Heavy Ion Therapy Research Integration

# Linear or Lineal?

## HOW LINEAL ENERGY IS RELATED TO LINEAR ENERGY TRANSFER AND HOW IT IS NOT

GIULIO MAGRIN, MEDAUSTRON ION THERAPY CENTER

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

# Agenda

**Motivation**

**First part**

- Definitions and playing with the concepts
- Discussion and Q&A

**Second part**

- Clinical use
- Outlook and comments
- Discussion and Q&A

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# Motivation and goals

Ion beams are commonly used in therapy

**The dose** is not sufficient to describe the radiation fields

To describe the biological effectiveness, it is necessary to classify the radiation in terms of **radiation quality** considering how its energy is deposited in micrometric or nanometric volumes.

- Q. Can we know PRECISELY the mechanisms that link radiation quality to clinical outcomes?
- A. No. But still it is essential.

Our goal is to find an **univocal** way to describe radiation quality and, from this, to find correlations **to the outcomes** on patients.

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# First Part

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# Radiation Quality

Let us start from the general concept of ***radiation quality*** which, in its more general forms, can be stated as:

“…*the nature and velocity of the charged particles that deliver the dose*”

OR, equivalently:

“*the type and energy of the particles crossing the site*”

Those are very simple definitions which emphasize how different particles and same particles at different energies may lead to rather different effects on cells.

It is unfeasible to provide this RQ experimentally

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# Radiation quality **specifiers**

*Linear Energy Transfer, LET*

Used in clinical applications

*Lineal energy, y*

Several experimental studies in clinical beams but never directly used in clinics

# Linear Energy Transfer as defined by ICRU (85)

The *linear energy transfer* or *restricted linear electronic stopping power*, $L_\Delta$, of a material, for charged particles of a given type and energy, is the quotient of $dE_\Delta$ by $dl$, where $dE_\Delta$ is the mean energy lost by the charged particles due to electronic interactions in traversing a distance $dl$, minus the mean sum of the kinetic energies in excess of $\Delta$ of all the electrons released by the charged particles, thus

$$L_\Delta = dE_\Delta / dl$$

Unit: keV·µm$^{-1}$ .

[ICRU report 85: Fundamental quantities and units for ionizing radiation Get access, International Commission on Radiation Units and Measurements, JICRU 11-1 (2011) https://doi.org/10.1093/rpd/ncs077]

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# Lineal Energy as defined by ICRU (85)

The *lineal energy*, *y*, is the quotient of $\varepsilon_s$, by $\bar{l}$ , where $\varepsilon_s$ is the energy imparted to the matter in a given volume by a single energy-deposition event and $\bar{l}$ is the mean chord length of that volume, thus

$$y = \varepsilon_s / \bar{l} \qquad \text{Unit: keV}\cdot\mu\text{m}^{-1}$$

- the energy imparted $\varepsilon_S$ is the sum of all energy deposits $\varepsilon_i$: $\varepsilon_S = \sum_i \varepsilon_i$,
  - the energy deposit in a single interaction is $\varepsilon_i = \varepsilon_{in} - \varepsilon_{out} + Q$;
    - where $\varepsilon_{in}$ is the energy of the incident ionizing particle (excluding rest energy); $\varepsilon_{out}$ is the sum of the energies of all charged and uncharged ionizing particles leaving the interaction; Q is the change in the rest energies of the nucleus and of all elementary particles involved in the interaction ($Q > 0$: decrease of rest energy)
- and $\bar{l}$ is mean length of randomly oriented chords (uniform isotropic randomness) through that volume (this definition is under discussion and could be revised).

[ICRU 85 https://doi.org/10.1093/rpd/ncs077]

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# Radiation quality specifiers

*Linear energy Transfer, LET*

*Lineal energy, y*

Both are describing the energy exchanged from the primary ionizing particles crossing the medium of very small sizes

# Different ‘energies’ of LET and y

| *LET* | *y* |
|---|---|
| is a *non-stochastic* quantity | is a *stochastic* quantity |
| *LET* is (generally) *computed* | *y* is (generally) *experimental* |
| considers energy *transferred* in the collision | considers the energy *imparted* to the site |
| only *electronic* collisions are examined | both, *electronic* and *nuclear* interactions are examined |
| the cuts on delta rays are in *energy* | the cuts on delta rays are in *range* |

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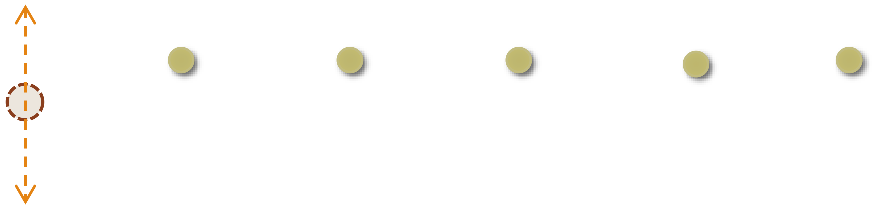
# Stochasticity

*LET* is non stochastic:

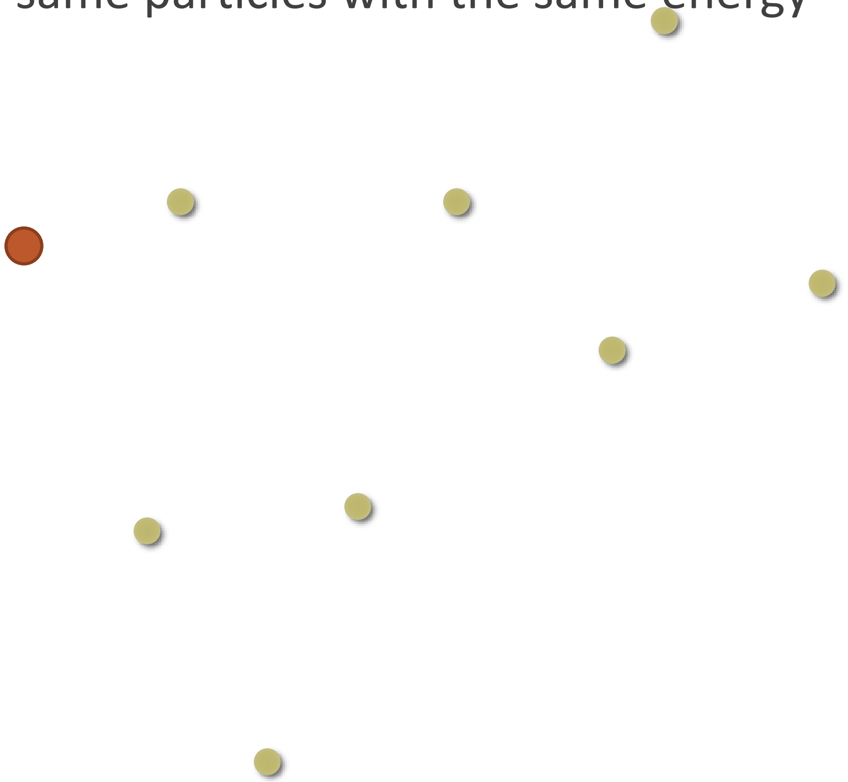
A particle, defined in type and energy has a unique value of LET. **LET here is not $\bar{L}_D$ or $\bar{L}_T$**



(very simplified illustration)

*y* is stochastic

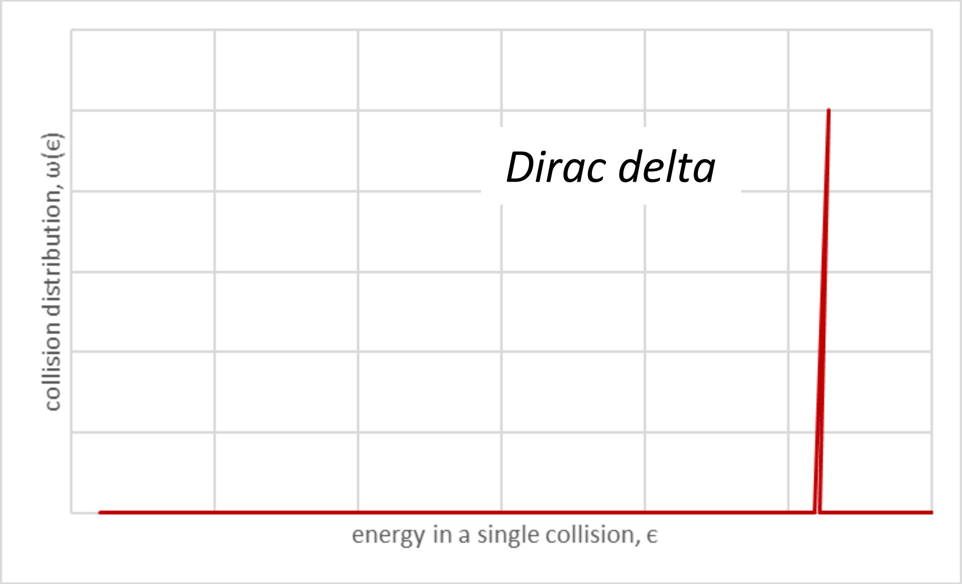
The same particles with the same energy



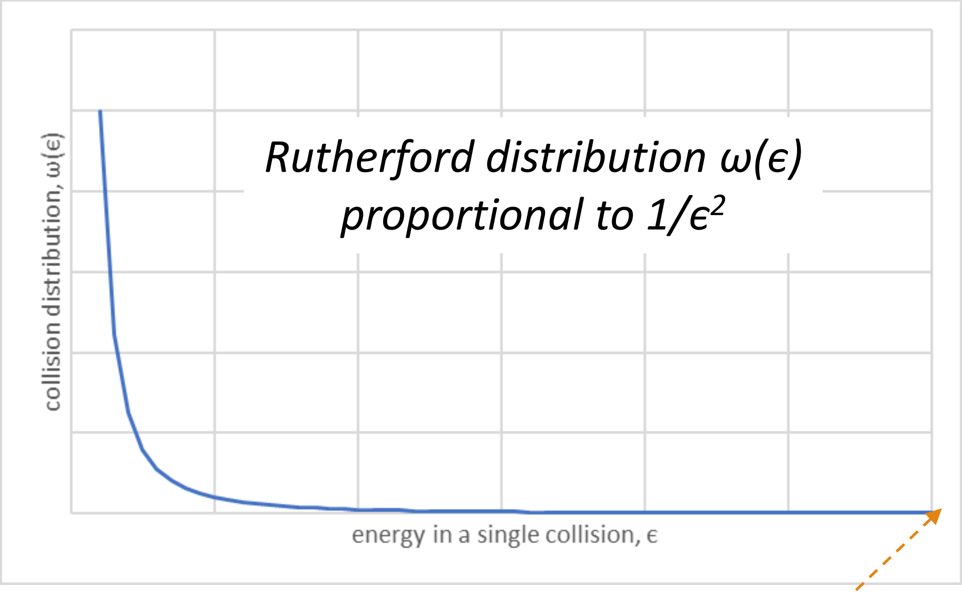
# Stochasticity

## distribution of energy exchanged in a **single electronic collision**:

*LET*



*y*



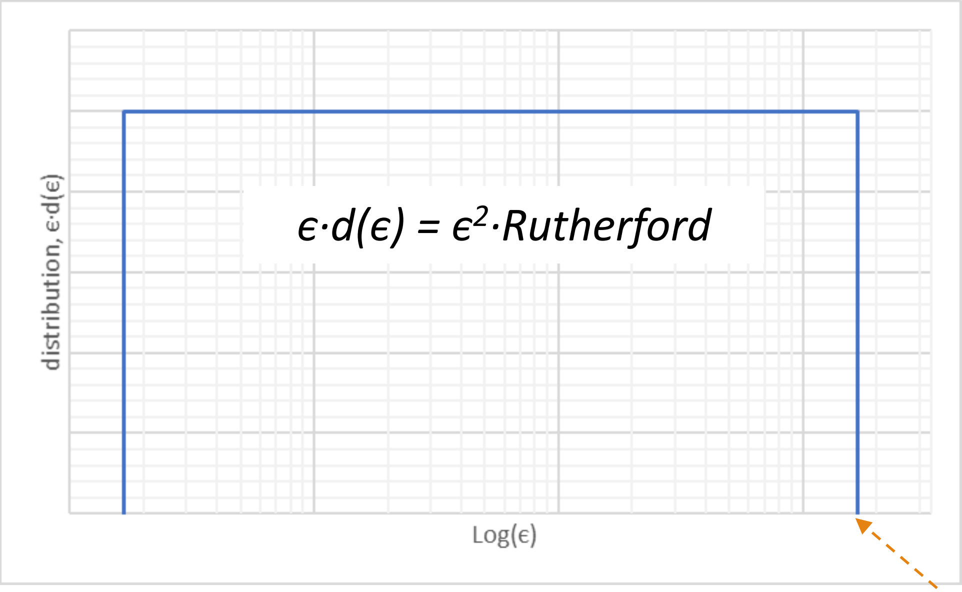
The distribution continues above zero for values of $\epsilon$ hundreds or thousands times larger.

# Stochasticity

## distribution of energy exchanged in a single electronic collision:

*LET*

*y*



$\epsilon \cdot d(\epsilon) = \epsilon^2 \cdot Rutherford$

Different representations

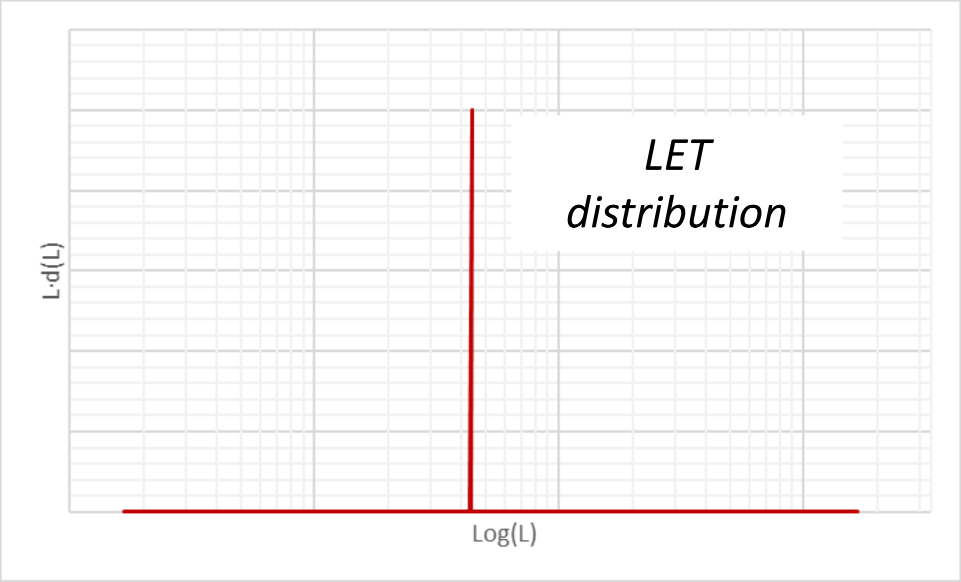
The maximum value of ϵ is proportional to the energy of the ion

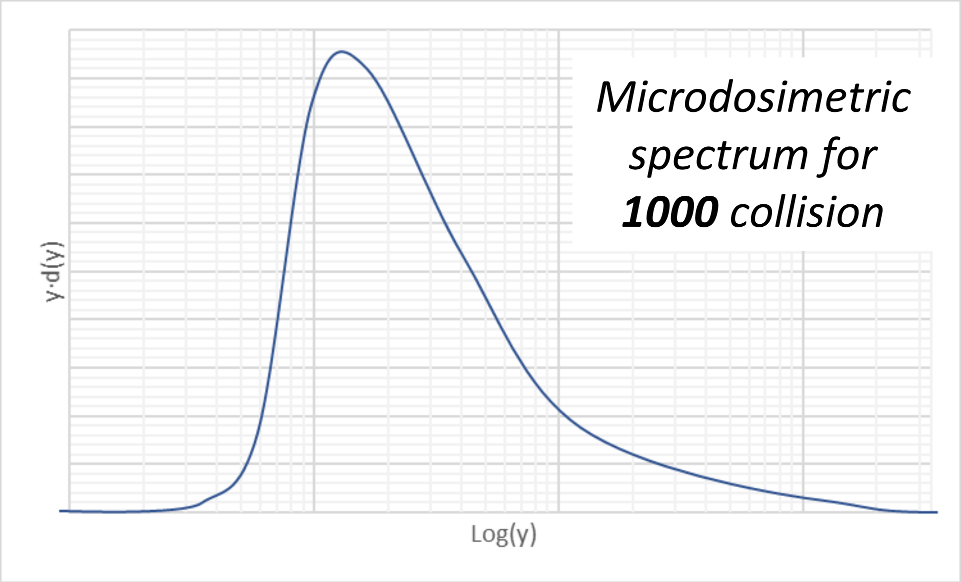
# Stochasticity

## distribution of energy in multiple electronic collisions:

*LET*

*y*





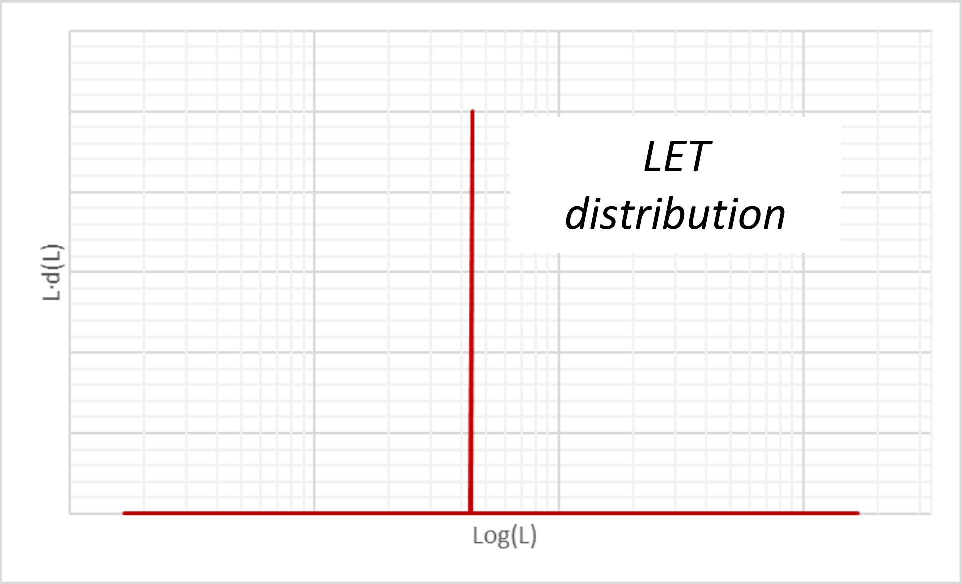
The theorem of central limit assures that the distribution, which represent multiple electronic collisions of the primary particle, progressively approximates the Gaussian distribution with the increasing of the number of collisions

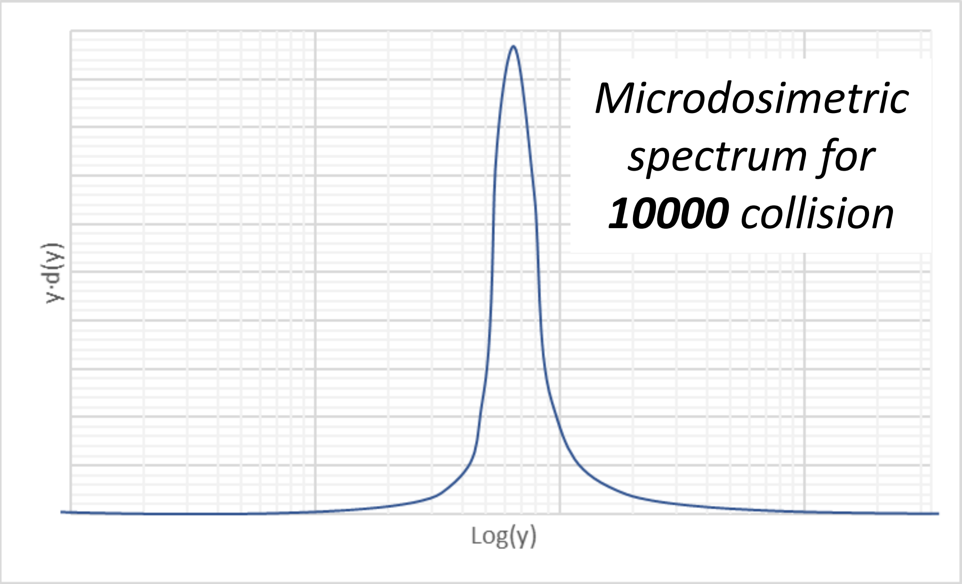
# Stochasticity

## multiple electronic collision:

*LET*

*y*





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# More on the ‘energies’ of LET and y

*LET*

energy *transferred* in *electronic* collisions

= electronic stopping power

$$-\left.\frac{dE}{dx}\right|_{elec.} = LET$$

same quantity, different users

*y*

energy *imparted* in electronic + nuclear interactions

For the energies used in ion-beam therapy, the electronic component is the most important; and the nuclear interactions assumed to be negligible.

# Different ‘energies’ of LET and y

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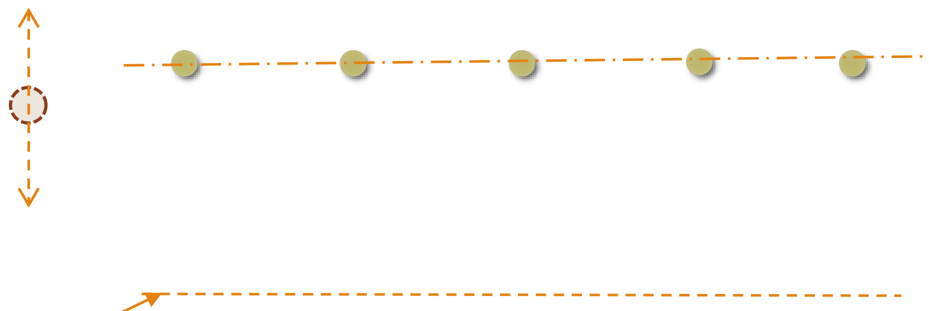
# Delta-ray cutoff

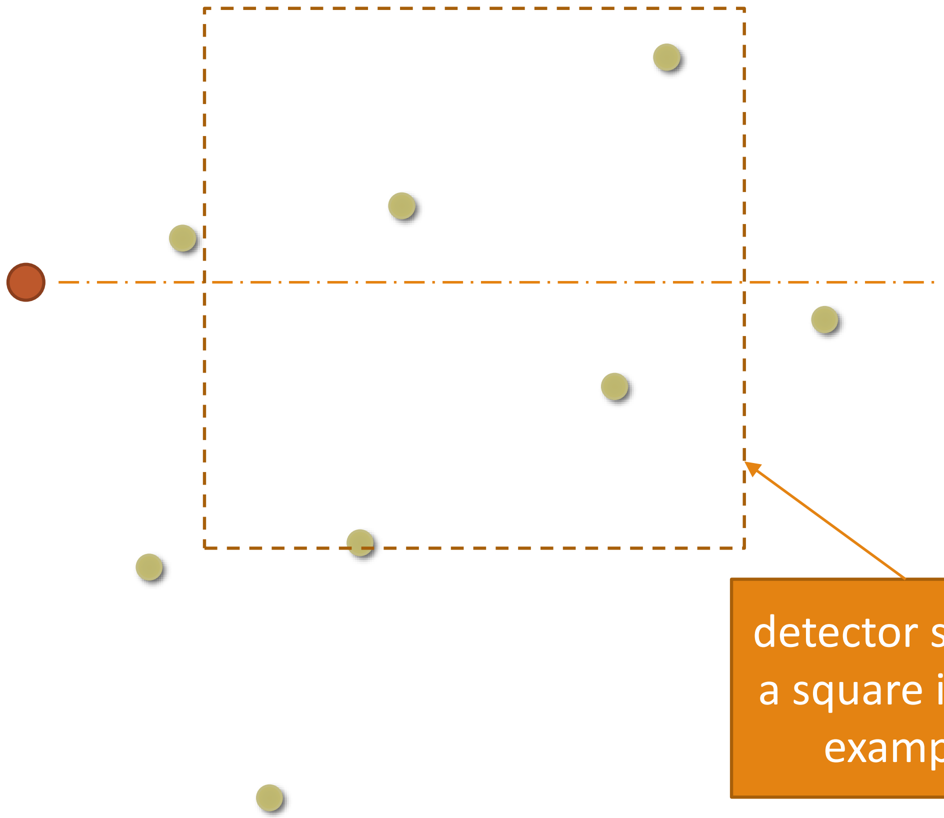
*restricted LET:* energy cutoff



energy threshold for instance 100 eV in “LET$_{100}$”

(very simplified illustration)

*y:* geometric cutoff



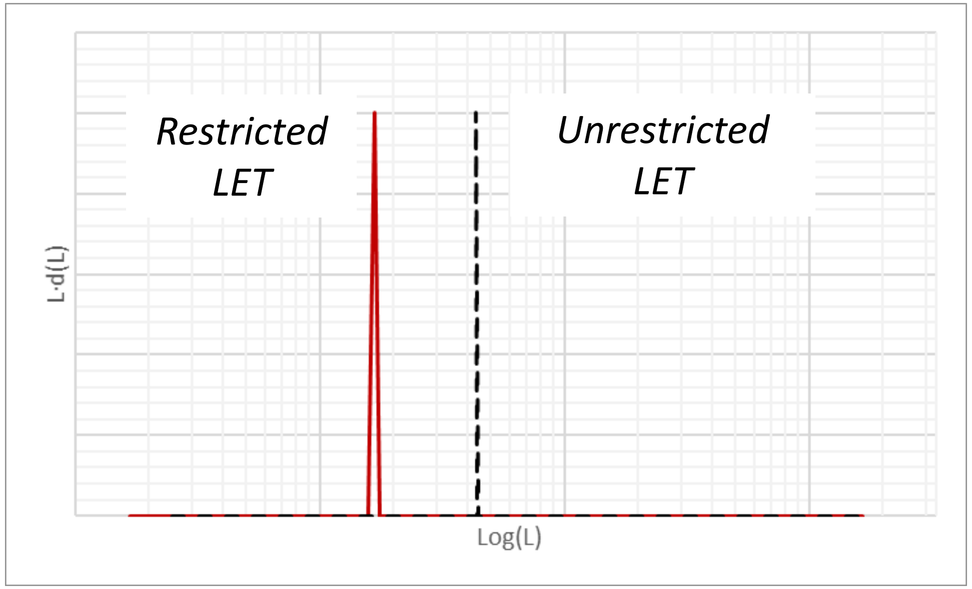
detector shape: a square in this example

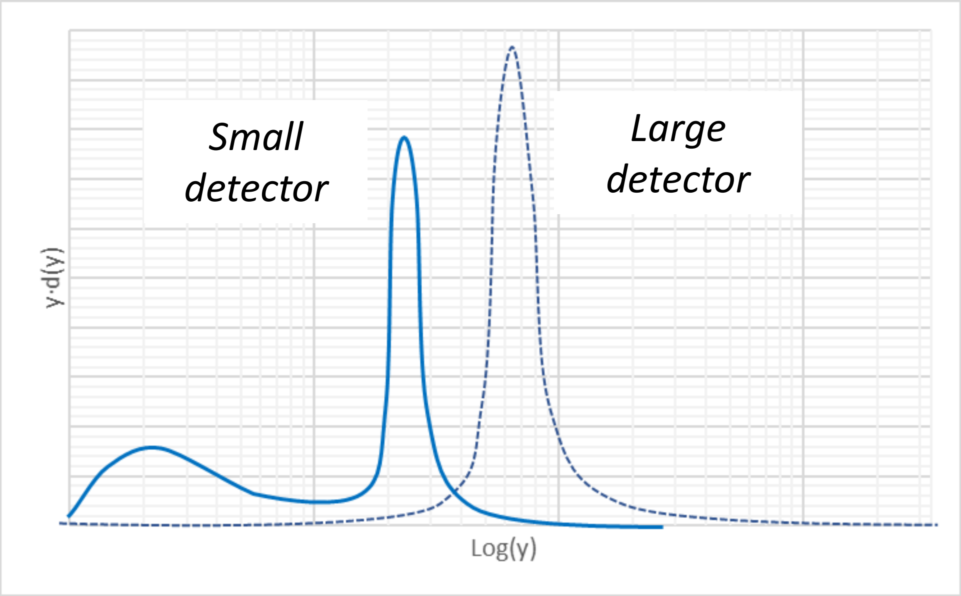
# Delta-ray escape

## for multiple electronic collisions:

*Restricted LET*

*y*





***In ion beam therapy, always unrestricted LET is used***

*In smaller detector higher escape.*

*The partial tracks of externa delta rays maintain the energy equilibrium*

[Magrin et al. 2022, J. Nucl. Eng. 2022, 3, 128–151. https://doi.org/10.3390/jne3020008]A

# Second Part

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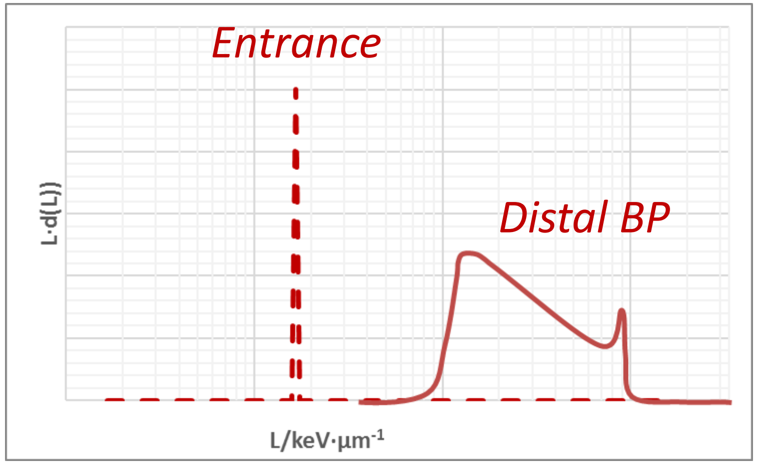
# Ion beams

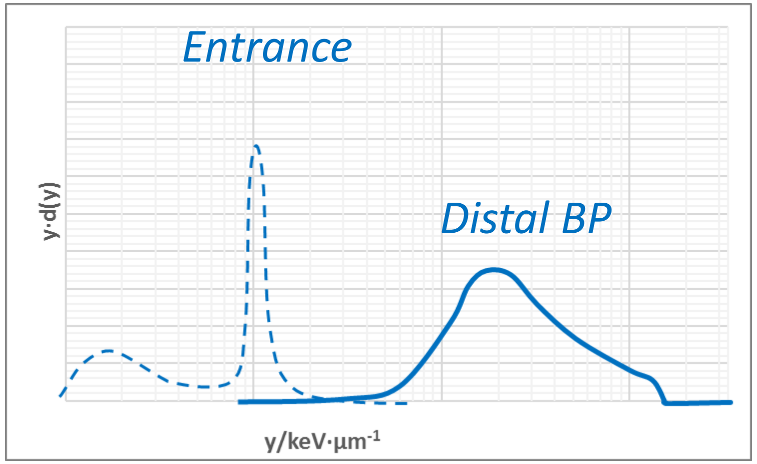
At the entrance for high-energy beams, the beam is monoenergetic: LET and y change slowly with the depth and they can be represented as a Dirac delta and a quasi-Gaussian

Penetrating the target, the particle energies are more heterogeneous, the nature of the radiation quality is expressed by distributions in large intervals of keV·µm$^{-1}$.

*Unrestricted LET*

- *y*

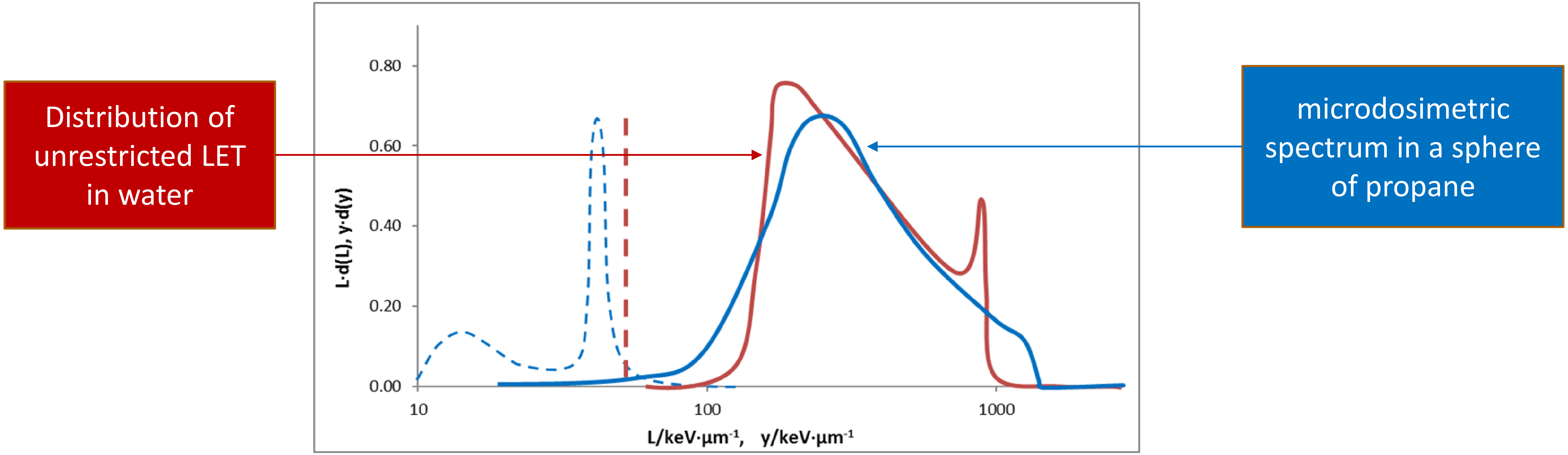




At high energy, the LET density distribution is the overlap of Dirac delta distributions

The microdosimetric spectrum is also affected by the shape of the detector.

# Ion beams



- Despite the different profiles, there is a common trend of the LET distributions and the lineal energy spectra: at the higher depths higher energy densities.
- The transformations from LET distribution to *y* spectra can be done analytically considering the shape and the material of the microdosimeter. [Magrin, Phys. Med. Biol. 63 (2018 ) 215021]

# Radiation Quality and Ion-Beam therapy

The microdosimetric Relative Biological Effectiveness: **$\mathbf{RBE_{\mu D}}$**

**L**(ocal) **E**(ffect) **M**(odel)

**M**(icrodosimetric) **K**(kinetic) **M**(odel)

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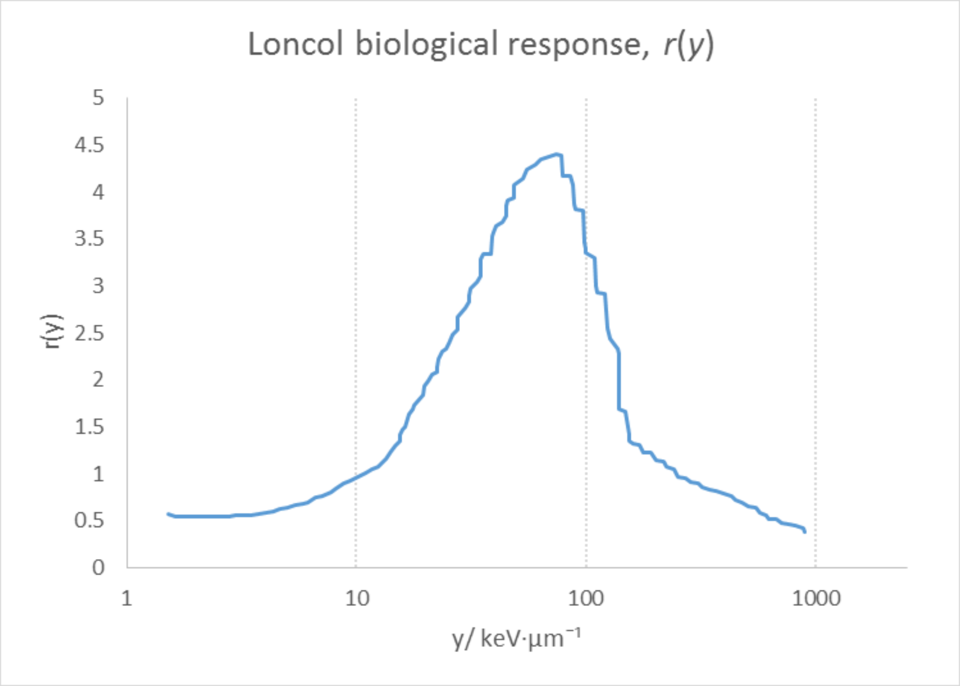
# Microdosimetric Relative Biological Effectiveness, RBE$_\mu$



$$RBE_{\mu D} = \int_0^\infty r(y) \cdot d(y)\, dy$$

## function, *r*(*y*)

***r*(*y*)** computed **unfolding radiobiological data** collected in photon, neutron, and proton radiation.

Proposed by Pihet in 1990 [1],

Used by Loncol in 1994 [2]

Revisited by Parisi in 2020 [3]

[1] P Pihet et al., Radiat Prot Dosimetry, 31-1/4 (1990) 437-42
[2] T Loncol et al., Radiat Prot Dosimetry, 52-1/4 (1994) 347-352
[3] A Parisi et al. Phys Med Biol, 65-23 (2020) 235010

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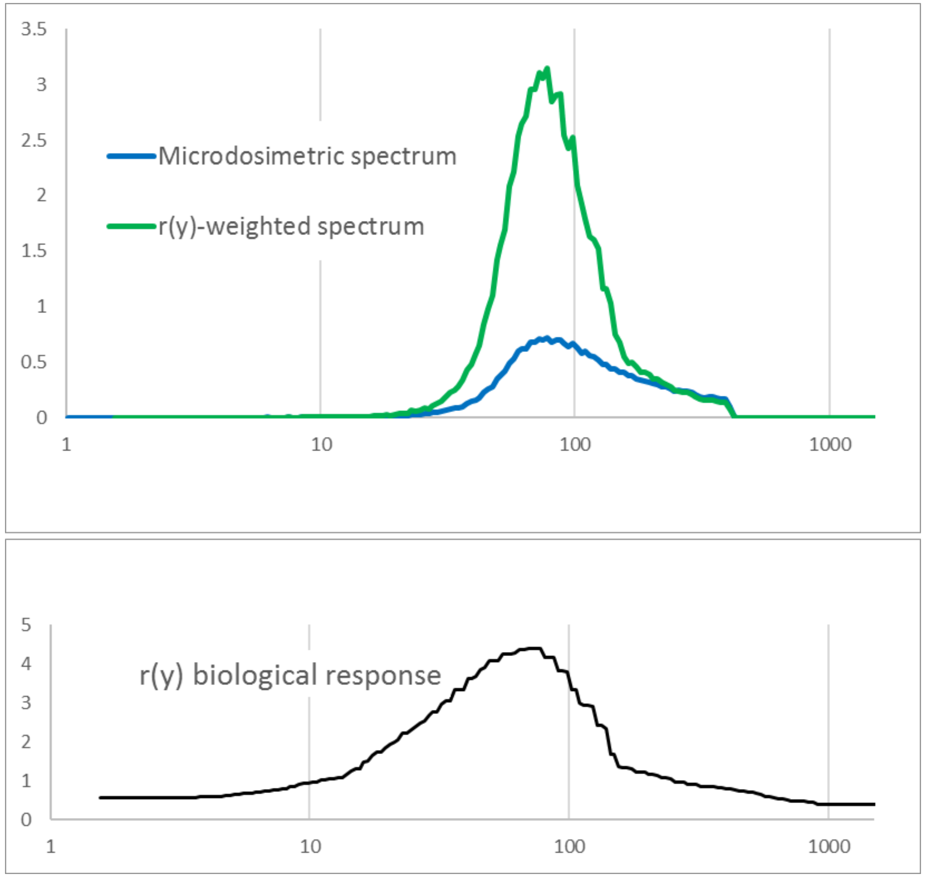
# Microdosimetric Relative Biological Effectiveness, $RBE_\mu$



$$RBE_{\mu D} = \int_0^\infty r(y) \cdot d(y)\, dy$$

The integral ($RBE_{\mu D}$) is larger for microdosimetric spectra which have large contributions in the interval between 30 keV·$\mu m^{-1}$ and 200 keV·$\mu m^{-1}$

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# Radiation Quality and Treatment Planning

- Radiation quality in clinics is **only present in** the (black box) of the **Treatment Planning Systems**
- Radiation quality computations through models, the Local Effect Model and Microdosimetric Kinetic Model

**LEM**:

- **Amorphous track structure**

**MKM**:

- Input from **saturated dose-mean lineal energy, y***

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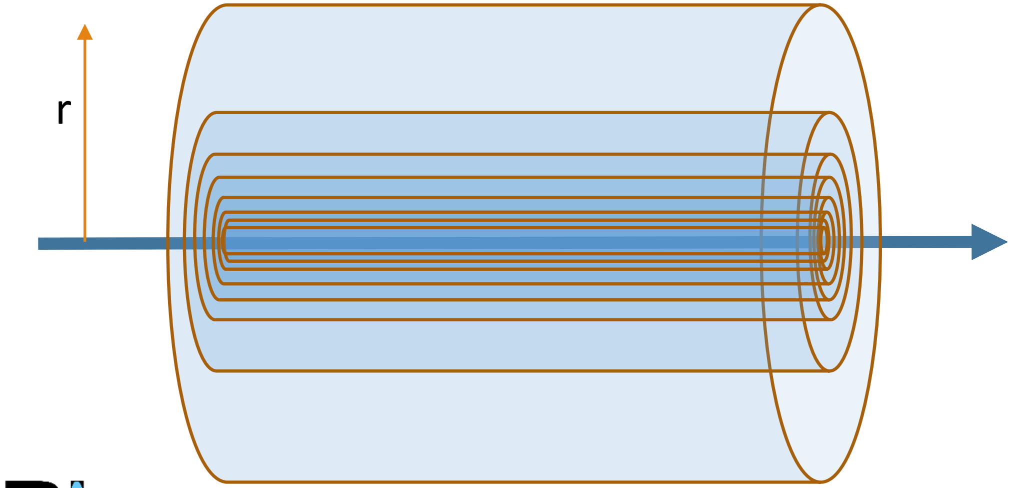
# Local Effect Model



LEM predicts the effects of high-LET radiation based on the known effects of low-LET radiation:

The amorphous track structure approach with local dose
D(r) ~ $1/r^2$

Toward nanodosimetry specification (microdosimetry deals with the whole particle track, nanodosimetry with the sub-structure of the track)

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# Microdosimetric Kinetic Model

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The RBE$_{10}$
(10% survival dose of HSG cells):

$$RBE_{10} = \frac{D_{10,R}}{D_{10}} = \frac{2\beta D_{10,R}}{\sqrt{\alpha^2 + 9.21\beta}\boxed{-\alpha}}$$

The “microdosimetric” **saturation-corrected dose-mean lineal energy**, $y^*$, is used in the survival fractions, $S = e^{-(\alpha D + \beta D^2)}$:

$$\boxed{\alpha = \alpha_o + \frac{\beta}{\rho \pi r_d^2}\, \boldsymbol{y}^*}$$

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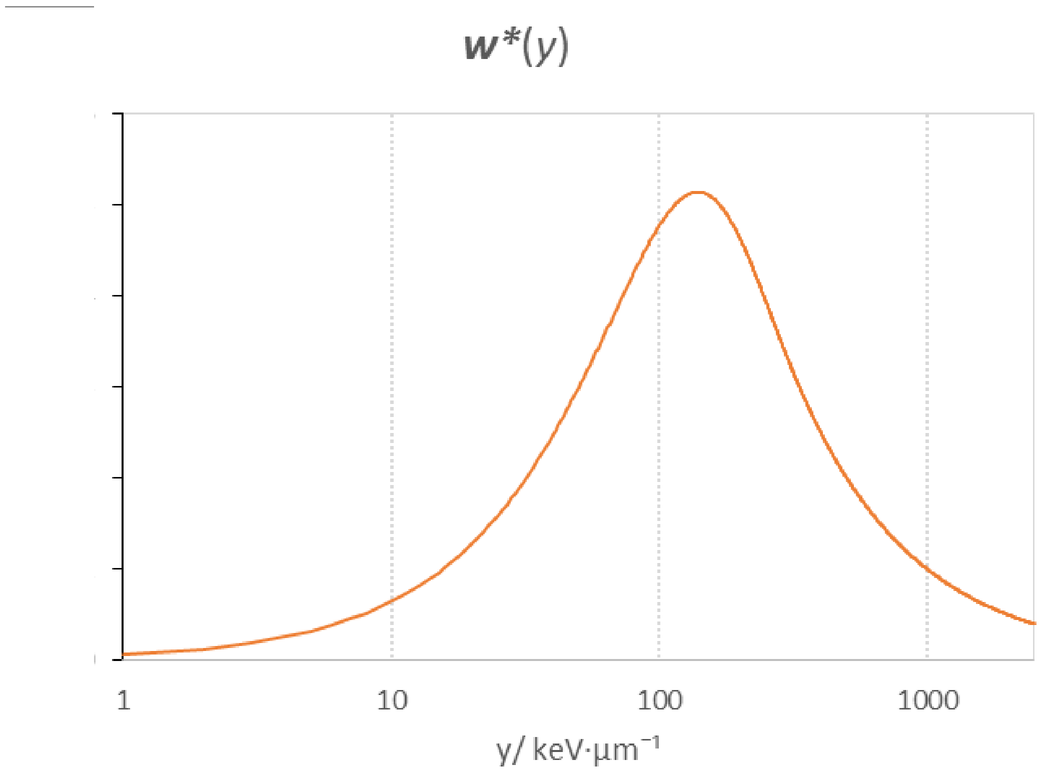
[Hawkins 1994, 2003]

# Microdosimetric Kinetic Model



$$y^* = \frac{y_0^2 \int_0^\infty \left(1 - e^{-y^2/y_0^2}\right) f(y)\,dy}{\int_0^\infty y f(y)\,dy}$$

— $w^*(y)$, Saturation correction weighting function, for $y_0$ = 124 keV·µm$^{-1}$

$$y^* \propto \int_0^\infty w^*(y) \cdot d(y)\,dy$$

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# Outlook and comments

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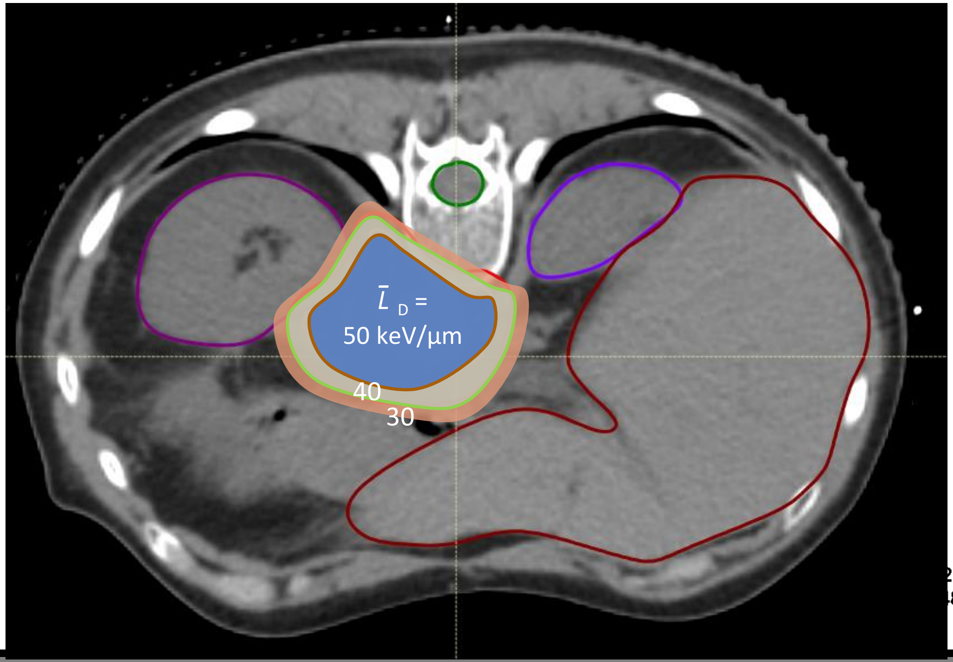
# Insights from retrospective clinical studies

The quantity in use as radiation quality specifier is Linear Energy Transfer (or LET) expressed as mean values in dose $\bar{L}_D$ and track $\bar{L}_T$, or probability density distributions $\boldsymbol{f}(\boldsymbol{L})$ and $\boldsymbol{d}(\boldsymbol{L})$

Retrospective studies which identify the regions of lack of tumor control after the irradiation:

- Correlation of local $\bar{L}_D$ values
  - in pancreatic tumor
    [Hagiwara Y et al., Clinical and Translational Radiation Oncology 21 (2020) 19–24. Doi: 10.1016/j.ctro.2019.11.002.]
  - in chondrosarcomas
    [Matsumoto S, et al. ,Anticancer Res. 2020; 40(11):6429-6435. Doi: 10.21873/anticanres.14664.]
  - in sacral chordoma
    [Molinelli S, et al. Radiother Oncol. 2021;163:209-214. Doi: 10.1016/j.radonc.2021.08.024.]



The figure is only illustrative, not from the research

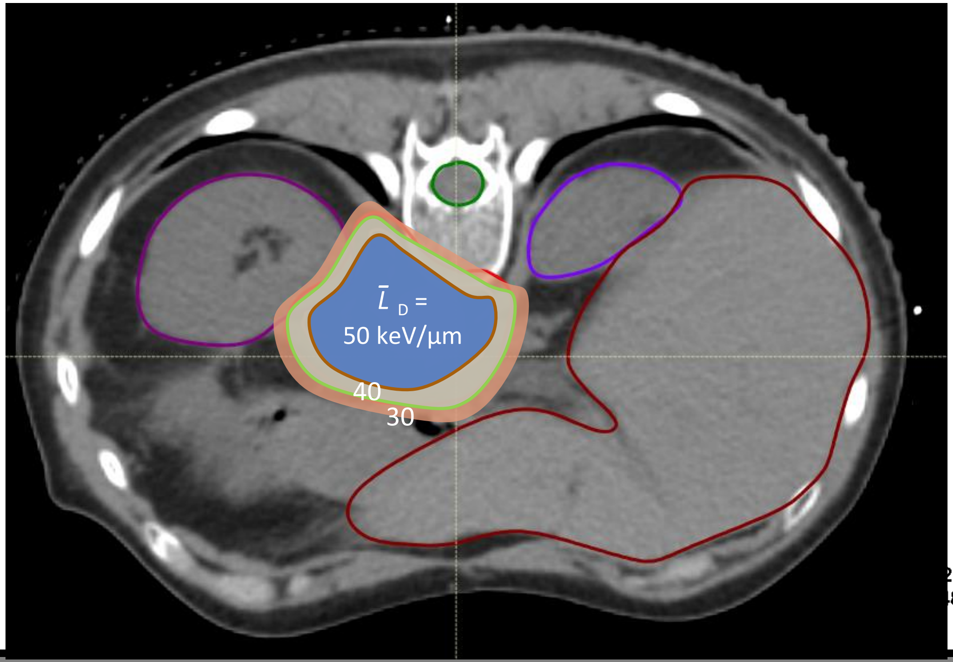
# Insights from retrospective clinical studies

Hagiwara: Retrospective studies in patients wth pancreatic tumor

Minimum value of dose-averaged LET above 50 keV·µm$^{-1}$ within the GTV has a significant association with local control of primary pancreatic cancers

Some radiation quality observations:

- **This clinical outcome cannot be described thought RBE**
- **High-LET values play a fundamental role**
- **Radiation quality is assessed with mean LET values. What advantage would be to used entire distributions?**



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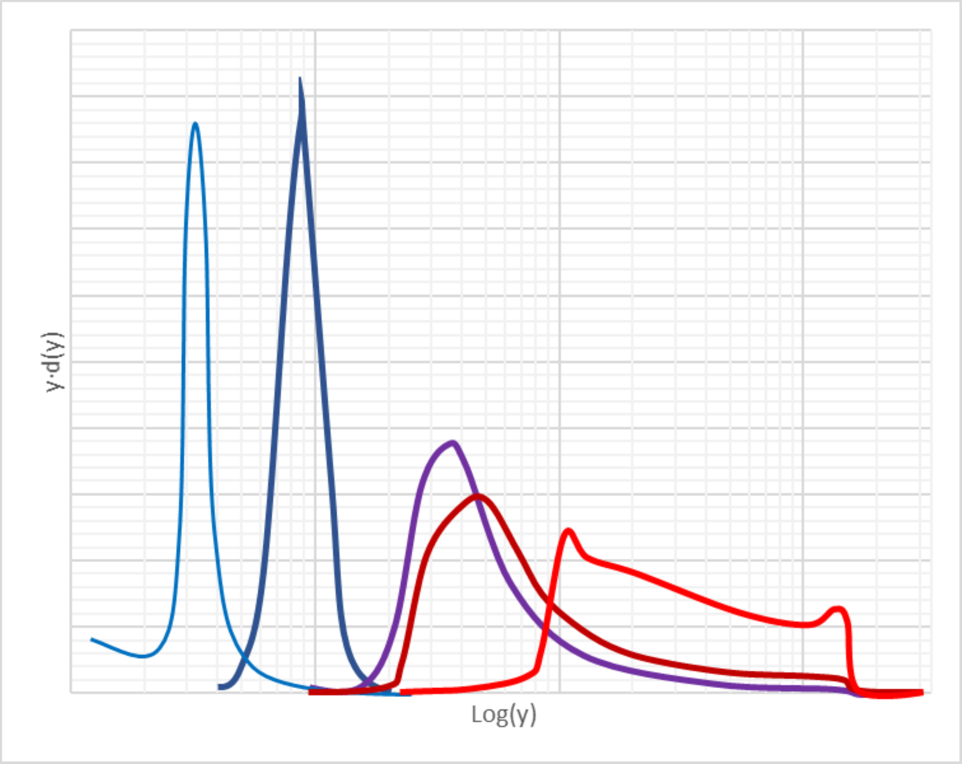
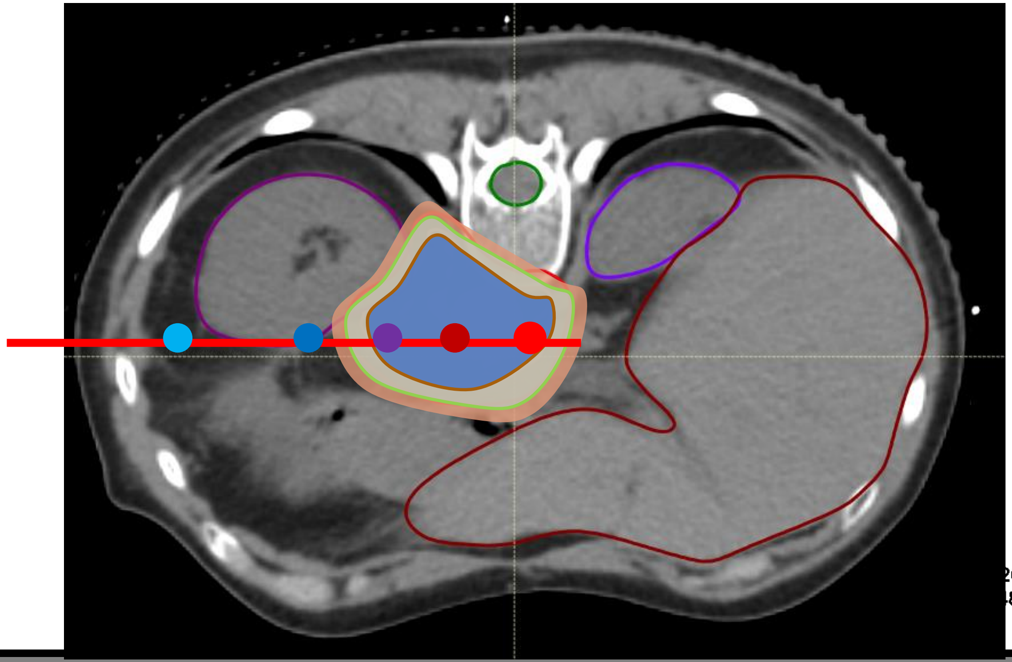
# Microdosimetric contribution





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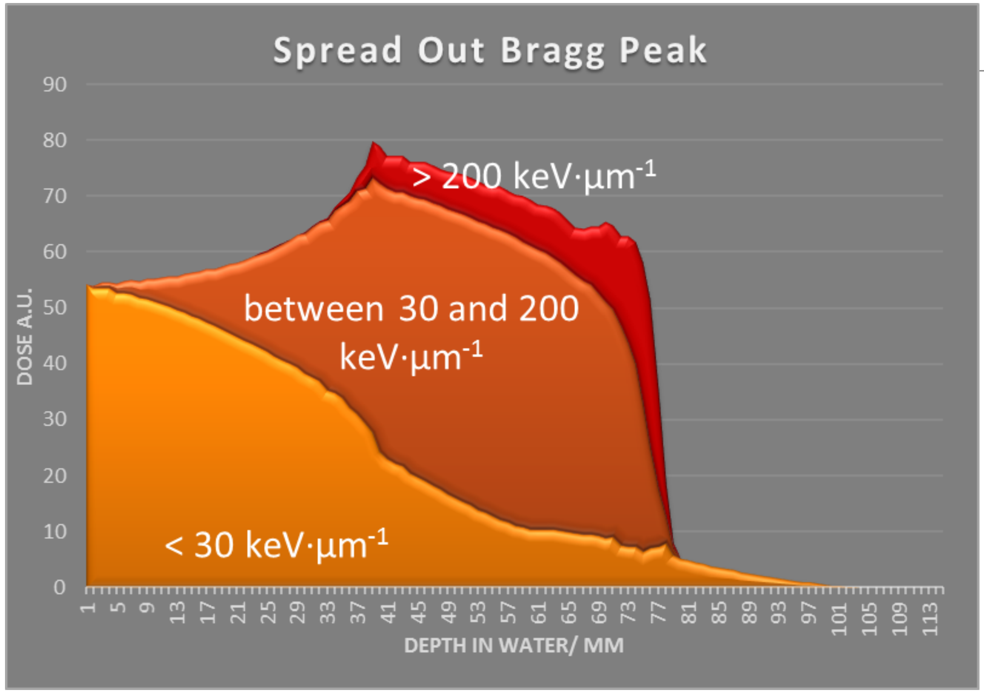
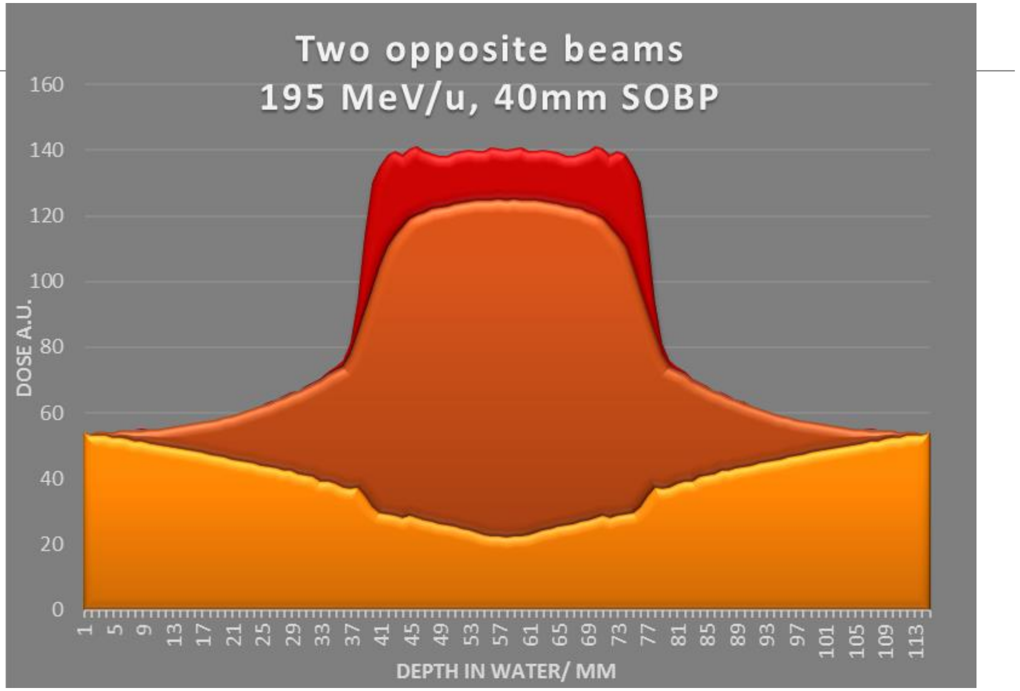
# Microdosimetric spectra and SOPB





- The spread out Bragg peak can be redesigned indicating the partial contribution to the dose from radiation from different radiation quality (lineal energy or LET) intervals.
- The probability density spectra are recombined according to the irradiation from multi-portal plans

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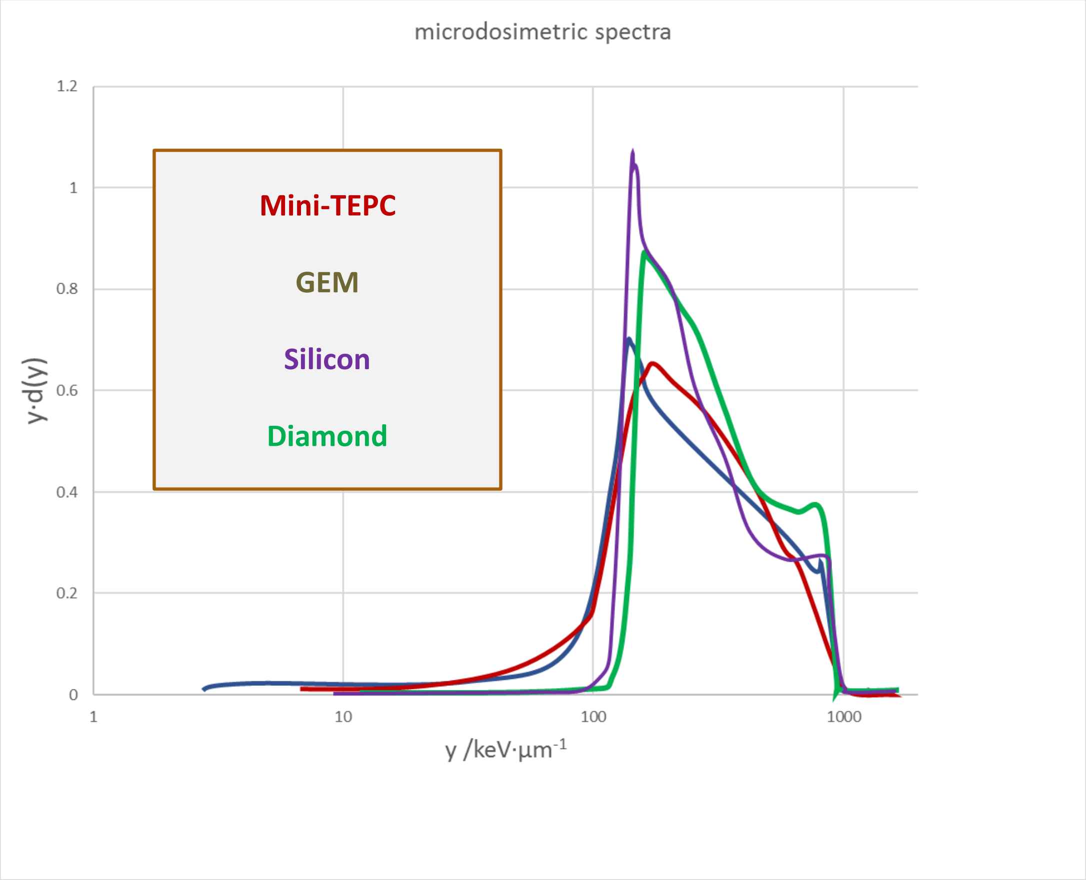
# Different microdosimeters

Microdosimetric spectra at the distal edge of the 62 MeV/u 12C

Laboratori del Sud, INFN Catania, Italy

Relative uncertainty of $\bar{y}_D$: ±13%

- The differences depend on the characteristics of the detectors: shape, size, and material
- Need of a unique reference
- Common work of the research groups to converge



P Colautti et al., Physica Medica, 52(2018) 113-121

# Intrinsic limit of radiation quality

We cannot think at a simple function linking radiation quality to clinical outcomes

Factors not related to radiation quality:

- integral dose
- dose fractionation and repair mechanisms
- patient-specific effects
- dose-rate effects
- bystander effects

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# Thanks

"This material was prepared and presented within the HITRIplus **Specialised Course on Heavy Ion Therapy Research,** and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the author (giulio.magrin@medaustron.at).

# EXTRA SLIDES

# Linear Energy Transfer as defined by ICRU (85)

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$$L_\Delta = dE_\Delta / dl$$

Unit: $\mathrm{keV \cdot \mu m^{-1}}$ .

[ICRU report 85: Fundamental quantities and units for ionizing radiation Get access, International Commission on Radiation Units and Measurements, JICRU 11-1 (2011) https://doi.org/10.1093/rpd/ncs077]

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$$y = \varepsilon_s / \bar{l}$$

Unit: keV·μm$^{-1}$

- the energy imparted $\varepsilon_S$ is the sum of all energy deposits $\varepsilon_i$: $\varepsilon_S = \sum_i \varepsilon_i$,
  - the energy deposit in a single interaction is $\varepsilon_i = \varepsilon_{in} - \varepsilon_{out} + Q$;
    - where $\varepsilon_{in}$ is the energy of the incident ionizing particle (excluding rest energy); $\varepsilon_{out}$ is the sum of the energies of all charged and uncharged ionizing particles leaving the interaction; Q is the change in the rest energies of the nucleus and of all elementary particles involved in the interaction ($Q > 0$: decrease of rest energy)
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HITRI plus
Heavy Ion Therapy Research Integration

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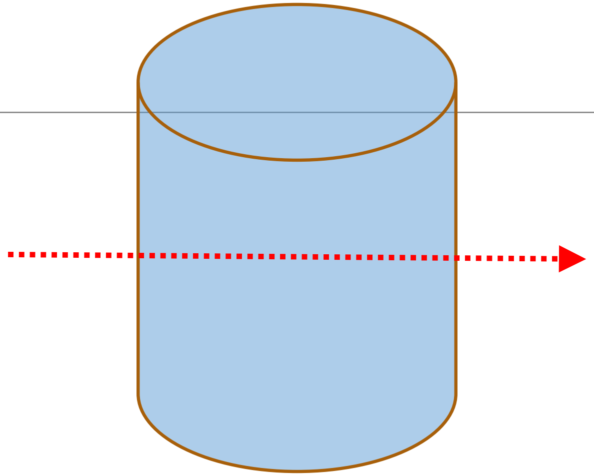
$L$: **LET**;
$\ell$: **chord length**;
$S$: the energy loss **straggling**;
$F$: **Fano** factor;
*det*: **detector** dependent factors as gas multiplication in TEPC or non-uniform response in solid-state;
*elec*: read-out **electronics**



Uncertainties not represented by variances:

- $\delta$: **delta-ray escape**
- R: **variation of LET** in small ranges
- *s.p.*: **stopping power** tables

$V_y$ , variance of the lineal energy and correlations (in relative terms)

$$V_y = V_L + V_\ell + V_\ell \cdot V_L + V_S + V_F + V_{det} + V_{elec}$$

$$C_\delta, \quad C_R, \quad C_{s.p.}$$

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