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Update on the NanOx biophysical model: Current status and perspectives

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AG GdR Mi2B
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- 1 The rationale for biophysical models
- 2 General features of the NanOx model
- 3 NanOx: Implementation for hadrontherapy
- 4 NanOx: Implementation for low-energy ions
- 5 Ongoing and future work with NanOx

The rationale for biophysical models

- At a given dose, **ions** are biologically **more effective than photons**...

$$\text{RBE} = \frac{D_r}{D_i} \Big|_{\text{isoeffect}}$$

But the **biological response depends on many factors**

- Specific modeling approaches / approximations required for external and internal radiotherapies (RTs):
 - ▶ **Hadrontherapy** (p of $\sim 70\text{-}250$ MeV, ^{12}C of $\sim 100\text{-}400$ MeV/n)
 - ▶ **TAT** (α -particles of 4-9 MeV); **BNCT** (α -particles, $^7\text{Li} < 2$ MeV)

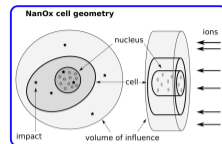
- Several biophysical models have been developed (mainly for hadrontherapy), including:

- ▶ **LEM I-IV**
- ▶ **MKM** and variants
- ▶ **RMF**
- ▶ **BIANCA**
- ▶ **GSM2**
- ▶ **ANAKIN**

NanOx

The Nanodosimetry and Oxidative stress (NanOx) model

- Considers the stochastic nature of radiation interactions
- Sensitive volume (SV): cell nucleus
- Biological endpoint: cell survival probability to 2 types of events

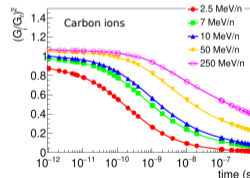
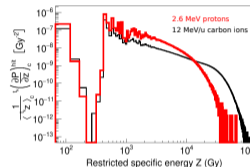


| | Local lethal events (LLE) | Global events (GE) |
|----------------|-----------------------------|---|
| Interpretation | Complex, irreparable damage | Accumulation of sublethal damage / oxidative stress |
| Scale | Nanometric | Micrometric |
| Evaluation | Specific energy* | Chemical yields* |

*Evaluated from Monte Carlo (MC) simulations with LPCHEM (Gervais et al. 2006)

- Cell survival for the irradiation configuration c_K :

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



Cell geometry, specific energy spectrum in nanometric targets and chemical yields of OH^\bullet

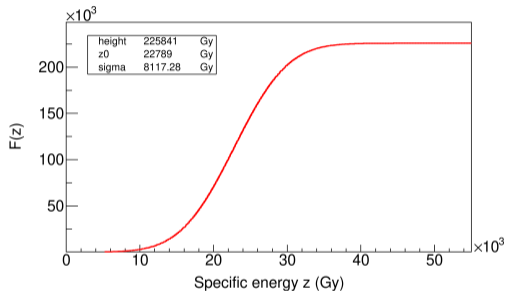
NanOx model: Main parameters and input data

| Parameter | Source |
|--|---|
| SV geometry | Cell microscopy images |
| α_R, β_R | Cell irradiations with photons |
| Effective local lethal function (ELLF) | At least 3 survival curves covering intermediate and high LET: 1 x-rays + 2 ions |

Effective local lethal function (ELLF)

- Shows a threshold and saturation effects ([Monini et al. 2020](#))
- Parametrization with an error function:

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

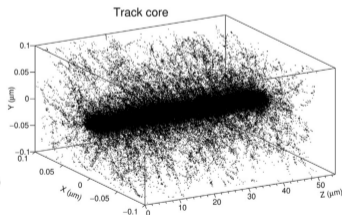
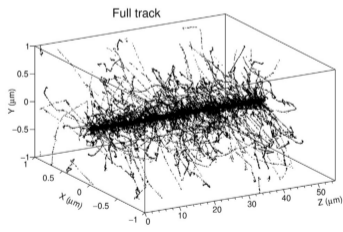


The ELLF determined for the V79 cell line

NanOx: Implementation for hadrontherapy (Cunha et al. 2017)

Basic assumptions:

- SV with cylindrical geometry and ion beam parallel to the SV axis
- Irradiation in **“track-segment”** conditions
- Ion tracks characterized by a **“core”** and a **“penumbra”**



A C ion track of 12 MeV/n and a zoom on its core
(Alcocer-Ávila et al. 2023)

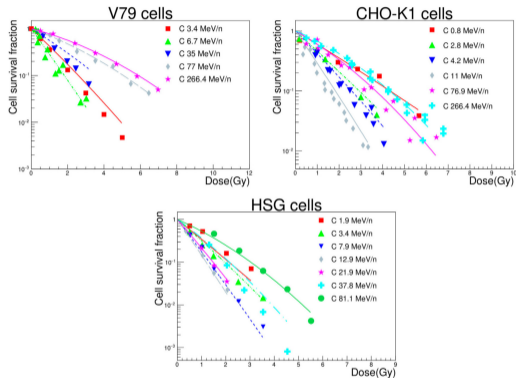
The survival fraction for each type of event is computed as:

$${}^cK S_{LLE} = \exp\left(-\alpha_c \cdot Z_c \cdot \frac{V_c}{V_s} - \alpha_p \cdot Z_p \cdot \frac{V_p}{V_s}\right)$$

$${}^cK S_{GE} = \exp\left[-\frac{\beta_r}{\eta^2} \left(Z_c \cdot \frac{G_c}{G_r} \cdot \frac{V_c}{V_s} + Z_p \cdot \frac{G_p}{G_r} \cdot \frac{V_p}{V_s}\right)^2\right]$$

Benchmarking of NanOx predictions for hadrontherapy

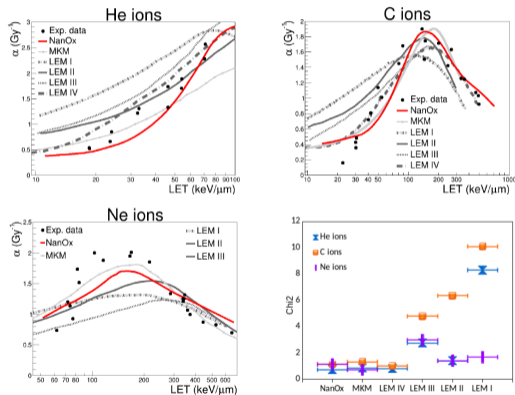
- Main output of NanOx: cell survival curves



Survival curves for cells irradiated by C ions. NanOx: lines (Alcocer-Ávila et al. 2022); experiments: symbols

- LQ fit to NanOx results $\rightarrow \alpha, \beta$

- NanOx predictions for 3 cell lines irradiated by monoenergetic ions were often more accurate than the ones of other models

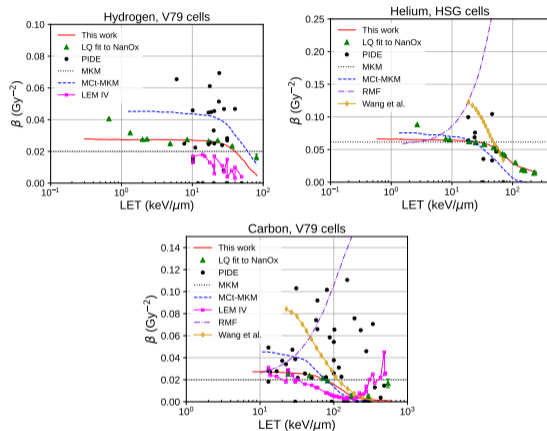


NanOx predictions of α for HSG cells (Monini et al. 2019)

Analytical expression for computing the β coefficient

- The β coefficient of cell survival curves is difficult to calculate with accuracy
- A fast method for computing β for ions with energies between ~ 1 –25 MeV/n was recently proposed
- NanOx predicts the decrease of β when the LET increases

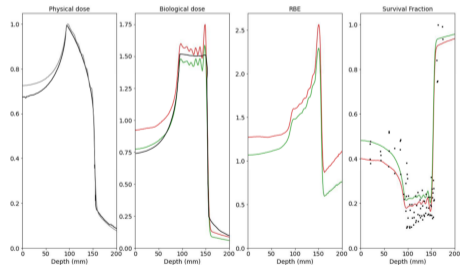
$$\beta \approx \beta_r (\text{RCE})^2 \left[1 - \frac{\alpha \cdot a \cdot \text{LET}}{\sigma_0} \right]^2 \cdot \frac{\left(1 + \frac{m_1}{2} \right)}{\left(1 - m_1 \right)^2}$$



β as a function of LET for HSG and V79 cells irradiated by protons, He and C ions (Alcocer-Ávila et al. in preparation)

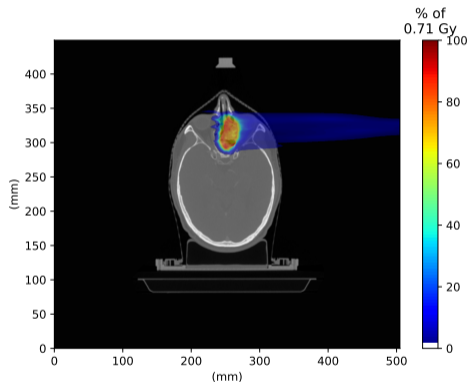
Towards a clinical application of NanOx: the BioDoseActor

- Ali et al. 2022 developed the **BioDoseActor** in GATE for computing the biological dose for clinical beams in hadrontherapy
- First tested by simulating the 320 MeV/u carbon-ion beamline at HIBMC (Japan) 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)

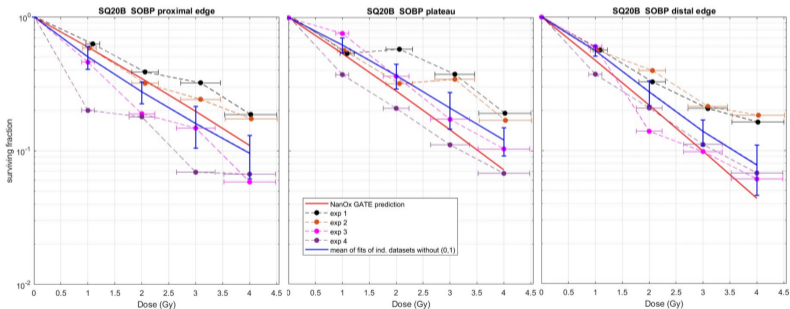
- Recently extended to 3D for reproducing patient treatment plannings



Biological dose simulated with GATE/NanOx

Investigating the biological response to irradiations with He ions

- ARRONAX beamline simulated in GATE
- Irradiation of SQ20B (tumor) cells in a He ion SOBP
- Calculation of cell survival fractions with the BioDoseActor and NanOx
- NanOx predictions described the experimental data relatively well considering the variability observed between experiments
- The model might underestimate cell survival at high doses and in the distal edge



Irradiation of SQ20B cells in a helium SOBP: comparison of measured surviving fractions with NanOx predictions for three irradiation settings (Berger et al. in preparation)

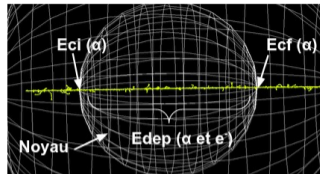
Adaptation of the NanOx formalism for low-energy ions

- NanOx was adapted for calculations with the low-energy, short-range ions found in TAT and BNCT (Alcocer-Ávila et al. 2024)

→ “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 an α -particle's kinetic energy when traversing a SV

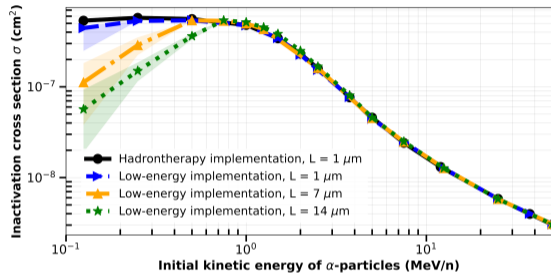
- Calculation based on the integration of LLE and GE along the ions' path in the SV

$${}_{t_k, t_k} n^* = \int_{t_k E_f}^{t_k E_i} {}_{t_N, t_k} \left(\frac{dn^*}{dE} \right) dE = \phi(t_k E_i) - \phi(t_k E_f)$$

$${}_{t_k} \tilde{Z} = \frac{\eta}{m_s} [\psi(t_k E_i) - \psi(t_k E_f)]$$

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

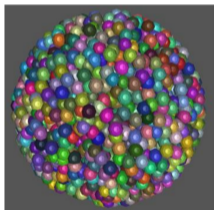
- NanOx implementations for hadrontherapy and low-energy ions were compared by computing the inactivation cross section (ICS)
- Both approaches agree for $E \gtrsim 1$ MeV/n
- For $E \lesssim 1$ MeV/n, the low-energy implementation predicts decreasing inactivation cross sections
- The impact of target geometry becomes noticeable at low energies
- This shows that NanOx offers a consistent framework for all ion-based RTs



Inactivation cross section as a function of the initial kinetic energy of α -particles (Alcocer-Ávila et al. 2024)

First applications of NanOx to TAT

- Dosimetric *in silico* study of ^{211}At for TAT (Levrague et al. in preparation)
- 3D multicellular geometry (spheroid)
- Simulations coupling CPOP + Geant4 + NanOx

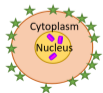


Membrane

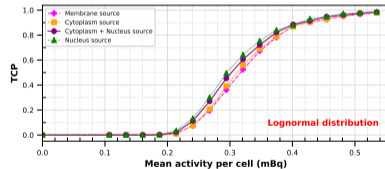
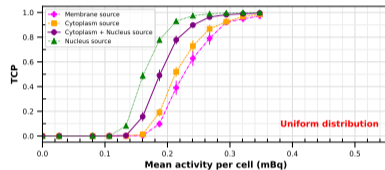
Cytoplasm

Homogeneous

Nucleus



- Study of the influence on RBE and TCP of various intracellular distributions of the radionuclide



TCP calculée dans un sphéroïde de 95 μm de rayon (cellules HSG), compacté à 75%, traité à l'At-211, en fonction de l'activité moyenne par cellule

Summary of ongoing and future work with NanOx

Irradiations with low-energy ions

- Simulations of irradiation platforms (Radio-gaaff, α -particle sources) to determine the **parameters needed for** experiments in conditions of **partial cell traversal**
- Calculations of cell survival will be extended to **realistic cell geometries and other SVs**

TAT

- Need of further calculations and comparisons with in vitro and in vivo experiments
- The impact on biological endpoints of complex heterogeneous distributions of the α -emitters should be explored in detail

BNCT

- Preliminary results comparing the cell survival predictions of NanOx with measurements at the ILL seem promising, but more modeling and experimental work is needed (Pedrosa-Rivera et al., in preparation)

Impact of physical processes on predictions

- The **influence on biological endpoints of physical processes** such as inner-shell ionization and the set of ionization cross sections used in the simulations is under study
→ **PhD thesis of Camila Strubbia**

Thank you for your attention

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