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The PICTURE project: toward biological dose prediction of targeted radiotherapies emitting short-range ions, 19th International Congress on Neutron Capture Therapy

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The project

In Radioelement-Based Therapies (RBT), such as alpha targeted therapy and BNCT, the distribution of radio-emitters and the cell geometry impact the biological effect produced by the treatment. It is therefore of utmost importance to consider models capable of predicting precisely the biological dose in RBTs, considering different scales for dosimetry (tissues, micro and nanometric) and different cellular sensitive volumes.

The PICTURE project will address this topic by the extension of the **NanOx biophysical model** to include both an improved consideration of the low-energy ion biological effects in different tissues and the consideration of extra-nuclear sensitive volumes in the response of cell depth. Based on results of **cell irradiation experiments** in different conditions, the NanOx model will be able to characterize the tissue response to low-energy light ions and predict the response of an applied RBT.

PICTURE
(Planning Innovative Cancer Therapies Using RadioElements)

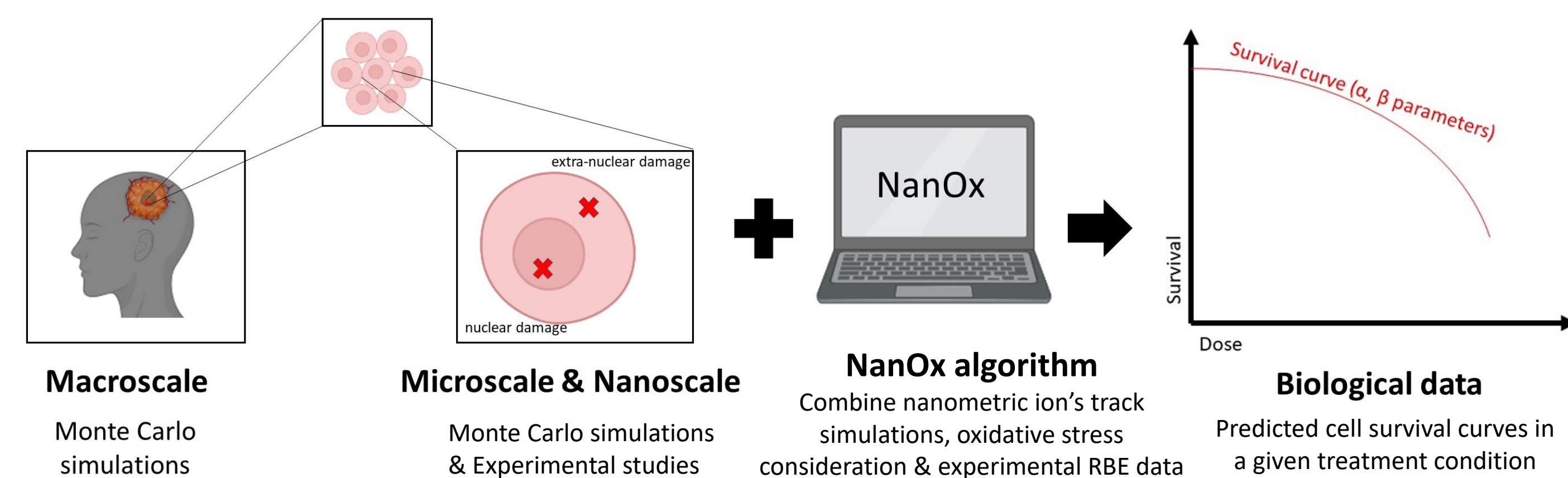


Figure 1. Outline of the project. Different scenarios and cell geometries simulated with Monte Carlo combined with experimental data will be included in the NanOx algorithm to predict the cell survival parameters for light-ion irradiations. The modified NanOx model will finally be used to improve the biological dose prediction in RBTs.

Hypotheses and Objectives

Main objective

For α -radioimmunotherapy (RIT) and BNCT, to better understand at which scale the distribution of radioelements in the tissues and in the cells need to be known.

How? by studying the impact of the cell geometry and the microdistribution of the radioelements on the biological dose calculations. Cell survival will be modelled with NanOx, based on track-structure simulations and irradiation experiments.

NanOx algorithm

Several biophysical models, like LEM, MKM and NanOx, have been developed to estimate the RBE of ions in hadrontherapy. The NanOx model [Cunha 2017; Monini 2019, 2020] considers the full stochasticity of energy deposition at both nano- and micro-metric scales. It is fulfilled in the modeling of the number of radiation impacts associated to a given dose, of the dose-deposition pattern along the track and of the inter-track processes. The final cell survival is a combination of local lethal events described in terms of nanodosimetry, and global events that result from the oxidative stress and accumulation of sublethal damage.

However, it is currently not adapted to predict precisely the effect of low-energy ions (< 10 MeV) of interest in RBTs, and the cell damage are only considered in the cell nucleus.

Objectives

Light ion effect prediction
Intra and extra-nucleus sensitive volumes

Input

Monte Carlo simulation
Experimental Data

Scales: Nanoscale (nucleus and extra-nucleus); Microscale (oxidative effects); Macroscale (from Monte Carlo simulations); Lethal fraction (from experimental data)

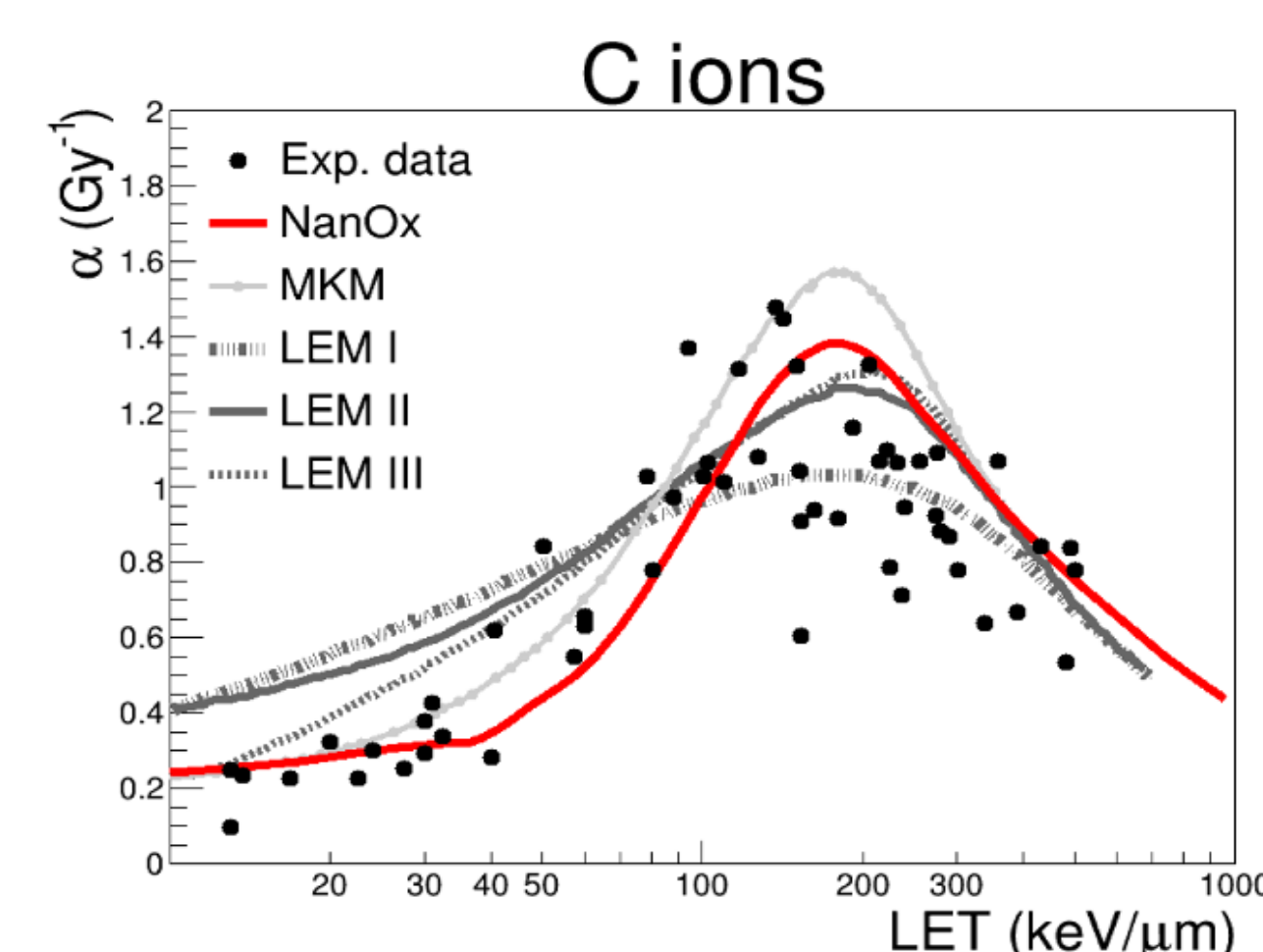


Figure 2 Comparison of the pool of experimental α values of V79 cells for monoenergetic carbon ion irradiations with those predicted by MKM, the three earlier versions of LEM, and NanOx [Monini et al. 2019]

Modeling of the biological dose distribution

Simulation tools: Geant4, Geant4-DNA (G4DNA) and NanOx.

Geant4/G4DNA

Macroscopic dosimetry simulations
Microscopic energy depositions of high-LET particles
Different distribution scenarios at the cellular scale in realistic cell geometries

NanOx

Cell survival predictions

Steps:

- 1- Macroscopic: calculation of mixed field of ions in depth for BNCT.
- 2- Microscopic: Influence of intra and extra cellular distributions of radioelements and of cell geometry (microscopy images) on cell survival for α -RIT and BNCT.
- 3- Implementation in NanOx of the cell survival experimental measurements with partial and full traversal cell irradiations for proton, alpha and Li-ion beams.

Final goal

Determine lethal function for each sensitive volume in NanOx tool.

Experimental studies

Biology: Cell survival curve determinations in ion irradiations for 3 cancer cell lines

Irradiation platform & beams

Radiograaff beamline [Constanzo 2014] at ALTO Tandem (Orsay, France).
3 to 10 MeV/n protons, alpha and Li-ions

Dosimetry:

GATE simulations & experimental meas. (Si detectors, scintillators, Films...)

Final goal

Firstly, obtain the biological effect of light-ions. Secondly, obtain separately the biological effects due to nucleus and extra-nucleus damage events.

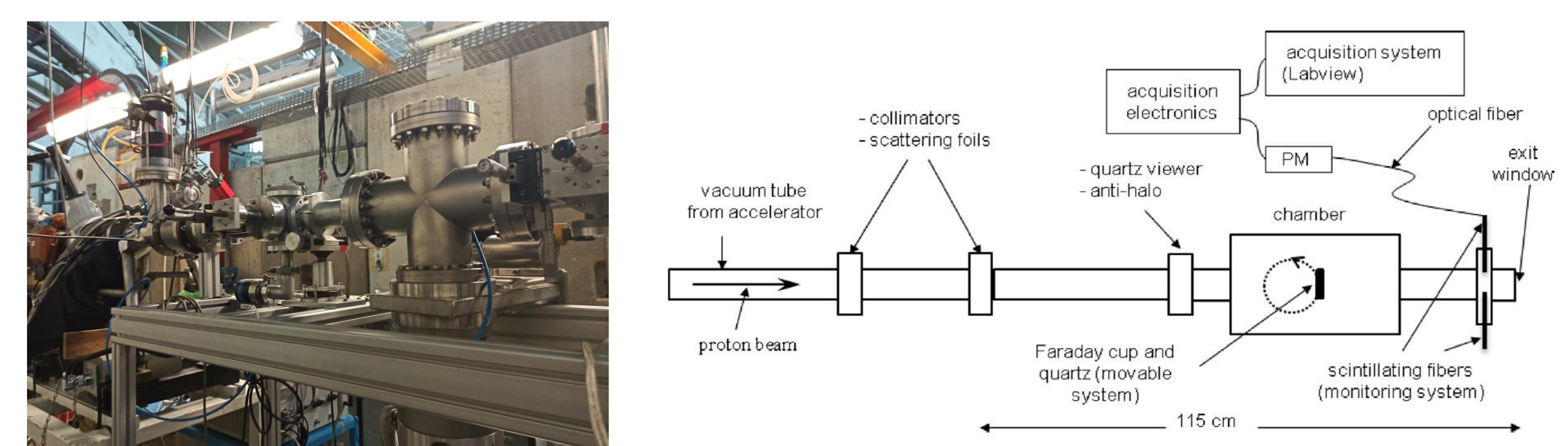


Figure 3. Radiograaff beamline installed at ALTO Tandem platform, where cell irradiation with protons, alpha particles and Li-ions will take place in order to get biological data to implement in the NanOx model.

Conclusions

This highly pluri-disciplinary project (biophysics modeling, G4-DNA Monte Carlo simulations, experimental radiobiology, instrumentation, computing science for imaging) will provide important knowledge on the radiobiological mechanisms and guidelines for future treatment planning systems and the optimization of RBT.

PICTURE project will try to answer the question:

Do we need information at sub-cellular, cellular or tissue scale to model precisely cell survival during α -RIT and BNCT radiotherapies?

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