make "full predictions" where there are no data

1. open questions

5. applications
(mechanisms, hadrontherapy)

cell death
& chromosome damage



2. examples of models

4. model validation

3. the BIANCA model/code

A possible approach for mixed fields

LQ fit of simulated survival curves

↙

Table of α and β coefficients for different particle types and energies

↙

FLUKA approach to mixed fields

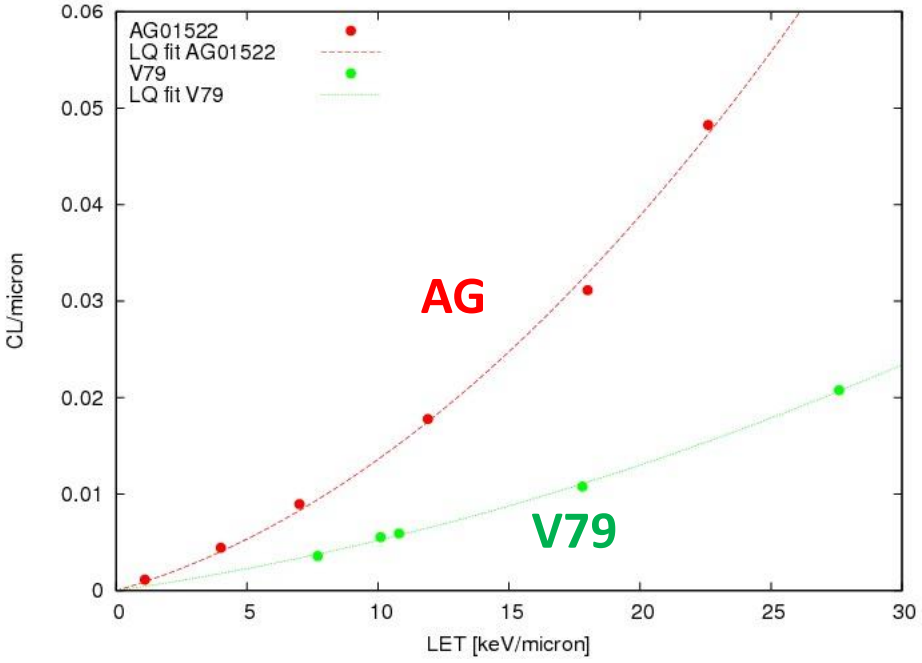
$$\alpha_{mix} = \frac{\sum d_i \alpha_i}{D}$$

$$\sqrt{\beta_{mix}} = \frac{\sum d_i \sqrt{\beta_i}}{D}$$

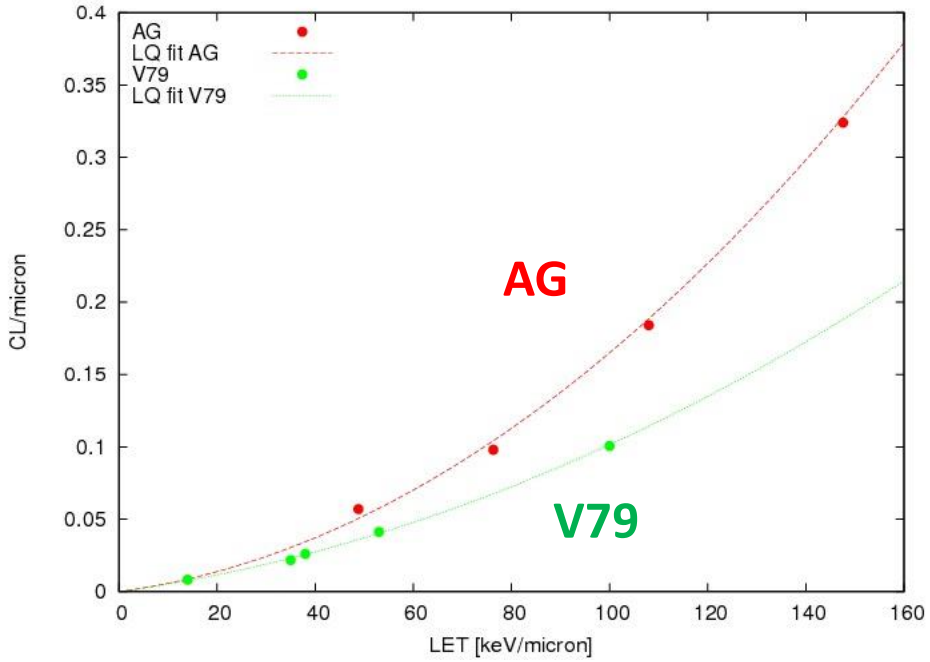
Characterization of DNA Cluster Lesions -I

CL/μm as a function of LET

protons



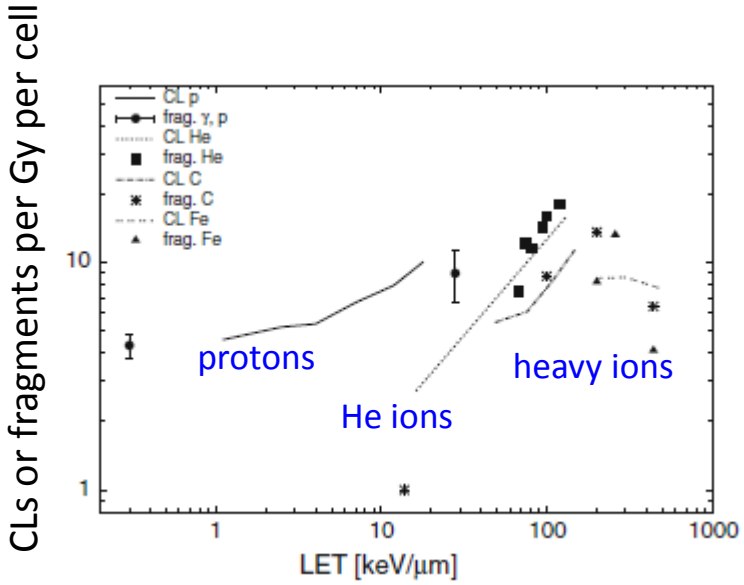
Carbon



- **dependence on LET:** CLs increase with LET (in a L-Q fashion), consistent with the increase of energy deposition clustering
- **dependence on cell line:** for a given radiation quality, normal cells have more CLs than radioresistant cells
- **application:** (LQ) fitting of CLs ⇒ cell death and aberrations can be predicted also at LET values for which there are no experimental data

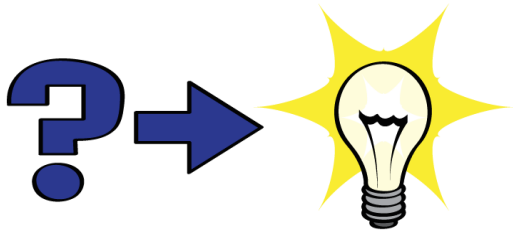
Applications for mechanisms

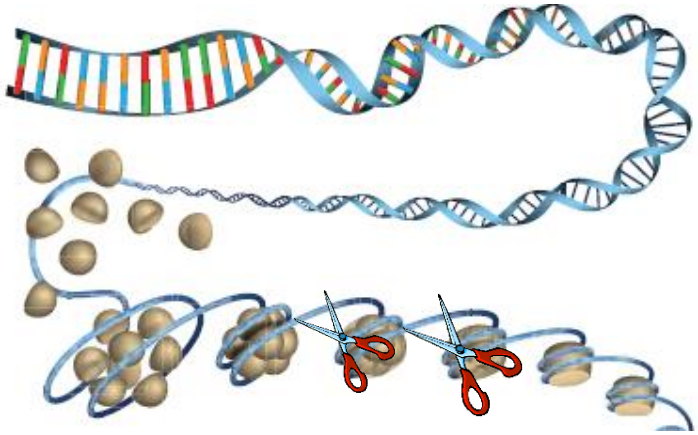
comparison between CLs and DNA fragments with different dimensions



(Carante et al. 2015, Radiat Environ Biophys)

- *finding: dependence of CLs on radiation quality (=particle type and LET) is analogous to that of DNA fragments with dimensions of ~0.2-1 kilo-base-pair*
- *hypothesis: these fragments are good candidates as DNA critical damage (confirming Rydberg et al. 1996)*





(Ou et al. 2017, Science 2017)

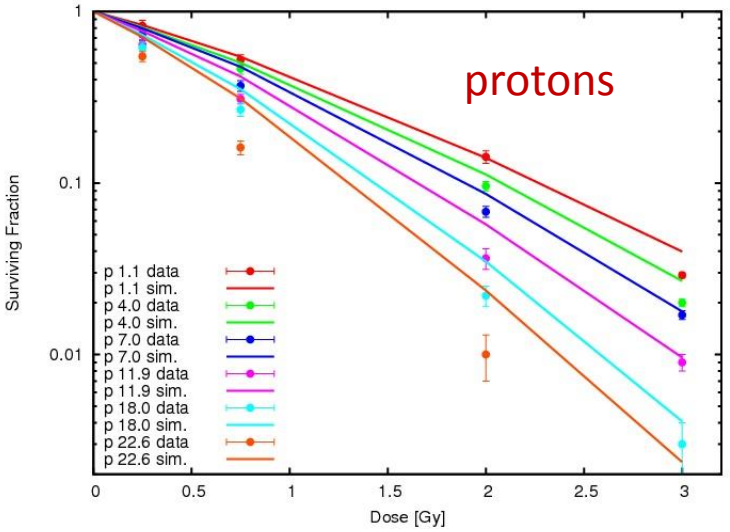
Predicting the survival of AG01522 cells from the survival of V79 cells

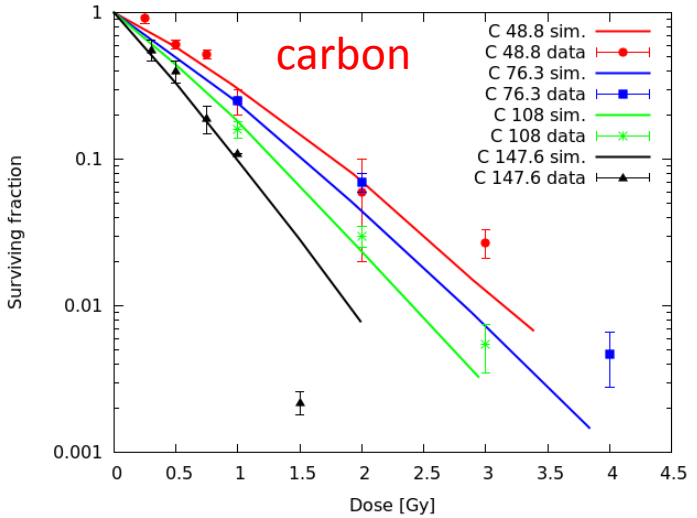
$$(CL/\mu m)_{AG,\,ion} = (CL/\mu m)_{V79,\,ion} \frac{(CL/GyCell)_{AG,\,X}}{(CL/GyCell)_{V79,\,X}} \frac{V_{V79}}{V_{AG}}$$

no parameter adjustment!

target radiosensitivity

target geometry





(M. Carante 2017, PhD Thesis; exp. data from Chaudhary et al., Kavanagh et al., Hamada et al.)

Main simulation steps

Dose and CL/(Gy·Cell)

CL/Cell

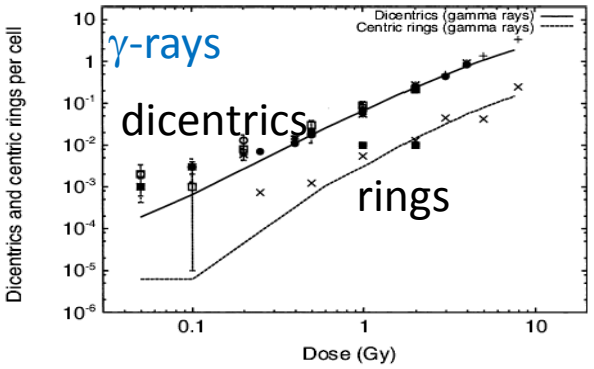
distributed in the cell nucleus according to radiation quality

- **identification of chromosomes and chromosome-arms hit by each CL**
- **un-rejoining *(with probability f)* or (mis-)rejoining of chromosome fragments**
- **scoring of chromosome aberrations**
- **repetition for many runs**

Surviving fraction S (D)

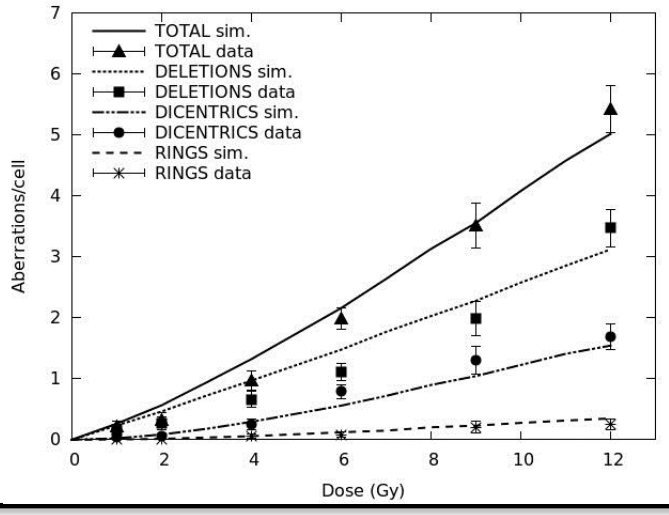
Comparison with chromosome aberration data

human lymphocytes



(Ballarini et al 2002, Radiat Prot Dosim)

human fibroblasts



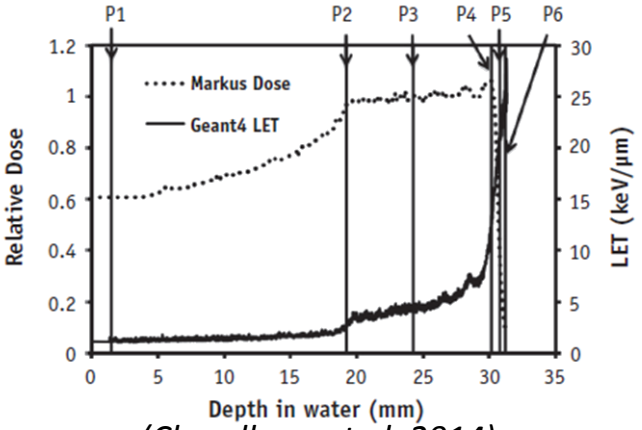
Microbeam (EU project "BioQuaRT", coordinated by H. Rabus)

	E (MeV)	LET (keV/μm)	ions/cell	aberrations/cell *(exp.)*	CLs/particle
α	10	90	10	0.61 *(0.60±0.06)*	0.69
α	20	37	25	0.35 *(0.36±0.04)*	0.20
p	10	5	200	0.35 *(0.36±0.06)*	0.024

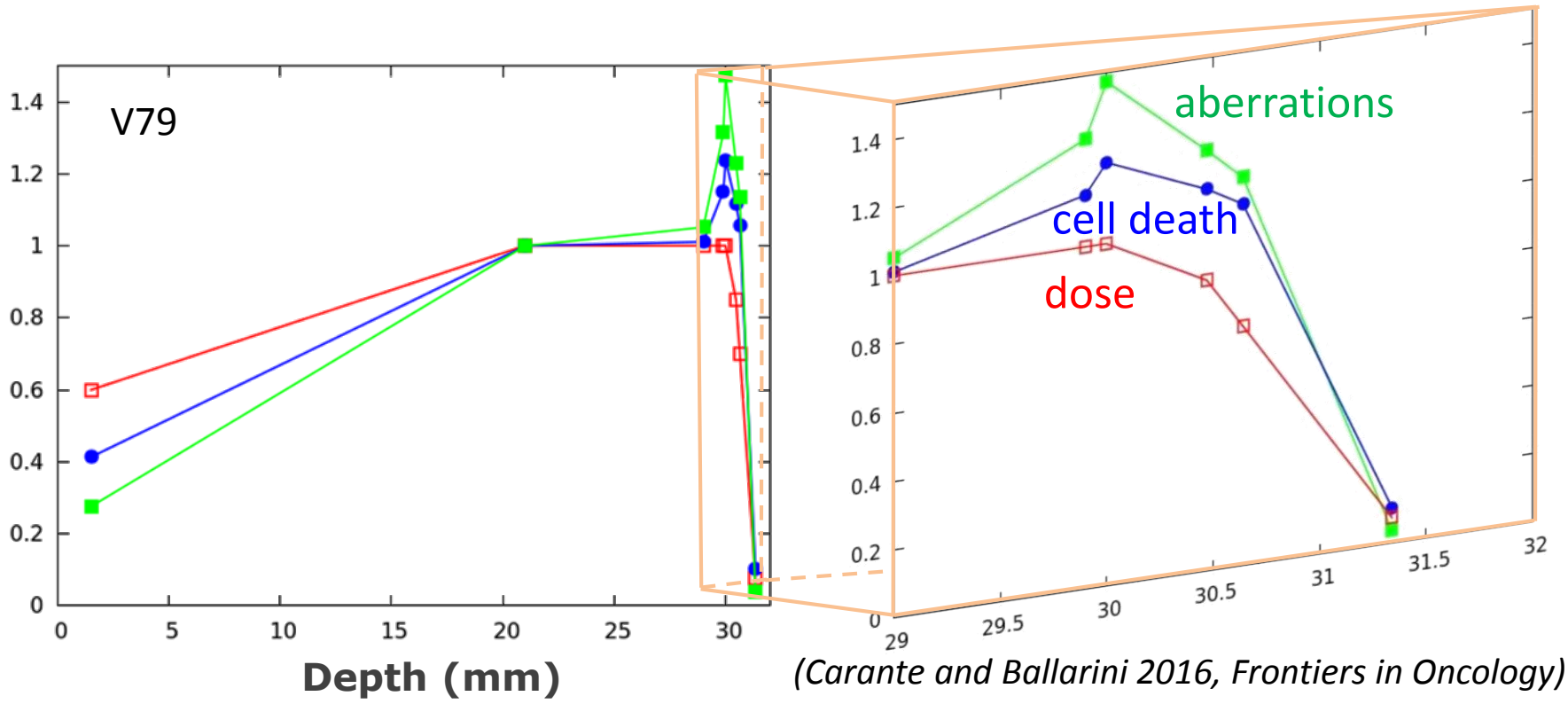
good agreement between calculated and observed chromosome aberrations; observed aberrations were interpreted in terms of CLs/particle

• the model/code can predict chromosome aberrations by different radiations in different cells

Cell death & chromosome damage for a proton SOBP @LNS, Catania



(Chaudhary et al. 2014)



(Carante and Ballarini 2016, Frontiers in Oncology)