Update on the NanOx biophysical model: Current status and perspectives

Mario Alcocer-Ávila[1], Victor Levrague[2], Thomas Berger[1], María Pedrosa-Rivera[3], Anthony Bertrand[1], Gersende Alphonse[4,5], Rachel Delorme[2], Étienne Testa[1] and Michaël Beuve[1]

[1]Université Claude Bernard Lyon 1, CNRS/IN2P3, IP2I Lyon, UMR 5822, Villeurbanne, France
[2]Université de Grenoble Alpes, CNRS, Grenoble INP, LPSC-IN2P3, Grenoble, France
[3]Depto de Física Atómica, Molecular y Nuclear, Facultad de Ciencias, Universidad de Granada, Granada, Spain
[4]Cellular and Molecular Radiobiology Laboratory, Lyon-Sud Medical School, UMR5822/IP2I, UCBL, Oullins, France
[5]Department of Biochemistry and Molecular Biology, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France

AG GdR Mi2B

October 11, 2024

Outline

The rationale for biophysical models

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

$$\mathrm{RBE} = \left.\frac{D_\mathrm{r}}{D_\mathrm{i}}\right|_{\mathrm{isoeffect}}$$

  But the biological response depends on many factors

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

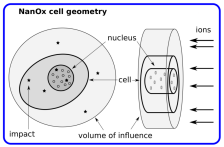
- Considers the stochastic nature of radiation interactions
- Sensitive volume (SV): cell nucleus
- Biological endpoint: cell survival probability to 2 types of events

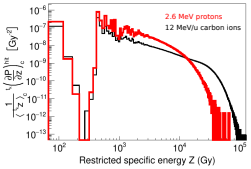
	Local lethal events (LLE)	Global events (GE)
Interpretation	Complex, irreparable damage	Accumulation of sublethal damage / oxidative stress
Scale	Nanometric	Micrometric
Evaluation	Specific energy*	Chemical yields*

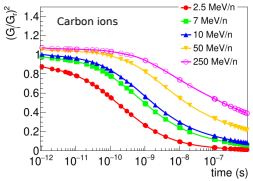
*Evaluated from Monte Carlo (MC) simulations with LPCHEM (Gervais et al. 2006)

- Cell survival for the irradiation configuration c_K:

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



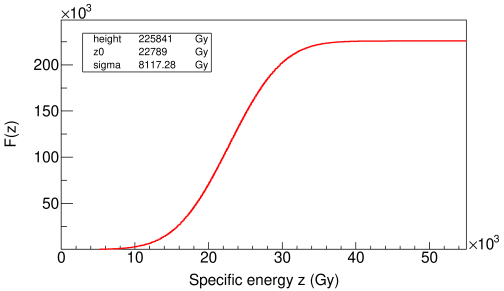




Cell geometry, specific energy spectrum in nanometric targets and chemical yields of $OH^{\bullet}$

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



The ELLF determined for the V79 cell line

Effective local lethal function (ELLF)

→ Shows a threshold and saturation effects (Monini et al. 2020)

→ Parametrization with an error function:

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

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

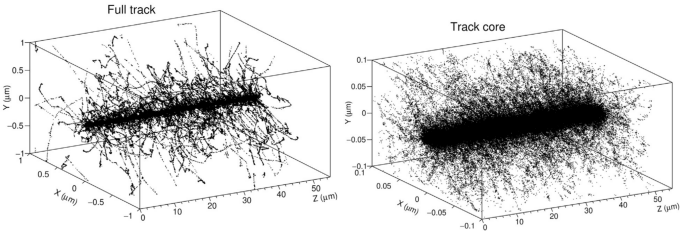
Basic assumptions:

- 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"**

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

$$ {}^{c\kappa}S_{\mathrm{LLE}} = \exp\left(-\alpha_{\mathrm{c}} \cdot Z_{\mathrm{c}} \cdot \frac{V_{\mathrm{c}}}{V_{\mathrm{s}}} - \alpha_{\mathrm{p}} \cdot Z_{\mathrm{p}} \cdot \frac{V_{\mathrm{p}}}{V_{\mathrm{s}}}\right) $$

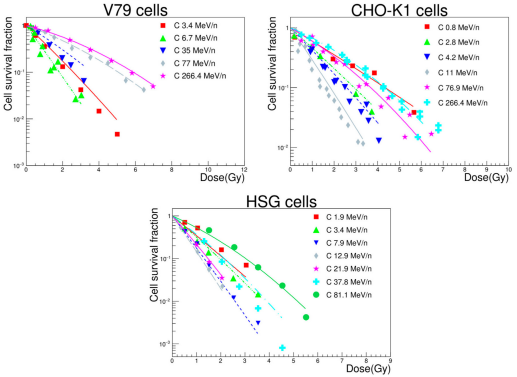
$$ {}^{c\kappa}S_{\mathrm{GE}} = \exp\left[-\frac{\beta_{\mathrm{r}}}{\eta^2}\left(Z_{\mathrm{c}} \cdot \frac{G_{\mathrm{c}}}{G_{\mathrm{r}}} \cdot \frac{V_{\mathrm{c}}}{V_{\mathrm{s}}} + Z_{\mathrm{p}} \cdot \frac{G_{\mathrm{p}}}{G_{\mathrm{r}}} \cdot \frac{V_{\mathrm{p}}}{V_{\mathrm{s}}}\right)^2\right] $$



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

Benchmarking of NanOx predictions for hadrontherapy

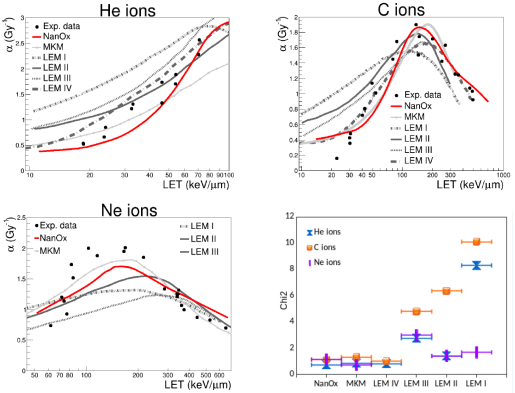
- Main output of NanOx: cell survival curves



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

- LQ fit to NanOx results → α, β

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

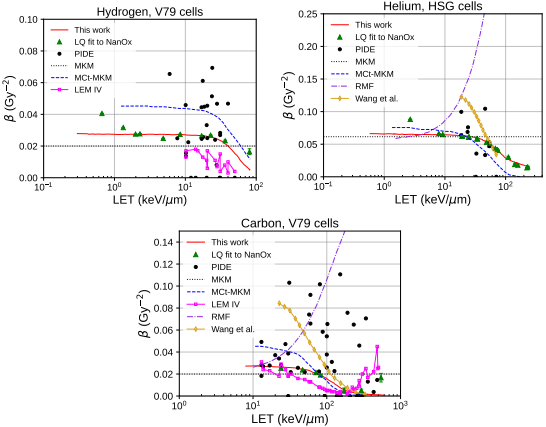


NanOx predictions of α for HSG cells (Monini et al. 2019)

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 $\sim$ 1–25 MeV/n was recently proposed
- NanOx predicts the decrease of β when the LET increases

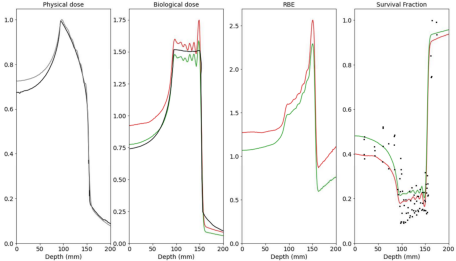
$$\beta \approx \beta_{\mathrm{r}}\,(\mathrm{RCE})^2 \left[1 - \frac{\alpha \cdot a \cdot \mathrm{LET}}{\sigma_0}\right]^2 \cdot \frac{\left(1 + \frac{m_1}{2}\right)}{(1 - m_1)^2}$$



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

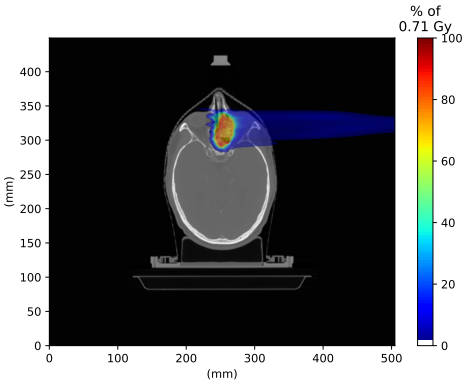
Towards a clinical application of NanOx: the BioDoseActor

- 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

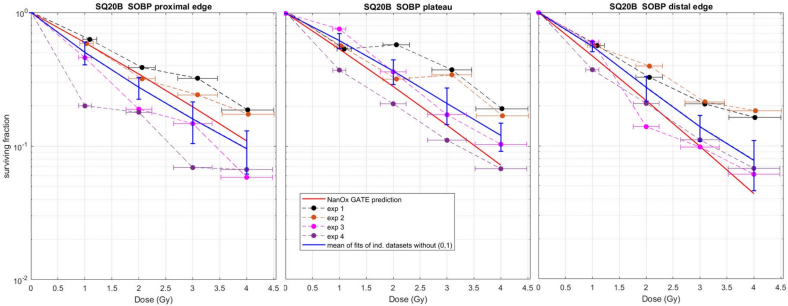


Biological dose simulated with GATE/NanOx

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)

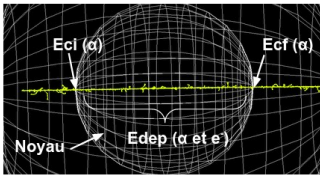
Adaptation of the NanOx formalism for low-energy ions

- 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

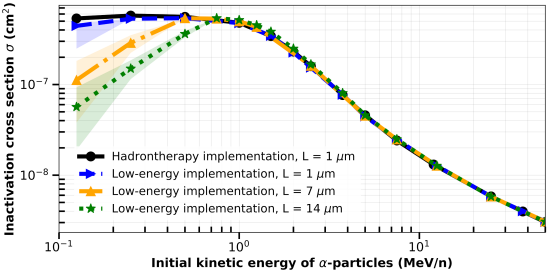
- Calculation based on the integration of LLE and GE along the ions' path in the SV

$$ {}^{t_N,t_k}n^* = \int_{{}^{t_k}E_\mathrm{f}}^{{}^{t_k}E_\mathrm{i}} {}^{t_N,t_k}\left(\frac{\mathrm{d}n^*}{\mathrm{d}E}\right)\mathrm{d}E = \phi({}^{t_k}E_\mathrm{i}) - \phi({}^{t_k}E_\mathrm{f}) $$

$$ {}^{t_k}\tilde{Z} = \frac{\eta}{m_\mathrm{s}}\left[\psi({}^{t_k}E_\mathrm{i}) - \psi({}^{t_k}E_\mathrm{f})\right] $$

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

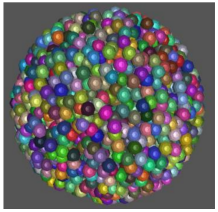
- NanOx implementations for hadrontherapy and low-energy ions were compared by computing the inactivation cross section (ICS)
- Both approaches agree for $E \gtrsim 1$ MeV/n
- For $E \lesssim 1$ MeV/n, the low-energy implementation predicts decreasing inactivation cross sections
- The impact of target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

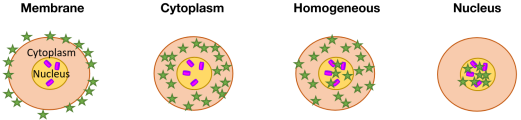


Inactivation cross section as a function of the initial kinetic energy of α-particles (Alcocer-Ávila et al. 2024)

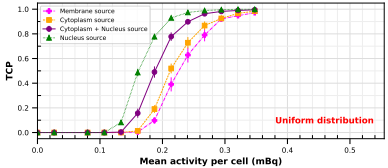
First applications of NanOx to TAT

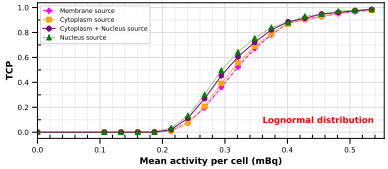
- Dosimetric *in silico* study of ^{211}At for TAT (Levrague et al. in preparation)
- 3D multicellular geometry (spheroid)
- Simulations coupling CPOP + Geant4 + NanOx





- 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 (Radiograaff, 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

References I

Alcocer-Ávila, M, E Testa, and M Beuve (in preparation). "Analytical expression of the β coefficient of cell survival curves predicted by the NanOx model". In.

Alcocer-Ávila, M et al. (2022). "Cell Survival Prediction in Hadrontherapy with the NanOx Biophysical Model". In: *Front Phys* 10, p. 1011063. DOI: 10.3389/fphy.2022.1011063.

Alcocer-Ávila, M et al. (2023). "Formalism of the NanOx biophysical model for radiotherapy applications". In: *Front Phys* 11. DOI: 10.3389/fphy.2023.1011062.

Alcocer-Ávila, M et al. (2024). "Biophysical modeling of low-energy ion irradiations with NanOx". In: *Med Phys*. DOI: 10.1002/mp.17407.

Ali, Yasmine et al. (2022). "Estimate of the Biological Dose in Hadrontherapy Using GATE". In: *Cancers* 14.7, p. 1667. DOI: 10.3390/cancers14071667.

Berger, T et al. (in preparation). "Surviving fraction of SQ20B cells in a helium spread out Bragg peak: comparison of experimental data with predictions of the NanOx model". In.

Cunha, M et al. (2017). "NanOx, a new model to predict cell survival in the context of particle therapy". In: *Phys Med Biol* 62.4, pp. 1248–1268. DOI: 10.1088/1361-6560/aa54c9.

Gervais, B. et al. (2006). "Numerical simulation of multiple ionization and high LET effects in liquid water radiolysis". In: *Radiat Phys Chem* 75.4, pp. 493–513. DOI: 10.1016/j.radphyschem.2005.09.015.

Levrague, V et al. (in preparation). "Impact of intracellular radionuclide distribution in a Monte Carlo biophysical 3D multi-cellular model for Targeted Alpha Therapy". In.

Monini, Caterina et al. (2019). "Comparison of Biophysical Models with Experimental Data for Three Cell Lines in Response to Irradiation with Monoenergetic Ions". In: *Phys Imaging Radiat Oncol* 12, pp. 17–21. DOI: 10.1016/j.phro.2019.10.004.

References II

Monini, Caterina et al. (2020). "Determination of the Effective Local Lethal Function for the NanOx Model". In: *Radiat Res* 193.4, p. 331. DOI: 10.1667/RR15463.1.