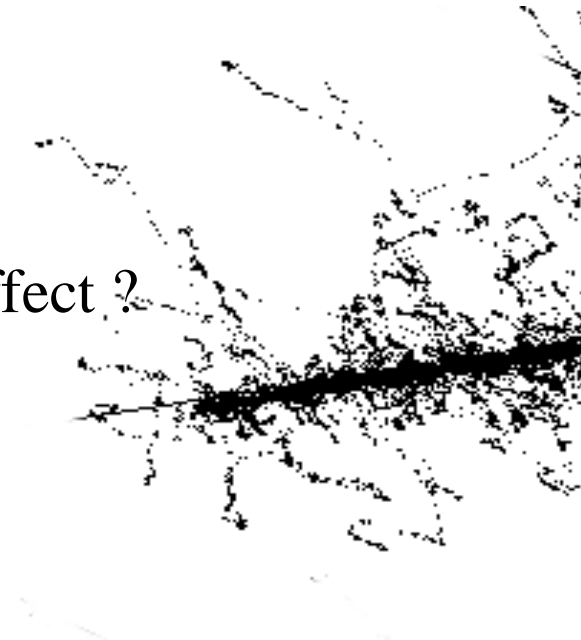


NanOx, a new multiscale model to predict biological effects of ionizing radiation

M. Beuve (PRISME, IPNL)



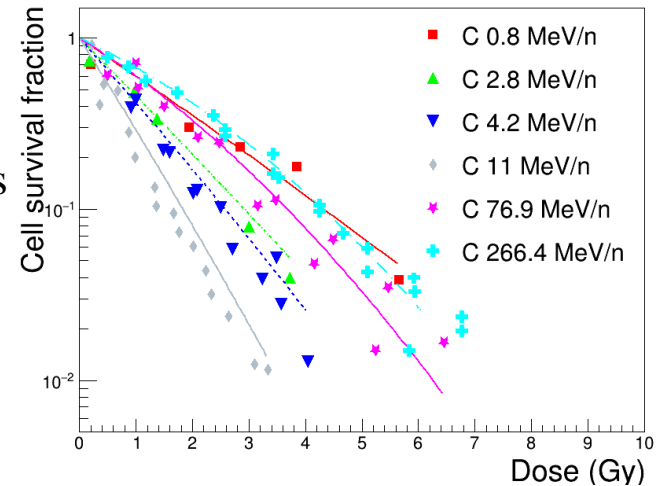
- **NanOx... to predict what ?**
- Results
- Characteristic features of the model
- Theoretical framework in brief
 - Non-local events
 - Local lethal events, threshold effect ?
- Towards a clinical application



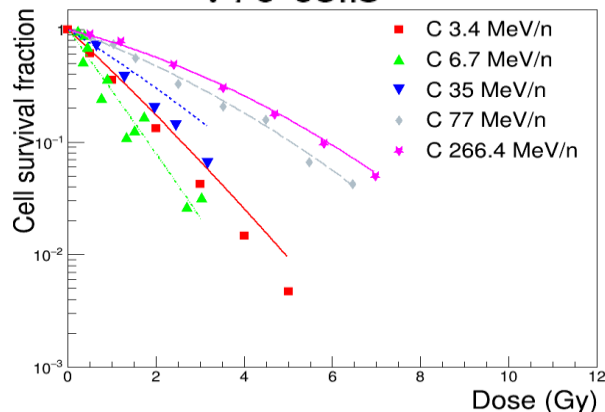
cell survival

- Interesting endpoint
 - integrates all death pathways
 - allows to derive Tumor Control Probability
 - Linked to deterministic effects in healthy tissues
- Depends on:
 - Particle type, energy and LET
 - Cell type, environment, phase
 - Dose, dose per fraction ...

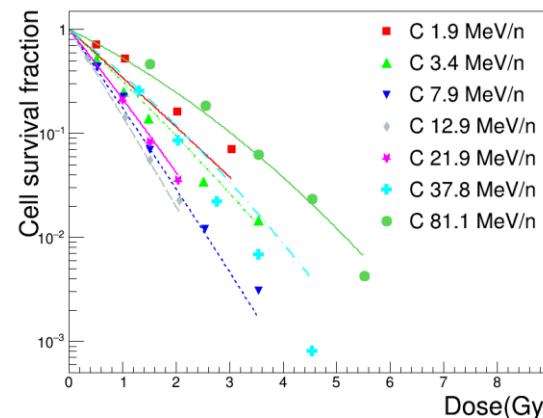
CHO-K1 cells



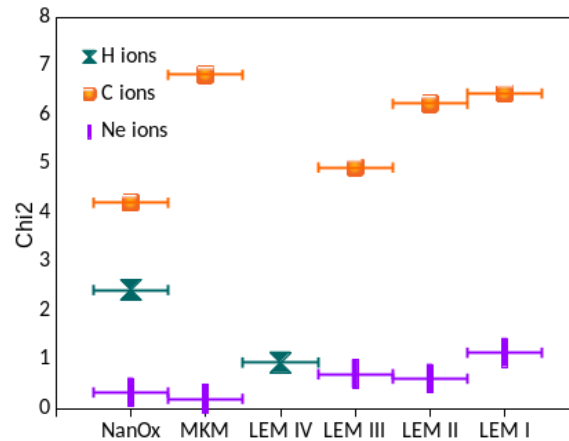
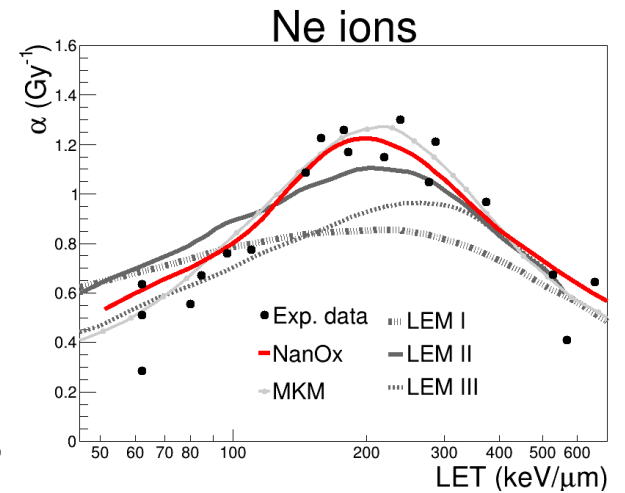
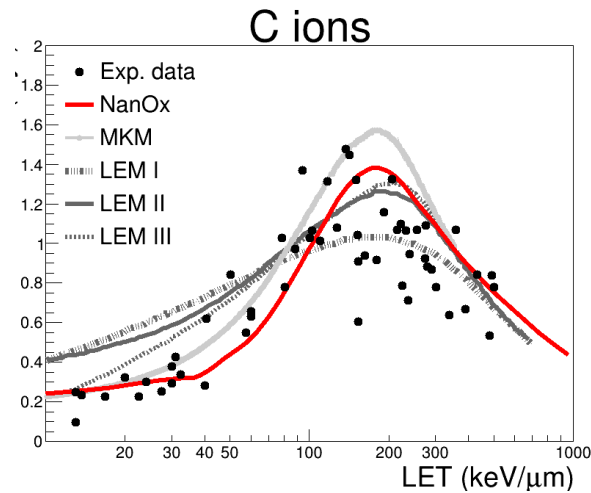
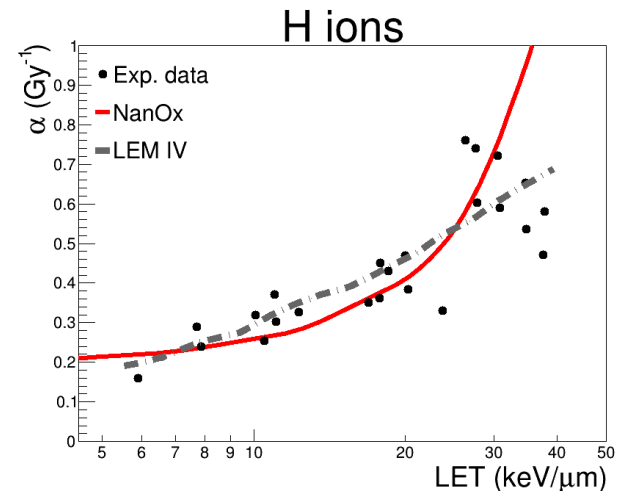
V79 cells



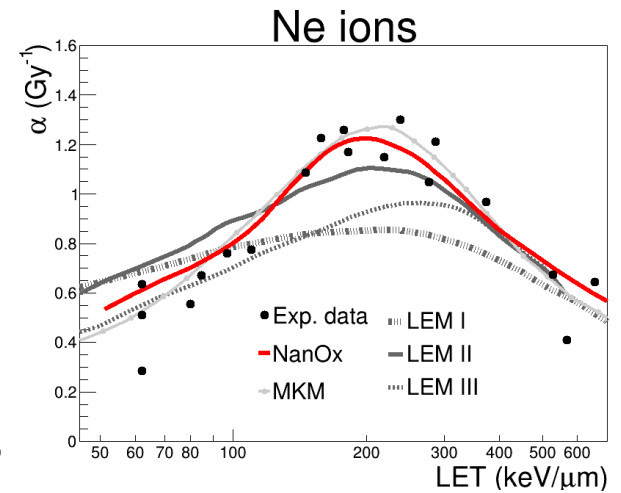
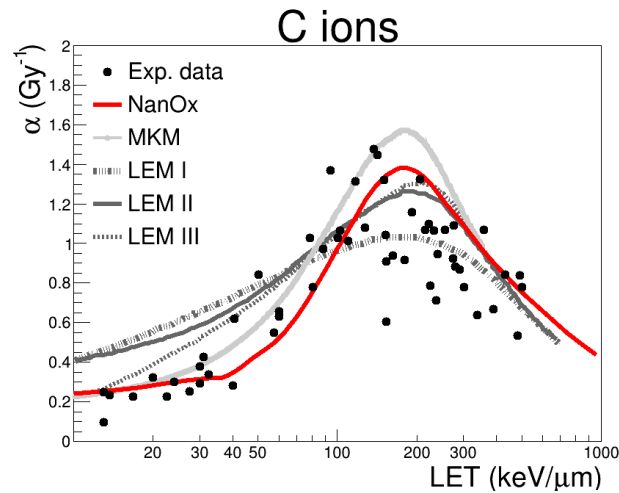
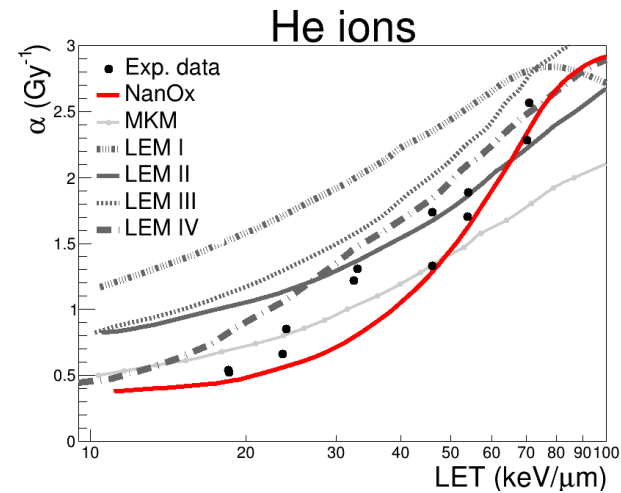
HSG



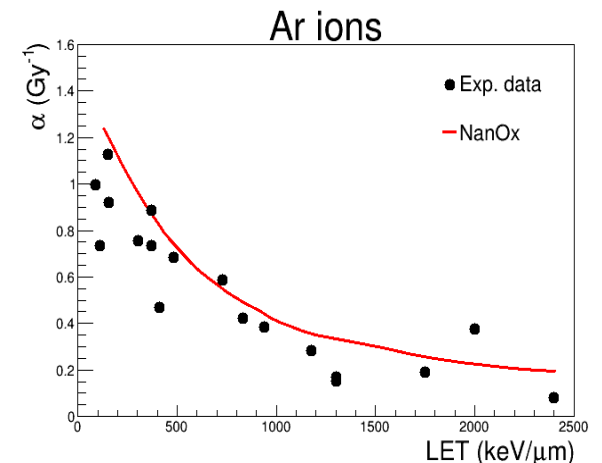
V79 cells, $\alpha(\text{LET})$



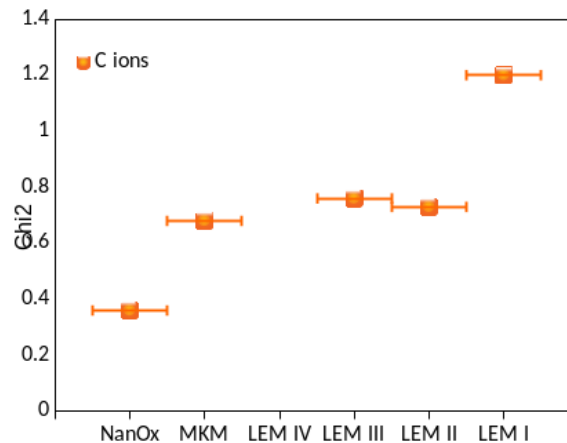
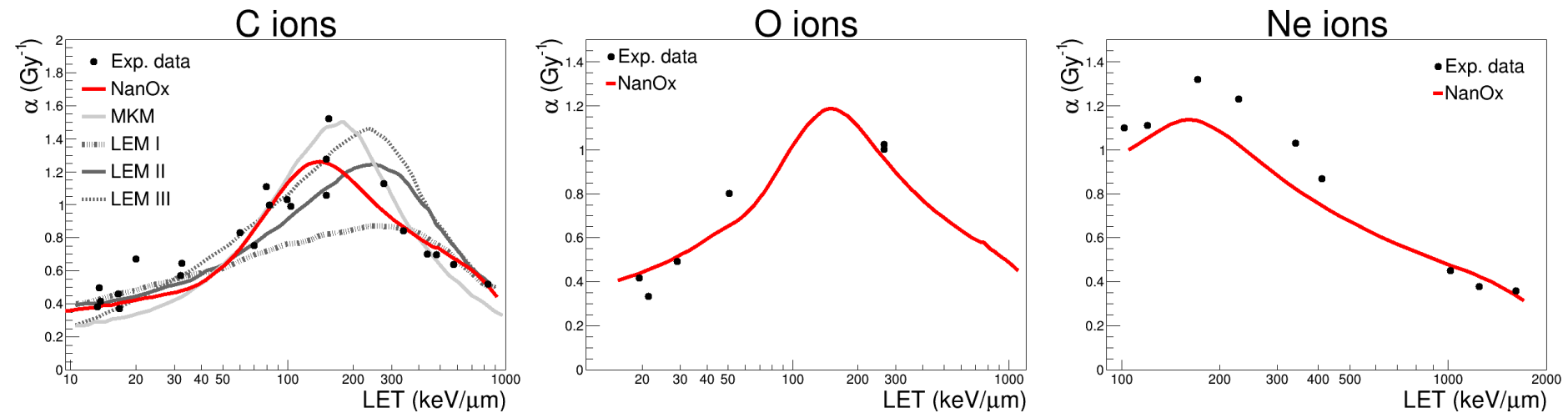
V79 cells, $\alpha(\text{LET})$ up to Argon



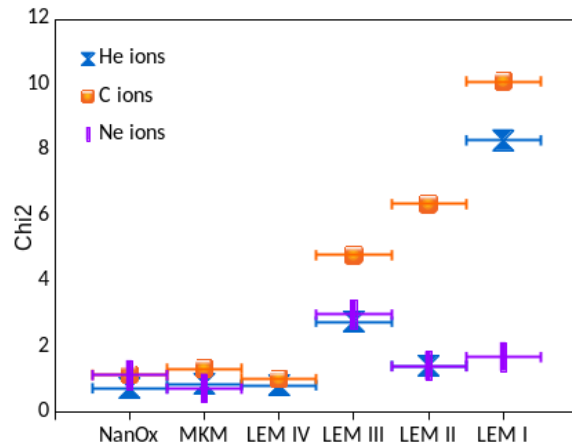
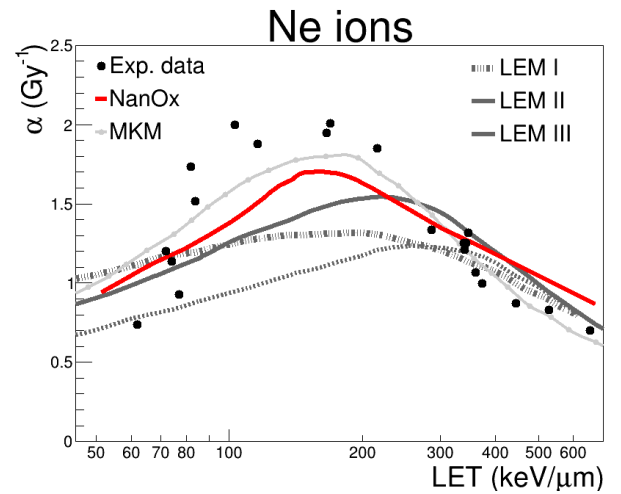
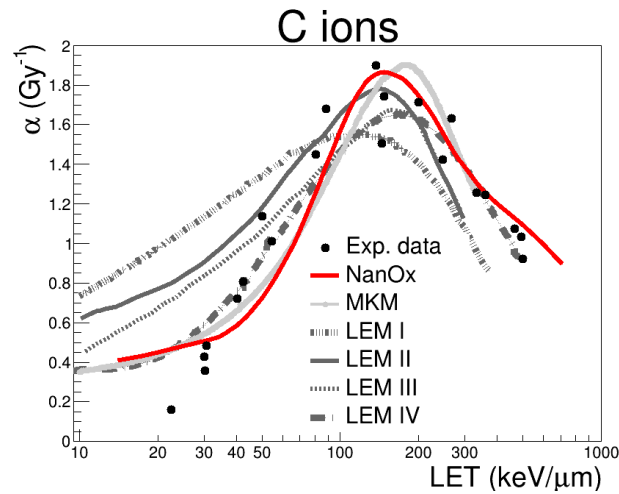
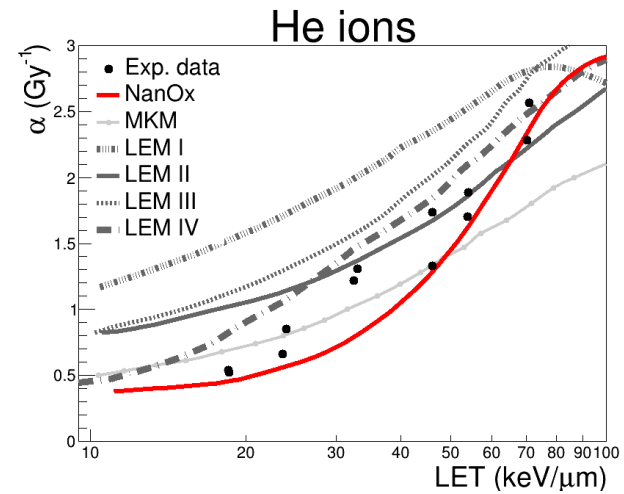
... up to Argon ions



CHO-K1 cells, α (LET)



HSG cells, $\alpha(\text{LET})$



- NanOx... to predict what ?
- Results
- **Characteristic features of the model**
- Theoretical framework
 - Non-local events
 - Local lethal events, threshold effect ?
- Towards a clinical application



NanOx: Statistical theory

- **C_N : Cell configurations**

- No explicit description of the communications between cells

- ⇒ One representative cell

- **C_K : Irradiation configurations**

- Ignoring beam-time structure

- No dose-rate effects

- Irradiation configurations

- K : fluctuating number of tracks

- C_K : Positions + tracks details

$$S(D) = \sum_{K=0}^{\infty} P(K, D) \times \langle S \rangle_{C_K, C_N}^{C_K, C_N}$$

NanOx: Multi-scale model

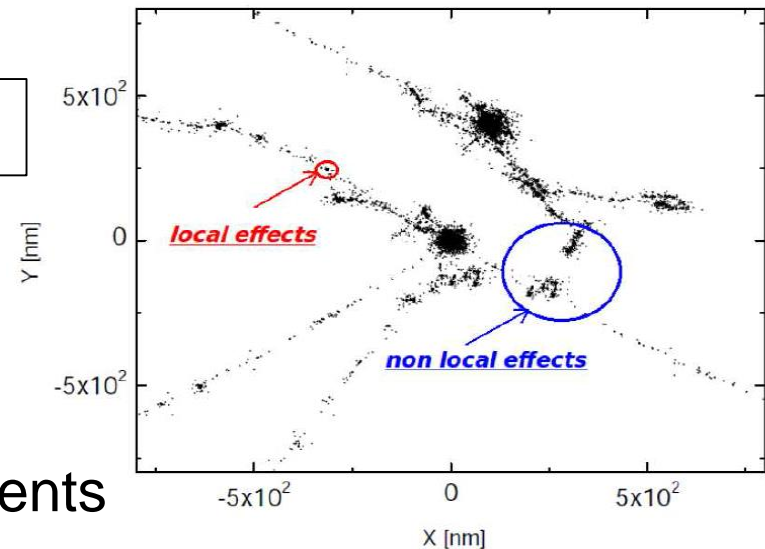
- Full statistical model
 - Dramatic computer resource
 - patient : 2 Gray in $10 \times 10 \times 10 \text{ cm}^3$
 - $6 \cdot 10^{17}$ ionizations!
 - Cell in flasks : 5 Gray in $5 \times 5 \times 0.1 \text{ cm}^3$
 - $1,5 \cdot 10^{16}$ ionizations !//
- Multi-scale approach
 - Simplifications and approximations

NanOx: Local and non local effects

Postulate:

$${}^{CK,CN}S = {}^{CK,CN}S_{local} \times {}^{CK,CN}S_{non-local}$$

- Local lethal events
 - Non correlated biological events
 - Inducing directly cell killing
 - Produced by physic-chemical events at local scale
 - *complex DNA lesions (10 nm),*
 - *histones (30 nm),*
 - *telomeres (100 nm)*
- Non-Local events : The other events



Local scale = Spatial extension small enough so that the induced physical events are due to one incident particle when irradiating with clinical doses.

(<10Gy) \Rightarrow size \ll 1 μ m

\Rightarrow **nanoscale**

Nanox: Non-local effects

- Literature:
 - Microdosimetry \Rightarrow interaction of two sub-lesions
 - Two-stage model [Kundrat *et al.*] \Rightarrow statistics in impact number
 - Ion-kill / γ -kill [Katz *et al.*] inter-track effects
 - \Rightarrow Micrometric target + multi target theory



- Our idea: Test a (new) concept of global events
- “Accumulation of sub-lethal damage, oxidative stress, non-targeted events... that are difficult to manage”
- *Postulate: Global events*

$${}^{CK}S_{non-local} = {}^{CK}S_{global}$$

$${}^{CK}S_{global} = g({}^{CK}X)$$

${}^{CK}X$ characterizing the global effects at global scale

Nanox: Non-local effects

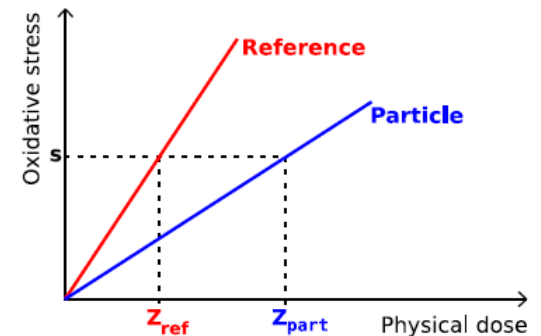
Oxidative stress

- $X = Y$ (Y for yield in the sensitive volume)
- LQ: $S(Y) = \exp(-aY-bY^2)$
- $Y = \text{yield of } \text{OH}^\bullet \text{ at } 10^{-11} \text{ s}$

Chemical specific energy

- $\check{Z} = \text{RCE} \times Z$
- RCE = relative chemical efficiency
- $S_G = \exp(-\alpha_G D - \beta_G D^2)$

Note: we set $\alpha_G = 0$ and $\beta_G = \beta_r / \eta$



Nanox: Local lethal effects

- **Postulate : Local lethal events**

- Represented by the activation of a local target
- N targets distributed in sensitive volume
- Probability for target activation:
 - a simple function $f(\text{CK}_Z)$ of a local quantity CK_X
 - CK_X : restricted specific energy at local scale

$$S_L = \prod_{i=1}^N (1 - f(\text{CK}_X x_i))$$

- Definition: **Effective local function**

$$F(x) = -N \times \ln(1 - f(x))$$

F as a linear combination

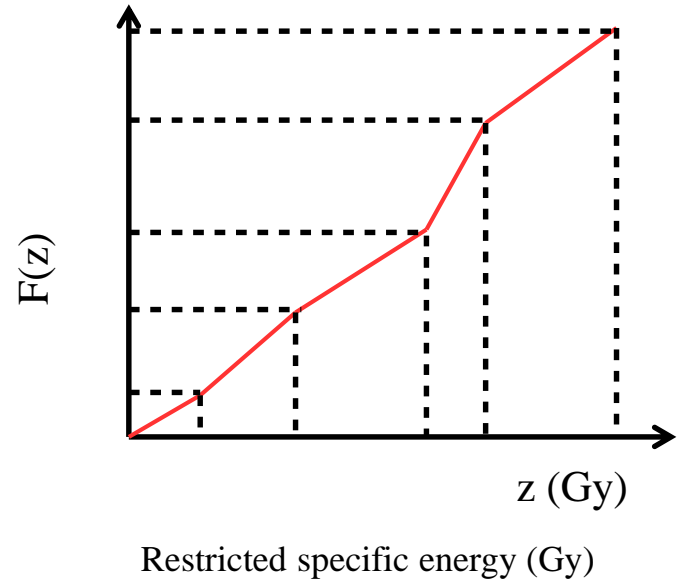
I. Decomposition on a basis:

$$F(z) = \sum_i \omega_i F_i(z)$$

II. Physical constraint: $F(z)$ increasing function

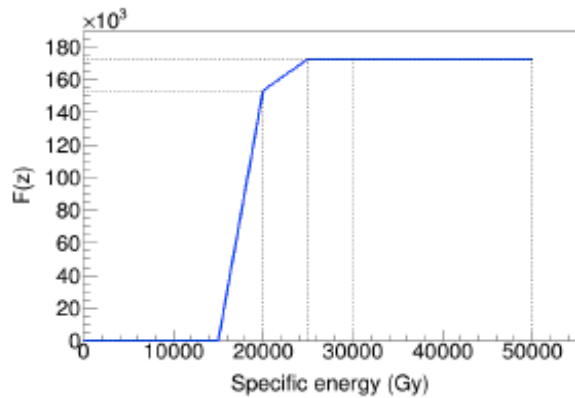
III. Experimental data constraint

=> to optimize the weights of the linear combination

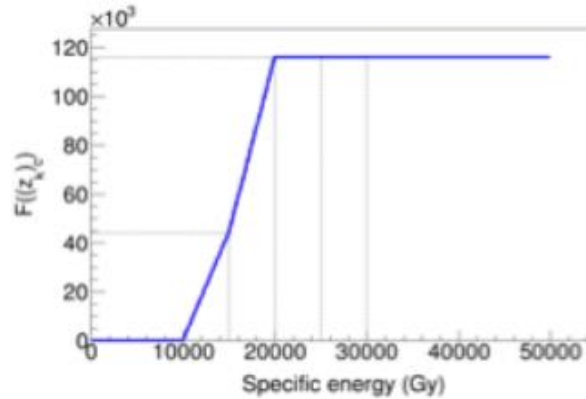


Lethal function: Results

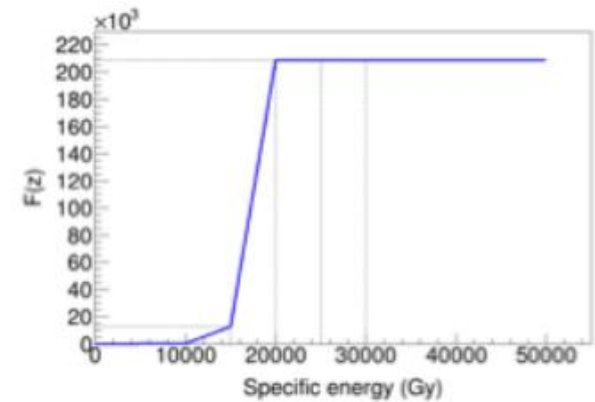
V 79 cells



CHO-K1 cells

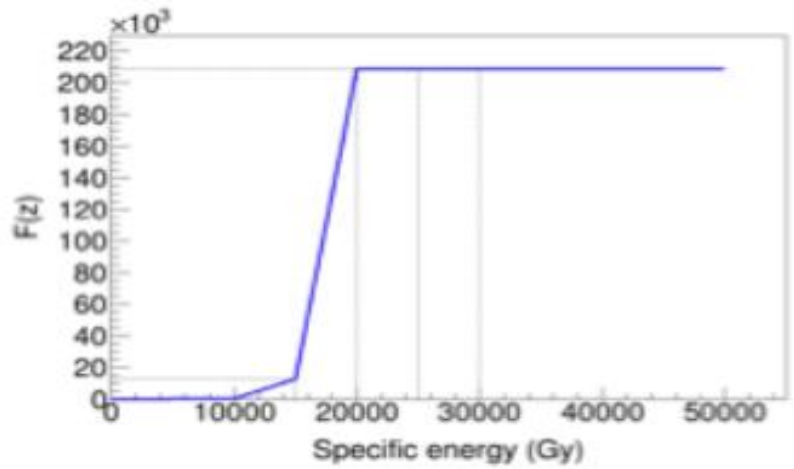
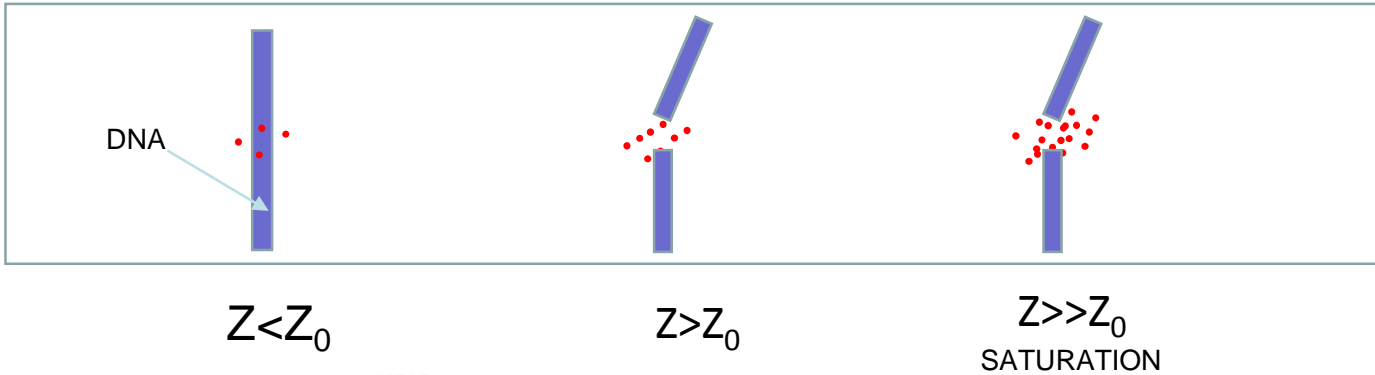


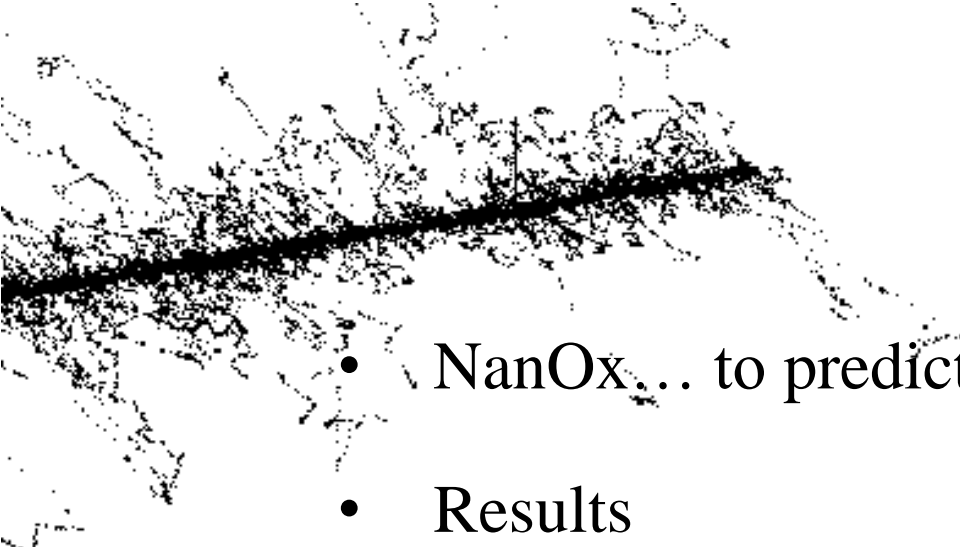
HSG cells



Threshold saturation

Biological interpretation?



- 
- NanOx... to predict what ?
 - Results
 - Characteristic features of the model
 - Theoretical framework
 - Non-local events
 - Local lethal events, threshold effect?
 - **Towards a clinical application**

Parametric lethal function

Erf-like function

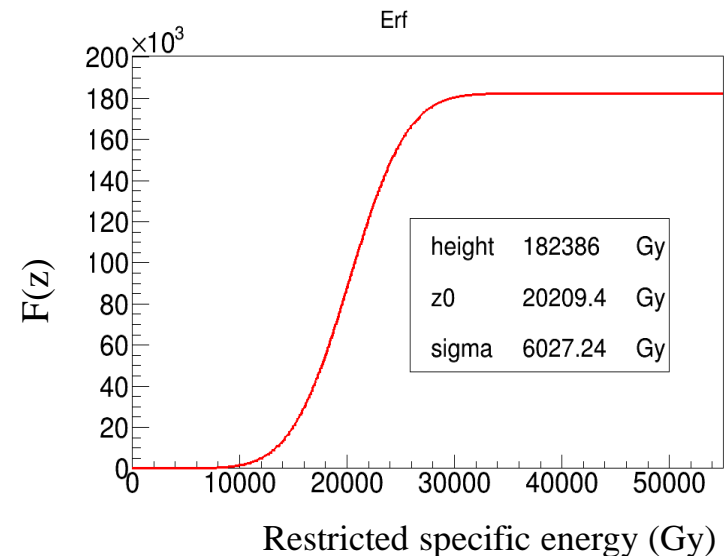
- Easier to manage, compatible with clinical application
- Few free parameters

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

h : maximal value

z_0 : threshold position

σ : width of the increase, less important



NanOx parameters

Study of the influence of Nanox parameters: Monini et al.,
Cancer (Basel) 2018 Mar 21;10(4). pii: E87

It is possible to get good agreement between NanOx predictions and experimental data (for V79, HSG and CHO-K1 cell lines) with only 5 biological data :

- Nuclear size of the cells
- $\alpha_{\text{ref}}, \beta_{\text{ref}}$ (photons)
- α ion high LET
- α ion intermediate LET

Conclusion

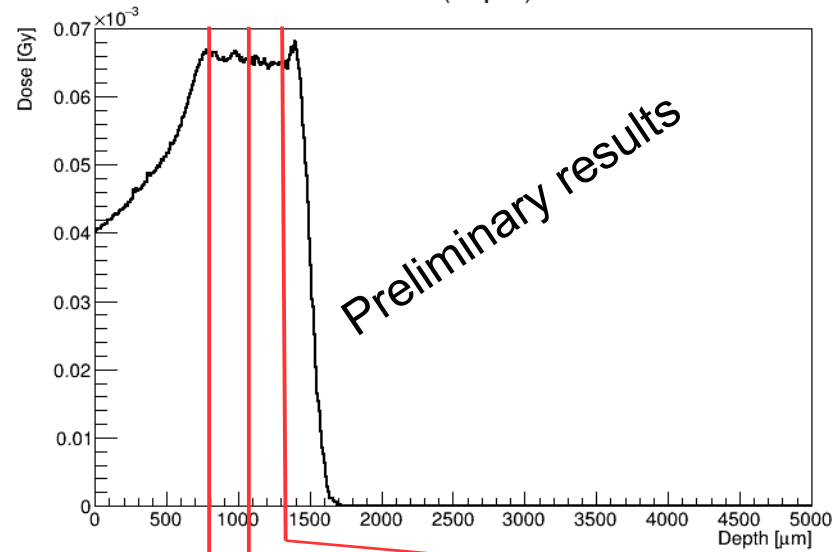
- NanOx: full stochastic and multiscale model (from nano scale)
- Innovative features
 - New quantities: restricted specific energy, RCE and chemical specific energy
 - Effect of threshold and saturation in the local effects
- Good agreement with experimental data for V79, CHO-K1, HSG
 - Better $(\chi)^2$ score than MKM and LEM
- Compatible with clinical application

Perspectives

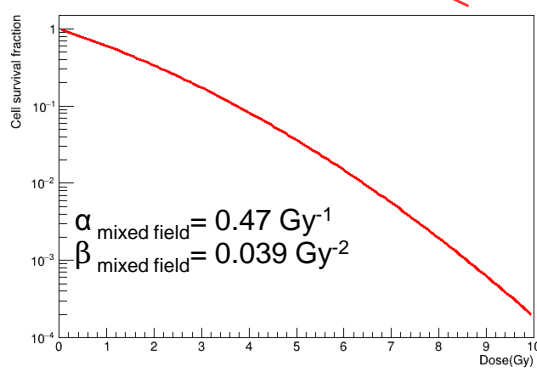
- First version: room for improvement
 - lethal function
 - global function
 - consider other non-local events...
- Challenging with other experimental data
 - Measurement with biologists of the team:
 - Raadiograaff, GANIL, INFN-LEGNARO ...
 - Evaluation in clinical conditions (SOBP)
 - CNAO ?, NIRS
 - Arronax: SOBP of Helium in progress

SOBP:ARRONAX

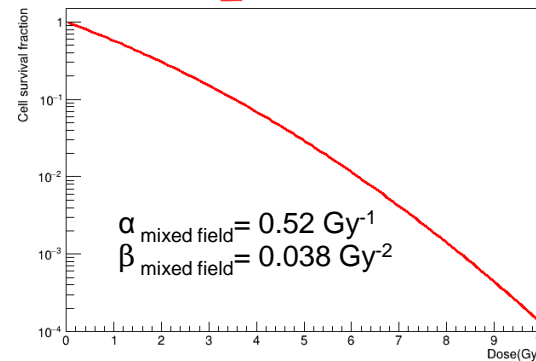
Dose (depth)



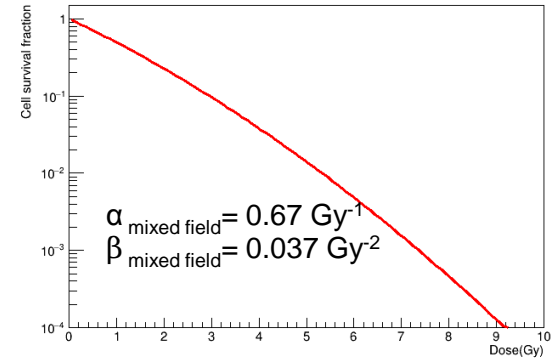
Mixed Field, x1



Mixed Field, x2



Mixed Field, x3



Outlook

Incorporation into Geant4 DNA and Gate
at multiple levels:

- **Macroscopic level:** table of Nanox prediction
 - ⇒ application for hadrontherapy
 - Collab. : LPC Clermont; CREATIS => 3D biological Dose
 - Collab. : LIRIS => 4D Biological Dose
- **Microscopic level:** Nanox calculations by trajectories
 - ⇒ applications for BNCT, vectorized radiotherapy, better description of low energy fragments in hadrontherapy
 - Collab. : LPSC Grenoble, Univ. of Rosario (Argentina)
- **Nanosopic level:**
 - nanotargets in realistic cell geometry
 - realistic representation of nano targets (DNA, lysosomes, mitochondria..)
 - introduction of biological mechanisms

Partners



CiMap

- **Collaborators**

- biologists of the team
- LPC Clermont
- CIMAP (Caen)
- LNL (Legnaro)
- Arronax/Subatech (Nantes)

- (C Rodriguez *et al.*)
- (L Maigne *et al.*)
- (B. Gervais, E. Balanzat)
- (R. Cherubini *et al.*)
- (C. Koumier *et al.*)

- **Acknowledgements**



INSTITUT
NATIONAL
DU CANCER

- INCA
- Labex Primes
- GdR MI2B



Backup

NanOx parameters

- α ion high LET
- α ion intermediate LET
- $\alpha_{\text{ref}}, \beta_{\text{ref}}$ (photons)
- Nuclear size of the cells



Experimental evidence		Fixed	
Fit	Simple measure	Cell line independent	To be studied
H	Micro targets size	t_{RCE}	Nano targets size
z_0	β_{ref}		α_{G}
σ			

F(z) {

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

Nanox: Local lethal effects

- What could be x?
 - ionization, core ionization, energy, radical productions, local heating...
- Simplifications
 - **Restrictive specific energy** deposited into a target by CK
 - $CK_X = CK_Z$:
 - Monte Carlo simulation
 - ✓ Gervais et al. 2006,
 - Beuve et al. 2009
 - Target :
 - Cylinder// Beam axis
 - Radius=Length= **10nm**
 - Uniformly distributed over the sensitive volume
 - Sensitive volume
 - Cylinder
 - Size: cell nucleus

$$Z = \frac{1}{m} \sum_{j \in R} \varepsilon_j, \quad (R = \text{restricted events})$$

