NanOx^{TM}: a new multiscale model to predict ion RBE in hadrontherapy

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Probability of cell survival

Surviving fraction of irradiated cells:

- integrates all death pathways

- allows to derive Tumor Control Probability

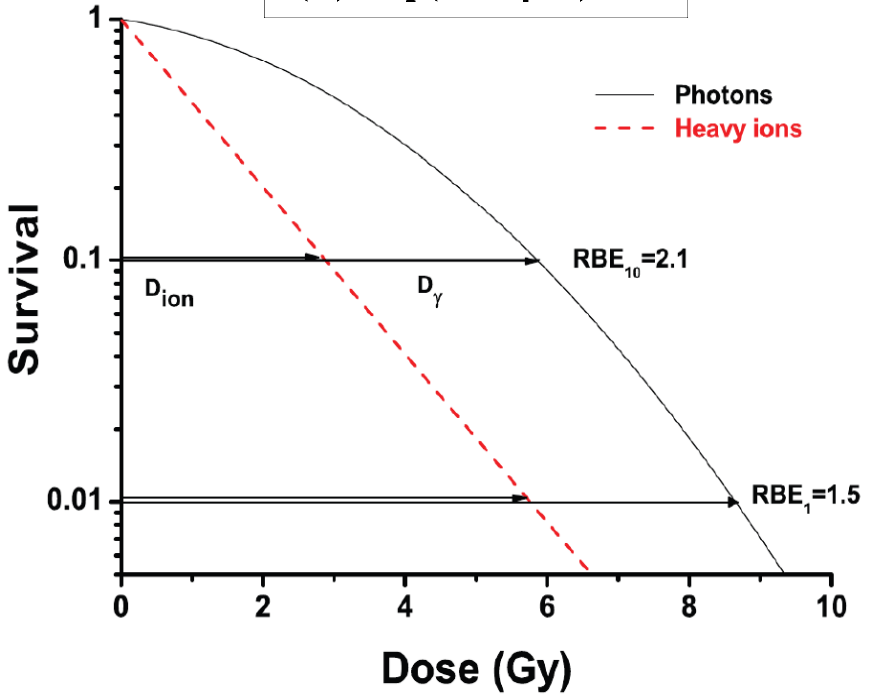
It depends on:

- Particle type, energy and LET
- Cell type, environment, phase
- Cell oxygenation state
- Dose, dose per fraction ...

MODELING REQUIRED !

RBE= $D_{photons}/D_{ions}$ for a given survival level

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



Prog. Part. Nucl. Phys. 45, S473–S544.

Biophysical modeling

3 approaches implemented in TPSs:

- **Local Effect Model** (LEM I)
- **modified Microdosimetric Kinetic Model**
- **empirical procedure developed at NIRS**

led to the succes of hadrontherapy

Present, however, some limitations:

- The pattern of dose deposition at nm scale should be taken into account
  → micrometric observables or radial dose do not consider the stochastic nature of radiation at local scale, even if they facilitate the model implementation
- A theory based only on local events can not reproduce shoulders in S(D) curves

Biophysical modeling

Model	Dosimetry		Stochastic effects		
	Nano	Micro	Nb impacts	Inter-track	Intra-track
MKM		x			x
mMKM		x			
LEM IV		x	x		
LEM I, II, III	x		x		

Biophysical modeling

Model	Dosimetry		Stochastic effects		
	Nano	Micro	Nb impacts	Inter-track	Intra-track
MKM		x			x
mMKM		x			
LEM IV		x	x		
LEM I, II, III	x		x		
NanOx™	**x**	**x**	**x**	**x**	**x**

NanOx™ : **NAN**odosimetry and **OX**idative stress

- Keeps on the notion of lethal local effects
- Accounts for fluctuations of dose at multiscale
- Considers radical production

NanOx™

Decomposed in a list of

- Postulates
- Simplifications
- Approximations

To help in analysis and criticism,

to test approximations,

to make evolution easier

$$\left(\frac{\partial P}{\partial Z}\right)_p^{c_{K_{out}}} = \prod_{k_{out}=1}^{K_{out}} \left(\frac{\partial P}{\partial Z}\right)_p^{c_{k_{out}}}$$

$$S(K_{in},K_{out}) = \int_0^\infty \int_0^\infty \int_0^\infty \exp(-{}^{c_{K_{in}},c_{K_{out}}}n^*) \times \exp(-\alpha_G{}^{c_{K_{in}},c_{K_{out}}}\bar{Z} - \beta_G{}^{c_{K_{in}},c_{K_{out}}}\bar{Z}$$
$$^{c_{K_{out}}}\left(\frac{\partial P}{\partial Z}\right)_p {}^{c_{K_{in}}}\left(\frac{\partial^2 P}{\partial Z_c \partial Z_p}\right) \times \mathrm{d}({}^{c_{K_{in}}}Z)_c \,\mathrm{d}({}^{c_{K_{in}}}Z)_p \,\mathrm{d}({}^{c_{K_{out}}}Z)_p$$

$$^{c_{K_{in}}}\left(\frac{\partial^2 P}{\partial Z_c \partial Z_p}\right) = \prod_{k_{in}=1}^{K_{in}} {}^{c_{k_{in}}}\left(\frac{\partial^2 P}{\partial Z_c \partial Z_p}\right)$$

NanOx™

Decomposed in a list of

- Postulates
- Simplifications
- Approximatio

$$^{c_{K_{in}},c_{K_{out}}}n^* = (^{t_k}\alpha)_c\frac{V_c}{V_s}\times K_{in}\times(^{t_k}Z)_c + \alpha_{r,L}\frac{V_p}{V_s}\times(^{c_{K_{in}},c_{K_{out}}}Z)_p$$

$$^{c_{K_{in}},c_{K_{out}}}\bar{Z} = \frac{(^{t_k}G)_c}{G_r}\frac{V_c}{V_s}\times K_{in}\times(^{t_k}Z)_c + \frac{V_p}{V_s}\times(^{c_{K_{in}},c_{K_{out}}}Z)_p$$

$$(^{c_{K_{in}}}Z)_c = \sum_{k_{in}=1}^{K_{in}}(^{c_{k_{in}}}Z)_c$$

$$(^{c_{K_{in}},c_{K_{out}}}Z)_p = \sum_{k_{in}=1}^{K_{in}}(^{c_{k_{in}}}Z)_p + \sum_{K_{out}=1}^{K_{out}}(^{c_{k_{out}}}Z)_p$$

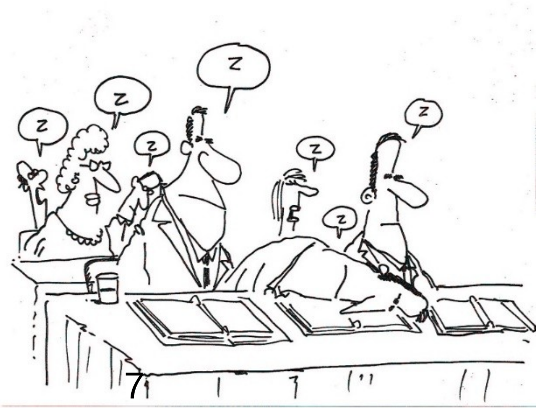
$$^{c_{K_{out}}}\left(\frac{\partial P}{\partial Z}\right)_p = \prod_{k_{out}=1}^{K_{out}}{}^{c_{k_{out}}}\left(\frac{\partial P}{\partial Z}\right)_p$$

$$S(K_{in},K_{out}) = \int_0^\infty\int_0^\infty\int_0^\infty \exp(-{}^{c_{K_{in}},c_{K_{out}}}n^*)\times\exp(-\alpha_G\,{}^{c_{K_{in}},c_{K_{out}}}\bar{Z} - \beta_G\,{}^{c_{K_{in}},c_{K_{out}}}\bar{Z}) \; {}^{c_{K_{out}}}\left(\frac{\partial P}{\partial Z}\right)_p {}^{c_{K_{in}}}\left(\frac{\partial^2 P}{\partial Z_c\partial Z_p}\right)\times \mathrm{d}(^{c_{K_{in}}}Z)_c\,\mathrm{d}(^{c_{K_{in}}}Z)_p\,\mathrm{d}(^{c_{K_{out}}}Z)_p$$

$$^{c_{K_{in}}}\left(\frac{\partial^2 P}{\partial Z_c\partial Z_p}\right) = \prod_{k_{in}=1}^{K_{in}}{}^{c_{k_{in}}}\left(\frac{\partial^2 P}{\partial Z_c\partial Z_p}\right)$$

… .hard to digest!

→ Simplified version



NanOx™: Statistical theory

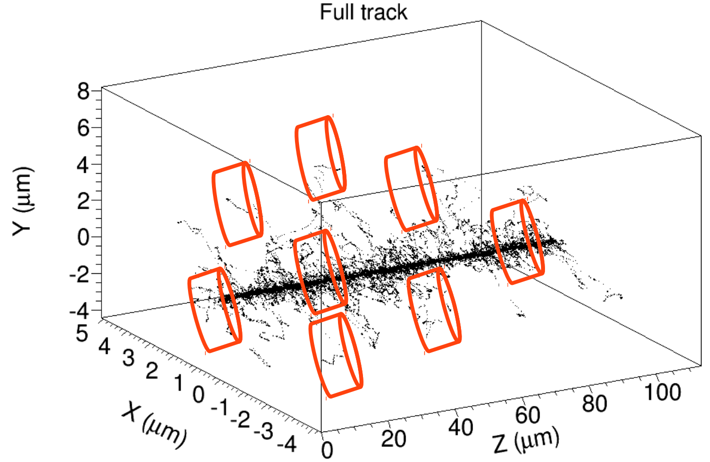
Goal: calculation of mean number of surviving cells $n=\langle n\rangle_{Ci,\,Ck}$

Ci: cell configuration

- Spatial distribution of cells, environment
- For each cell: geometry, cycle state, oxygenation state

Ck: irradiation configuration

- Dose, type of particle, energy, interaction positions
- For each impact, track details
    - \- energy transfers
    - \- radical production



C 12 MeV/n in water, targets not in scale!

NanOx™: Statistical theory

Goal: calculation of mean number of surviving cells n=<n>$_{\mathbf{Ci,\ Ck}}$

<u>Ci: cell configuration</u>

- Spatial distribution of cells, environment
- For each cell: geometry, cycle state, oxygenation state

simplifications:

No explicit description of the communication between cells

neither of the cellular state

→ One representative cell on an average state

NanOx™: Statistical theory

Goal: calculation of mean number of surviving cells n=<n>$_{Ci, Ck}$

Ck: irradiation configuration

- Dose, type of particle, energy, interaction positions
- For each impact, track details
  - energy transfers
  - radical production

simplifications:

Ignoring beam-time structure (dose-rate effects)

Given K: fluctuating number of tracks

CK: position + tracks details

$$\bar{S}\,(D) = \sum_{K=0}^{\infty} P(K,D) * \langle {}^{CK}S \rangle_{CK}$$

NanOx™: local, non-local effects

Factorization of the probability of cell survival:

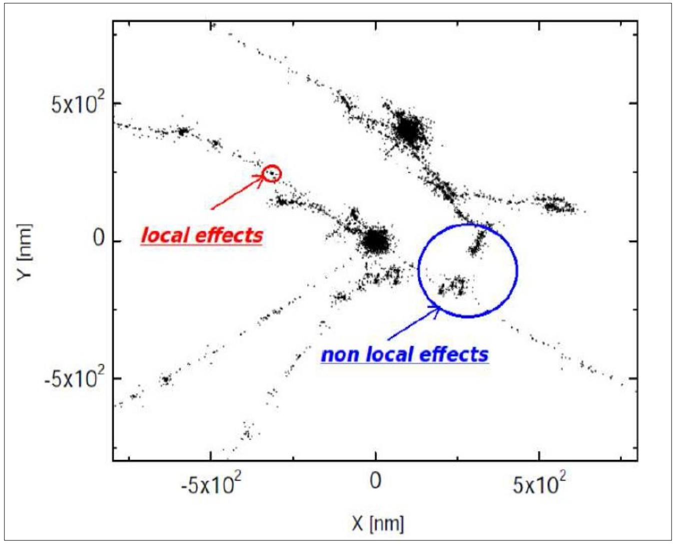
$$\boxed{{}^{\mathrm{CK}}S = {}^{\mathrm{CK}}S_{local} * {}^{\mathrm{CK}}S_{non-local}}$$

- **Local lethal events**

  Produced by physico-chemical events at local scale:

  - *complex DNA lesions (10 nm)*
  - *histones (30 nm)*
  - *telomeres (100 nm)*

  Induce directly cell killing



- **Non-local events**

  Accumulation of sub-lethal damage, oxydative stress, non-targeted events… that are difficult for cells to manage

NanOx™: local effects

Local lethal events represented by the activation of 1 among N local targets

Probability of activation: simple function f(x) such that $^{c_N,c_K}S_L = \prod_{k=1}^{K}\prod_{i=1}^{N}(1 - f(^{c_i,c_k}x))$

^{CiCk}x : observable characterizing the irradiation at local scale
ionization, energy, radical production, local heating…
deposited by the irradiation configuration C*k* in the target *i*

More convenient function for the practical implementation of the model:

Effective lethal function F(x)= -N ln(1-f(x)) ,

which allows to express the effective number of local lethal events:

$$n^* = \frac{1}{N}\sum_{i=0}^{N} F(^{c_i,c_K}x)$$

$$\Rightarrow {}^{c_K}S_L = e^{-n^*}$$

NanOx™: local effects

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${}^{CiCk}x$: observable characterizing the irradiation at local scale
ionization, energy, radical production, local heating…
deposited by the irradiation configuration C*k* in the target *i*

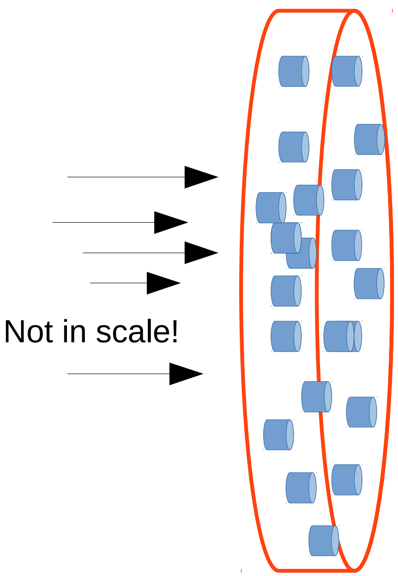
simplifications:

${}^{CiCk}x = {}^{CiCk}z$ specific energy deposited into a nano target

LQD Monte Carlo Code, Gervais et al. 2006

- Nano targets :
  Cylinders // Beam axis, R=L=10nm
  Uniformly distributed over the sensitive volume

- Micro targets: sensitive volumes
  Cylinders, same size than cell nucleus



NanOx™: local effects

Local lethal events represented by the activation of 1 among N local targets

Probability of activation: simple function f(x) such that ${}^{c_N,c_K}S_L = \prod_{k=1}^{K} \prod_{i=1}^{N} (1 - f({}^{c_i,c_k}x))$

$\boxed{\begin{array}{l} {}^{CiCk}x : \text{observable characterizing the irradiation at local scale} \\ \quad\quad \text{ionization, energy, radical production, local heating…} \\ \quad\quad \text{deposited by the irradiation configuration C}k \text{ in the target } i \end{array}}$

More convenient function for the practical implementation of the model:

$\boxed{\text{Effective lethal function} \quad F(x) = -N \ln(1-f(x))}$,

….. What is F(x) ??

NanOx™: non-local effects

Non-local events are harmful, but not able to cause cell death on their own

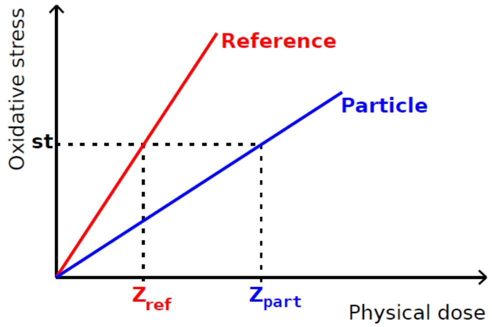
$${}^{CK}S_{non-local} = g({}^{CK}X)$$

${}^{CK}X$= quantity characterizing the irradiation at larger scale than ${}^{CK}x$, in the global volume

simplifications:

Non-local events → *Global* events represented by the production of radical species
- triggers oxidative stress
- induces a significant part of DNA sublethal damage

A convenient observable: chemical specific energy $\boxed{{}^{CK}X = {}^{CK}\tilde{Z} = \sum_{k=1}^{K} {}^{Ck}RCE \cdot {}^{Ck}Z}$,

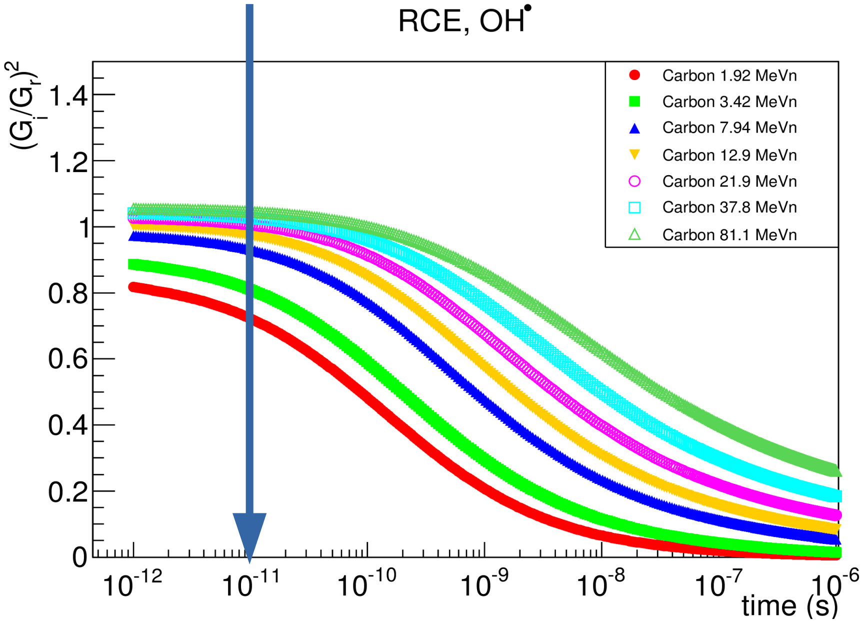


RCE: relative chemical efficiency for a given level of oxidative stress wrt a reference radiation (photons)

$$\mathrm{RCE}_{\mathrm{st}} = \left(\frac{Z_{\mathrm{r}}}{Z}\right)_{\mathrm{st}}$$

A convenient volume: sensitive volume (micro targets ~ cells nuclei)

NanOx™: non-local effects



LQD, PHYCHEML, PHYCHEM
Monte Carlo Code, Gervais et al. 2006,Colliaux et al. 2010

- RCE defined in terms of chemical yields of hydroxyl radical ($OH^{\bullet}$), one of the most effective reactive species in causing cell damage
- t_{RCE} set to 10^{-11}s to roughly characterize the primary ROS production

A well-known global function: $\boxed{{}^{c\kappa}S_G({}^{c\kappa}\tilde{Z}) = C_{\mathrm{norm}} \cdot \exp(-\alpha_G \cdot {}^{c\kappa}\tilde{Z} - \beta_G \cdot {}^{c\kappa}\tilde{Z}^2)}$

$\alpha_G=0$ in this first version of the model

$\beta_G=\beta_r/\eta^2$ where β_r is issued from the LQ fit of cell survival to reference radiation

and $\eta=\langle Z\rangle/D$

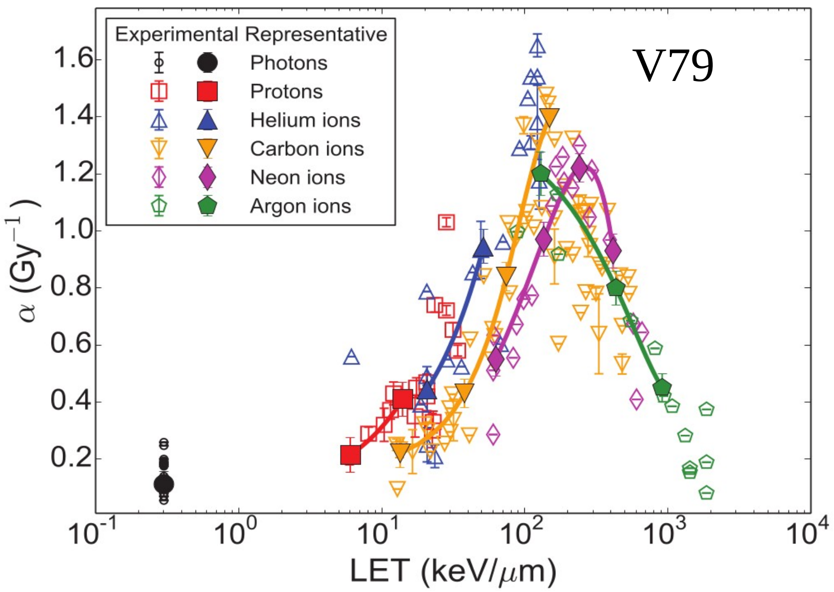
Results

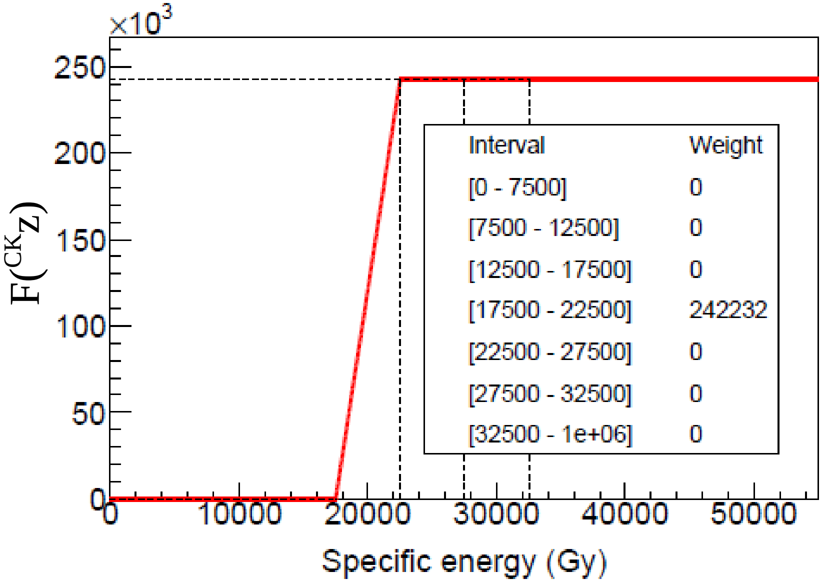
Effective lethal function

Effective lethal function $F(z) = -N \ln(1-f(z))$

Experiment based derivation of F(z)

- Decomposition on a basis: $F(z)=\sum_i \omega_i F^i(z)$
- Physical constraint: F(z) increasing function
- Optimization of ω_i coefficients to minimize disagreement with experimental data





NanOx™: effective lethal function

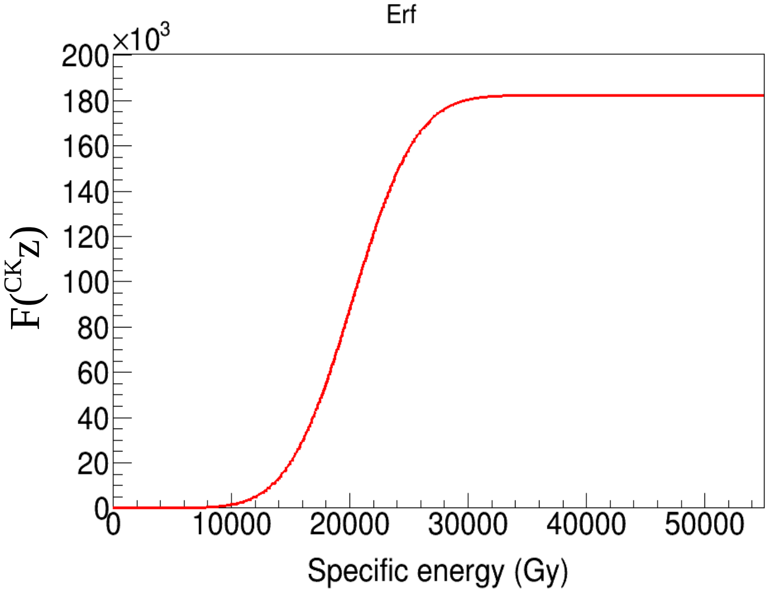
Conclusion on the "experimental" derivation of F(z) :

threshold and saturation

Building up a parametric lethal function : error function

- Easier to manage, compatible with clinical application
- Few free parameters

$$F({}^{c_K}z) = \frac{h}{2}\left[1 + \mathrm{erf}\left(\frac{{}^{c_K}z - {}^{c_K}z_0}{\sigma}\right)\right]$$



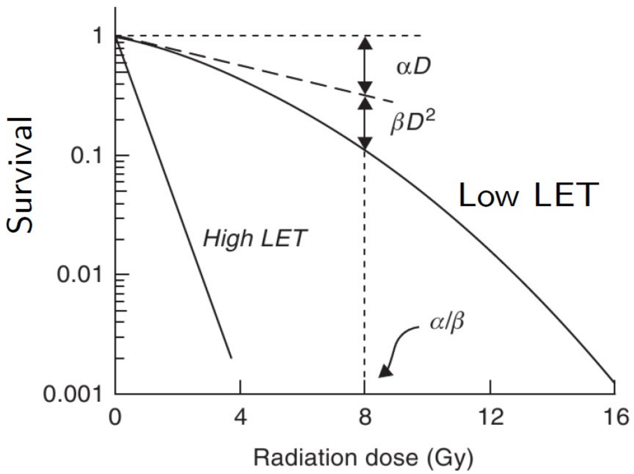
H : maximal value
z_0 : threshold position
σ : width of the increase, less important

NanOx™: modeling via F(z) ??

Relevant cross checks for the effective lethal function, and thus for $^{CK}S_{local}$

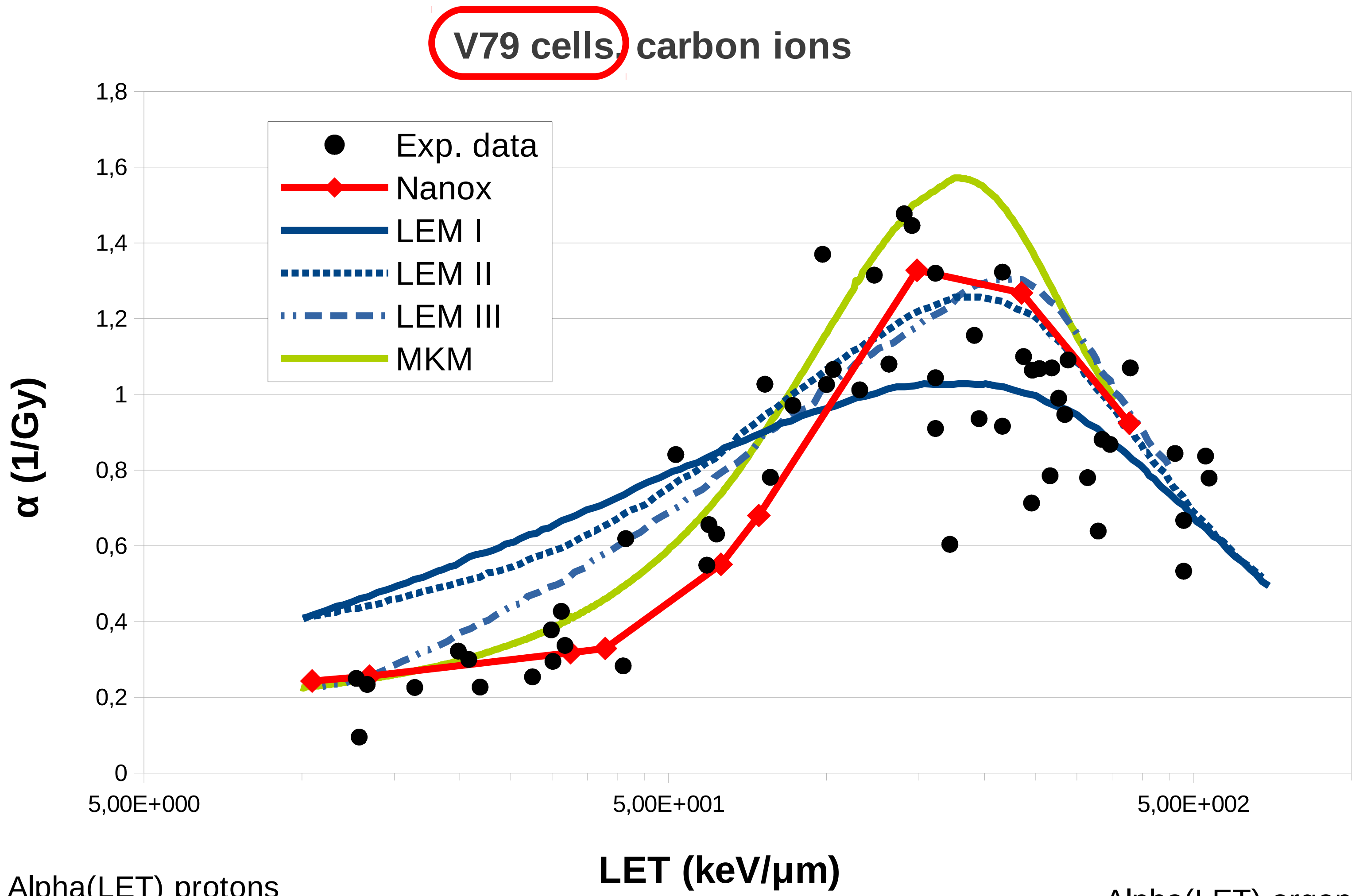
- α(LET) distributions
- Slope of the cell survival curves

since $S(D) = \langle ^{CK}S_{local} \times ^{CK}S_{non-local} \rangle_{CK}$

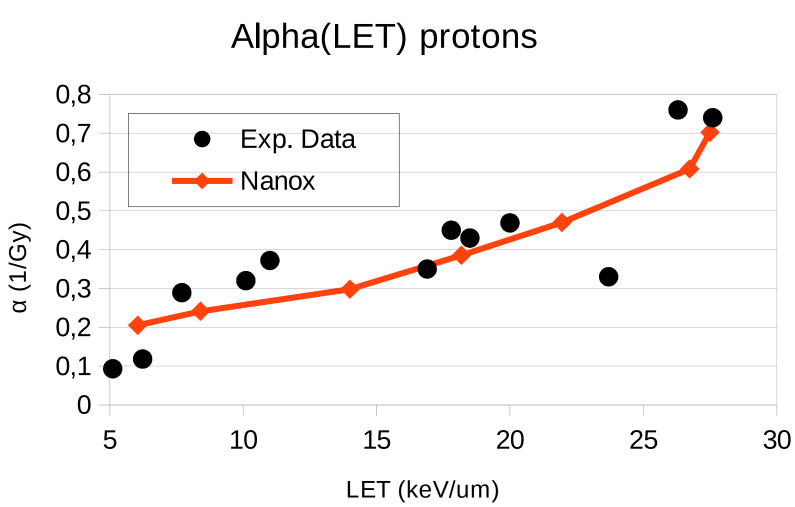


Application to several cell lines

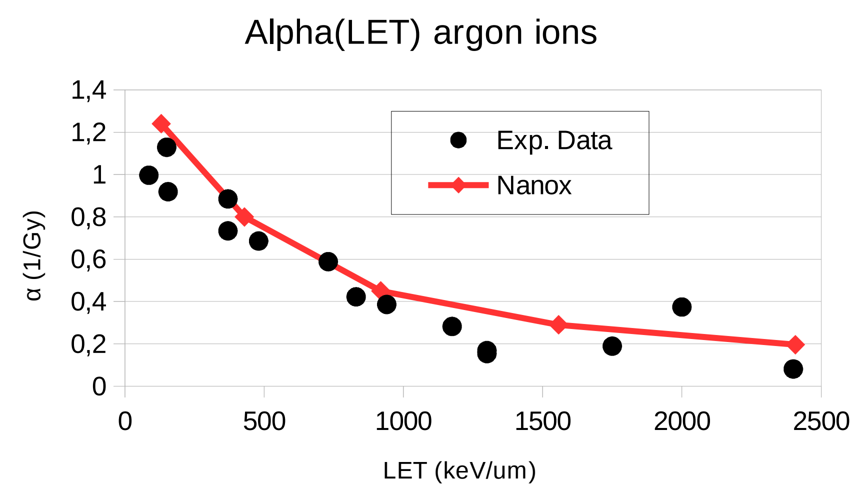
	Description	H	z_0 (Gy)	σ (Gy)
V79	lung fibroblasts, chinese hamsters	225841	22789	8117.3
CHO-K1	ovary, chinese hamster	104810	14507.2	2781.4
HSG	salivary glands, human	179439	15653.5	549.3



V79 cells, carbon ions
Exp. data
Nanox
LEM I
LEM II
LEM III
MKM
α (1/Gy)
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
5,00E+000
5,00E+001
5,00E+002
LET (keV/µm)

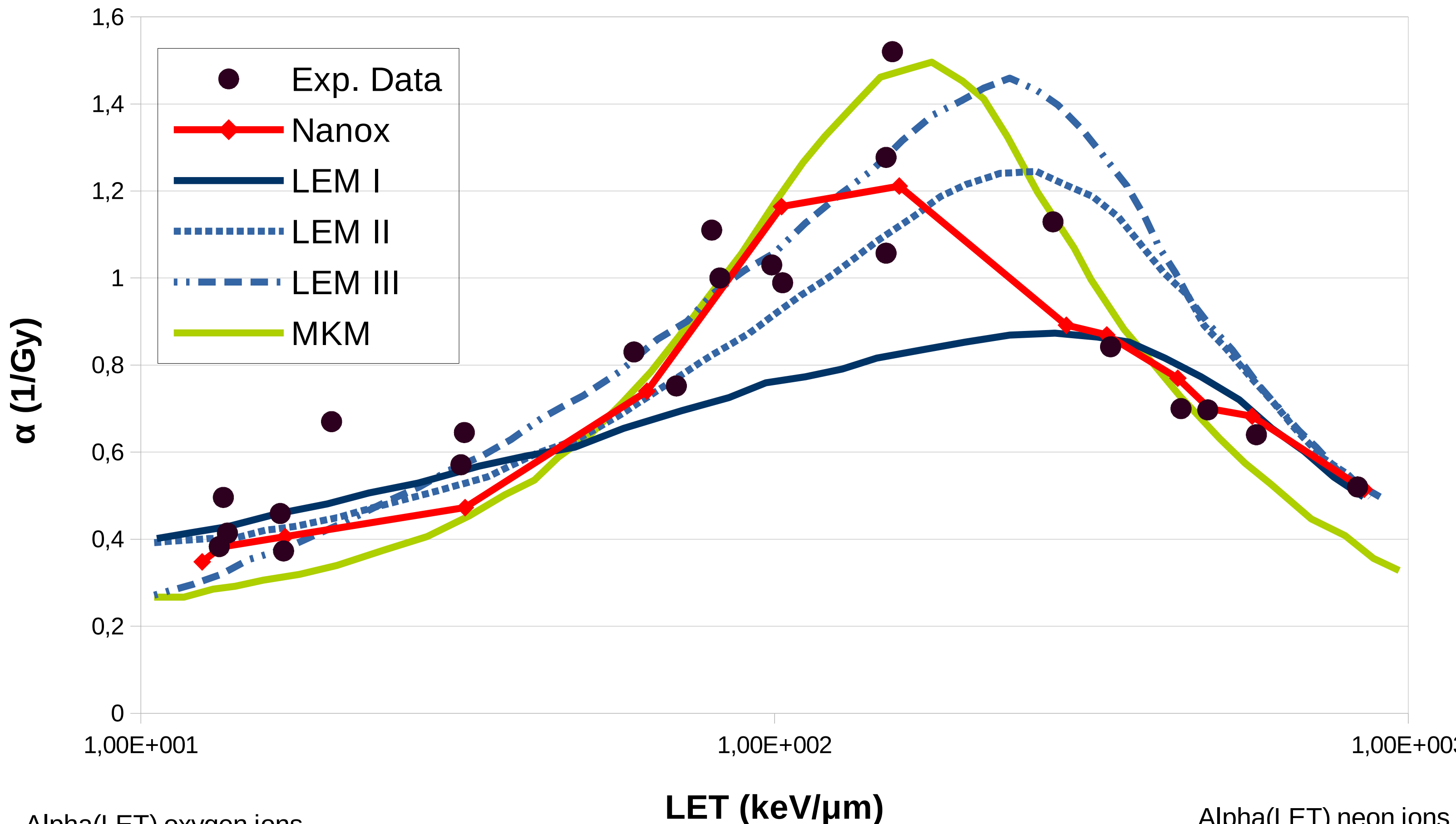


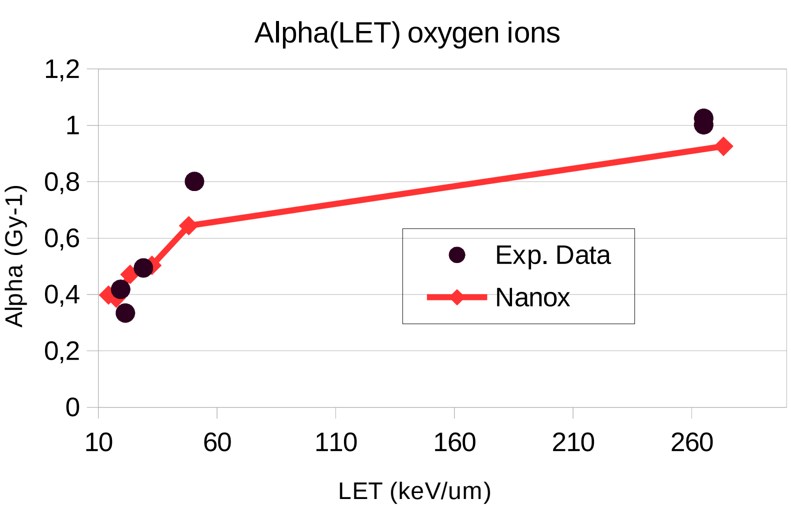
Alpha(LET) protons
Exp. Data
Nanox
α (1/Gy)
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
5
10
15
20
25
30
LET (keV/um)

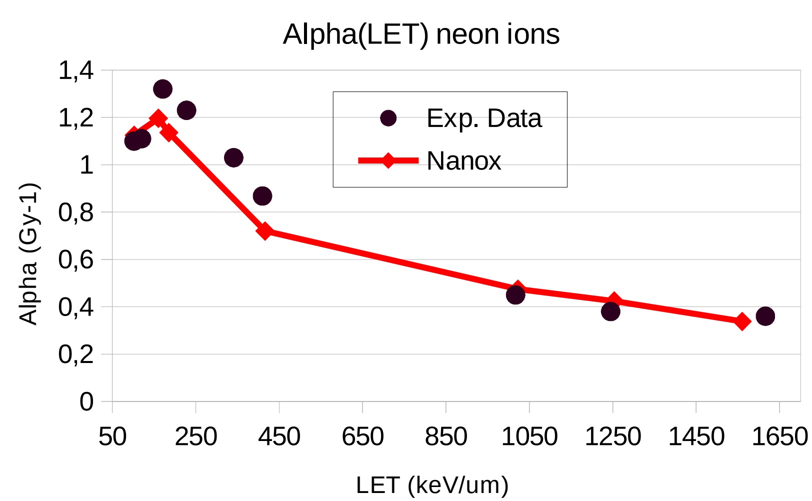


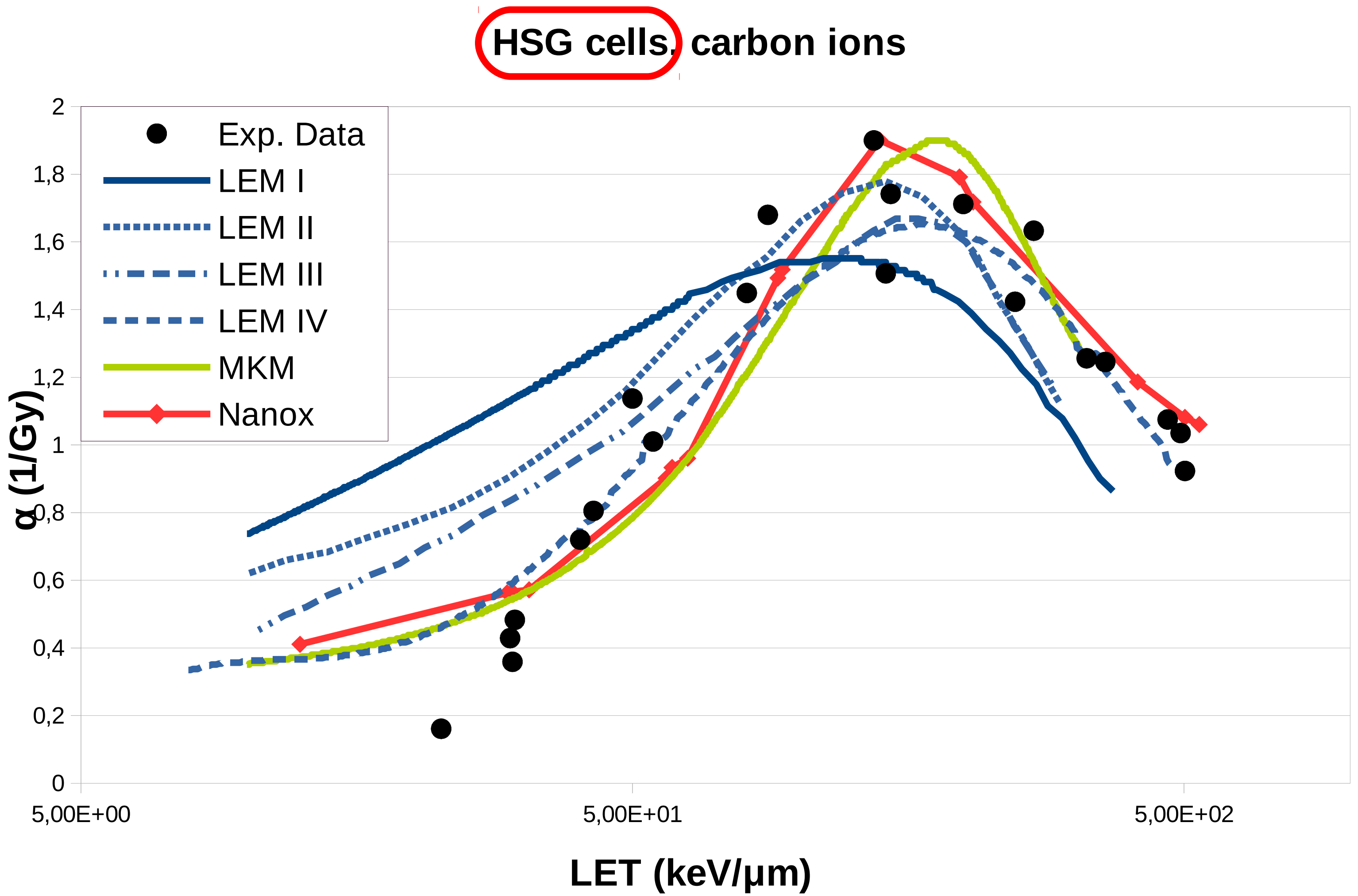
Alpha(LET) argon ions
Exp. Data
Nanox
α (1/Gy)
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0
500
1000
1500
2000
2500
LET (keV/um)

CHO-K1 cells, carbon ions









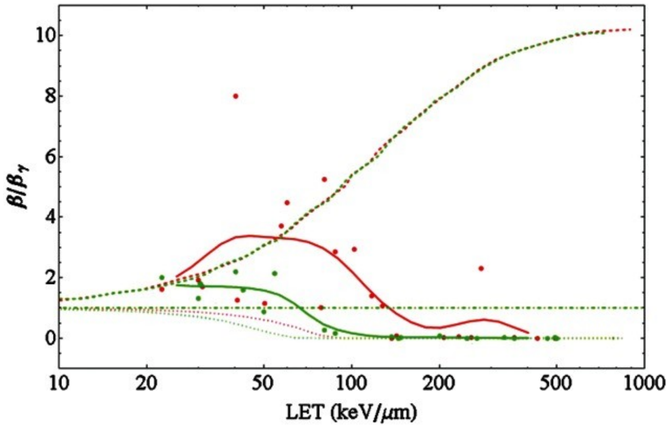
Modeling of local effects, in conclusion:

- Good agreement with experimental data
- NanOx™ is consistent with LEM and MKM

NanOx^{TM}: modeling via $g(\tilde{Z})$??

Relevant cross checks for the global function, and thus for $^{CK}S_{non\text{-}local}$

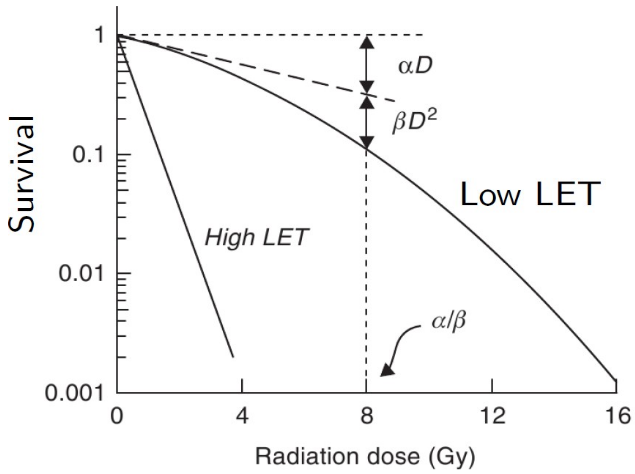
- β(LET) distributions: chaotic behavior…



Friedrich et al. 2013
Ratio of β(LET) of carbon ions to that of photons for V79 cells (red) and HSG cells (green), as measured by Furusawa et al. 2000. The dashed, dotted and dashed–dotted lines show model predictions of RMF, LEM and MKM respectively.

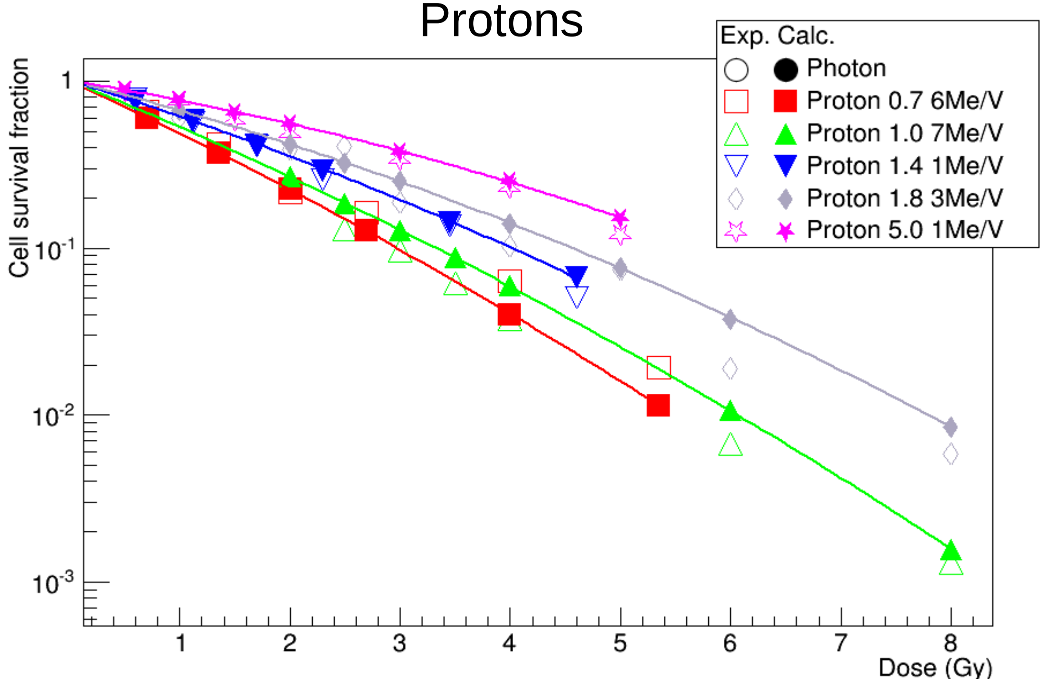
- Shoulder of the cell survival curves

since $S(D) = \langle ^{CK}S_{local} \times ^{CK}S_{non-local} \rangle_{CK}$

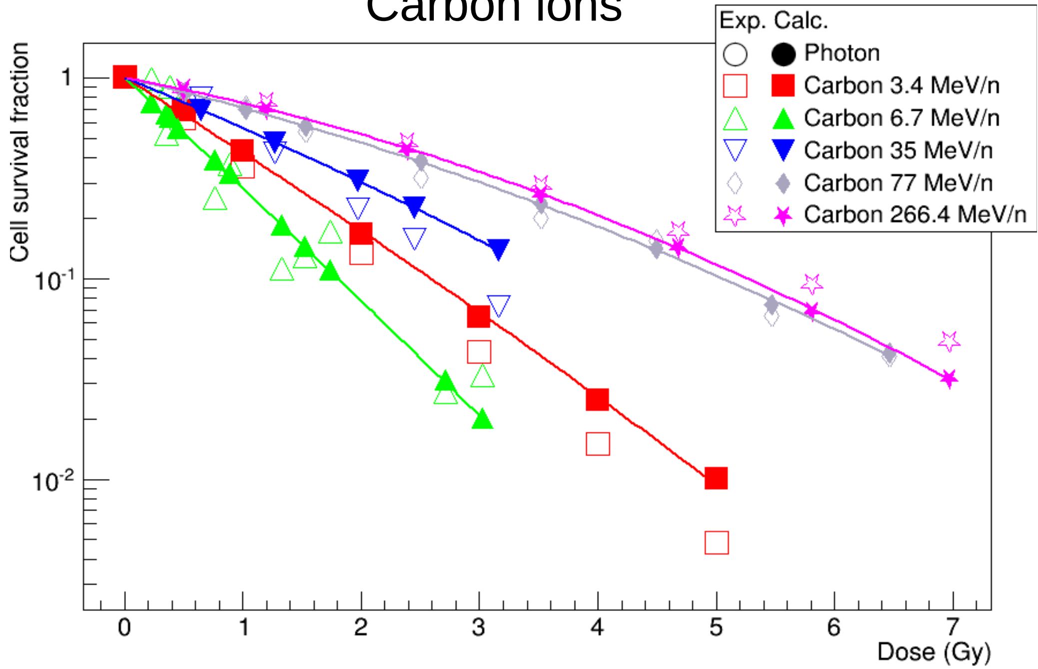


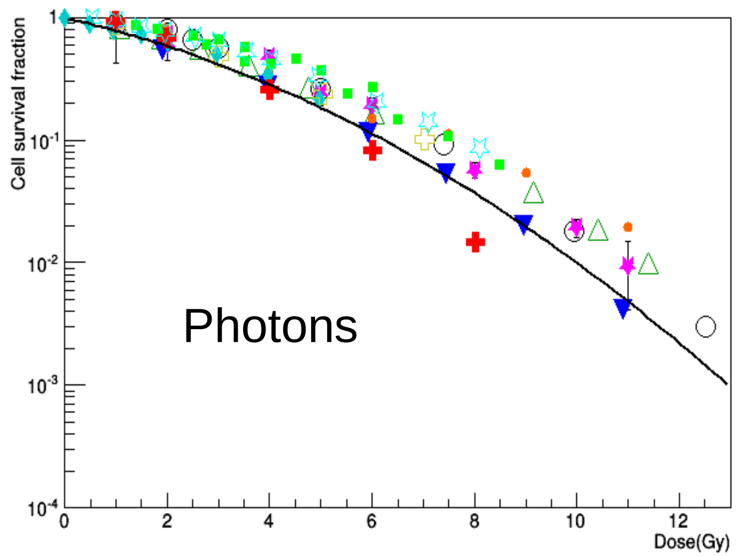
S(D) for V79 cells

Protons

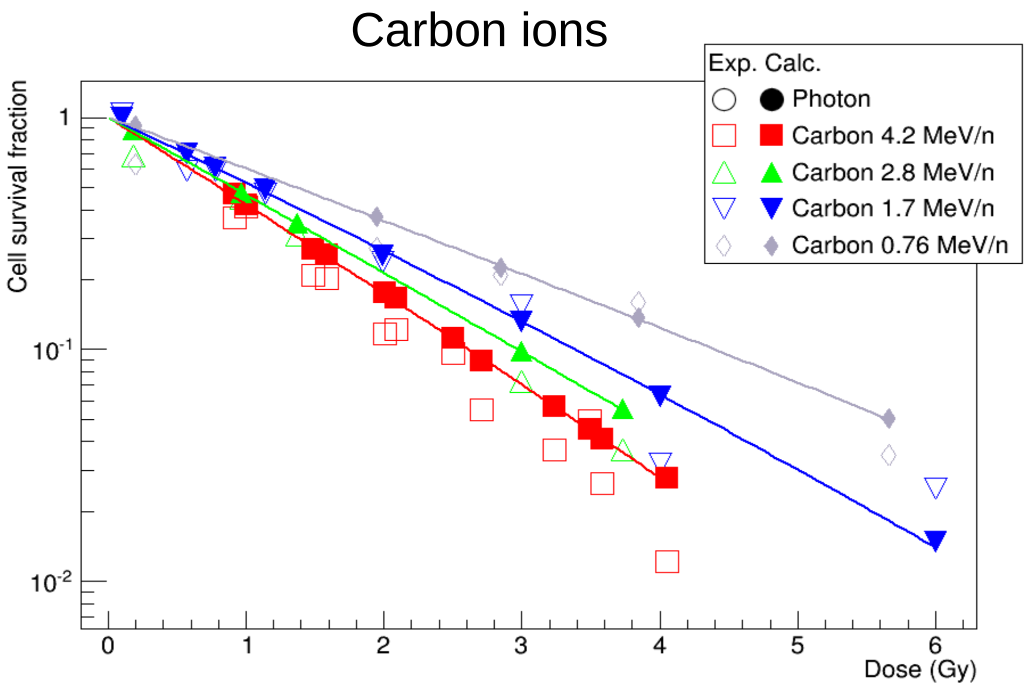


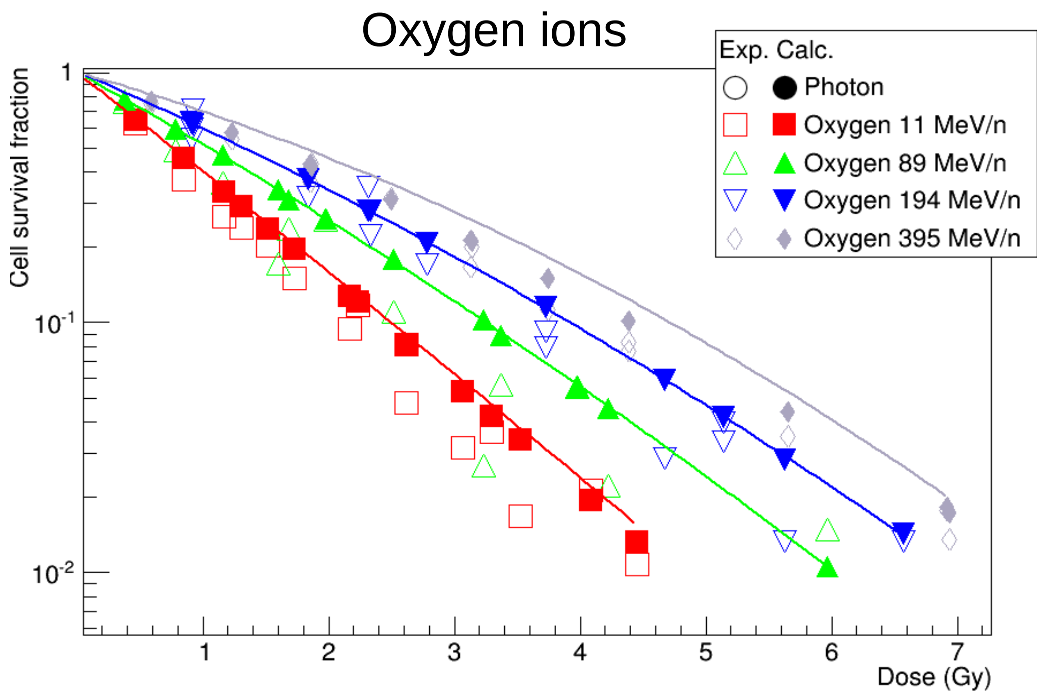
Carbon ions

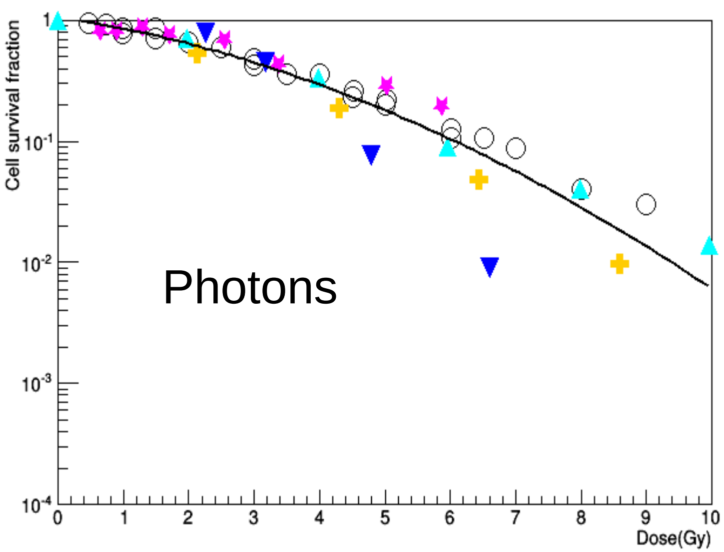




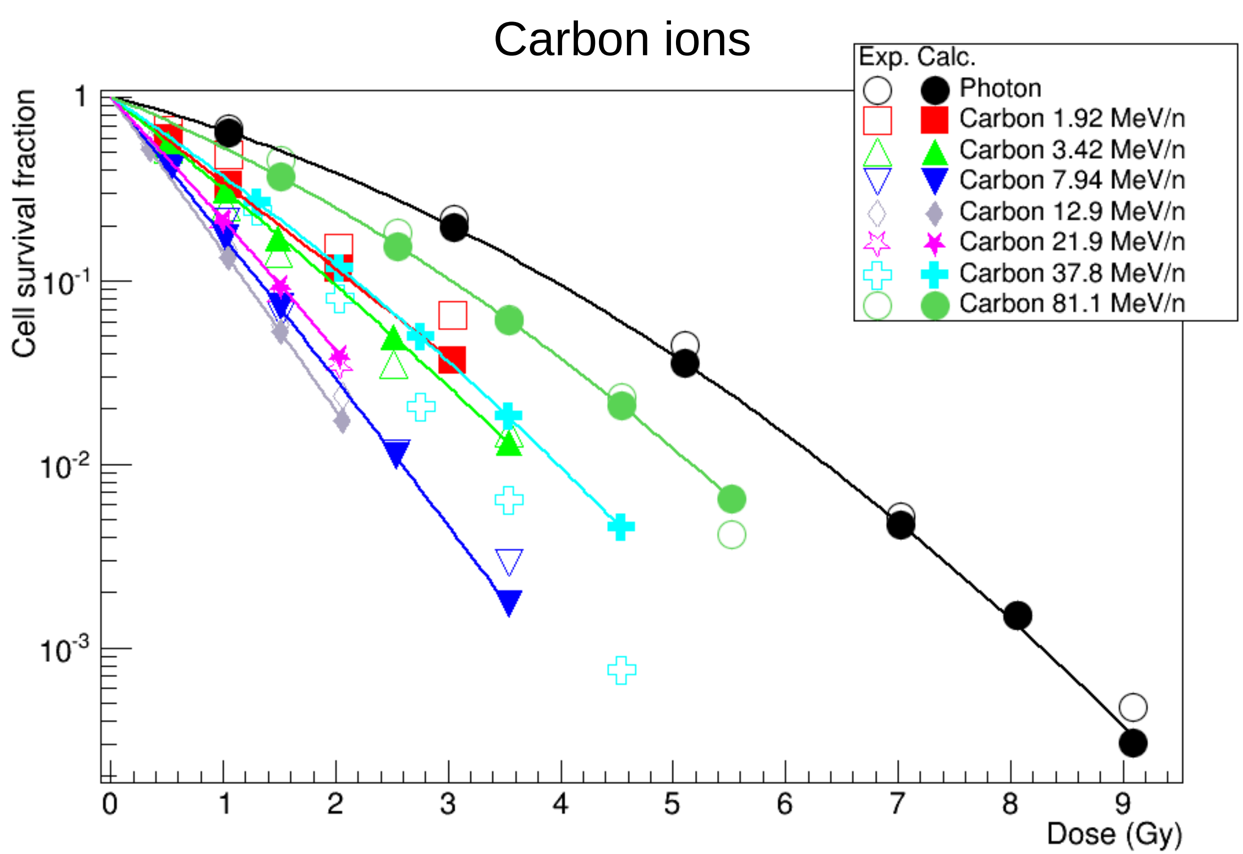
S(D) for CHO-K1 cells







S(D) for HSG cells



Modeling of global effects, in conclusion:
Rather good agreement with experimental data for a large LET range

NanOx™ parameters

Input
• α ion high LET • α ion intermediate LET • α_{ref}, β_{ref} (photons) • Nuclear size of the cells

	Experimental evidence (cell line - dependent)		Fixed (~ cell line - independent)
	Fit	Simple measure	
	H	Nuclear size of the cells	Nano targets size
F(z)	z_0	β_{ref}	t_{RCE}
	σ		α_G

→ **Modeling relies on 5 parameters associated to a specific cell line!**

Conclusion

- Threshold and saturation effects in the effective lethal function
- Statistical effects considered at nanometric and micrometric scales
- Reasonable number of parameters for clinical application
- Accurate determination of LQ parameters

  α : correct description of overkill effect

  β : increases with decreasing LET

Outlook

- Further characterization of the model with monoenergetic irradiations
  - parameters' influence and dependence on cell line
  - evaluation/relaxation of some approximations/simplifications

- Towards clinics: S(D) in SOBP
  - α and β tables → implementation into a TPS and Geant4-DNA/Gate
  - parameters' influence and dependence on cell line
  - benchmark against LEM and MKM

- Innovative therapies:
  - Survey the application of the model for neutron beam therapy, photoactivation of nanoparticles, internal vectorized radiotherapy ...

Thank you !

MKM and mMKM parameters

MKM average number of lethal lesions : $L_n=(\alpha_0+z_{1D}\beta)D+\beta D^2$

- α_0 and β: LQ parameters to photon survival
- mean specific energy for a single event in a domain of diameter d:
  $z_{1D}= <E^2>/m<E> + 0.229*LET/d^2$

(non Poisson correction does not introduce other parameters)

mMKM average number of lethal lesions : $L_n=(\alpha_0+z^*_{1D}\beta)D+\beta D^2$

- saturation-corrected mean specific energy for a single event in a domain d z^*_{1D} expressed in terms of z, β, $R_{nucleus}$, R_{domain}

⇩

3/4 parameters but microdosimetry used to describe events that take place at nm scale

LEM parameters

LEM average number of lethal lesions : $L_n = -\int dV/V \ln(S_x z[d(x,y,z)])$

Input :
- Volume of sensitive targets
- Survival curve after photons irradiation

$$S_X(D) = \begin{cases} \exp(-\alpha_X D - \beta_X D^2) & : D \le D_t \\ S_t \exp(-s[\eta(D)(D - D_t)]) & : D > D_t \end{cases}$$

- Radial dose distribution

$$D(r) = \begin{cases} \lambda \frac{\mathrm{LET}}{r_{\min}^2} & : r < r_{\min} \\ \lambda \frac{\mathrm{LET}}{r^2} & : r_{\min} \le r \le r_{\max} \\ 0 & : r > r_{\max} \end{cases}$$

r_{min}=10nm
r_{max} delta-rays

⇨ **The modeling requires the determination of 4 parameters:**
α, β, $R_{nucleus}$, D_t

Biological targets