The NanOx framework for predicting the biological effects of ion irradiations

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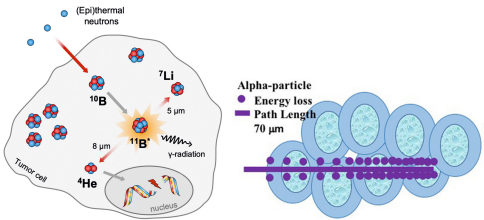
Outline

Ion-based innovative radiotherapies (RTs) and biophysical models

- At a given dose, ions are biologically more effective than photons. Rationale for ion-based innovative radiotherapies.
- High-energy ions: Hadrontherapy (e.g. ^{12}C of ∼100-400 MeV/n).
- Low-energy ions: TAT (α-particles of 4-9 MeV); BNCT (α-particles, $^{7}Li < 2$ MeV).

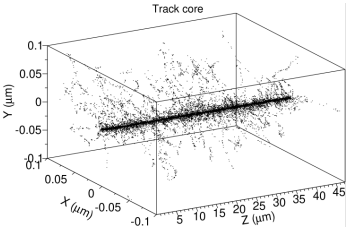


The energy and range of emitted radiations is different in BNCT (left) and TAT (right) (Naskar et al. 2021; Hoppenz et al. 2020)

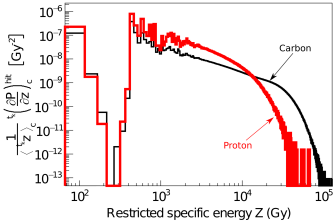
- Biophysical models are needed to predict the RBE of ions and optimize treatments.
- Current models in clinical use are the local effect model I (LEM I, Scholz et al. 1997) and the modified microdosimetric kinetic model (mMKM, Inaniwa et al. 2010).
- Other biophysical models have been developed, including:
  - RMF (Carlson et al. 2008)
  - BIANCA (Carante et al. 2018).
  - GSM2 (Cordoni et al. 2022).
  - ANAKIN (Cordoni et al. 2023).
  - NanOx (Cunha et al. 2017).

The NANodosimetry and OXydative stress (NanOx) model

- Predicts cell survival to ionizing radiation.
- Considers:
  - Stochastic nature of energy deposition (micrometric and nanometric scales).
  - Sublethal damage and oxidative stress induced by free radicals (e.g., $^{\bullet}OH$).
- Cell survival depends on two types of events:
  - Local lethal events (LLE) → inactivation of nanometric targets (≈ irreparable DNA damage).
  - Global events (GE)→ accumulation of sublethal lesions and oxidative stress.



Track of a 2.6 MeV proton in water.



Probability distributions of specific energy in a nanometric target for a 2.6 MeV proton and a 12 MeV/u carbon ion (Alcocer-Ávila et al. 2022).

NanOx parameters

- NanOx can be applied to high- and low-energy ion irradiations.
- In both cases the predictions of the model are based on 5 parameters:
  - The geometry of the sensitive volume (SV). For hadrontherapy only the radius of the cell nucleus is needed. For BNCT and TAT a more detailed geometry is required.
  - The quadratic coefficient β_G computed from reference radiation (photons).
  - The 3 parameters (z_0, σ, h) of the effective local lethal function (ELLF), used for calculating the survival to local lethal events.

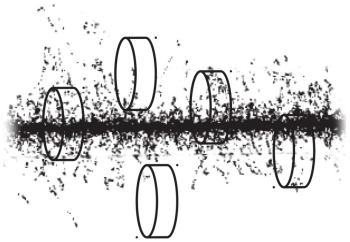


Illustration of cell irradiation in hadrontherapy

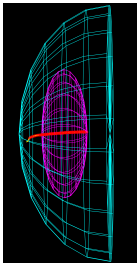
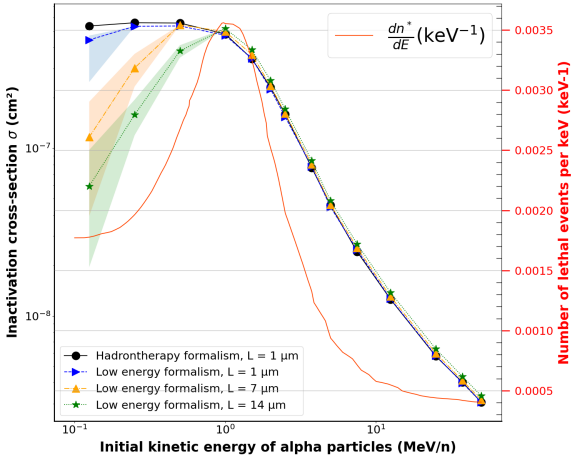


Illustration of a low-energy track within a cell geometry

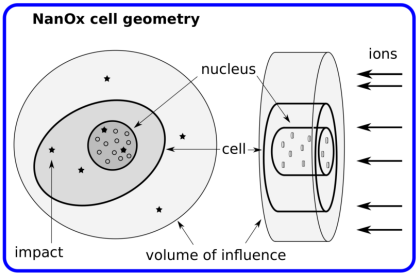
Comparison of NanOx predictions for high- and low-energy ions

- The NanOx formalisms for hadrontherapy and low-energy ion were compared by computing the inactivation cross section as a function of the initial kinetic energy of ions.
- Both approaches agree for E $>$ 1 MeV/n.
- For E $<$ 1 MeV/n, the low-energy formalism predicts decreasing inactivation cross sections.
- The influence of target geometry also becomes noticeable at low energies.
- This shows that NanOx offers a **consistent framework** for all ion-based RTs.



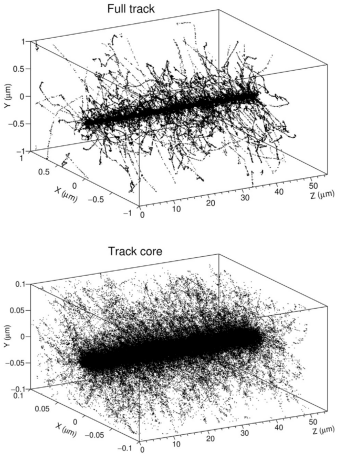
Basic assumptions in NanOx for hadrontherapy

- One SV: the cell nucleus.
- SV with cylindrical geometry and ion beam parallel to the SV axis.
- Irradiation in **"track-segment" conditions**.



Cell geometry used in NanOx calculations for hadrontherapy (Alcocer-Ávila et al. 2022)

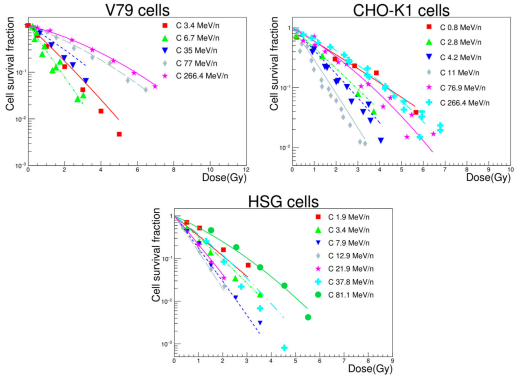
- Presence in ion tracks of a **"core"** and a **"penumbra"**.



A carbon ion track of 12 MeV/n and a zoom on its core

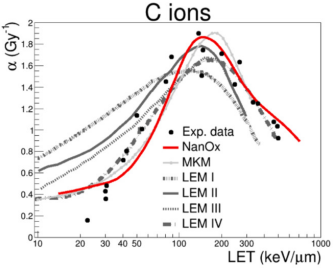
Benchmarking of NanOx predictions for hadrontherapy

- The main output of NanOx are the cell surviving fractions as a function of dose.



Survival curves for V79, CHO-K1 and HSG cells irradiated by carbon ions of various energies. NanOx: solid and dashed lines; experimental data (Friedrich et al. 2021): filled symbols (Alcocer-Ávila et al. 2022)

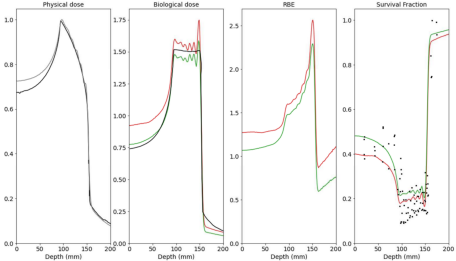
- A LQ fit can be applied to NanOx predictions to construct tables of α and β coefficients for use in TPS.
- A study showed that NanOx predictions are more often more accurate than the ones of other biophysical models.



α values of HSG cells for carbon ions. Experimental data (symbols) is compared to the predictions of several biophysical models (lines) (Monini et al. 2019)

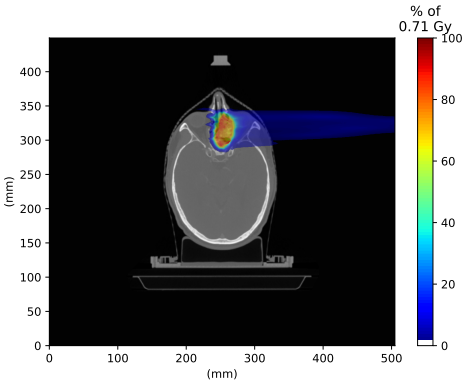
Towards a clinical application of NanOx: the BioDoseActor

- Ali et al. 2022 developed the **BioDoseActor** module in GATE for computing the biological dose for clinical beams in hadrontherapy.
- First tested for the Hyogo Ion Beam Medical Center (HIBMC) 320 MeV/u carbon-ion beam line using NanOx and the mMKM.



Physical dose (grey), biological dose, RBE and survival fractions provided by BioDoseActor as a function of target depth: NanOx (red), mMKM (green) and experimental data (black)

- Recently extended to 3D for reproducing patient treatment plannings.



Biological dose simulated with GATE/NanOx

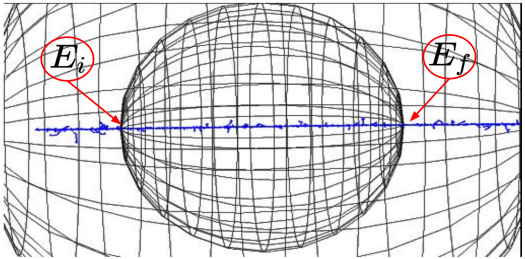
Adaptation of the NanOx formalism for low-energy ions

NanOx was adapted for calculations with the low-energy, short-range ions found in TAT and BNCT.

→ "Track-segment" approximation no longer valid

Need of considering:

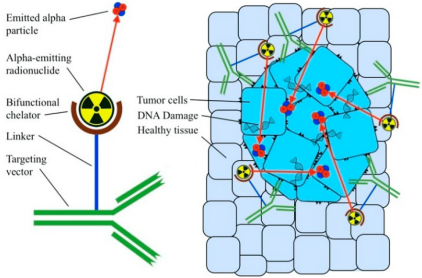
- The energy loss of the ion in the SV.
- The change in the number of lethal events as a function of the ion's energy.
- The impact of cell geometry and the distribution of the therapeutic agent.



Change in ion's kinetic energy when traversing a SV

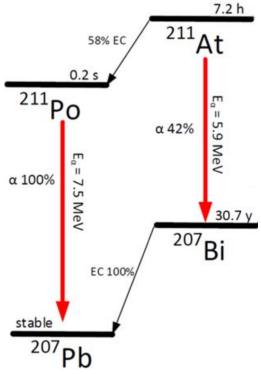
Work on targeted alpha therapy (TAT)

- TAT exploits the properties of α-particles emitted by various radionuclides to destroy cancer cells.
- α-particles with energies of 4-9 MeV, high-LET (55-225 keV/μm) and short range (30-100 μm) (Hofmann et al. 2020).



Basis of TAT (Nelson et al. 2020)

- Victor Levrague PhD thesis (LPSC, Grenoble).
- Dosimetric study of ^{211}At for TAT.

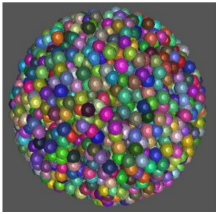


Decay scheme of ^{211}At (Abel et al. 2019)

Multicellular target modeling for TAT

Coupling of **Geant4 + CPOP + NanOx**:

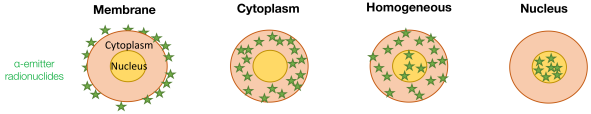
- Geant4 provides the physics for ion transport.
- CPOP to generate multicellular geometry (spheroid).
- NanOx to compute cell survival and tumor control probability (TCP).



Multicellular geometry simulated in the study with the CPOP code (Maigne et al. 2021)

Calculations considering:

- The energy loss of α-particles in the SV: algorithm recovering the energy of primary ions at the entrance (E_i) and exit (E_f) of the SV.
- An spheroid of 95 μm radius, 75% compaction.
- The cell nucleus as the only SV.
- ^{211}At uniformly distributed in different cell compartments.



Different investigated distributions of the radionuclide

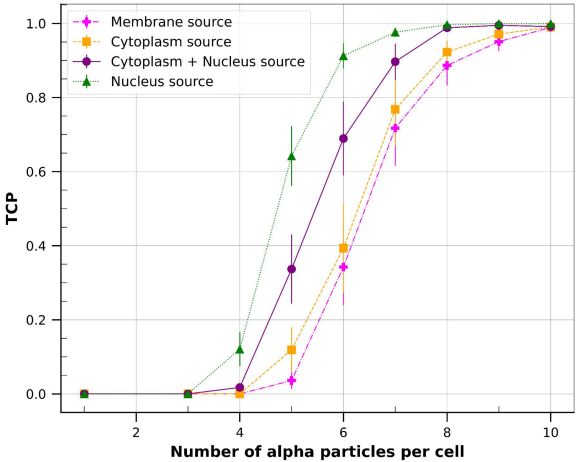
Tumor Control Probability (TCP) results

- TCP computed from NanOx cell surviving fractions as:

$$\mathrm{TCP} = \prod_{i=1}^{n} (1 - S_i)$$

- The TCP was plotted as a function of the number of α-particles per cell.

- Main finding:
  - The intracellular distribution of the radionuclide may impact the TCP for low radionuclide concentrations, low compaction spheroids, and for small tumors (i.e. with radius < 50 μm).



TCP for 4 intracellular distributions of ^{211}At and different number of α-particles per cell

Summary of ongoing and future work

Ongoing work and outlook for TAT and BNCT modeling

- Calculations in TAT will be compared with experimental data (e.g. Neti et al. 2007).
- Further TAT studies will be performed to evaluate the impact on TCP of radionuclide distribution inside the tumor, including its diffusion kinetics.
- Inclusion of a second (extranuclear) SV to predict the biological effects due to the irradiation of specific cell compartments. The model parameters will be adjusted on new experimental data to characterize the sensitivity of both SVs.
- The NanOx formalism is being adapted to take into account all radiation contributions to the biological dose in BNCT.

Other future work on the NanOx model may focus on:

- Response to high doses and high dose-rates (e.g. applications in FLASH RT).
- Irradiation under hypoxia conditions.
- Indirect effects of irradiations, e.g. bystander and abscopal effects.

Thank you for your attention

Team and collaborations

- IP2I @ Lyon: Étienne Testa, Michaël Beuve
- LRCM @ Lyon: Claire Rodriguez-Lafrasse, Gersende Alphonse, Anne-Sophie Wozny
- LIRIS @ Lyon: Hamid Ladjal
- LPSC @ Grenoble: Rachel Delorme, Victor Levrague, María Pedrosa-Rivera
- LPC @ Clermont-Ferrand: Lydia Maigne, Alexis Pereda

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BACKUP SLIDES

NanOx: Cell survival calculation in hadrontherapy

- The average cell surviving fraction is computed as:

$$\overline{S(D)} = \sum_{K=0}^{\infty} P(K, D) \cdot \langle {}^{c_K}S \rangle_{c_K}$$

$P(K, D)$: probability to have K impacts at dose D
$\langle {}^{c_K}S \rangle_{c_K}$: mean survival over all configurations.

- The surviving fraction includes the contribution of local and global lethal events, considered as independent:

$${}^{c_K}S = {}^{c_K}S_{LLE} \times {}^{c_K}S_{GE}$$

- NanOx has been applied for computing surviving fractions of several cell lines (e.g. HSG, CHO-K1, V79, SQ20B) irradiated by photons and different ions (Monini et al. 2017).

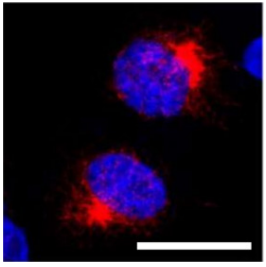


Image of HSG cells (Kim et al. 2019)

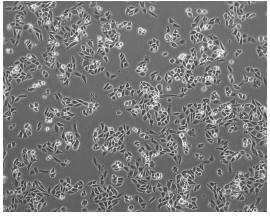


Image of CHO-K1 cells

Cell survival to local lethal events

- The modeling of LLE is based on the inactivation of a single local target among N distributed uniformly in the SV.
- Local targets modeled as cylinders with diameter $d_{\mathrm{t}} = 20$ nm and length $L_{\mathrm{t}} = 10$ nm
- NanOx calculations are based on the **effective number of local lethal events (ENLLE)**:

$$ {}^{\mathrm{c}_i,\mathrm{c}_k}n^* = -\ln\left(1 - {}^{\mathrm{c}_i}f({}^{\mathrm{c}_i,\mathrm{c}_k}z)\right) $$

${}^{\mathrm{c}_i}f({}^{\mathrm{c}_i,\mathrm{c}_k}z)$: probability that target i is inactivated after an impact with configuration c_k inducing the **restricted specific energy** ${}^{\mathrm{c}_i,\mathrm{c}_k}z$ in i

- The cell surviving fraction to LLE for a configuration c_K of radiation impacts can be expressed in terms of an **effective local lethal function (ELLF)** $F(z)$:

$$ {}^{\mathrm{c}_K}S_{\mathrm{L}} = \prod_{k=1}^{K} \exp\left(-F\left({}^{\mathrm{c}_k}z\right)\right) $$

with:

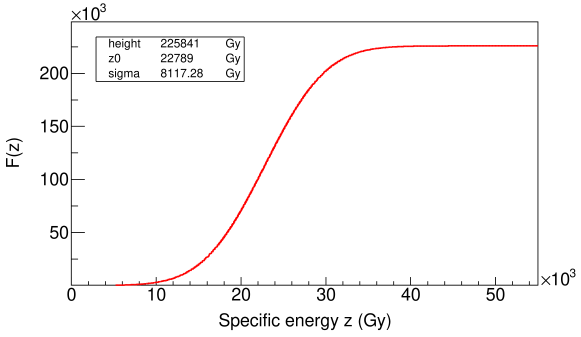
$$ F(z) = -N\ln\left(1 - f(z)\right) $$

The effective local lethal function (ELLF)

- The ELLF characterizes the response of each cell line by means of 3 free parameters (z_0, σ, h) determined through a fit to experimental values of α (Monini et al. 2020).

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

z_0: threshold of the function
σ: extent of the increase
h: height of the response



Effective local lethal function for the V79 cell line

Cell survival to global events

- The computation of the cell survival to GE uses the notion of **chemical specific energy,** $\tilde{Z}$:

$$^{c_\kappa}\tilde{Z} = {}^{c_\kappa}\mathrm{RCE} \cdot {}^{c_\kappa}Z$$

  $^{c_\kappa}\mathrm{RCE}$ is the **relative chemical effectiveness**, defined as the ratio of the **chemical yield** (i.e., number of reactive chemical species generated per 100 eV) of the ion, $^{c_\kappa}G$, to that of reference radiation, G_r:

$$^{c_\kappa}\mathrm{RCE} = \frac{^{c_\kappa}G}{G_\mathrm{r}}$$

- These quantities are obtained from MC simulations with the LQD/PHYCHEML/CHEM codes (Gervais et al. 2006).

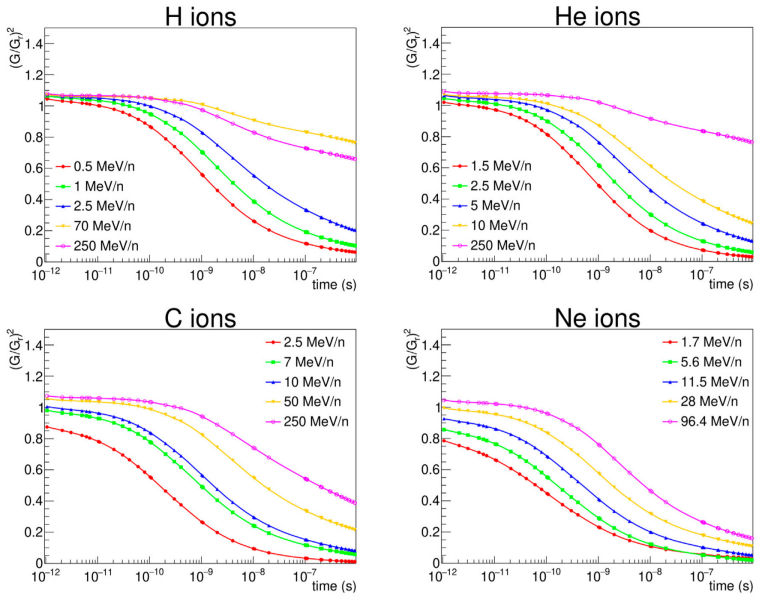
- Currently only primary $^\bullet\mathrm{OH}$ are considered for cell survival calculation.

- The cell surviving fraction to GE for a configuration c_K of radiation impacts is then:

$$^{c_\kappa}S_\mathrm{G} = \exp\left(-\alpha_\mathrm{G}\,{}^{c_\kappa}\tilde{Z} - \beta_\mathrm{G}\,{}^{c_\kappa}\tilde{Z}^2\right)$$

- α_G and β_G are determined for each cell line from cell survival curves for reference radiation.

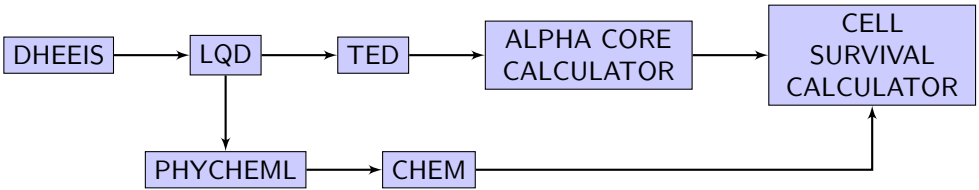
- We currently set $\alpha_\mathrm{G} = 0\ \mathrm{Gy}^{-1}$ to perform an independent adjustment of local and global events.



RCE[2] as a function of time for hydrogen, helium, carbon and neon ions of different energies (Alcocer-Ávila et al. 2023)

The NanOx codes

- From a practical point of view, NanOx simulations require the use of several codes, as shown in the diagram below:



- TED, ALPHA CORE CALCULATOR and CELL SURVIVAL CALCULATOR are fully written in C++; the other codes are written in C.
- In terms of performance the bottleneck of a full NanOx calculation is usually located at the beginning and end of the process: the calculations with the codes DHEEIS and CELL SURVIVAL CALCULATOR can take several hours.
- All codes run in sequential mode (no parallelization implemented yet).

Planning Innovative Cancer Therapies Using RadioElements (PICTURE)

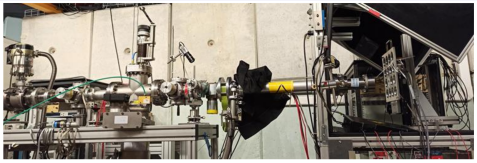
Aim: To contribute to the **optimization of innovative RTs based on low-energy ion irradiations** (e.g., TAT and BNCT)

Evaluating the impact on biological dose of:

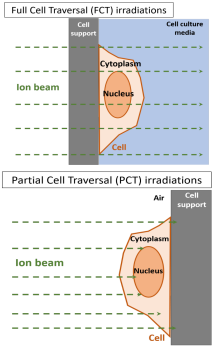
- Cell geometry.
- Microdistribution of therapeutic agents.
- Radioinduced events in sensitive sites other than the cell nucleus (extranuclear SV).

→ **Experimental part:** irradiations in full and partial cell traversal conditions.

→ **Modeling part:** extension of NanOx, coupling with Geant4/Geant4-DNA including realistic cell geometries obtained from microscopy images.

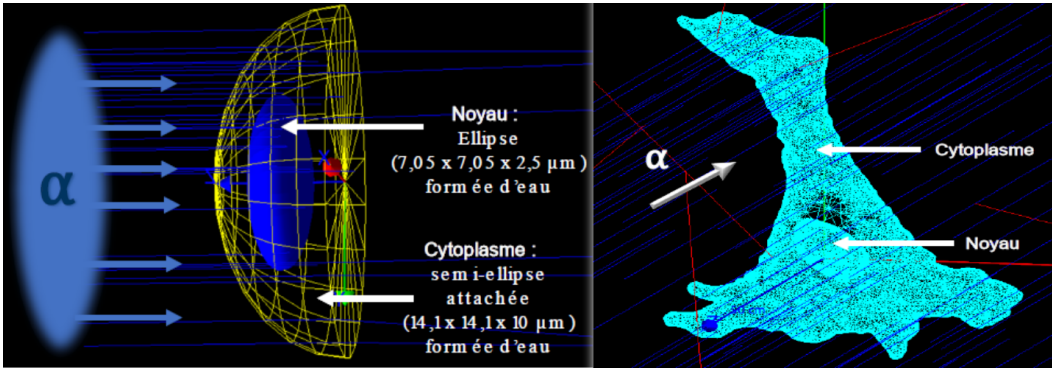


Radiograaff line at the ALTO platform.



Irradiations in full and partial cell traversal conditions.

Examples of cell geometries



Simplified and 3D microscopy cell models in GATE

Overview of the NanOx formalism for low-energy ions

For low-energy ions, the number of LLE and GE will vary as a function of the ion's energy across the SV. Main hypothesis are:

1. Narrow tracks.
2. Negligible fluctuations from one radiation configuration to another (average over a large number of particles of the same type T_{k} and energy E_{k}).

- The cell survival to LLE and GE can be computed from the effective number of local lethal events and the concentration of primary reactive chemical species, respectively.

- The ENLLE is given by:

$$ {}^{\mathrm{t}_N,\mathrm{t}_k}n^* = \int_{{}^{\mathrm{t}_k}E_{\mathrm{f}}}^{{}^{\mathrm{t}_k}E_{\mathrm{i}}} {}^{\mathrm{t}_N,\mathrm{t}_k}\left(\frac{\mathrm{d}n^*}{\mathrm{d}E}\right)\mathrm{d}E $$

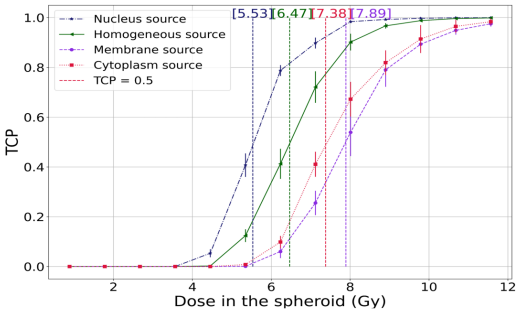
  where ${}^{\mathrm{t}_k}E_{\mathrm{i}}$, ${}^{\mathrm{t}_k}E_{\mathrm{f}}$ denote the energy of the ion at the beginning and end of the track in the SV.

- Similarly, for GE the concentration of primary reactive chemical species is expressed as:

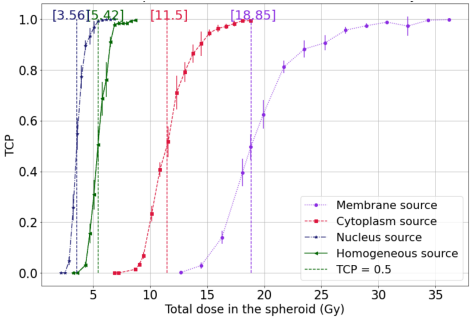
$$ {}^{\mathrm{t}_k}Y = \frac{1}{m_{\mathrm{s}}}\int_{{}^{\mathrm{t}_k}E_{\mathrm{f}}}^{{}^{\mathrm{t}_k}E_{\mathrm{i}}} {}^{\mathrm{t}_k}G(E)\mathrm{d}E $$

  with m_{s} the mass of the SV.

Examples of TCP prediction in TAT and BNCT



TCP as a function of the spheroid dose for ^{211}At



TCP as a function of spheroid dose for the CHO-K1 cell line for each distribution of ^{10}B