ICTR-PHE 2016

Uniting physics, biology and medicine for better healthcare

NanOx™: A new multiscale theoretical framework to predict cell survival in the context of particle therapy

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Context

Particle therapy

Use of ion beams to treat tumors

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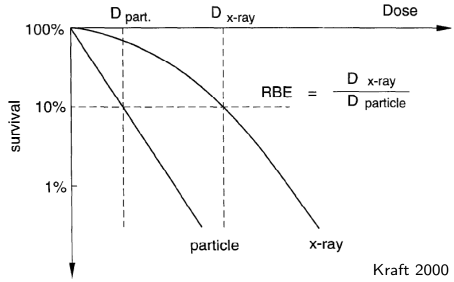
Particle therapy

Use of ion beams to treat tumors

$\Downarrow$

Enhanced biological effectiveness



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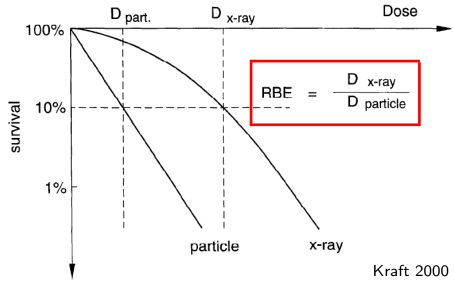

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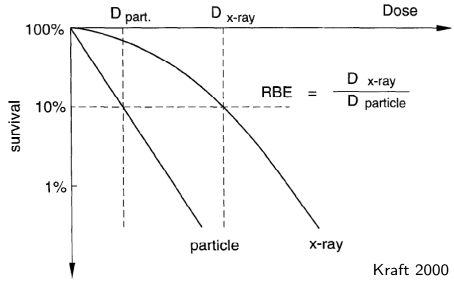

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Cell survival

- Described by the LQ model:

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

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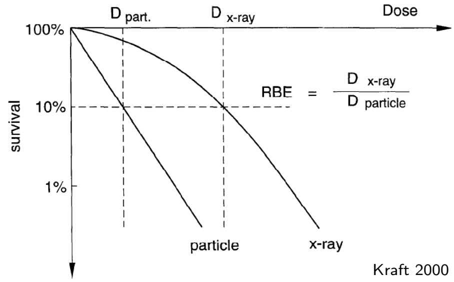

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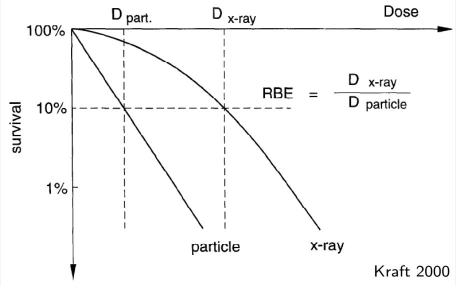

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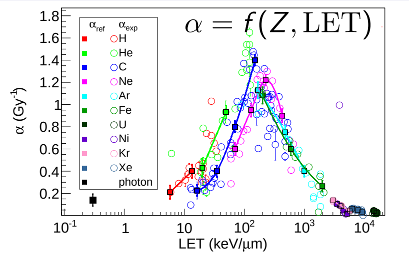

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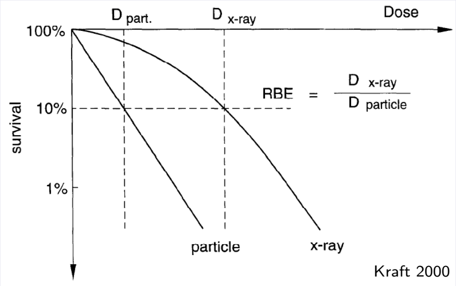

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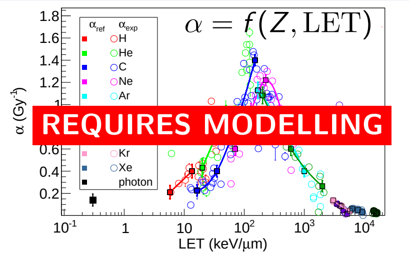

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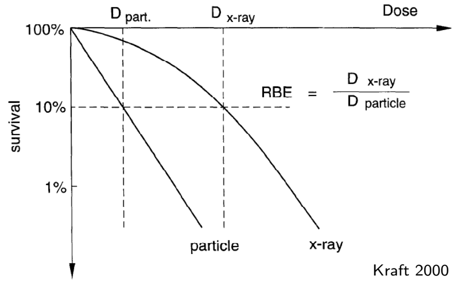

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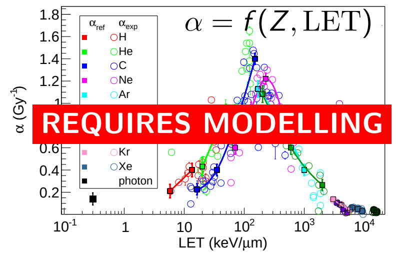

Current models (LEM, MKM) show limitations $\Longrightarrow$ Room for new models

NanOx™: Principles

Completely statistical theory

- Cell survival = $\langle S \rangle$ over many configurations of cells and radiation impacts
- Stochastic nature of radiation at multiple scales

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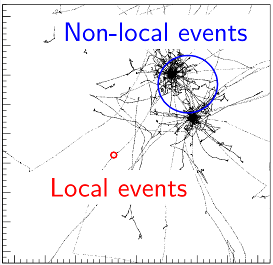

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Definition	Directly lethal	The rest
Scale	Nanometric	Micrometric
Biological interpretation	Severe damage to DNA, membranes, cell organelles	Accumulation of oxidative stress Sublethal lesions

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⇓ Nanometric targets

⇓ Oxidative stress

NanOx™: Lethal function

Local lethal events

- Destruction of a local target
- N local targets in the cell sensitive volume
- Probability of destroying a target

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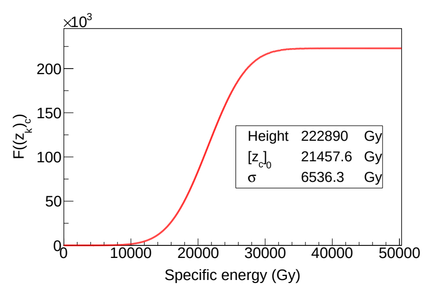
Parametric representation

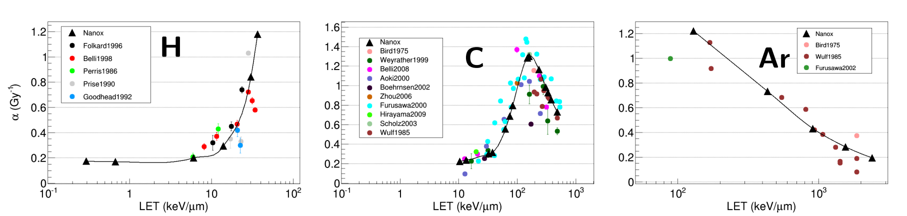
- Threshold and saturation
- Three parameters

$$F(z) = h \times \left[1 + \text{erf}\left(\frac{z - z_0}{\sigma}\right)\right]$$



Results: α coefficient

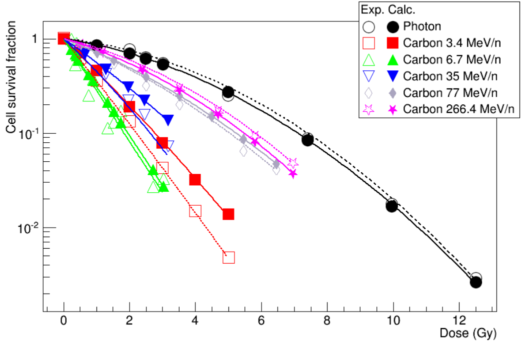
α distributions for H, C and Ar ions for V79 cells



- Good agreement
  – discrepancies lower than uncertainties in experimental data
- Overkill effect reproduced

Results: Cell survival

Cell survival to carbon ions for V79 cells



- Good agreement
- In particular the decrease of the shoulder with LET

Conclusions and outlook

Conclusions

- **New model based on**
  - Local/non-local events
  - Multiscale statistics $\rightarrow$ fully stochastic dose deposition
- **New concepts**
  - Non-local events: radical production
  - Chemical dose
- **First results**
  - Good agreement with V79 cells experimental data

Conclusions and outlook

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– **New model based on**

- Local/non-local events
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– **New concepts**

- Non-local events: radical production
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– **First results**

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Outlook

– **Further testing**

- Other cell lines
- Mixed fields and SOBP

– **Possible improvements**

- Further optimizing F
- Refine approximations

– **Contribution to PT**

- Implementation into a TPS
- Coupling with future nanodosimeters

Thank you

Sensitive volume

Postulate 1: Sensitive volume

The total cell survival is characterized by the irradiation effects in two volumes:

- One associated to local events
- Another one associated to non-local events

Simplifications

- **Simplification 2: Targets**
  - Uniformly and randomly distributed in the local events sensitive volume
  - Cylindrical
- **Simplification 3: Sensitive volume associated to local events**
  - Confined to the cell nucleus
  - Cylindrical
- **Simplification 4: Sensitive volume associated to non-local events**
  - Non-local sensitive volume = Local sensitive volume

Independent cell survival to local and non-local events

Postulate 2: Independent cell survival to local and non-local events

The probability of cell survival to local events is independent of that to non-local events. The survival of one cell is thus given by:

$$S = S_L \times S_{NL}$$

Survival to local events

Postulate 3: Survival to local events

The sensitive volume contains N targets and the inactivation of one of these targets causes the cell to die.

$$S_L = \prod_{i=1}^{N} (1 - f(z_i))$$

– $f(z_i)$: probability of inactivation of target i by the specific energy z
$= n_i$, the mean number of lethal events in target i

Number of effective lethal events (ELE)

The number of effective lethal events in a target is set as $n_i^* = \ln(1 - n_i)$.

$$S_L = e^{-n^*}$$

where n^* is the number of ELE in the cell.

Survival to non-local events

Postulate 4: Survival to non-local events

Non-local events are represented by global events

$$S_{NL} = S_G$$

Survival to non-local events

Simplification 5: Chemical effect chosen

The chemical effect is represented by the concentration of the $OH^{\bullet}$ radical after a time T_R from the impact of the radiation. RCE is then

$$\mathrm{RCE} = \frac{G_{part}}{G_{ref}}$$

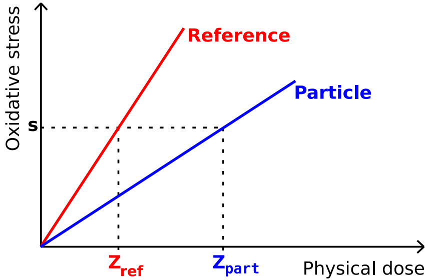
where $\frac{G_{part}}{G_{ref}}$ is the production yield of $OH^{\bullet}$ for the particle/reference

Postulate 6: Parametric shape of the global survival

S_G is represented by a "LQ" shape of the chemical dose:

$$S_G = e^{-\alpha_G \tilde{Z} - \beta_G \tilde{Z}^2}$$

where α_G and β_G are parameters to be defined for each cell line



For a level **s** of oxidative stress:

$$\mathrm{RCE_s} = \frac{Z_{ref}}{Z_{part}}$$

We have chosen X-rays as the reference radiation

Postulate 5: Chemical dose

S_G is a function of the chemical dose $\tilde{Z}$ deposited in the sensitive volume.

$$\tilde{Z} = \mathrm{RCE} \times Z$$

Coefficient α

Nanox implementation is computationally very time consuming

- S_L (and n^*) computation depends on simulating many nanometric targets

$\Rightarrow$ Trick: to compute n^* from the specific energy in the sensitive volume

Coefficient α

We define a coefficient α for a given radiation type from the expression

$$n^* = \alpha Z$$

- makes the link between nanoscopic and microscopic scales
- describes the efficiency of a given particle in creating lethal events

Coefficient α

At typical clinical doses (2 Gy)

- Photons: $n^* = \alpha Z$
- Ions: very heterogeneous energy deposition pattern

$$n_c^* = \alpha_c Z_c$$
$$n_p^* = \alpha_p Z_p$$

– Z_c: specific energy in the sensitive volume from track core events
– Z_p: specific energy in the sensitive volume from track penumbra events

Approximation

α_p is set as independent of the ion and is approximated by:

$$\alpha_p = \alpha_{\text{X-rays}}$$