Planning Innovative Cancer Therapies Using RadioElements:
the PICTURE project

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Workshop CNAO-IN2P3 – Pavia, November 26, 2021

Targeted radiotherapies with emission of short-range ions

Therapies

- Alpha Targeted Radiation Therapy (α-TRT)
- Boron Neutron Capture Therapy (BNCT): $^{10}B(n,^{7}Li)\alpha$

	α-TRT	BNCT
Radionucl.	^{223}Ra, ^{225}Ac, $^{212/213}Bi$, $^{211}At\ldots$	^{10}B
α energies	5–9 MeV	a few MeV
α ranges	40–100 µm (a few cells)	5–9 µm
LET (keV/µm)	60–100	>200

Common difficulties in biological dose predictions

- Low-range ions = need for considering the heterogeneity of dose deposition at the cellular level
- Question of the relevant sensitive target at the cell level due to this heterogeneity (nucleus, cytoplasm, membrane…)
- Need for multiscale modeling and adapted biophys. models

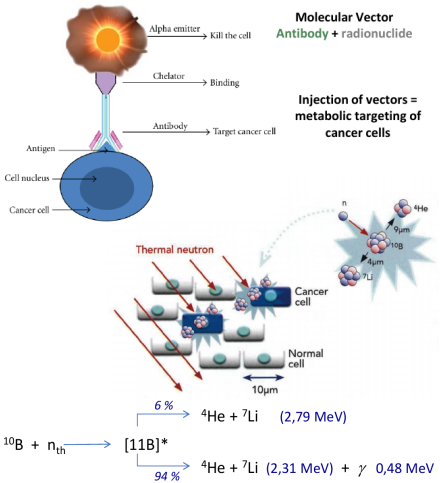


Fig. 1: α-TRT (top) and BNCT (bottom)

PICTURE project (collab. IP2I, LPSC, LIRIS)

Objective and funding

- Improve the biological dose prediction for targeted RT involving short-range ions (BNCT & α-TRT)
- 3-year ANR-INCA project (2 postdocs 30 months): March 2021–March-2024

(Main) Material & Methods

- Coupling multiscale Monte Carlo simulations (G4-DNA, GATE/G4) and the NanOx biophysical model
- Perform dedicated radiobiology experiments to constraint NanOx parameters

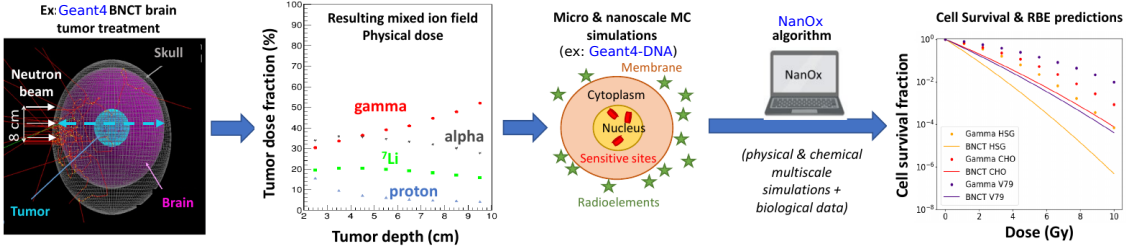


Fig. 2: Modeling workflow

NanOx model: "Nanodosimetry and Oxidative Stress" [Cunha 2017]

Main assumptions

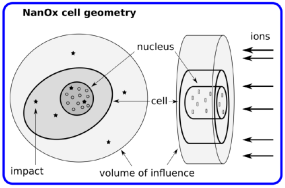
- Sensitive volume: cell nucleus
- 2 types of biological events:

	Local lethal events (LLE)	Global events (GE)
Event	Inactivation of nanometric targets	Oxidative stress in the sensitive volume
Scale	Nanometric	Micrometric
Evaluation	Specific energy*	Production of chemical species*

  - *: evaluated from Monte Carlo simulation (LPCHEM code [Gervais 2006])
- Cell survival for the configuration c_K (ion impacts, target positions, track structures): ${}^{c_K}S = {}^{c_K}S_{LLE} \times {}^{c_K}S_{GE}$

Full modeling of radiation stochastic effects

- Average cell surviving fraction: $\overline{S(D)} = \sum_{K=0}^{\infty} P(K,D) \cdot \langle {}^{c_K}S \rangle$
  - $P(K,D)$: probability to have K impacts with a dose D
  - $\langle {}^{c_K}S \rangle_{c_K}$: mean survival over all configurations c_K



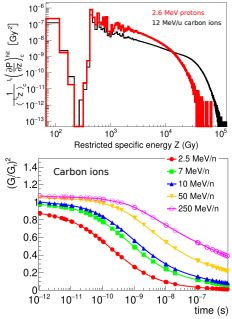


Fig. 3: Cell geometry, specific energy spectra and $OH^{\bullet}$ prod.

NanOx model: Main parameters and input data

Main parameters	Cell nucleus diameter	Effective lethal function of nanometric targets
Main input data	Cell microscopy	$\sim$ 3 cell survival curves 1 RX + 2 ions (intermediate and high LET ions)

Effective lethal function

- Construction from basis (increasing) functions

$\Rightarrow$ Demonstration of threshold and saturation effects [Monini 2020]

$\Rightarrow$ Parametrization with an error function (3 parameters)

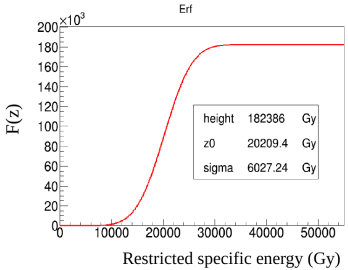


Fig. 4: Effective lethal function of V79 cell line

NanOx model: Results ("for hadrontherapy") and current limitations for targeted RT

Main parameters and required input data

- "NanOx predictions for three cell lines irradiated by monoenergetic ions were more often more accurate than the ones issued from 5 other biophysical models (MKM, LEM I–IV)" [Monini 2019]

Current limitations for targeted RT

- Developed for hadrontherapy (ion energy 50-400 MeV/nucleons): not adapted to low-energy predictions ⇒ Low-energy data need
- Need for implementation of an extra-nuclear sensitive volume

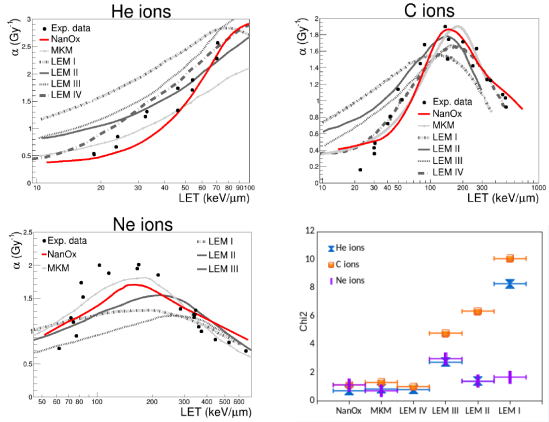


Fig. 5: NanOx predictions of α coefficients for HSG cell [Monini 2019]

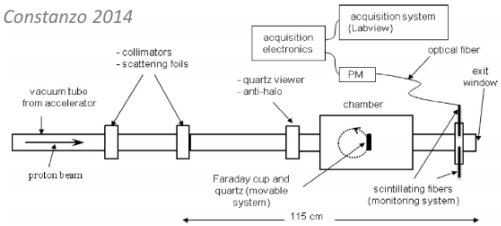
Radiobiology experiments: Current status of the Radiograaff beamline

Original objective

- Cell irradiations with 3 MeV proton beams (for the 4 MV VdG accelerator in Lyon)

Design

- Double scattering foils and collimation system (broad beam ~ 2 cm^2, $\pm 3\%$ homogeneity)
- Dose monitoring systems (Faraday cup, quartz, scintillating fibers)
- Thermostatic sample-support adapted to living cells



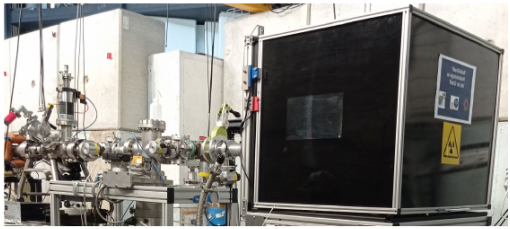


Fig. 6: The Radiograaff beamline

Specific biological experiments needed for PICTURE

Biological measurements

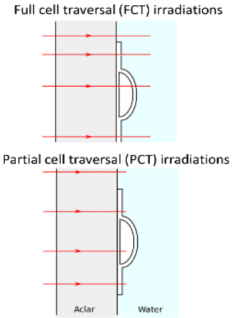
- Cell survival curves (clonogenic assay after irradiation)
- 3 different mammalian cell lines: CHO-K1, SQ20B and U87

Beams

- p 3MeV (for biol. reference)
- 4 energies ^{4}He (12–35 MeV)
- 4 energies ^{7}Li (25–50 MeV)

Full and partial cell traversal

- Objective: Distinguish the contribution of nuclear and extra-nuclear sensitive volumes
- Prospective experiments (very precise dosimetry and ion-range control)



Summary and Perspectives

Objective of the PICTURE project

- Improve the biological dose prediction for BNCT and α-TRT

Material and Methods

- Coupling multiscale Monte Carlo simulations (G4-DNA, GATE/G4) and the NanOx biophysical model
- Adaptation of NanOx $\Rightarrow$ 2 sensitive volumes: nuclear and extra-nuclear sensitive volumes
- Cell survival measurements to constraint NanOx parameters:
  - ^{4}He (12–35 MeV), ^{7}Li (25–50 MeV)
  - 2 irradiation configurations: full and partial cell traversal
- Cell confocal microscopy: 3D cell geometry $\Rightarrow$ Realistic cell modeling in MC simulations

Perspectives of collaboration

$\Rightarrow$ Radiobiology experiments

$\Rightarrow$ Biological dose modeling