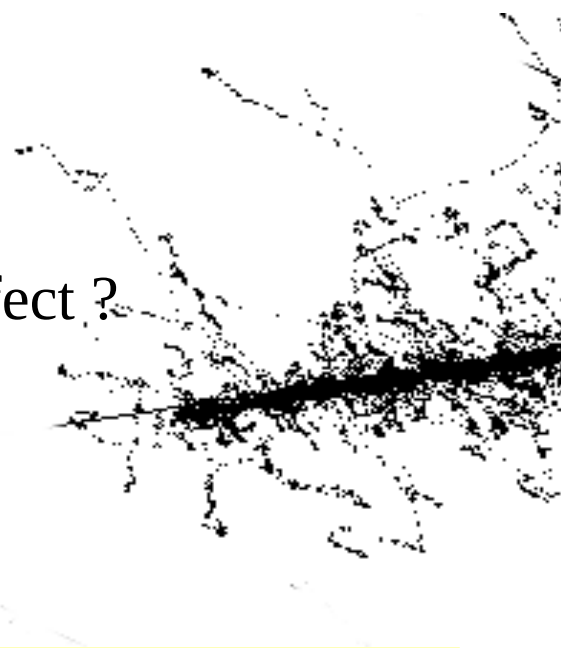
NanOx, a new multiscale model to predict biological effects of ionizing radiation

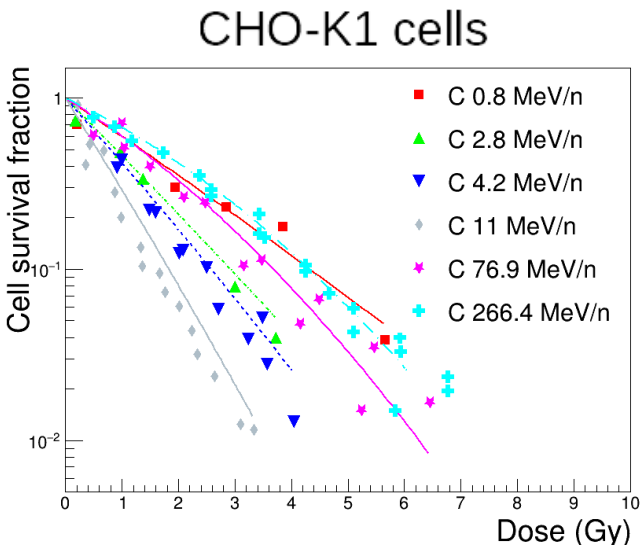
M. Beuve (PRISME, IPNL)

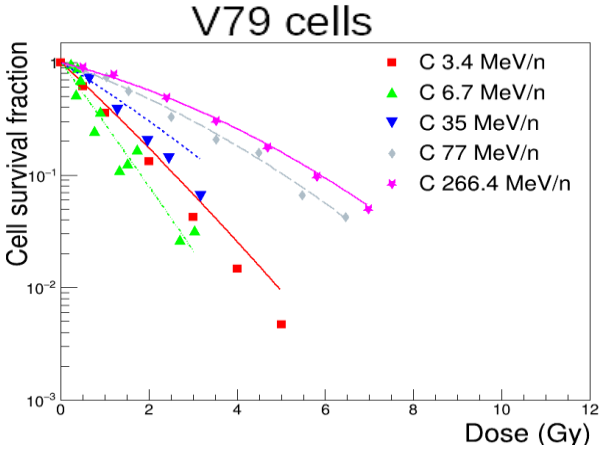
- **NanOx… to predict what ?**
- Results
- Characteristic features of the model
- Theoretical framework in brief
  - Non-local events
  - Local lethal events, threshold effect ?
- Towards a clinical application

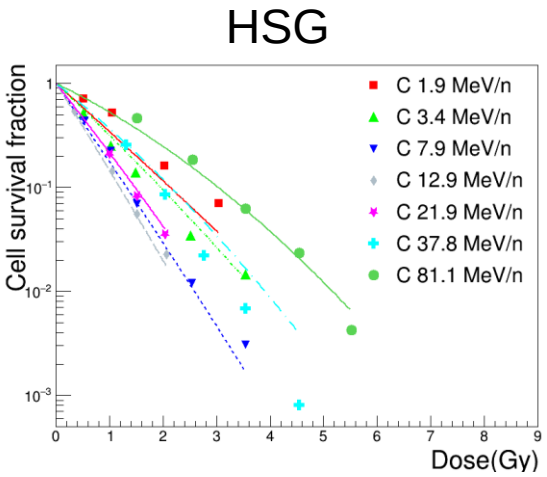


cell survival

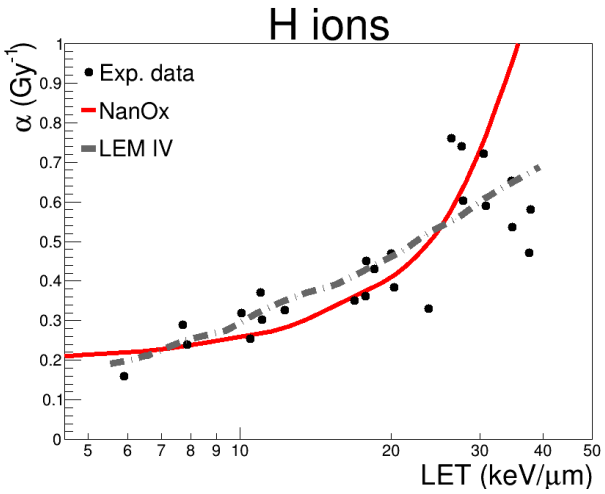
- Interesting endpoint
  - → integrates all death pathways
  - → allows to derive Tumor Control Probability
  - → Linked to deterministic effects in healthy tissues
- Depends on:
  - Particle type, energy and LET
  - Cell type, environment, phase
  - Dose, dose per fraction …

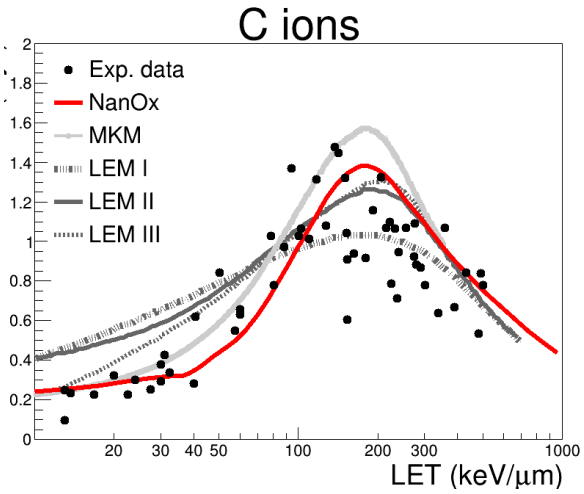


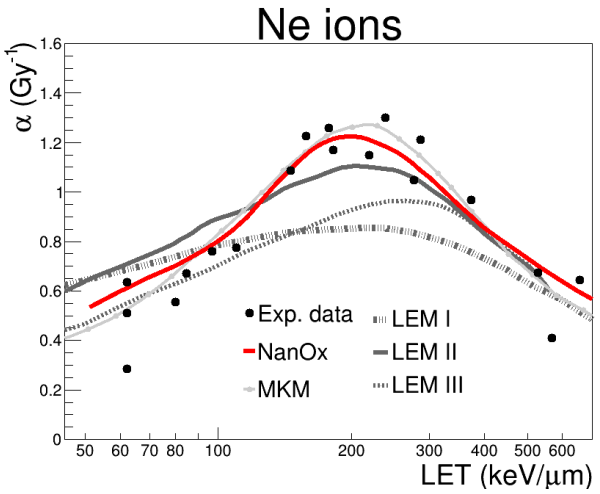


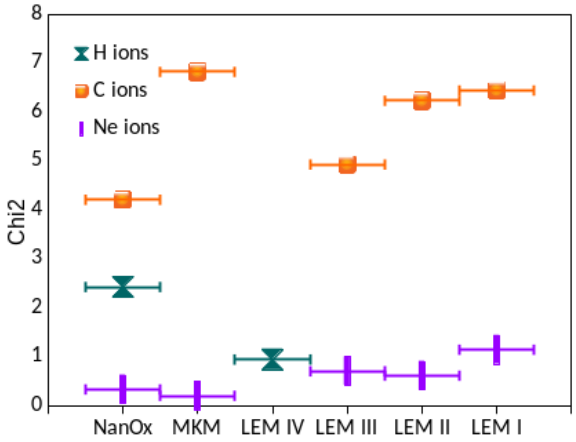


V79 cells, α(LET)

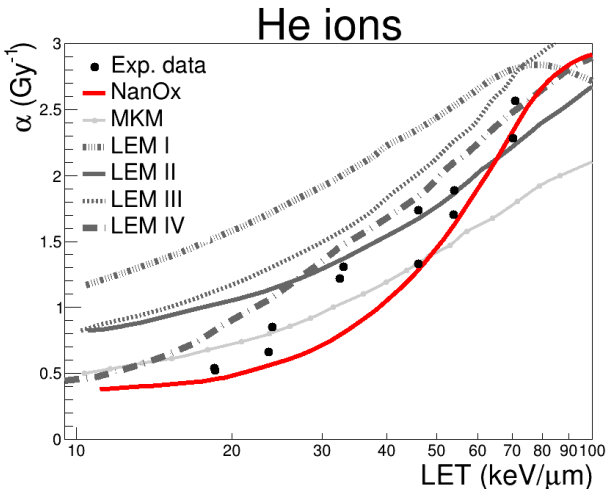


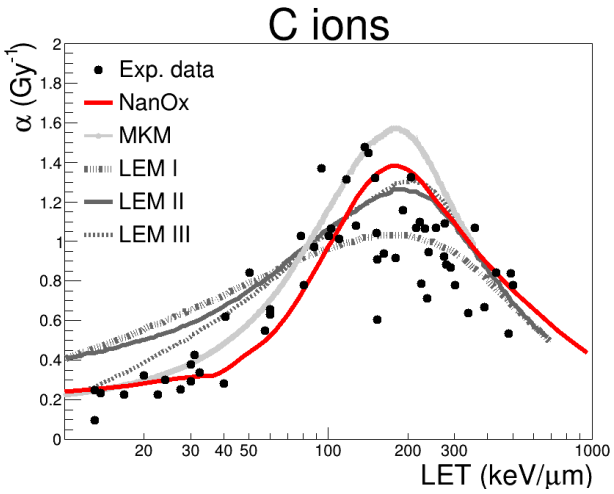


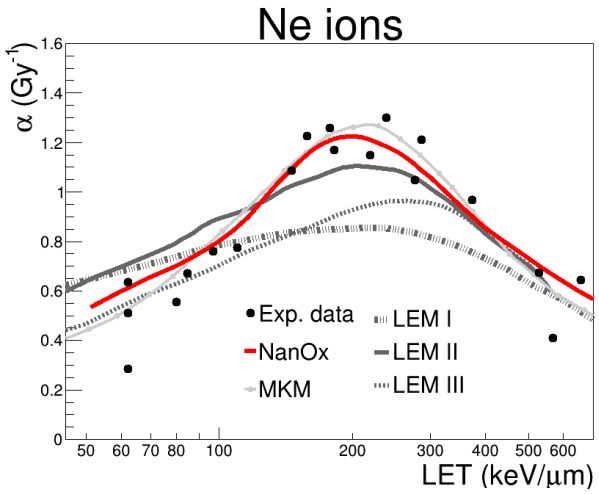




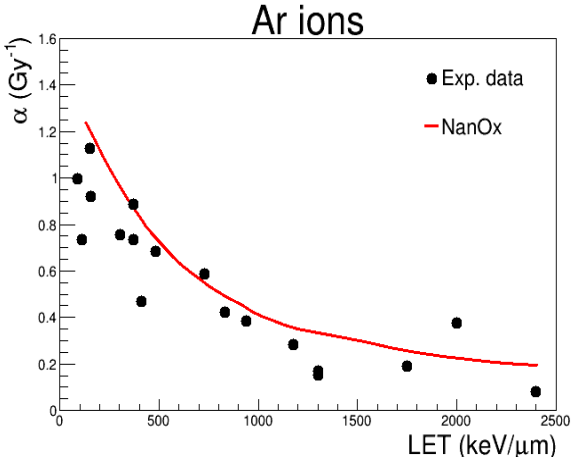
V79 cells, α(LET) up to Argon





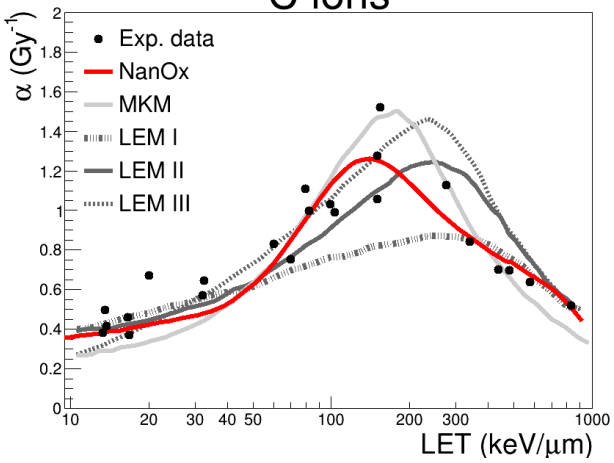


… up to Argon ions

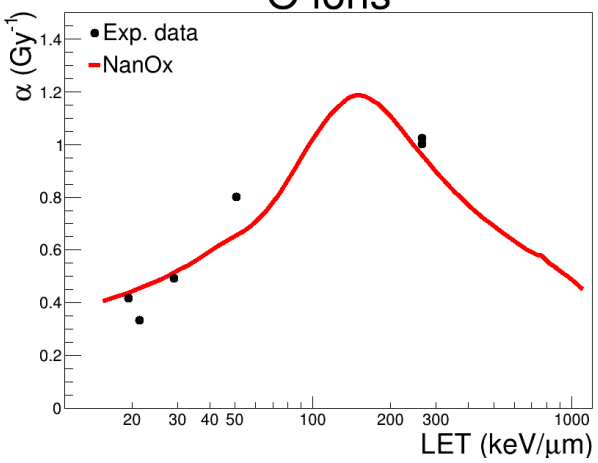


CHO-K1 cells, α(LET)

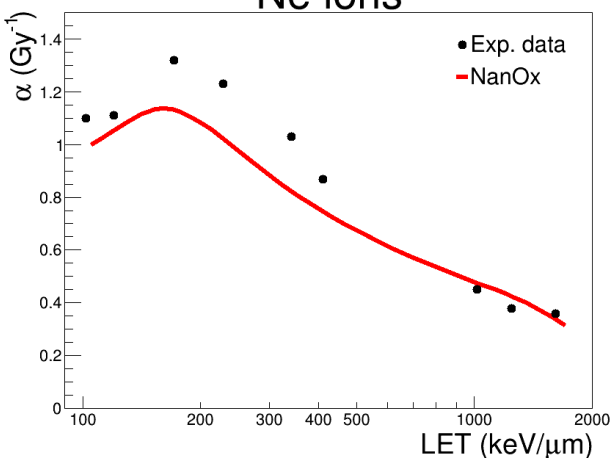
C ions

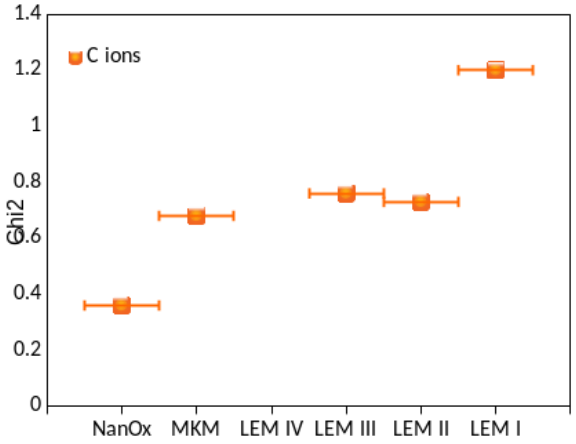


O ions

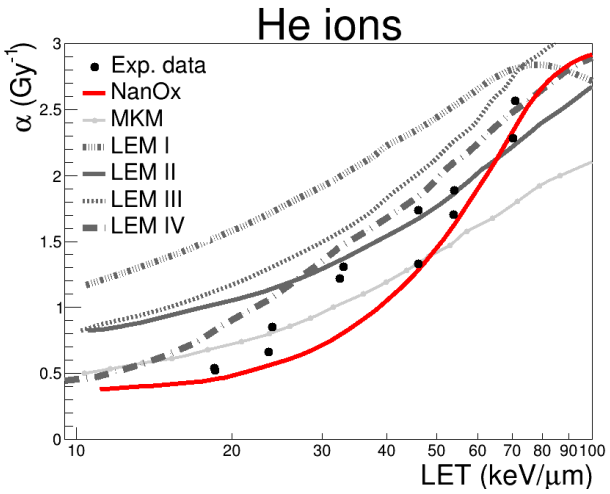


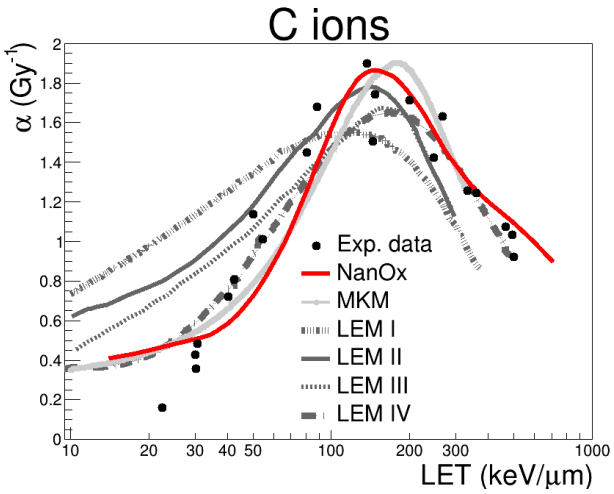
Ne ions

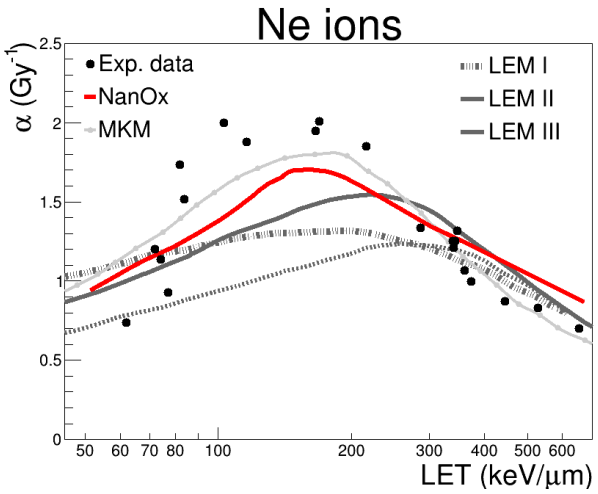


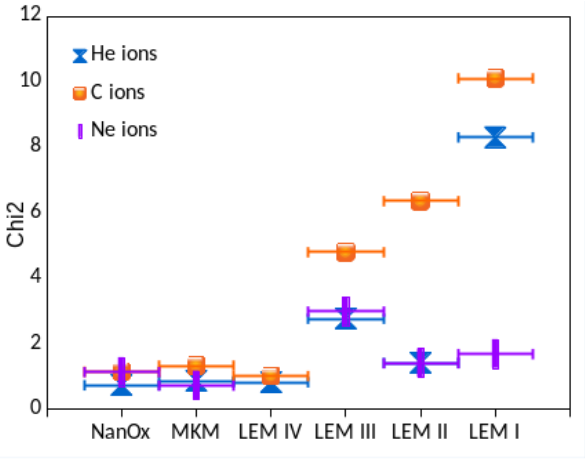


HSG cells, α(LET)









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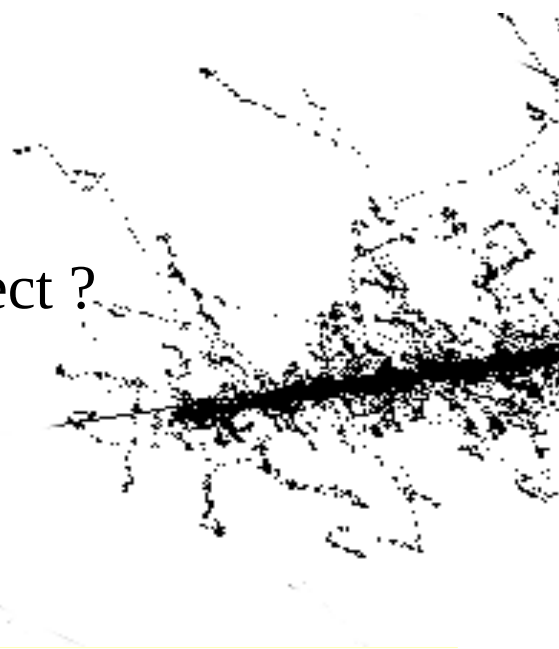
- Towards a clinical application



NanOx: Statistical theory

- **C_N : Cell configurations**
  - No explicit description of the communications between cells

  ⇒<u>One representative cell</u>

- **C_K: Irradiation configurations**
  - Ignoring beam-time structure
    - No dose-rate effects
  - Irradiation configurations
    - K : fluctuating number of tracks
    - C_K : Positions + tracks details

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

NanOx: Multi-scale model

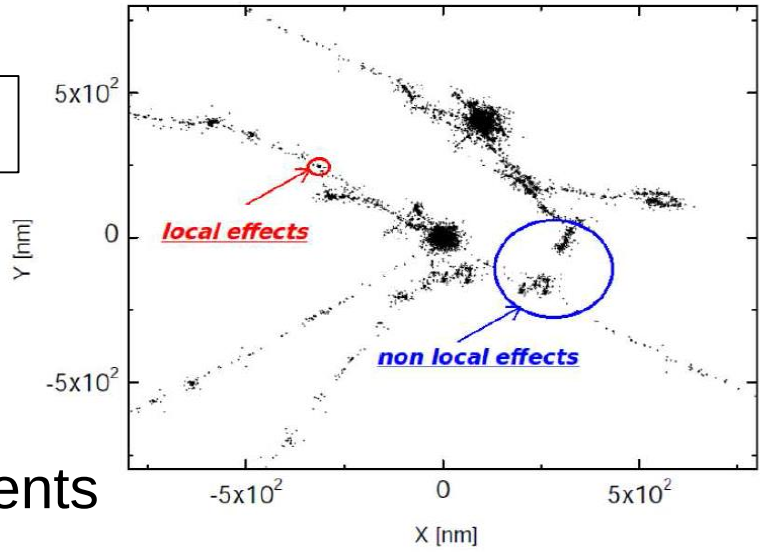
- Full statistical model
  - Dramatic computer resource
  - patient : 2 Gray in 10x10x10 cm^3
    - 6.10^{17} ionizations!
  - Cell in flasks : 5 Gray in 5x5x0.1cm^3
    - $1,5.10^{16}$ ionizations !//
- Multi-scale approach
  - Simplifications and approximations

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) ⇒ size ≪ 1 µm

⇒ **nanoscale**

Nanox: Non-local effects

- Literature:
  - Microdosimetry ⇒ interaction of two sub-lesions
  - Two-stage model [Kundrat *et al.*] ⇒ statistics in impact number
  - Ion-kill / γ-kill [Katz *et al.*] inter-track effects

    ⇒ 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*

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

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

^{CK}X characterizing the global effects at <u>global</u> scale

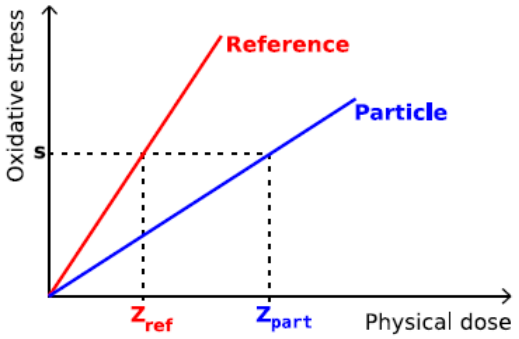
Nanox: Non-local effects

Oxidative stress

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

Chemical specific energy

- $\check{Z}$=RCE x 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 $f(^{CK}z)$ of a local quantity ^{CK}x
    - ^{CK}x : restricted specific energy at local scale

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

- Definition: **Effective local function**

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

F as a linear combination

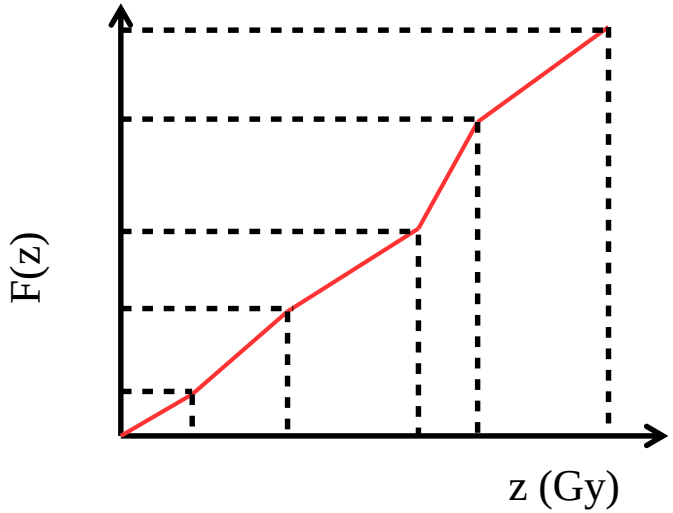
I. Decomposition on a basis:

$F(z)=\sum_i \omega_i F^i(z)$

II. Physical constraint: F(z) increasing function

III. Experimental data constraint

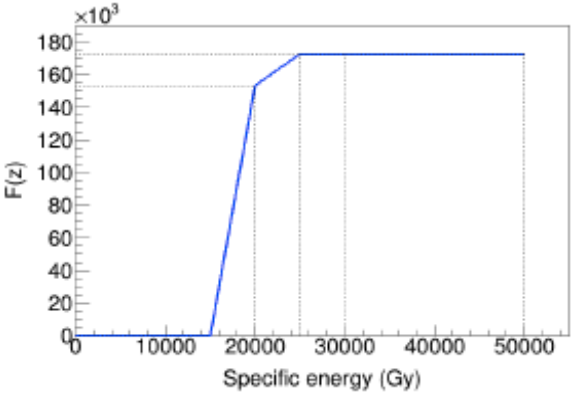
=> to optimize the weights of the liner combination



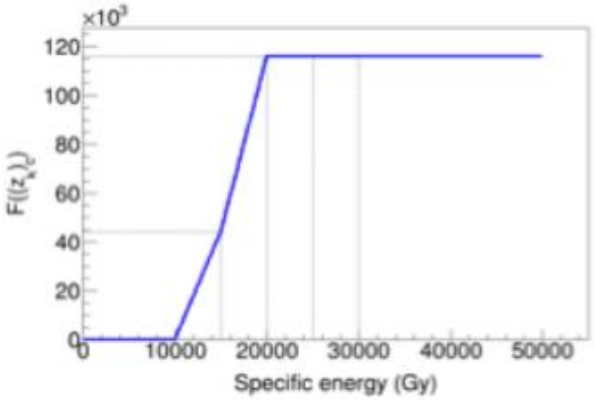
Restricted specific energy (Gy)

Lethal function: Results

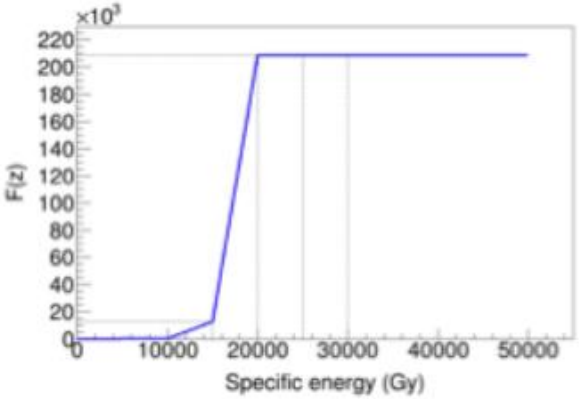
V 79 cells



CHO-K1 cells

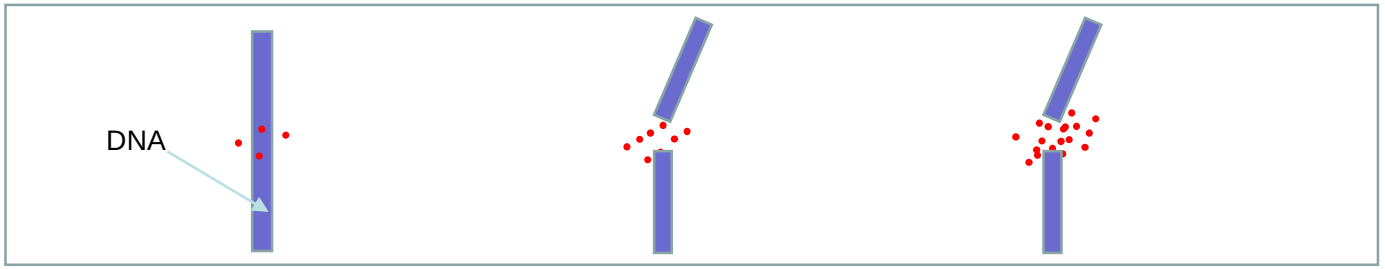


HSG cells

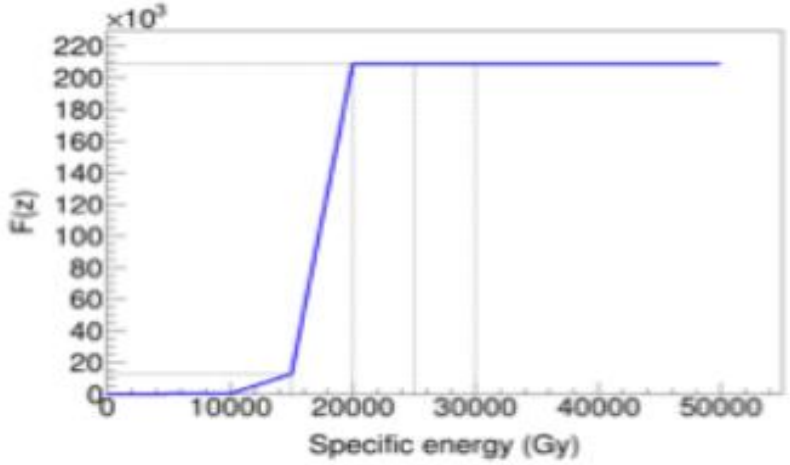


Threshold saturation

Biological interpretation?



$Z<Z_0$ $Z>Z_0$ $Z>>Z_0$ SATURATION



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- **Towards a clinical application**

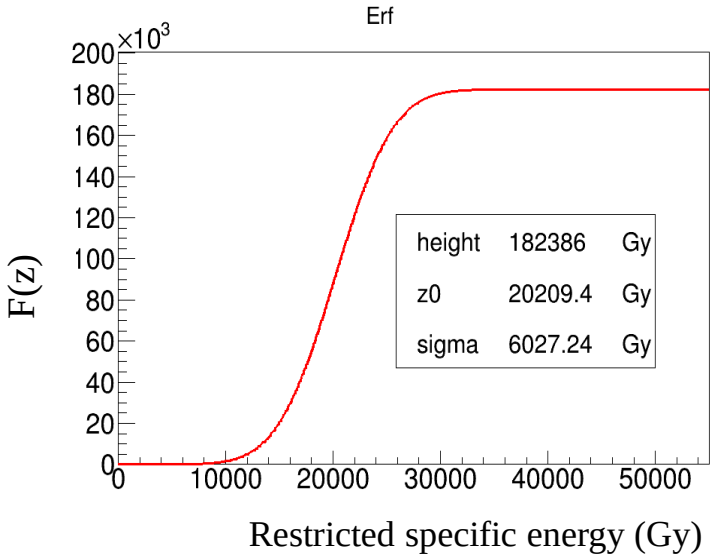
Parametric lethal function

Erf-like 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 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
- α_{ref}, β_{ref} (photons)
- α ion high LET
- α ion intermediate LET

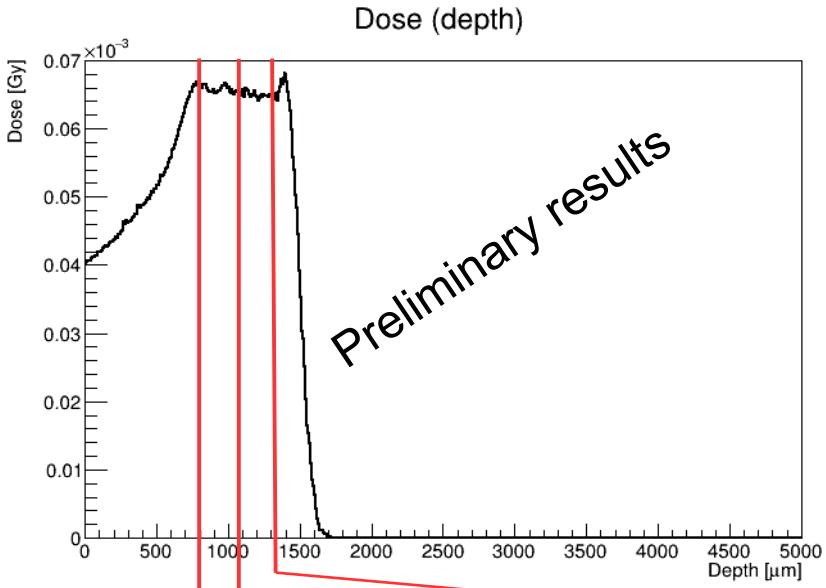
Conclusion

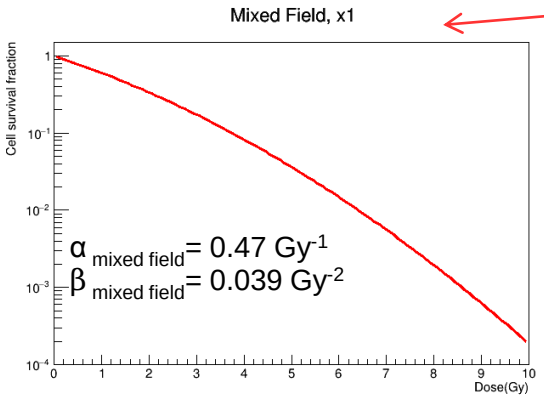
- NanOx: full stochastic and multiscale model (from nano scale)
- Innovative features
  - New quantities: restricted specific energy, RCE and chemical specific energy
  - Effect of threshold and saturation in the local effects
- Good agreement with experimental dat for V79, CHO-K1, HSG
  - Better $(\chi)^2$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

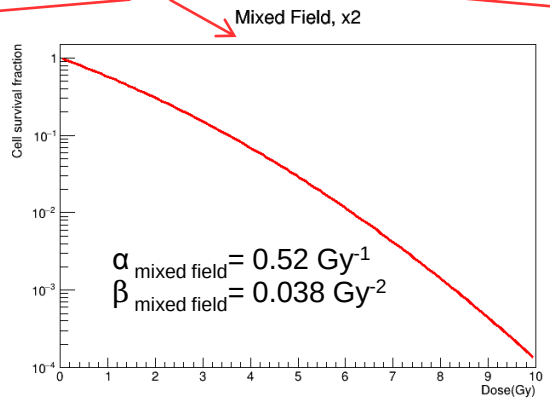
Perspectives

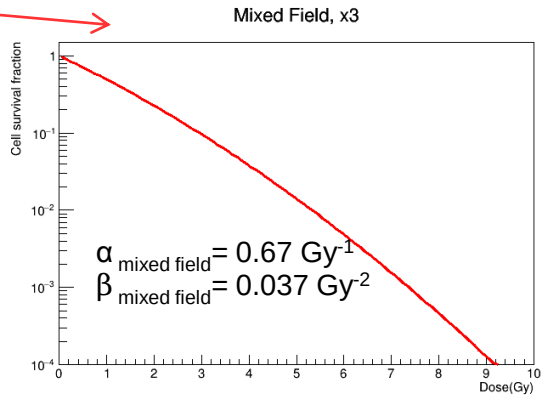
- First version: room for improvement
  - lethal function
  - global function
  - consider other non-local events…
- Challenging with other experimental data
  - Mesurement with biologists of the team:
    - Raadiograaff, GANIL, INFN-LEGNARO …
  - Evaluation in clinical conditions (SOBP)
    - CNAO ?,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

SOBP:ARRONAX









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)

- **Nanoscopic level**:
  - nanotargets in realistic cell geometry
  - realistic representation of nano targets (DNA, lyososmes, mitochondria..)
  - introduction of biological mechanisms

Partners

- **Collaborators**
  - biologists of the team (C Rodriguez *et al.*)
  - LPC Clermont (L Maigne *et al.*)
  - CIMAP (Caen) (B. Gervais, E. Balanzat)
  - LNL (Legnaro) (R. Cherubini et al)
  - Arronax/Subatech (Nantes) (C. Koumier et al)

- **Acknowledgements**
  - INCA
  - Labex Primes
  - GdR MI2B

Backup

NanOx parameters

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

	Experimental evidence		Fixed	
	Fit	**Simple measure**	**Cell line independent**	**To be studied**
F(z)	**H**	**Micro targets size**	t_{RCE}	Nano targets size
	z_0	**β_{ref}**		α_G
	σ			

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

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

  - Target :
    - Cylinder// Beam axis
    - Radius=Length= **10nm**
    - Uniformly distributed over the sensitive volume
  - Sensitive volume
    - Cylinder
    - Size: cell nucleus